PhD thesis

Patients Reported Outcomes for Symptom Management in Patients with Metastatic Malignant Melanoma receiving immunotherapy

- design, execution, and evaluation of a randomized controlled trial

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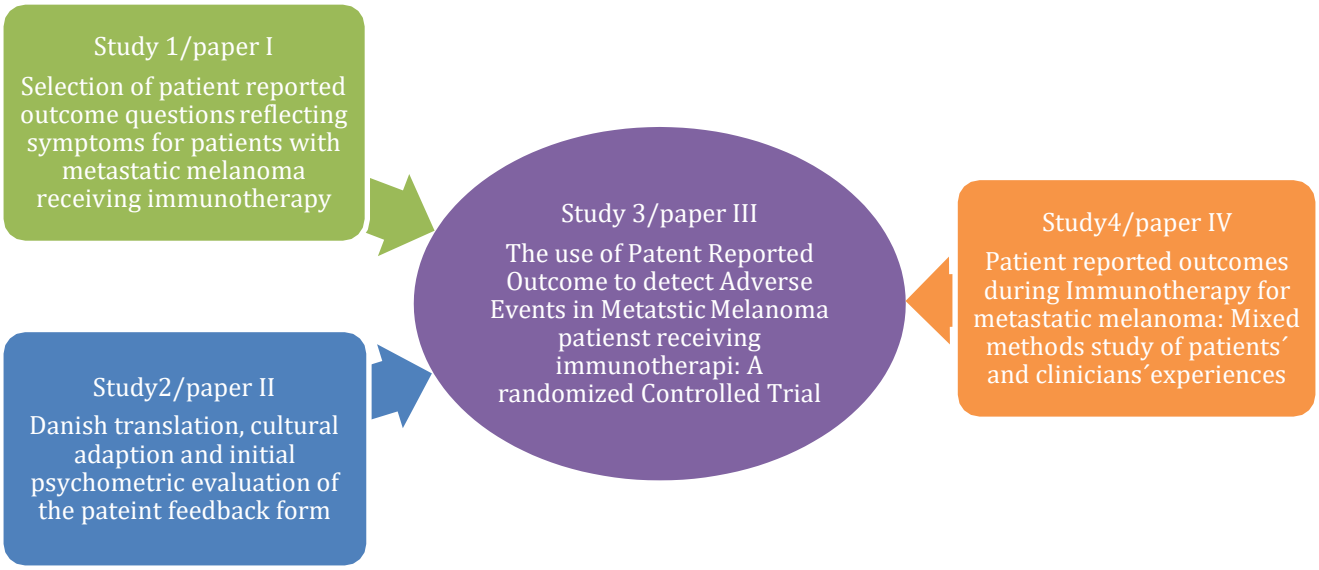
Preface and thesis outline

This PhD project consists of four studies using both quantitative and qualitative methods. The center of the thesis is a randomized clinical trial PROMelanoma with the primary aim of reducing the number of severe adverse events for melanoma patients who receive immunotherapy by using an e-Health intervention. In order to initiate the randomized controlled trial (RCT) and explore its endpoints, two supporting studies were carried out. First, through a thorough selection process, the items to be used in the trial were chosen from the PRO-CTCAE library (Study 1). Second, our study group translated an American questionnaire and validated it in a Danish context, according to existing guidelines, making it possible to evaluate the e-Health intervention from a patient perspective (Study 2). The third study was the RCT, where 146 melanoma patients were recruited between January 2017 and May 2019 at the Department of Oncology, Odense University Hospital (Study 3). Finally, a fourth study was undertaken where the patients participating in the RCT and their treating clinicians evaluated their experience through a survey and interviews (Study 4).



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Lærke Kjær Tolstrup December 2019

List of papers

Paper 1

Tolstrup LK, Bastholt L, Zwisler AD, Dieperink KB, Pappot H. Selection of patient-reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. ***Journal of patient-reported outcomes. 2019 Mar 21;3(1):19.***

Paper 2

Tolstrup LK, Pappot H, Zangger G, Bastholt L, Zwisler A-D, Dieperink KB. Danish translation, cultural adaption, and initial psychometric evaluation of the patient feedback form.
Health and quality of life outcomes. 2018 April 27;16(1):77.

Paper 3

Tolstrup LK, Bastholt L, Möller S, Zwisler, AD, Dieperink KB, Pappot H.
The use patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: A randomized controlled trial
Manuscript

Paper 4

Tolstrup LK, Pappot H, Bastholt L, Zwisler, AD, Dieperink KB.
Patient-reported outcomes during immunotherapy for metastatic melanoma: Mixed methods study of patients' and clinicians' experiences
In review, Journal of Medical Internet Research

Abbreviations:

CPI	Check-Point Inhibitor
CTLA-4	Cytotoxic T lymphocyte-Associated antigen 4 pathway
PD1	Programmed cell Death protein 1
PFS	Progression-Free Survival
OS	Overall survival
FDA	Food and Drug Administration
AEs	Adverse Events
AE	Adverse Event
NCI	National Cancer Institute
CTCAE	Common Terminology Criteria for Adverse Events
QoL	Quality of Life
ALAT	Alanine Aminotransferase
ASAT	Aspartate Aminotransferase
PRO	Patient-reported outcomes
PROM	Patient-Reported Outcome Measures
PREM	Patient-Reported Experience Measures
RCT	Randomized Controlled Trial
PRO-CTCAE	Patient Reported Outcomes-CTCAE
SPCs	Summary of Product Characteristics
EMA	European Medicines Agency

Contents

1. Introduction

1.1 Malignant melanoma

Worldwide, the incidence of melanoma of the skin continues to rise [1]. The increase is predominantly due to increased exposure to ultraviolet radiation/change in sun exposure patterns, ozone depletion [2, 3], and an aging population [4]. Cutaneous melanoma is the most lethal skin cancer worldwide [5]. In alignment with the global trend, the number of Danes who are diagnosed with malignant melanoma has also increased significantly during the last 50 years. Melanoma of the skin is the 19th most commonly occurring cancer in men and women, and Denmark had the highest incidence rate of melanoma in women in 2018 and the fourth-highest rate for both sexes in the world [6]. In Denmark, approximately 2300 new cases are reported every year. Most melanomas are diagnosed as primary tumors that have not metastasized [7], and they are cured by surgical intervention (stages 1 and 2). A little over 230 patients have resectable stage 3 or 4 disease, which means that they are also cured by surgical intervention, but have a high risk of recurrence. These patients are candidates for adjuvant immunotherapy. Another 400 patients are diagnosed with metastatic disease [8], where surgery alone can no longer be performed with curative intent (unresectable stages 3 and 4) either at initial diagnosis or during follow-up.

1.2 Treatment

Until recently, being diagnosed with metastatic malignant melanoma meant very poor prospects because the disease did not respond to existing treatments such as Interferon and cytotoxic chemotherapy. In a review from 2011, Garbe et al. concluded [9] that the median survival for patients with stage IV metastatic disease was around eight months, and less than 10% were alive after five years. However, the emergence of new anti-neoplastic treatments to this patient population has changed the scene drastically. Today, being diagnosed with metastatic melanoma no longer equals a death sentence. New systemic treatments for metastatic disease have emerged over the last ten years and have been approved for melanoma treatment. The three main groups of systemic drugs that are currently used are cytotoxic chemotherapy, targeted therapy, and immunotherapy. The efficacy of cytotoxic chemotherapy is very poor [7]. However, when it comes to targeted therapies [10, 11], and immunotherapy using checkpoint inhibitors (CPIs) [12-14], significant increases in survival have been found in large randomized clinical trials [15] with a five-year s urvival of up to 52% [16]. Because this

thesis deals with immunotherapy, alone or in combination, the following will focus on immunotherapy only.

1.3 The immune system and checkpoint inhibitors

In a normal state, the immune system detects and attacks organisms such as cancer cells that invade the body and cause disease. Immune checkpoints work by shutting down the immune system to prevent autoimmunity from occurring [17] and damage healthy cells. Thus, by stepping on the brakes, immune checkpoints ensure that the immune system does not harm the normal cells when responding to foreign invaders [18]. The downside of this mechanism, however, is that it may also hinder continued T-cell activation and prevent these cells from recognizing tumor antigens and killing tumor cells. This fact means that cancer cells can sometimes avoid immune recognition [17] through interaction with the checkpoints. The immune checkpoint inhibitors (CPIs) works by blocking these checkpoints so that the immune system continues to be activated. In this way, the brakes on the immune system are removed, and the patient´s own immune system is stimulated to recognize and attack the cancer cells [19, 20]. This overactivation of the immune system can trigger auto-immune side effects because the patient´s own immune system may also attack healthy cells. The two most relevant CPIs in relation to cancer therapy and melanoma so far are the anti-cytotoxic T lymphocyte-associated antigen 4 pathway (anti-CTLA-4) and anti-programmed cell death protein 1 (anti-PD-1). They will be described below.

1.4 Metastatic setting

1.4.1 Anti-CTLA-4 - Ipilimumab

Ipilimumab was the first drug to change the metastatic melanoma treatment strategy. Two studies showed increased OS with Ipilimumab compared to a peptide [21] vaccine or placebo [22] with response rates of 10-15 % [22, 23]. These results led to approval by the FDA and in Denmark in 2011 for the treatment of melanoma patients with metastatic disease. The toxicity profile of this drug can be severe since up 27% of the patients experience severe (grade 3 and 4) adverse events (AEs) [24]. When first introduced, Ipilimumab was used as first-line treatment for patients with metastatic disease, but as monotherapy, it is now only used as second or third-line therapy in Denmark.

1.4.2 Anti-PD1 - Pembrolizumab/Nivolumab

Pembrolizumab and Nivolumab were approved by the FDA in 2014 and in Denmark in 2015 for patients with metastatic melanoma. Today, these PD-1 inhibitors are the most advanced in terms of clinical development [25]. They have superseded Ipilimumab as a first-line treatment for patients with unresectable disease – either as a monotherapy or in combination with Ipilimumab [7]. Studies demonstrate that both Pembrolizumab and Nivolumab are superior to Ipilimumab in terms of both progression-free survival (PFS) and overall survival (OS) [24, 26]. The two drugs are comparable for efficacy and toxicity profiles and can be used interchangeably. For these drugs, 12-16 % of the patients experience severe toxicities (Table 1).

1.4.3 Combination therapy

Anti-CTLA-4 and anti-PD1 drugs combined are indicated for first-line treatment in patients with metastatic disease who have low PD-L1 expression in their tumor cells [7]. The Checkmate-067 trial showed a significantly longer PFS compared to Ipilimumab and Nivolumab as monotherapy in PD-L1 negative tumors [24]. The combination was approved by the FDA in 2015 and in Denmark in 2017 for PD-L1-negative patients. The latest update has shown a 5-year survival OS of more than 50% [16]. The combined therapy has, however, also resulted in an increased risk of severe toxicity. Over half of the patients experience severe AEs [24, 27].

1.5 Adjuvant setting

When it comes to the treatment of melanoma, it is not only in the metastatic setting that treatment options have improved. CPIs now also play a role when it comes to adjuvant treatment in patients surgically treated for regionally metastatic (stage 3) or distant metastatic melanoma. Until 2018, the standard of care consisted of clinical surveillance (watch and wait). The first drug to fundamentally change the scene was Ipilimumab. In 951 melanoma patients with resected melanoma at high risk of recurrence (stage IIIa, IIIb, or IIIc disease), PFS and OS at five years were significantly improved in favor of the patients who had received Ipilimumab compared with the placebo [28, 29]. However, more than half of the patients experienced severe AEs [28]. Ipilimumab was never approved in Europe as an adjuvant treatment. In December 2018, the CPIs, Pembrolizumab, and Nivolumab, were approved as adjuvant treatment. Nivolumab and Pembrolizumab had proven to increase progression-free survival (PFS) when compared to Ipilimumab/placebo [30, 31]. Moreover, they are less toxic.

1.6 Adverse events

As mentioned above, patients who receive cancer treatment may experience treatment- related toxicity. Treatment toxicities are also known as side effects, symptoms, or adverse events. In the following, they will be referred to as adverse events (AEs). An adverse event (AE) is an unexpected medical problem that occurs during treatment with a drug **[32]**. AEs may present themselves as mild, moderate, or severe. The American National Cancer Institute (NCI) has developed standardized definitions for adverse events – CTCAE (Common Criteria for adverse events) to enable clinicians to describe the severity of organ toxicity for patients receiving cancer therapy [33]. In this grading system, AEs are graded according to their severity. Grade 1 is a mild symptom, grade 2 a moderate symptom, and grades 3 and 4 typically represent severe and/or life-threatening symptoms. The mild and moderate symptoms are not severe, and if they require treatment, it is usually a local or minor intervention. With proper handling, the patient can continue treatment. Severe AEs, on the other hand, result in medical interventions, hospitalizations, and treatment discontinuation. Urgent intervention is often required [33]. The AEs that patients experience when treated with CPIs are unique and differ significantly from the ones patients who receive other kinds of antineoplastic therapies (cytotoxic chemotherapy, targeted therapy, radiotherapy) experience. They may potentially be life-threatening [21] if not detected promptly [21, 34]. When patients experience severe AEs (grade 3 or 4), treatment is either withheld or discontinued [35]. For AEs, they must be detected and treated in an adequate and timely manner, enabling relevant treatment to be initiated before they develop into severe AEs [25] and become potentially lethal and/or treatment-limiting. Table 1 provides an overview of AEs related to treatment with the relevant CPIs.

Checkpoint inhibitors	Any grade	Grade 3 or 4
Anti-CTLA-4 [21, 24, 26, 27] Ipilimumab	73-93%	20-27%
Anti-PD1 [26, 31, 36, 37] Pembrolizumab	67-80%	10-14%
Anti-PD1 [12, 13, 24, 30] Nivolumab	68-73%	9-16%
Anti-CTLA-4 + Anti-PD1 [24, 27] Ipilimumab+Nivolumab	91-96%	54-55%

Table 1 Treatment-related AEs described in prospective randomized trials.

1.6.1 Skin-related toxicity

Skin-related AEs often occur early and are one of the most commonly observed AEs [38]. It includes AEs such as vitiligo, autoimmune skin diseases, and rashes. Almost half of the patients who receive Ipilimumab experience skin-related AEs [38], whereas, for patients treated with anti-PD1, the number who experienced skin toxicity was around 18-25% [24, 38, 39]. Rash is, by far, the most common cutaneous AE seen with CPIs [40]. There are various kinds of rash, such as erythematous, reticular, edematous, or maculopapular rashes [38]. In this study, the term rash is used for all the various kinds, both because the patients cannot distinguish between them, and in published papers, the overall term rash is used [21, 27, 36]. As with many other the AEs related to CPIs, early detection is crucial to prevent exacerbation of the skin-toxicity, limit treatment interruption, and reduce the quality of life QoL [41].

1.6.2 Gastro-intestinal toxicity

Almost one-third of patients receiving Ipilimumab develop treatment-related diarrhea [21]. About 40% of the patients receiving the combination therapy experience gastrointestinal toxicity, including almost 10% with severe diarrhea or colitis [25]. Diarrhea is characterized by frequent and watery bowel movements [33], and the number stools determine the severity. Colitis, on the other hand, is associated with blood or mucus in the stool and/or abdominal pain [42]. However, the distinction between diarrhea and colitis is not always clear cut, and the terms of severe diarrhea and colitis are sometimes used interchangeably. Treatment for diarrhea/colitis must be provided promptly [42]. If it is not detected and treated early, patients may have to be hospitalized and treated with high doses of steroids and other immune-

suppressive agents – sometimes for a considerable period of time and with an impact on their quality of life (QoL).

1.6.3 Hepatic toxicity

Liver toxicity often presents itself in the form of elevated alanine transferase (ALAT) or elevated aspartate aminotransferase (ASAT). In most cases, the patients do not have any symptoms, but in more severe cases, the patients experience fever, fatigue, or jaundice [43]. More than 30% of the patients who receive combination therapy experience an increase in liver enzymes, whereas approximately 14% of the patients experience a grade 3 or 4 AE [24]. Because of the asymptomatic nature, elevated liver enzymes are usually detected by the routine monitoring of liver tests that take place during treatment.

1.6.4 Endocrine toxicity

Patients may also develop AEs in the endocrine organs. Even though they are not the most commonly occurring AEs, they must be monitored closely, because they can become very severe [18], potentially life-threatening. Furthermore, their presence may result in a reduced QoL and reduced possibility of receiving further treatment [44]. Thus, it is vital that they are detected early and treated promptly. Patients who receive combination therapy have an increased risk of developing severe endocrine AEs [18]. Most of these are irreversible and require life-long substitution treatment [45]. The main endocrine AEs are hypophysitis, and thyroiditis [46]. They are described below.

Hypophysitis

Autoimmune hypophysitis is one of the most common endocrine AE among patients treated with anti-CTLA-4 [47]. It occurs in up to 13% of the patients treated in clinical trials [46]. When Ipilimumab and Nivolumab are combined, it seems to occur more frequently compared to monotherapy [46]. The most common symptoms are not very specific. They include muscle weakness, fatigue, headache [18], but also mental status changes, anorexia, nausea, memory difficulties, visual disturbances, arthralgia have been reported [18, 38, 47]. If patients are treated promptly with hormone replacement, the symptoms will quickly reverse [47]. Because of the risk of secondary adrenal insufficiency, making early detection is crucial.

Thyroiditis

Hyperthyroidism and hypothyroidism are the most common endocrine AE in patients treated with a PD1-inhibitor [18]. When the thyroid gland function is affected, the patients typically

experience first a short period of hyperthyroidism, usually asymptomatic, before they become hypothyroid [48], albeit a minority of patients develop hypothyroidism that is not preceded by hyperthyroidism [45]. Accordingly, the term thyroiditis is used as the patients often experience both, and the term covers both symptom complexes [48].

1.6.5 Other immune-related adverse events

As illustrated in Figure 1, there are a lot of other AEs that patients may experience. Almost all organs may be affected by the treatment. Fatigue is a very common AE which occurs in up to 42% of the patients [21]. Other AEs that also occur and can be disturbing to the patients and impact their QoL are diabetes mellitus, arthritis, myositis, vitiligo, ocular disorders, pneumonitis, nausea, and constipation.

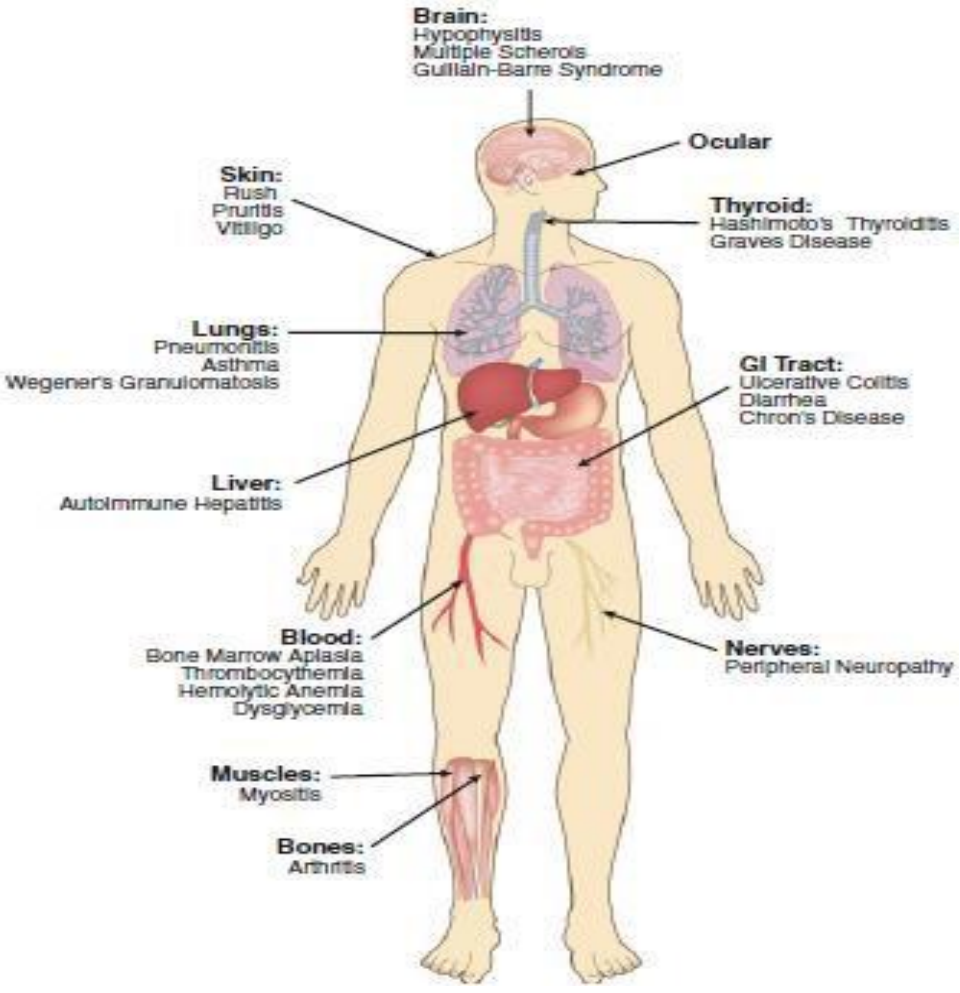


Fig.1 Reprinted from [25] with permission. Springer International Publishing, 2018. All rights reserved.

1.6.6 Onset

When it comes to time to onset of AEs, there is variation between the different CPIs. For anti-CTLA, the majority of AEs occur within the first three months after treatment start [38, 49], which is also true for the combination therapy (anti-CTLA-4 + anti-PD1) [27]. For patients receiving anti-PD1, the most AEs occur within the first six months [26, 39]. Late effects are also reported with these treatments. Actually, the first onset of AEs related to immunotherapy has been reported as long as one year after the discontinuation of treatment [35], and recent studies elucidate that delayed immune-related AEs may be an under-recognized phenomenon [50]. Although it would be interesting to explore the long-term side effects of CPIs, it is beyond the scope of this thesis, where the focus is on the large proportion of AEs that occur within the first 24 weeks of treatment.

1.6.7 Early detection

The relevant AEs have been described above, and it has been elucidated how they can become very severe. Furthermore, it has been emphasized that early detection is crucial so that mild or moderate AEs are managed in time, preventing them from becoming severe with all the problems this severity entails. In order to optimize early detection, we hypothesized that if melanoma patients were more intensively involved in the reporting of the symptoms they experienced while on treatment with immunotherapy, the number of grade 3 or 4 AEs might be reduced. In the following section, the focus will be on patient-reported outcomes (PROs), how they are used in various ways, and how they will be used in this study.

2. Patient-reported outcomes

In recent years, there has been an increased awareness within the health care system of the fact that patients may not be sufficiently involved when it comes to treatment and care. The Danish National Survey of Patient Experiences (Danish acronym: LUP) from 2018 stresses that the dimension "patient involvement" is the most poorly rated area of all of the dimensions rated by the patients in the survey [51] although Danish regions recommend that treatment and care should be planned *with* the patient and not *for* the patient [52]. Moreover, the Region of Southern Denmark emphasizes that the patient must be an actively qualified and willing partner in his or her cancer treatment and the development of the health care system [53]. Thus, both politicians, as well as patient organizations, wish for patients to be more engaged. According to the patient organization, "Danish patients," individual patient involvement is when patients are involved in their own course of treatment considering individual needs and preferences. This outcome is obtained through dialogue and decisions related to treatment and care [54]. When it comes to cancer treatment, there has also been an increased focus on involving the patient. One of the ways in which to engage the patient more is to use PROs. "*A PRO is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else)*" [55]. PRO can be seen as a good opportunity to systematically gather information on the patients´ perspective by combining the clinical and patient-experienced focus [56]. Patient reporting can be used in various ways. Patient-reported experience measures (PREMs) that capture the patients´ experience with and perception of treatment and care. The Danish National Survey of Patient Experiences is an example of this phenomenon. The other group is patient-reported outcome measures (PROMs) that describe how patients experience their symptoms, QoL, and functioning. Questionnaires such as EORCT-QLQ-30 and 5Q-5D are typical examples of this. In this project, there will be examples of both a PROM and a PREM questionnaire (Fig. 2).

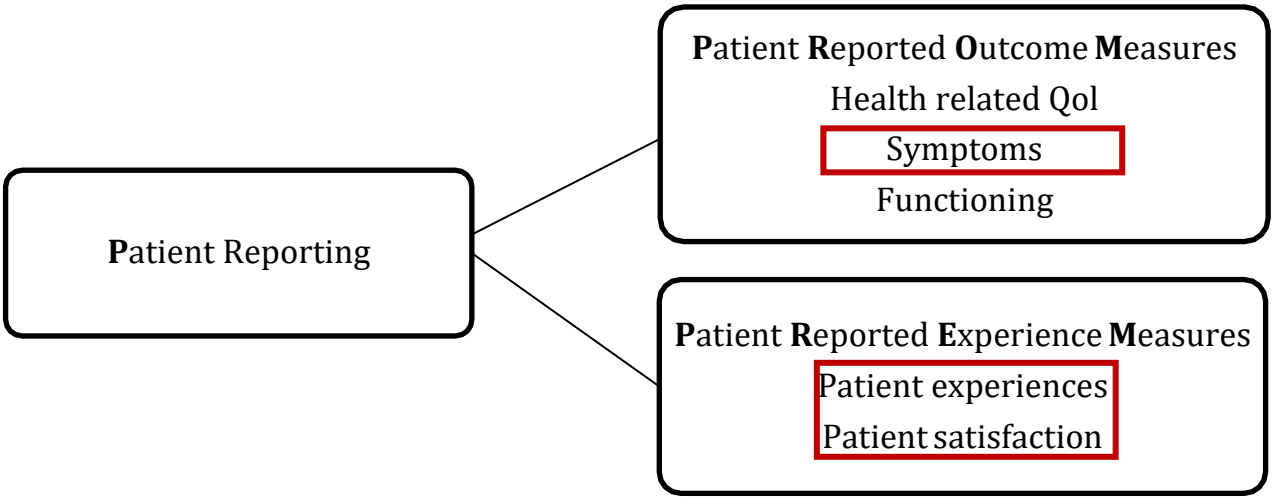


Fig. 2 Overview of patient-reported outcome measures and patient-reported experience measures. The red boxes illustrate the focus of the PhD-project

2.1 Active vs. passive PRO

The use of PROs in connection with clinical trials has increased significantly within the last decades [57]. In cancer trials, PRO-data has typically been collected to evaluate QoL and capture the most common treatment-related toxicities [58]. These data have often been collected prospectively, but not analyzed until the trials have ended [58]. The European Medicines Agency describes, for example, how there may be possible add-on value from licensure perspective of PRO-data to traditional efficacy and safety data in benefit-risk assessment [59]. In some studies, PRO endpoints have contributed to the interpretation of clinical trial results and led to regulatory approval of a specific drug [57]. Thus, it has primarily been used in the passive sense to generate population-based data and not be beneficial for the patients who deliver the PRO information directly. Rather it has benefitted future patients. Today, however, the collection of PRO-data is increasingly used actively; it is collected and used in real-time when the patient is actually seen at the clinic, where it is used to inform clinical decision making and enhance care for the individual patient, for example, by detecting physical or psychological issues that may otherwise be overlooked [60].

2.2 PRO and clinical outcomes

Because of the shift described above, the collection pf PRO-data has become more challenging because patient reporting has to be meaningful for both clinicians and patients and useable in real-time consultations [61]. It looks as if this challenge is partly met. Even though there are significant gaps in the evidence-base, there is growing evidence that when PROs are collected in routine cancer care, patient-centered care is improved [62]. Studies suggest that when patient reports are included in the patient-physician talk, symptom control and patient satisfaction are improved [63]. Other studies indicate that consultations are streamlined, and communication facilitated [64], QoL improved [63], and the risk of late side effects reduced [65]. Kotronoulas et al. conclude, in a review from 2014, describing 26 controlled trials on different cancer diagnoses, that when it comes to PROM-interventions, statistically significant findings were not found very often, and the effect sizes were mainly small-to-moderate and that more research is warranted [66]. Berry et al. also found that symptom distress was not alleviated by frequent patient reports plus tailored self-care instructions such as seeking assistance in managing troublesome issues compared to usual care [67]. Thus, there is a need for further investigation of the value of PROs concerning clinical outcomes.

Moreover, even though PRO has been used more extensively in the field of routine clinical cancer treatment within the last decades, and improvements have taken place, standardization is still lacking [68]; a lot of different systems are, for example, used to collect patient data and the implementation also varies [69]. As alluded to earlier, the focus of the PRO-tools used in routine cancer care or clinical trials differs; the focus can be on health- related QoL, physical symptoms, treatment toxicities, or psychosocial problems. In this thesis, the focus will be on PRO in connection with symptom management (Fig. 2).

2.3 PRO and symptom management

Evidence suggests that clinicians´ reporting of symptomatic AEs lacks reliability and that they tend to underreport the incidence and severity of symptoms compared to patients´ direct response. Moreover, patient self-reporting is truer to the patient perspective because the report has not been interpreted by a clinician [55, 70]. Furthermore, studies demonstrate that the numbers of AEs reported are greater when the report comes directly from the patient, rather than form the clinician [71]. Also, patients might have his or her AEs evaluated by different doctors each time they come to the clinic, which may further reduce the credibility of toxicity-

monitoring further [72]. Some studies describe how PROs can be useful in the early detection and monitoring of symptoms [68]. Some studies even describe how the derived effects of using PROs, i.e., early detection and the adequate treatment of disease and treatment-related symptoms, have resulted in prolonged survival [73] and early detection of relapse [74]. The U.S. Food and Drug Administration (FDA) Guidance for Industry also recommends using PRO in situations where the patients know best, for example, concerning symptomatic AEs [75]. PRO-tools have been used to monitor symptoms arising from anti- cancer agents, such as chemotherapy and radiotherapy. In some cases, the EORCT QOL-C30 has been used to capture some symptoms [76]. The Functional Assessment of Cancer Therapy (FACT) questionnaire includes symptoms such as nausea, headache, and anorexia, and it even has a melanoma-specific module [77]. The MD Anderson Symptom Inventory (MDASI) captures the 13 most important symptoms about cancer and treatment [78] (a melanoma-specific module does not exist). Only a limited number of AEs, however, are covered in these questionnaires, and they are not specifically designed for capturing AEs. By using PROs in connection with immunotherapy, there is a possibility of improving the understanding of the impact that immunotherapy has on the patients [79]. Selecting the right tool is a challenge, however, since none of the existing questionnaires are designed and suitable for patients who receive immunotherapy. In a recent review, Hall et al. [80] suggest that a new PRO-tool for symptom- monitoring is needed that can adequately capture the toxicity that patients experience when receiving immune CPIs. This need for a tailored PRO-tool is stressed by Kluetz et al. [81], who argue that in order for a PRO to be meaningful, it must reflect the relevant symptomology of the treatment under investigation. Thus, there was a need for a questionnaire specifically designed for detecting AE´s in melanoma patients receiving immunotherapy, which led to the item selection study (study1).

2.4 The PRO-CTCAE library

The American National Cancer Institute (NCI) has developed standardized definitions for AEs – Common Criteria for adverse events (CTCAE) to describe the severity of organ toxicity for patients receiving cancer therapy [82]. The system consists of 780 AEs and was at the beginning, primarily used in clinical trials to provide standardization in the evaluation of treatment-related toxicity. Today it is also used in routine cancer treatment. The CTCAE consists of three general categories [70]: 1) laboratory-related events such as anemia, 2) measurable events, for example, increased blood pressure, or 3) symptomatic AEs such as diarrhea. However, the AEs are typically assessed by clinicians and may not align with patient reporting of symptoms [79].

Recognizing this difference between patient and clinician reporting, the NCI has developed the paper-based CTCAE scoring system for toxicity- monitoring into an electronic tool appropriate for patient self-reporting [70] to give a truer picture of patients´ symptoms. The AEs in which patients are able to report fall into the category of symptomatic toxicities and out of the 780 AEs described in the CTCAE, 78 are appropriate for self-monitoring and constitute now what has been labeled as the PRO-CTCAE. Because each AE is elicited using between one to three questions, 124 individual questions are representing the 78 AEs in the library [83]. The PRO-CTCAE library is a form builder that researchers and clinicians can use (free of charge) to generate custom-built forms by selecting precisely the items that fit the patient population under investigation. The PRO-CTCAE item library has been translated into Danish and linguistically validated in a Danish setting [84]. It is not the intention that the PRO-CTCAE should replace the traditional CTCAE assessment carried out by clinicians. Instead, it should serve as a supplement to increase understanding of toxicity and tolerability [58].

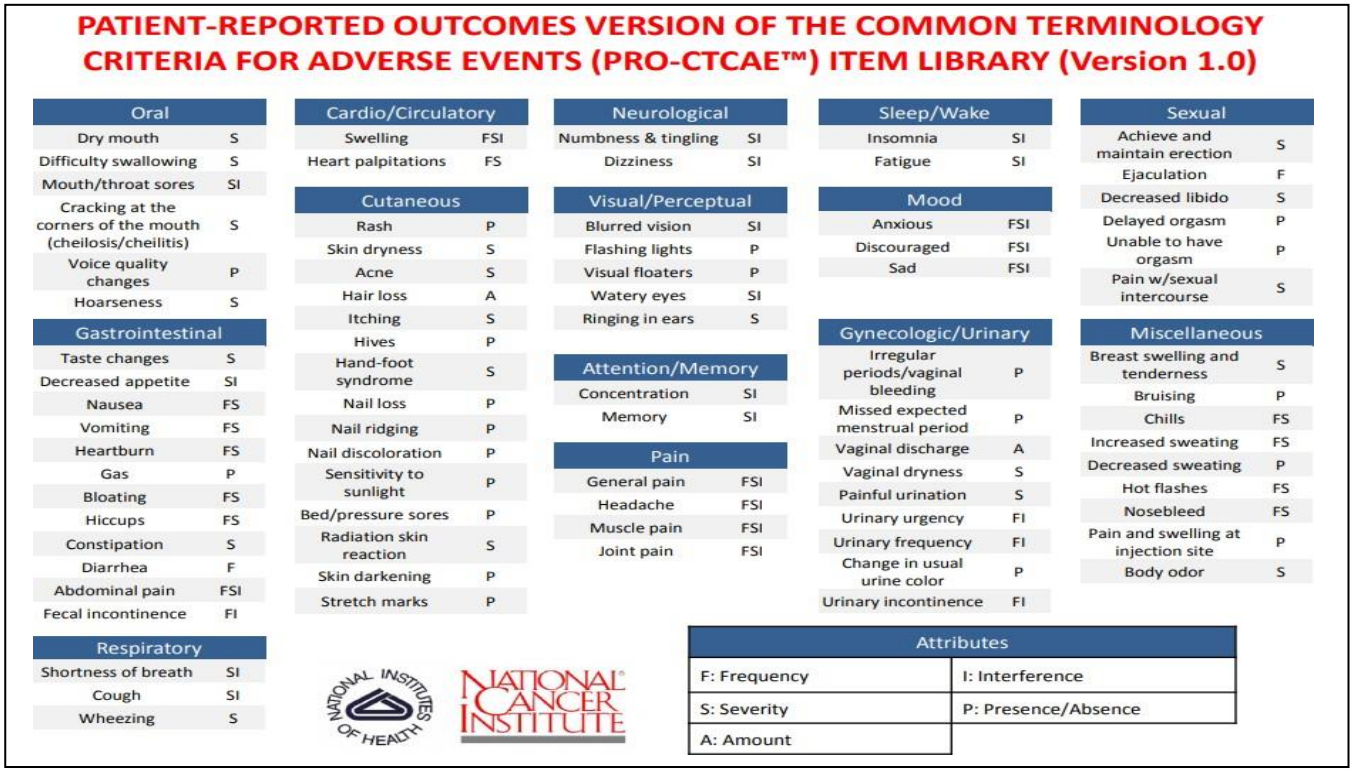


Fig. 3 An overview of the PRO-CTCAE item library. The items that were included in the RCT were selected from this library

Since the standard PRO-CTCAE recall period is seven days, it is recommended that it is filled out weekly [85], which is also the recall period that was chosen for this study. The PRO- CTCAE has been used in various studies to improve toxicity-monitoring for cancer patients receiving cytotoxic chemotherapy [63, 86], and the FDA considers it a promising tool that evaluates symptomatic AEs from the patient perspective [87]. It is not, however, in widespread use [68], and, to our knowledge, it has not been used in connection with CPIs, which makes it all the more interesting to explore. In this thesis, the use of a questionnaire designed from the PRO-CTCAE library, specifically for melanoma patients receiving immunotherapy (study I), will be used.

2.5 Electronic collection of PROs

Several studies have demonstrated that if the patients are properly trained, the fact that a PRO-tool is electronic does not constitute a problem, when it comes to recruiting and compliance. Several studies support the assessment that (even old and computer-naïve) patients are willing and able to answer electronic questionnaires [88-94]. This factor was important when designing this randomized controlled trial (RCT) because we knew that most of the patients eligible for this study are elderly. The average age of people, when diagnosed is 65 [95]. There are various methods for capturing electronic data. Data can be collected via the web, a handheld computer, a cell phone, or an interactive voice-response system. The development of IT-solutions has not only eased electronic data collection and made a patient- reported outcome more accessible to most patients. Compared to data collection with paper and pen, electronic data collection has also made patient reporting more accessible to clinicians, making it easier to include the patient response in a real-time consultation, minimize response burden, increase satisfaction and reduce the amount of missing data [69]. IT-solutions have also provided the patients with new ways of reporting their PRO-data, for example, their symptoms, outside the planned visits to the hospital [69] via a link to a webpage. However, additional research should be carried out to refine the technical solutions [96].

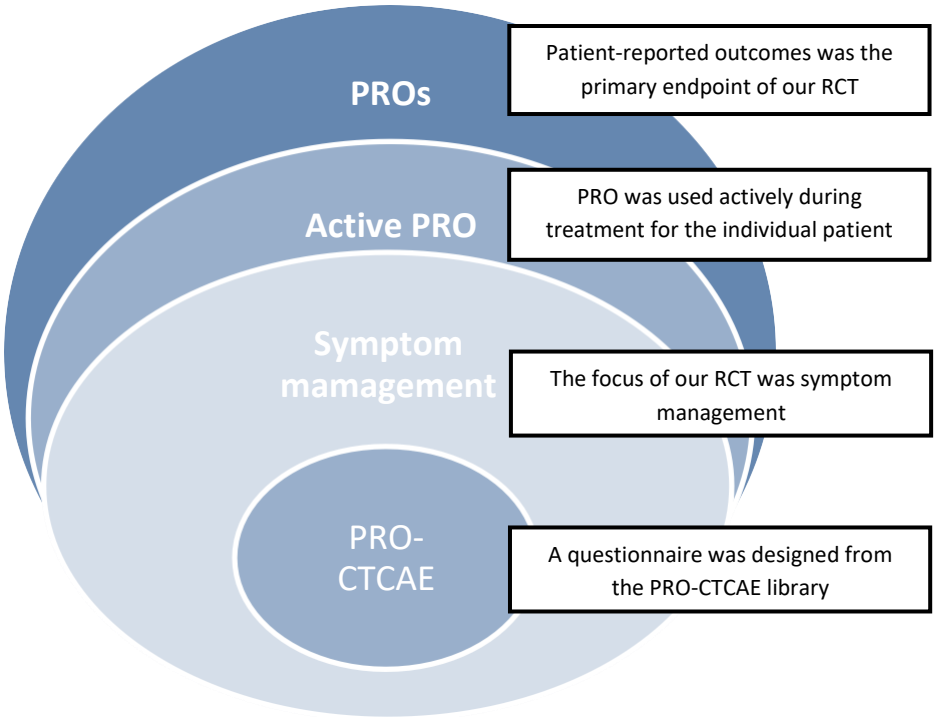


Fig. 4 The circle illustrates the choices about Patient-Reported Outcomes made in this project before initiating the RCT

2.6 Patients and clinician satisfaction

Not much is known about patients´ perception of the collection of PROs in the out-patient setting [97]. It is, however, important to measure patient satisfaction in order to find out if the use of a PRO is worthwhile, particularly if the intervention is to be implemented in standard care. An ideal electronic PRO platform is clinically relevant and easy for the patients to use [98], and it has to be a minimal burden to the staff [69]. In connection with the implementation of our RCT, we wanted to find out if these characteristics also applied to our e-Health intervention. In order to do so, we chose to use both qualitative and quantitative measures to evaluate the patient experience (study 4). We expected that using a standardized survey to examine general trends combined with interviews to give a more detailed insight would provide us with an understanding of the patients and clinician perspectives [99, 100]. Since we could not find an adequate questionnaire to use in our RCT to measure patient satisfaction with the e-Health intervention PROMelanoma, we decided to translate and validate an American feedback form (study 2). The American version of the Patient Feedback form was also used in connection with cancer patients [101, 102]. As it turned out, the form was originally developed and used to evaluate how patients experienced the electronic tracking of treatment-related toxicity using

the CTCAE adapted into a patient web-based patient-reporting system [94]. It can be seen as a forerunner of the PRO-CTCAE item library, which explains why the form appeared to be a perfect match when our study group searched for a fitting questionnaire to use in order to assess satisfaction with the intervention. Thus, face validity was high as the questionnaire seemed to measure what it was supposed to measure. The questionnaire seemed to be highly relevant and transparent and an adequate reflection of the construct to be measured [103], in this study: Patient satisfaction.

		Strongly Agree	Agree	Disagree	Strongly Disagree
3.	The questionnaire was easy to complete.	1	2	3	4
4.	Completing the questionnaire was useful.	1	2	3	4
5.	The questionnaire was easy to understand.	1	2	3	4
6.	Completing the questionnaire made it easier for me to remember my symptoms and side effects when I met with my doctor.	1	2	3	4
7.	Completing the questionnaire improved discussions with my doctor.	1	2	3	4
8.	My doctor used information from the questionnaire for my care.	1	2	3	4
9.	The quality of my care was improved because of the questionnaire.	1	2	3	4
10.	Communication with my doctor was improved because of the questionnaire.	1	2	3	4

Fig. 5 Selected questions from the Patient Feedback Form See appendix C for the entire questionnaire.

3. Aims and Hypothesis

The focus of this thesis is patient-reported outcomes for symptom management in patients with metastatic malignant melanoma receiving immunotherapy, including the design, execution, and evaluation of a randomized controlled trial. The thesis employs a mixed- methods approach using both qualitative and quantitative data. The first two studies are methods studies that include a literature search and a chart audit and a questionnaire translation and validation process. The third study is a randomized controlled trial, and the fourth study is an evaluation of the RCT, containing both quantitative data (a survey) and qualitative data (individual interviews and one focus group interview). A brief outline of the methodological and statistical considerations and results of the four studies will be presented in the methods and results section for each study. For more details, we refer to papers I-IV.

Study 1 - Item selection of relevant adverse events

The objective of this study was to elucidate the AEs that melanoma patients treated with immunotherapy experience and further identify the equivalent questions from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events library to include in the randomized controlled trial.

Hypothesis: It is possible to design a questionnaire from the PRO-CTCAE library specifically for melanoma patients receiving immunotherapy

Study 2 - Translation and validation of Patient Feedback Form

This study aimed to translate and culturally adapt the American "Patient Feedback Form" for Danish patients and to examine selected psychometric properties. The translated version of the form should be filled out by patients receiving the e-Health intervention in the randomized controlled trial.

Hypothesis: It is possible to carry out a proper translation and validation of the American Feedback Form and adapt it to a Danish setting

Study 3 - The randomized controlled trial

The primary endpoint was to examine if an e-Health intervention used weekly by patients receiving immunotherapy to supplement standard AE monitoring results in cutting the frequency of grade 3 or 4 AEs during treatment by 50% compared to patients who get a

standard AE monitoring every three weeks. Secondary endpoints were 1) to examine if more AEs are reported in the intervention group 2) to examine if the time patients experience grade 2 or higher toxicity, differs in the two groups to examine if there is a difference between the two groups when it comes to the number of 3) telephone consultations, 4) extra outpatient visits, 5) days in hospital, and 6) days on steroid therapy.

Hypothesis: Melanoma patients who report their adverse events to immunotherapy using PRO will experience an overall reduction of grade 3 and 4 events by 50% compared to patients who receive standard monitoring

Study 4 - Patient and clinician perspectives

This study aimed to examine how patients in the intervention of the randomized controlled trail and their treating clinicians experienced the use of the e-Health intervention.

Hypothesis: It is feasible to implement the e-Health intervention, PROMelanoma, in routine cancer care, and the satisfaction is high among patients and their treating clinicians.

4. Methods and results

In the following, the methods and results from the four studies that constitute the thesis will be described. Study 1 and study 2 were carried out between June 2016 till December 2016, leading up to the RCT, study 3, which recruited patients between January 2017 and May 2019. The evaluation of the intervention, study 4, was carried out simultaneously with the randomized controlled trial. Table 2 provides an overview of the studies.

	Study I	Study II	Study III	Study IV
Methods	Method study: Literature search, chart audit, and examination of product information	Method study: Translation, cultural adaption and psychometric testing of the Patient Feedback Form	Randomized controlled trial (PROMelanoma)	Mixed methods study to evaluate satisfaction with the e-Health intervention using a survey and interviews
Data	-Ten articles - 37 medical records - Product information of the relevant CPIs	Phase 1: - Seven cancer patients - Seven healthy persons Phase 2: - 95 prostate cancer patients	146 melanoma patients randomized between January 2017 and May 2019	- 57 patients included in the survey - 14 interviews with patients - One focus group interview with clinicians
Analysis	Adverse events were elucidated and their equivalent PRO-CTCAE items identified	Cognitive interviewing was used and initial psychometric testing performed	Poisson regression and negative binomial regression were used.	Descriptive statistics were used to describe results from the survey. Content analysis was used to analyze the Interviews
Results	28 items were included from the PRO-CTCAE library plus an additional item from the EORTC QLQ-30 resulting in a questionnaire specifically designed for melanoma patients	The translation and validation process resulted in a valid Danish version of the American Patient Feedback form	There was no difference between the two groups when it comes to the number of severe AEs. Patients in the intervention arm called more often.	Overall, patients and clinicians were satisfied with the tool. They believed it enhanced patients´ awareness of symptoms and increased the feeling of involvement.

Table 2 Overview of methods and results of the four studies

4. Study 1 – Selection of patient reported outcomes questions

As described in paper I, when creating a PRO and preparing the ideal instrument for assessing toxicity, it is important to select the symptoms that are most burdensome to the patients and occur most frequently [79]. In addition, they must be adapted to the toxicity-profile under investigation [81]. Another important factor is that it has to be easy to fill out, not too time-consuming and meaningful to the patients. In order to prepare the RCT, the objective of this study was to identify the symptoms appropriate for patient self-reporting and their equivalent PRO-questions to include from the PRO-CTCAE library.

4.1 Methods

Three initiatives were carried out. First, a literature research was performed in the three databases: Pubmed, Embase, and Cinahl, to establish the AEs described in international literature. Second, a chart audit was performed to see if the AEs found in medical records at the Department of Oncology at Odense University Hospital aligned with those found in international literature. Third, the Summary of Product Characteristics (SPCs) of the relevant CPIs were studied to make sure that no AEs were overlooked (Figure 6). See Paper I for further details.

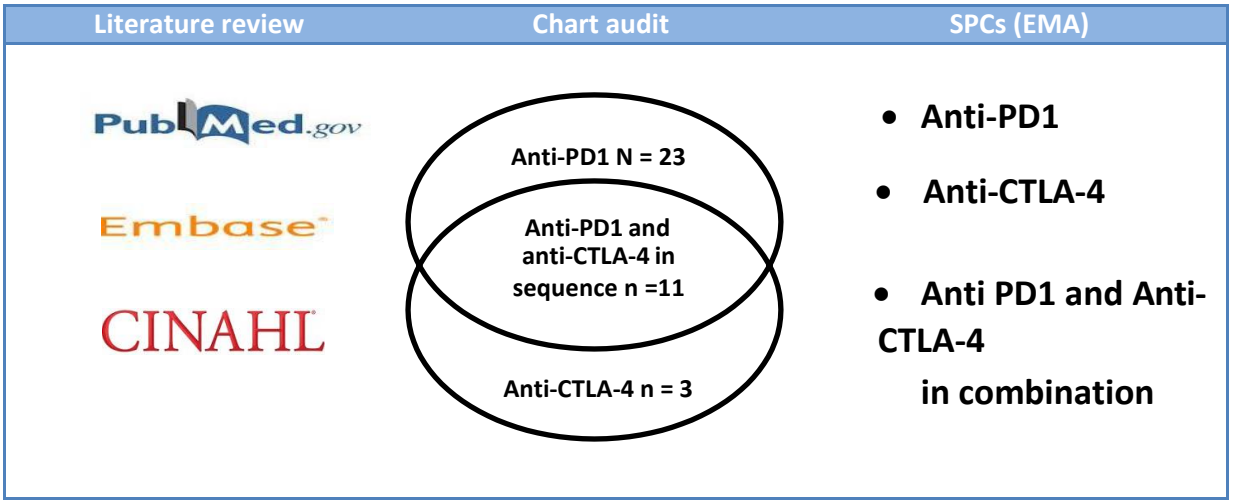


Fig. 6 Overviews of the three methods used to elucidate adverse events

Literature search: The literature search was performed in June 2016 (appendix A). Articles were included if the studies described were RCTs that 1) compared immunotherapy with chemotherapy or placebo, 2)compared immunotherapy in different doses, 3)compared different

immunotherapies, or [4]compared immunotherapy with other cancer therapies. In the search, the term "lung cancer" was also included because we, in the beginning, considered including this patent population in our randomized trial. During the title and abstract screening process, the group was excluded along with other cancer diagnoses as it was decided to focus only on melanoma patients in my thesis. Having performed a preliminary title and abstract screening, the second reviewer would take part in determining which references should move on to the full-text review. Hereafter, both reviewers would jointly decide which articles should be extracted and used in the study.

Chart Audit: A convenience sample of 37 medical records was examined with oral and written informed consent from patients between June and August 2016. All melanoma patients treated with either anti-PD-1 (Pembrolizumab) or anti-CTLA-4 (Ipilimumab) were asked to participate. The AEs identified in the medical records were found primarily in a pre-specified toxicity-monitoring form build upon the CTCAE grading scale v4 for physicians to evaluate the severity of AEs [104]. Moreover, free text notes in the medical records were examined.

SPCs: Finally, the SPCs from the European Medicines Agency (EMA) for Yervoy (Ipilimumab), Keytruda (Pembrolizumab), and Opdivo (Nivolumab) [105] were studied to ensure that no AEs had been overlooked.

Tablet set-up: Since the questions in the PRO-CTCAE library had already been validated in a Danish context among patients with seven different cancer types [84], there was no need to validate the chosen questions further. The set-up of the tablet, however, was to be decided. Accordingly, it was decided to make a small pilot study to test the tablet set-up to examine, i.e., if it was easy to use, not too time-consuming and if the alert function worked.

4.2 Results

The three data sources rendered a clear overview of the symptomology of the relevant CPIs. Having established the most frequent toxicities, we went on to identify the equivalent items to include from the PRO-CTCAE library. A total of 28 PRO-CTCAE questions were selected (Table 3). An extra question on blood in the stool, which was not a PRO-CTCAE item, was added because, albeit rare, it was important to detect as early signs of colitis. The question was

selected from the EORTC QLQ-30 – CR29 questionnaire (item no 38). The patients were to answer between 29 and 57 questions depending on how many toxicities they had experienced and how many supplementary questions were triggered. See paper I for further details on the item selection process and appendix B for a full overview of questions and sub-questions.

Vomiting	Constipation	Rash	Taste changes
Nausea	Hair loss	Itching	Skin dryness
Abdominal pain	Joint pain	Dizziness	Blurred vision
Diarrhea	Muscle pain	Headache	Hot flashes
Chills	Fatigue	General pain	Swelling
Decreased appetite	Shortness of breath	Pain/swelling injection site	Sad
Mouth/ throat sores	Cough	Numbness/ tingling	Discouraged
In addition to the 28 items from the PRO-CTCAE library, a question on blood in stool was included			

Table 3 Selected items from the PRO-CTCAE library reflecting relevant toxicities for patients receiving immunotherapy for malignant melanoma

4.2.1 Tablet set-up

Nine persons (four melanoma patients and five healthcare professionals) were asked to test the tablet set-up to examine if it was easy to use, not too time-consuming and if the alert function, which prompted the patients to contact the department when they reported an AE, was functional. Even though all the testers found the tablet easy to use, some changes were made as a result of the interviews. From the beginning, it had been decided to include an alert-function which prompted the patients to contact the out-patient clinic in case of an AE. The testers, however, found that it popped up too frequently. Accordingly, the alert function was removed for five items (*fatigue, skin dryness, hair loss, decreased appetite, and taste changes)*, because the patients did not have to react immediately to these AEs. Also, in the first version, the test respondents were annoyed that they had to answer the supplementary questions attached even though they had answered never or none to an item. Accordingly, the set-up was changed so that the attached question(s) would only be triggered if the patient had, in fact, experienced an AE. The estimated time for filling out the questionnaire adapted for melanoma patients receiving immunotherapy was approximately 10 minutes, depending on the number of experienced AEs and triggered questions. This result is in line with another Danish study with a similar number of PRO-CTCAE items, where the mean time for completing the questionnaire

was approximately seven minutes [106]. All of the testers found the tablet easy to use and the number of questions appropriate.

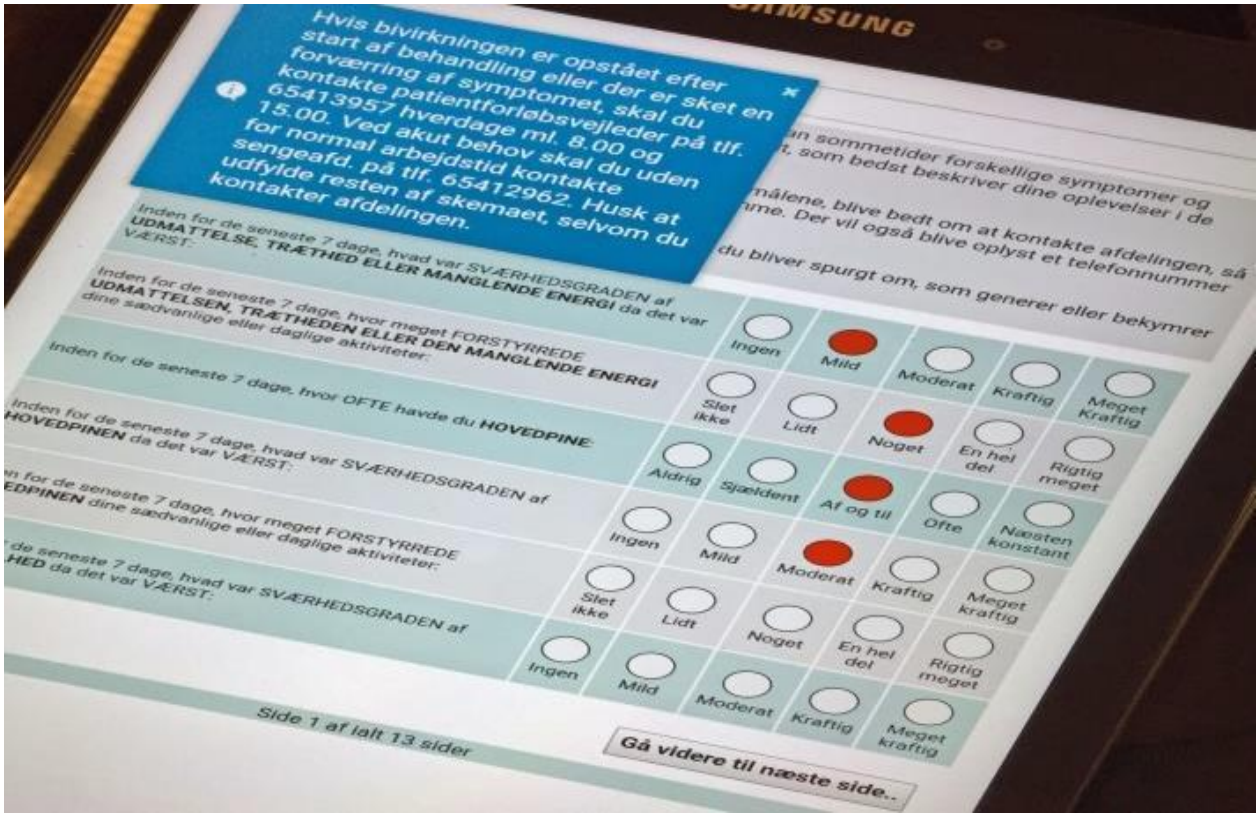


Fig. 7 Example of a page from the electronic questionnaire. The blue box in the left corner is the alert function telling the patient to contact the hospital

5. Study 2 – Translation and validation of the Patient Feedback Form

Because we would like the patients in our RCT to evaluate the e-Health intervention with a survey, we searched for a relevant PREM-questionnaire, as we wanted their experience investigated. As it was not possible to find a Danish questionnaire that fit the purpose, we decided to look abroad. As a result, an American Patient Feedback form [101] was chosen for this project as it includes all the relevant questions (appendix C).

5.1 Methods

Following existing guidelines, we translated the questionnaire into Danish and performed validation in Danish patients. See paper II and Figure 8 for further details.

Phase 1 consisted of several steps. First, the Patient Feedback Form was translated into Danish and culturally adapted according to existing guidelines, making it usable in a Danish setting [107, 108]. Moreover, the Patient Feedback Form was validated qualitatively [109] by performing cognitive interviewing with seven melanoma patients treated with immunotherapy and seven healthy persons. A combination of the "think aloud" method and "probing" was applied [109].

Phase 2 consisted of psychometric testing. In this study, a model population of a convenience sample of 102 men with prostate cancer in post-treatment control (54-73 years old) was chosen as respondents as they all had filled out the same PROM-questionnaire. In total, 95 persons were interviewed over the phone. No psychometric testing of the original version of the Patient Feedback Form had been carried out, and thus, the number of factors was unknown. It was not possible to make a confirmatory factor analysis. Accordingly, the psychometric evaluation comprised of an exploratory factor analysis (EFA) [110]. The number of latent factors were decided by evaluating the scree plot and the number of factors with Eigenvalues >1 [110]. Further, to assess internal consistency, Cronbach's Alpha (α) was evaluated. The level of α was considered: fair = 0.70-75; moderate = >0.75-0.80; good => 0.80- 0.85; excellent >0.85-0.90 [111]. Missing data was assessed by Little's Missing Completely at Random (MCAR) test [112]. Expectation-Maximization (EM) technique was used to impute data.

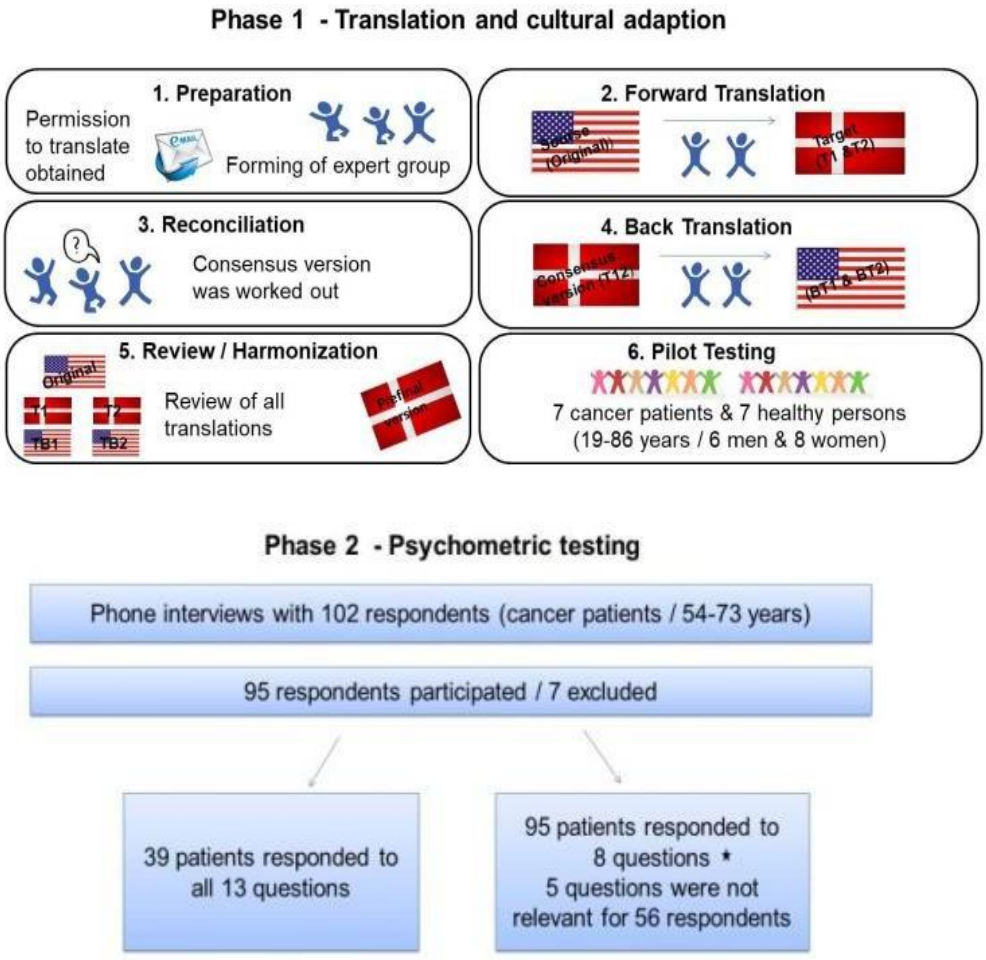


Fig 8 Overview of the translation and validation of the American Patient Feedback Form

5.2 Results

Phase 1: Overall, the forward and backward translation process went smoothly. Minor discrepancies, such as the use of synonyms and different word order, were found. However, the experts disagreed on whether or not the word "Feedback," which was included in the title, should be translated into Danish. Consequently, the project group decided to let the participants in the pilot test decide which word to use. Accordingly, the word was translated into Danish. One question about the time it took to fill out the form was changed slightly to make more sense. As a result of the cognitive interviews, the semantics of one of the questions was altered somewhat to adapt to Danish culture.

Phase 2: Among the 95 respondents, 56 respondents (58.9%) were not able to respond to all 13 items since they had been in touch with a clinician; five of the 13 items address this interaction. The MCAR test demonstrated that data were missing completely at random (p=0.307). The missing data were replaced by the EM method. The EFA was carried out as the KMO was 0.731, and Bartlett´s test significant (p<0.001). Four factors had an Eigen value >1, but only one factor was extracted as the Scree plot had a clear "elbow" (Fig. 9), showing one factor explaining 46.1% of the variance (Table 4). Three items had a factor load <0.4. The Cronbach's α was 0.89, which meant that the internal consistency was high. The inter-item correlations varied between -0.001-0.773, with items 2 and 5 having the lowest correlation and items 10 and 11 the highest.

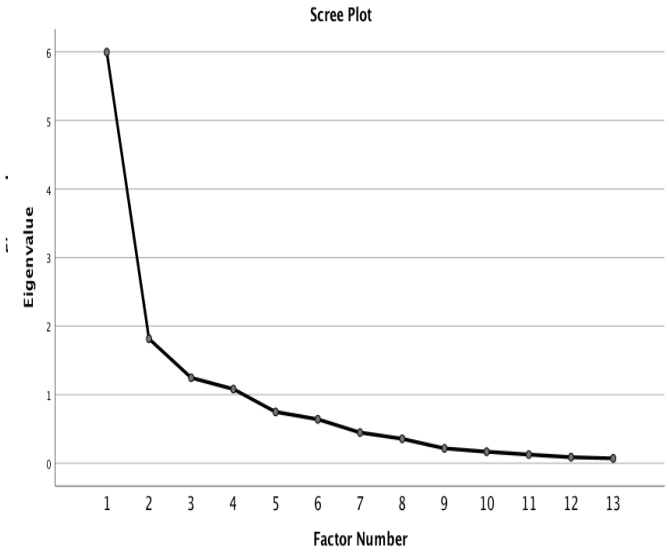


Fig. 9 Scree plot of eigenvalues according to factors in Patient Feedback Form

Factor	Initial Eigen Values	% of variance	Cumulative %
1	5.995	46.118	46.118
2	1.816	13.968	60.086
3	1.247	9.589	69.675
4	1.081	8.319	77.995
5	748	5.754	83.749
6	641	4.929	88.678
7	447	3.440	92.118
8	356	2.739	94.857
9	217	1.667	96.523
10	167	1.287	97.810
11	126	970	98.780
12	88	676	99.456
13	71	544	100.00

Table 4 Overview of factors in the Patient Feedback Form

The Danish version of the American Patient Feedback Form (appendix D) seems to be a valid tool for measuring patient satisfaction with PRO-interventions. However, additional psychometric testing could advantageously be carried out on a larger sample size.

6. Study 3 – A randomized controlled trial

6.1 Methods and patients

The RCT was designed as a pilot study to preliminary asses if the use of PRO by melanoma patients receiving immunotherapy could result in a reduction in the number of grade 3 or 4 AEs. Moreover, to investigate secondary endpoints which will be described below.

6.1.1 Recruitment

Recruitment took place at the Department of Oncology at Odense University Hospital between January 2017 and May 2019. The patients were introduced to the trial when they were informed about treatment with immunotherapy. See Table 5 for inclusion and exclusion criteria. Patients who were allocated to the intervention were given a tablet computer with a sim-card and trained in the self-reporting of symptoms. The baseline report was made in the outpatient clinic.

√ in the boxes – Yes or No		Yes	No
1.	Diagnosed with malignant melanoma	□	**STOP**
2.	Planned treatment with immunotherapy (metastatic or adjuvant)	□	**STOP**
3.	Men and women, age ≥ 18 years	□	**STOP**
4.	No serious or uncontrolled medical disorder that, in the opinion of the investigator, may impair ability to follow the protocol	□	**STOP**
5.	Be willing and able to comply with the electronic reporting of AEs on a weekly basis and the completion of quality of life questionnaires at baseline, 6 and 12 months.	□	**STOP**
6.	Be able to read and understand Danish	□	**STOP**
7.	Signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines	□	**STOP**

Table 5 Inclusion and exclusion criteria of the RCT

Patients were randomly assigned in a 1:1 ratio using the Open Patient data Explorative Network [113] to one of the following arms: standard toxicity assessment performed by a physician prior to treatment or standard toxicity assessment performed by a physician prior to treatment supplemented by weekly reporting at home.

6.1.2 Standard care/Intervention

In standard care, patients have their AEs assessed by a clinician prior to each treatment cycle. The patients are informed (orally and in writing) about the treatment and the toxicities which may occur during treatment. In addition to standard care, patients in the intervention had a tablet computer at their disposal with a sim-card. When the patients reported an AE, an alert was triggered for the majority of AEs telling the patient to contact the hospital. The alert was triggered when the patients reported a mild or higher symptom for 24 of the 29 items included in the questionnaire. The patient reports were not monitored by a clinician between visits. However, before the patient came to the outpatient clinic, the clinician would log into the Ambuflex system [114] to view the reports for the past weeks.

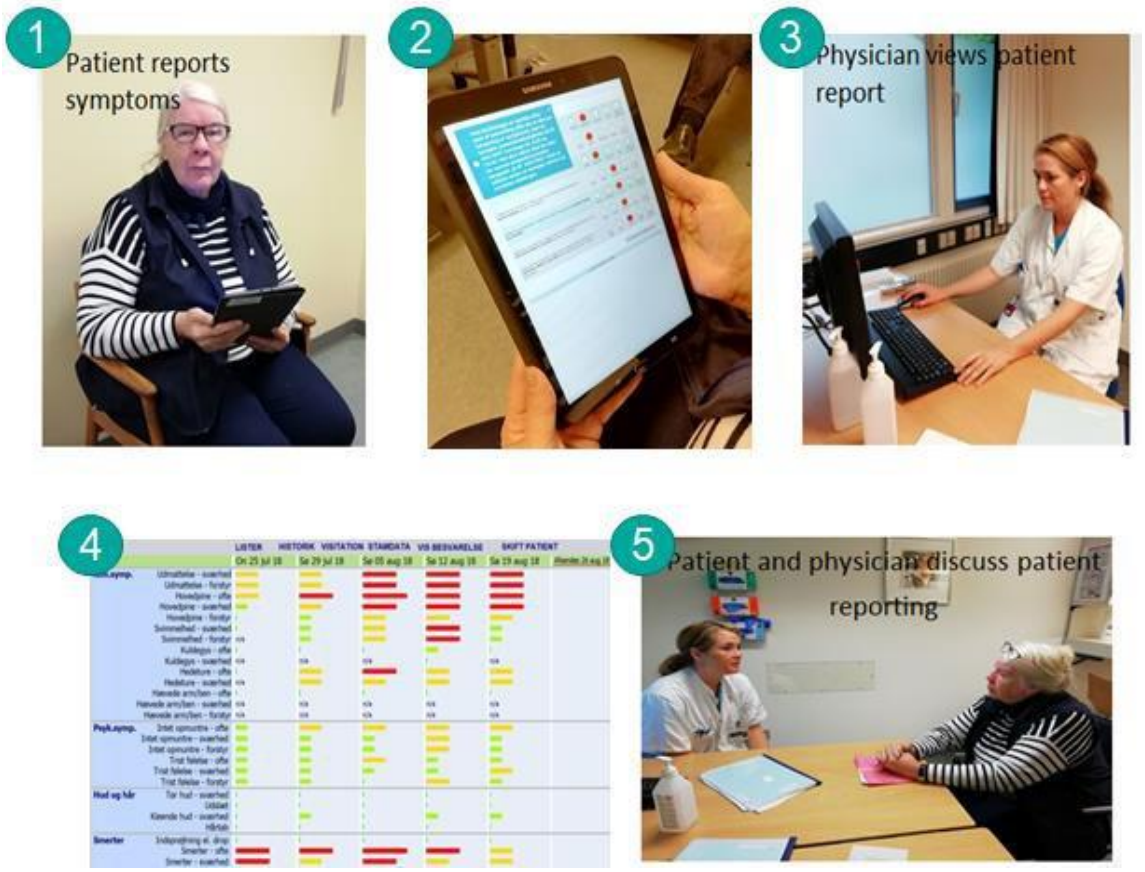


Fig. 10 Overview of the process of patient reporting

The questionnaire used in this study was designed from the PRO-CTCAE library. Detailed information on the development of the PRO-CTCAE library, and the selection of items is described above in the introduction and in paper I.

6.1.3 Primary and secondary outcomes

The Primary and secondary outcomes of the trial are described in Table 6.

Outcomes	
Primary outcomes	To investigate if the number of grade 3 or 4 AEs can be reduced by 50% by the use of PRO to report symptoms
Secondary outcomes	To investigate if more AEs are reported in the intervention group
	To investigate if the time patients experience grade 2 or higher toxicity differs
	To investigate if there is a difference in the number of telephone consultations
	To investigate if there is a difference in the number of extra outpatient visits
	To investigate if there is a difference in the number of days in hospital
	To investigate if there is a difference in the number of days in steroid treatment.

Table 6 Overview of primary and secondary outcomes

6.1.4 Statistical considerations

Since this trial was a pilot study evaluating a new health technology, a significance level of 0.2 [115] and a power of 0.64 was accepted to evaluate the endpoints. The planned sample size was 140 patients. Baseline characteristics and AEs by randomization groups were reported as counts and proportions. We compare number of AEs, phone contacts, and extra visits to the outpatient clinic by Poisson regression, respectively, negative binomial regression, in case of detected over dispersion. We compare total duration of grade 2 or higher AEs, duration of hospital stay and duration of steroid treatment by Wilcoxon rank sum test, and display the total length of grade 2 or higher AEs a Kaplan-Meier curve. All analyses were carried out in Stata 15.0 [116].

6.2 Results

As illustrated in the Consort diagram below (Fig. 11), 181 patients were found eligible for inclusion. Approximately 20% (n=35) declined to participate. Among these, 27 patients did not wish to be included either because they were not used to electronic devices or because they did not have the mental resources. The median age of the patients that declined to participate because of lack of IT-skills was 78 years, compared to 66 years in the randomized group. A total of 146 patients were randomized to the RCT. Two patients withdrew their consent, and six patients were excluded from the analysis. The last patient was included in May 2019.

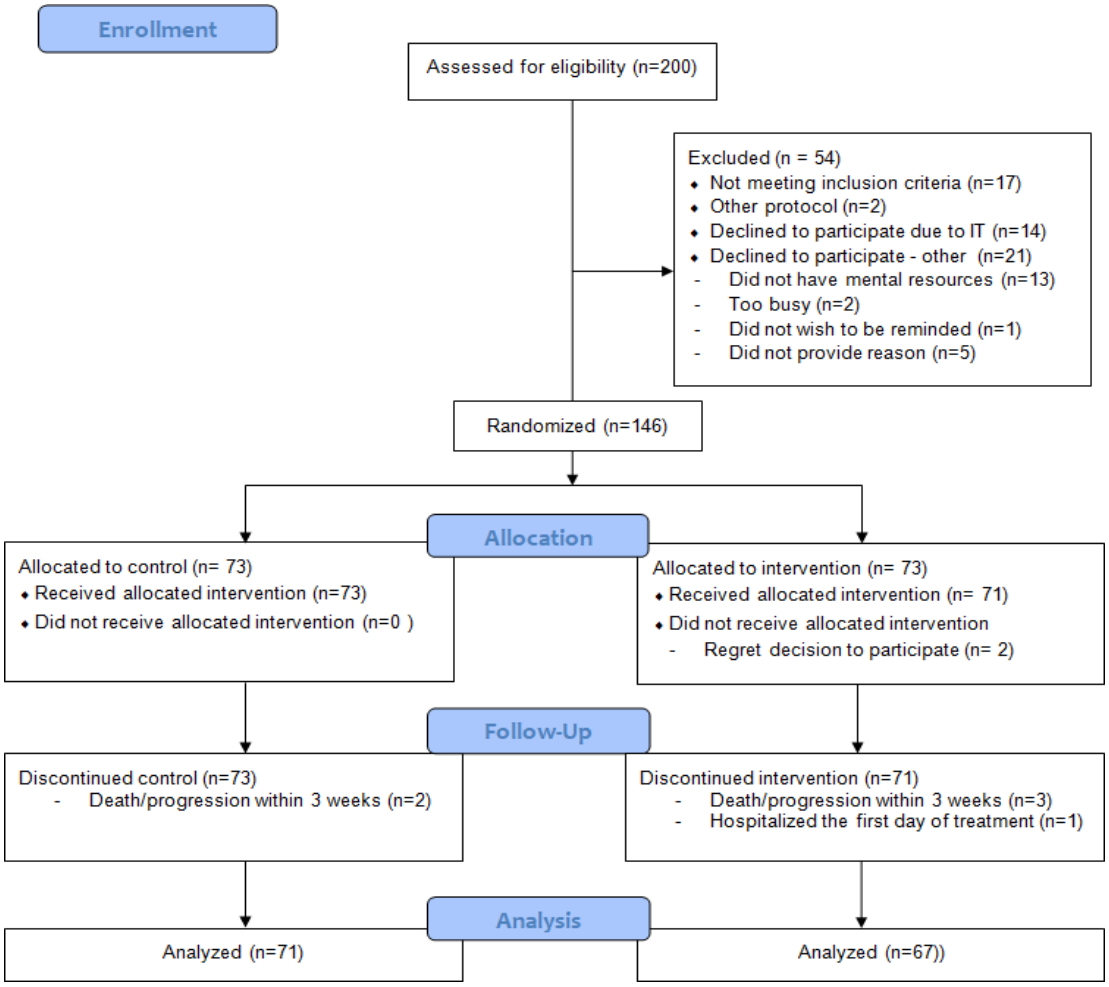


Fig 11 Consort diagram of inclusion process

Baseline characteristics between the control group and the intervention groups were compared. As illustrated in Table 7, there was no significant differneces between the groups. For further detail see paper III.

	Control N = 73 (%)	Intervention N=73 (%)	P-value
Age			
Median	66	66	0.957
Range	32- 83	34 - 87	
Sex			
Male	43 (59%)	35 (48%)	0.184
Female	30 (41%)	38 (52%)	
ECOG Performance Status			
0	52 (72%)	49 (69%)	0.582
1	19 (26%)	19 (27%)	
2	1 (1%)	3 (4%)	
Line of therapy			
Adjuvant	13 (18%)	11 (15%)	0.879
1st line	52 (71%)	52 (71%)	
2nd line	6 (8%)	6 (8%)	
3rd line	2 (3%)	4 (5%)	
Computer experience			
None	0 (0%)	3 (6%)	0.232
A little	16 (38%)	15 (32%)	
A lot	26 (62%)	29 (62%)	

Table 7 Overview of selected the baseline characteristics

6.2.1 Primary and secondary outcomes

We did not find a significant difference in the number of grade 3 or 4 AEs between the two groups. There was no difference in the number of overall AEs, or in the time the patients experienced grade 2 or higher toxicity either (Table 8).

Outcomes	P-value
Number of grade 3 or 4 adverse events	0.983
Overall number of adverse events	0.560
Duration of grade 2 or higher toxicity differs	0.516
Number of telephone consultations	0.009
Number of extra outpatient visits	0.156
Number of days in hospital	0.101
Number of days in steroid treatment.	0.004

Table 8 Differences in outcomes between control (n=71) and intervention (n=67) group

We did see a significant difference in the number of phone calls to the hospital as patients in the intervention group called more frequently. Thirteen patients (19%) represented almost half of the phone calls (47%) in the intervention group, which means that a minority of patients called frequently. There was also a tendency towards patients in the intervention group having more extra visits, which is in keeping with the higher number of phone calls. When it comes to the number of days in hospital there was a tendency (P = 0.101) that patients in the intervention group had more days in the hospital, compared to patients in the control group. Patients in the intervention group had significantly more days on steroid treatment (P= 0.004). However, only a little over one third of the patients received steroids or was admitted to the hospital.

7. Study 4 - Patients' and clinicians perspective on the e-Health intervention

A mixed-methods approach was applied to gain a deeper insight into the topic [99, 100]. For the quantitative part of the study, a questionnaire to measure patient satisfaction – the Patient Feedback Form [94, 101, 117] – was provided to patients who were randomized to the e- Health intervention. In addition, qualitative interviews with a subsample of these patients and one focus group interview with their treating clinicians were conducted.

7.1 Methods

7.1.1The e-Health intervention

As mentioned, the National Cancer Institute's PRO-CTCAE developed for patient self-reporting [118] was chosen as a PRO tool since the CTCAE grading scale [119] is well recognized within the medical oncology community [120] and used by clinical oncologists all over the world. The software platform AmbuFlex, which is specially developed for electronic PROs, was used [121]. The patients received a tablet with a SIM card to ensure internet access. The reporting would take place on the tablet, at home, once a week, which is the preferred recall period for PRO-CTCAE items [85], and continue for 24 weeks to ensure that the majority of symptoms were detected. If the patients experienced an AE, an alert would tell them to contact the department for 24 out of 29 AEs. As soon as the patients had responded to the questionnaire, the report was visible to the healthcare professionals in the outpatient clinic. Before the patients came to the outpatient clinic, the clinicians would log into the electronic system to see the patient's report.

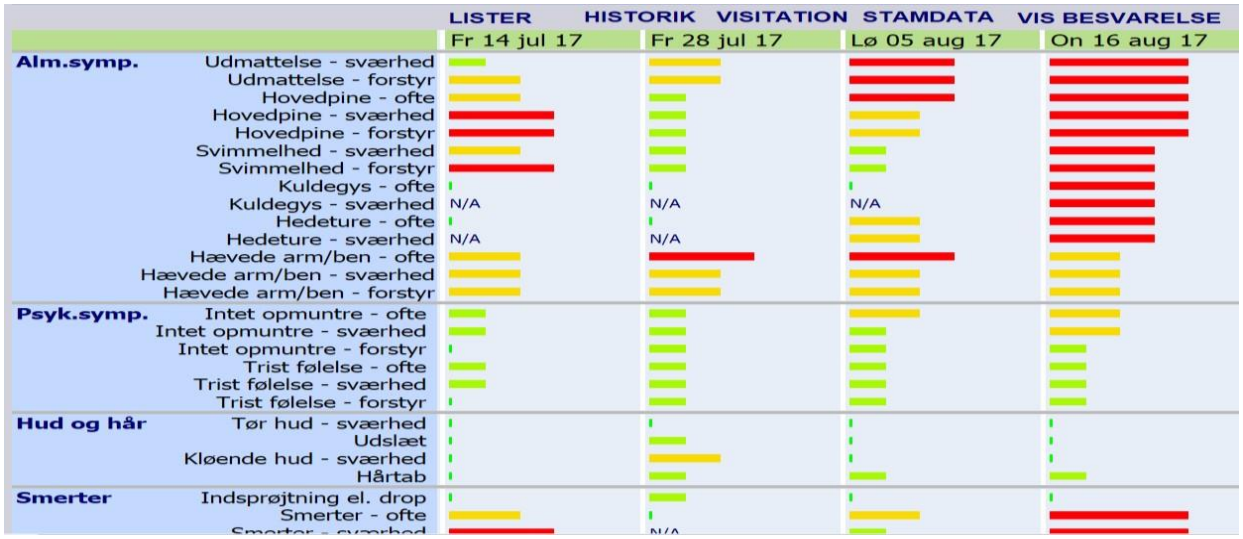


Fig. 12 Overview of the patient reports as viewed by the clinician

7.1.2 Interviews with patients

Patients were eligible for the qualitative part of the study if they had been randomized to the intervention in the RCT PROMelanoma and received one treatment cycle. A convenience sample of patients enrolled in the study, considering age and gender, were contacted over the phone and informed about this study between November 2017 and June 2018. A semi- structured interview guide was prepared (appendix E). The interviews were carried out by the same interviewer (LKT), who also carried out audiotaping and transcription. Four major categories were identified beforehand: The usefulness of the IT solution, the questionnaire, physician-patient communication, and involvement of relatives. A directed content analysis, as suggested by Hsieh and Shannon [122], was applied, using a deductive approach [123, 124]. Recruitment continued until no new information or no new themes were observed.

7.1.3 Survey

All patients in the intervention were asked to fill out the Patient Feedback Form [94, 101, 117] between January 2017 and April 2019, dealing with patient satisfaction relating to the e- Health intervention. The patients had completed the weekly PROMelanoma reporting at least three times. They had had the opportunity to discuss their report at least once with a physician before filling out the Patient Feedback Form. Data were analyzed using descriptive statistics.

7.1.4 Focus group interview with clinicians

A focus group interview was chosen as the preferred method for clinicians because the number of physicians and nurses caring for these patients was limited to a small selected group, which made a questionnaire pointless. For the same reason, only one interview was conducted. The interview was conducted in a semi-structured way [125] (appendix F). The purpose of the focus group was to explore the perspectives of the clinicians regarding the implementation and acceptability of the e-Health intervention in daily practice. The same approach – content analysis – was applied concerning the group interview, as described above [122].

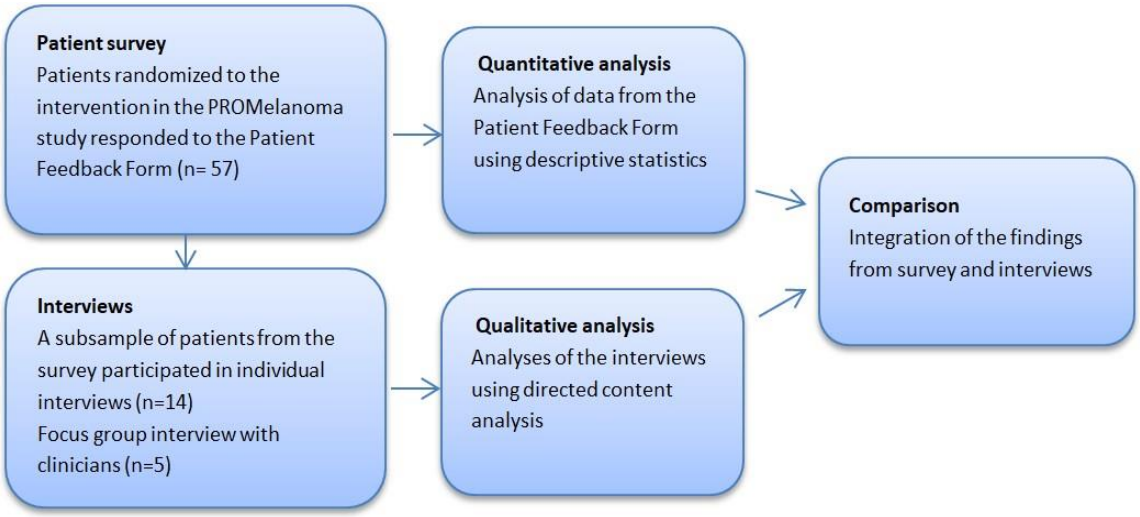
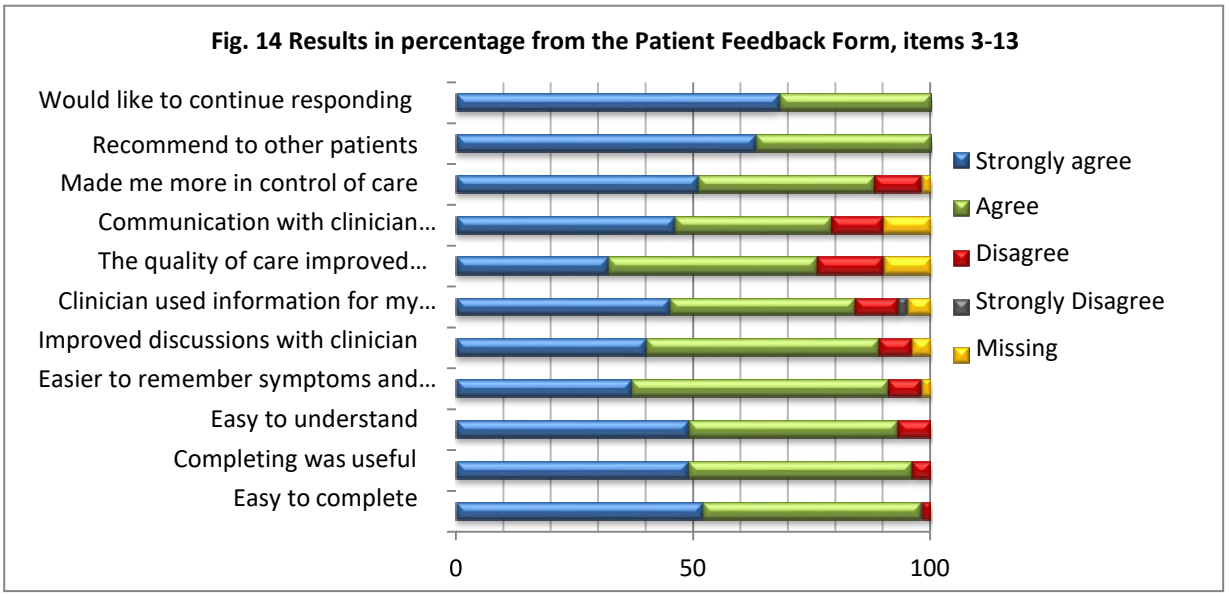


Fig. 13 Overview of the mixed methods study design, including a survey, individual interviews, and one focus group interview

7.2 Results

7.2.1 Survey:

Patients who were randomized to the intervention in the PROMelanoma study (n=70), median age 65 years old, 33 men/37 women), evaluated the e-Health intervention by completing the Patient Feedback Form. A total of 13 patients did not fill out the Patient Feedback Form because they did not wish to do the electronic reporting anyway (n=2), were hospitalized due to AEs, and never received the second treatment cycle (n=2), or the melanoma progressed quickly. It was unethical to ask them to participate (n=9). A total of 57 patients completed the questionnaire. Results from the survey can be found in Figure 14 below.



As demonstrated in Fig. 14, the patients participating in the survey were very satisfied with the e-Health intervention. For eight out of 13 questions, there was a satisfaction rate of over 90%. Only 75% of the patients agreed that the questionnaire improved the quality of care, which was the question with the lowest satisfaction rate. See Table 8 and paper IV for further details.

7.2.2 Patient interviews

Fourteen interviews were conducted. The median age of the patients was 67 years, range 41-79 – six men and eight women. The mean duration of the interviews was 20 minutes (range: 9 – 33). Three of the themes that were identified from the transcripts aligned with three of the predetermined categories: Usefulness of the IT solution, the questionnaire, and physician-patient communication. The fourth category, which was the involvement of relatives, never evolved into a theme because the vast majority of patients did not discuss the reporting with their relatives. The main findings of the patient interviews can be found in Table 8.

7.2.3 Focus group interview with clinicians

The focus group consisted of five clinicians: Three physicians and two nurses. They were all female and had a median age of 43 years. They all had a broad experience working with melanoma patients and dealing with AEs related to immunotherapy (6-11 years). All of them were used to including the patient reports in the consultation. In general, the clinicians believed that patient report increased the level of attention to AEs, and it made sense to include them in the patient-clinician talk. However, including the patient data, was also more time-consuming compared to a regular consultation and PRO-tool should be a supplement rather than a replacement.

7.2.4 Comparison between survey and patient interviews and focus group interview

Overall, the findings from the survey confirmed what had been established in the patient interviews. The patients reported that it was easy to fill out the questionnaire and that it made sense to do so. Moreover, it increased symptom awareness. A minority of the patients expressed in the interviews that they did not believe that the health care professionals had seen their reports when they came to the clinic. This result is in line with the data from the survey, where the majority experienced that the reported information was used in the consultation. Both patients and clinicians agreed that when the report was included, it helped to set an agenda for the consultation, prioritizing the most acute problems.

Survey (n = 57) % of patients who agree/strongly agree (Selected questions)	Interviews with patients (n = 14)	Focus group interview (n = 1 focus group/5 participants)
- The questionnaire was easy to complete (98 %) - Easier to remember symptoms and side effects (91%) - Clinicians used the information for my care (84%) - The quality of care was improved because of the questionnaire (75%) - Communication with clinician improved (78%) - Made me feel more in control of care (87) - Recommend to other patients (100%)	**1. The usefulness of the electronic solution** - Accessing and filling out the questionnaire was easy - Some patients needed a touch screen pen - Patients were asked to update the operating system of the tablet, but easy to discard - Patients contacted the clinic in case of technical issues - Only a few patients would have patients preferred a link **2. The questionnaire** - The number of items was appropriate - Half of the patient believed responding to the questionnaire was reassuring - Responding made it easier to remember symptoms and awareness was increased - The alert function popped up too frequently **3. Patient-physician communication** - Two-thirds believed that their reports had been seen and included in the consultation - Some did not know if a clinician had seen their reports - The majority did not believe they had more contact - The reporting made the patients feel more involved in treatment and care	- There was sometimes a discrepancy between how the patient and the physician graded a symptom - Inclusion of patient reporting was more time-consuming compared to an ordinary consultation - Patients were better prepared when they came to the clinic - Patients had an increased focus on symptoms and were more alert - The information which was given to the patients before treatment start was repeated when the patients responded to the questionnaire at home - The patients took part in setting the agenda for the consultation - Patient reporting should be a supplement, not a replacement - The e-Health intervention was a valuable tool, particularly for the patients who were normally reluctant to contact the hospital

Table 8 Main findings from the survey, patient interviews and focus group interview with clinicians

8. Discussion

In this PhD project, the use of patient-reported outcomes for symptom management in patients with metastatic melanoma receiving immunotherapy is investigated in detail, including design, execution, and evaluation of a randomized controlled pilot trial. We have succeeded in carrying out the planned trial within the expected timeframe. The in- and exclusion criteria made it easy to find eligible patients, and most patients were willing to participate. Only the eldest patients were hard to recruit, which is not quite what we expected, because, as mentioned in the introduction, many studies have demonstrated that the majority of older patients are, in fact, willing and capable of making online reporting [88-94]. Overall, patients recruited to the e-Health intervention were compliant (including the elderly), and the vast majority of patients adhered to the weekly reporting. Most of the time, clinicians included the patient responses in the outpatient consultation. Also, patient and clinician satisfaction was high. Patients believed that the electronic questionnaire was easy to access and fill out, and patients and clinicians agreed that attention to AEs was increased. Thus, in terms of feasibility, the PRO-intervention seemed to be a success. The fact that patients who received the intervention called the hospital more frequently, also suggests that the patients became more aware of their symptoms as was the intention. However, this increased focus did not result in a reduction in the number of grade 3 and 4 AEs when toxicity was assessed in the two groups. Thus, the use of PRO in this patient group and with this design did not improve clinical outcomes. This finding has also been reported by others as alluded to in the introduction [66, 67, 126], whereas others have demonstrated improvements [73, 74].

There may be various explanations for why we did not detect a difference. First, toxicity-monitoring was already carried out at a high level in the department where the study was performed; patients were informed on a detailed level, including written information on when to react in case of the occurrence of symptoms. Secondly, a relatively large proportion of grade 3 and 4 AEs are asymptomatic and thus not possible for the patients to detect. Thirdly, the design of the RCT may have been more complex. In the following, the design of the RCT will be discussed in more detail. Before that, I would like to touch upon the choices made about the questionnaire and item selection to explore if other options could have been chosen. We also collected QoL data in this project because the literature suggests that the use of PROs may impact patients' QoL. It was not possible, however, to include the results in this thesis because data collection is still ongoing, but the use of PRO concerning QoL will be discussed briefly at the end.

8.1 Questionnaires and item banks

When this study was planned, choosing the PRO-CTCAE library for designing a questionnaire for melanoma patients receiving immunotherapy was obvious for more reasons. First of all, it is built on the CTCAE-platform, which is used widely in oncology. Moreover, few PRO-tools are developed to monitor and provide support between visits [127], which is the case with the PRO-CTCAE library where the preferred recall period is one week [85]. Also, the fact that the PRO-CTCAE items had been validated in a Danish context [84] supported our decision. Other questionnaires also evaluate disease-related or treatment-related symptoms along with other domains (physical function, social role function, and psychological function) such as the EORTC QLQ-30, the FACT-questionnaire, and the SF-36. Albeit some of these questionnaires also have a diagnosis-specific supplement, they can be static and inflexible, and often they include items of limited relevance for the individual patient [58]. The advantage, however, of these established standard questionnaires is that that they do not require a lot of preparation, and it will be possible for researchers to compare their findings with those from other studies [128, 129].

Nevertheless, there is an increasing tendency to individualize questionnaires to fit various patient populations and the most important symptoms they may experience, which is also recommended [81]. This need may be met when selecting the relevant items from an item bank. Various item banks, such as the EORTC and the PROMIS, have also been developed and work in the same way as the PRO-CTCAE, providing flexibility for the user. It may be relevant to mention that none of these item banks, including the CTC-AE scoring system which the PRO-CTCAE is built upon, were originally developed to evaluate toxicities related to novel therapies such as immunotherapy and targeted therapy [96]. Fiteni et al. argue that even the latest version (CTCAE v5.0), which came out in 2017 – after the initiation of our RCT - remains insufficient when it comes to immunotherapy [96]. However, according to Mendoza, an ideal assessment tool should include the symptoms occurring most frequently and are most distressing to the patients [79]. We believe that the rigorous item selection process that we carried out as preparation of our RCT (described in Paper I), where we demonstrate that the most relevant and important immune-related toxicities are covered by the PRO-CTCAE [130], justifies our choice. However, work still needs to be done that evaluates the coverage of the CTCAE in detecting AEs, for example, by making an extension of the existing CTCAE [131], which again may affect the content of the PRO-CTCAE.

It may have been advantageous to include patients in the process of selecting the relevant items to include, which has been done in other studies [132] and was something we discussed when the RCT was designed. We planned on conducting interviews with patients to elucidate further the symptomatology of the CPIs relevant to this study, as suggested by Mendoza [79]. We decided against it, however, because the patients might mention several more rare symptoms which it would not be possible to include if we wanted to keep the number questions acceptable for weekly reporting. Instead, we made it possible for the patients to add symptoms that had not been included in the questionnaire so that rarer toxicities could also be detected. A similar study on the item selection process, identifying AEs of a prostate cancer population, concluded that asking the patients about their experiences only add little to the information obtained from the European Medicines Agency (EMA), FDA and RCTs [133], which supports our choice of not basing item selection on patient interviews.

8.2 The design of the RCT

When the RCT was planned, we decided that the department of Oncology at Odense University Hospital should be the only Danish site including patients because toxicity-monitoring may be different at the other oncology departments in Denmark. Moreover, data collection may be of a higher quality and it would be easier to make sure that all eligible patients were recruited. Furthermore, problems with having an IT-solution across different regions could be avoided. Realistically, we expected to be able to include approximately 140 patients in two years based on a report from the Danish Melanoma Group [134]. However, in order to achieve a good power, we would have needed to include twice as many patients or to find a larger difference in the number of severe AEs. Accordingly, we decided to conduct a pilot study which was based on a power of 0.64 and a level of significance of 0.20. Accepting this threshold for the level of significance provided us with the opportunity of making a preliminary assessment of the primary endpoint, which was reduction of severe AEs by 50%. According to Lee et al. when evaluating new health technologies a pilot study can be used not only to determine feasibility of the implementation of the new technology, but also to provide a preliminary assessment of benefit [114]. Thus, the results may indicate if the number of grade 3 or 4 events could be reduced, and thereby making a larger RCT worthwhile. In our RCT (this case), however, where the pilot study did not show any difference between the intervention group and the control group in the number of grade 3 or 4 AEs, it would not make sense, with our current clinical endpoints (in terms of clinical outcome), to prepare and conduct a larger RCT- or continue including patients to the trial.

As mentioned, few PRO-interventions are designed to monitor symptoms in between visits, but studies illustrate that patients are reluctant to contact the hospital outside scheduled appointments [127]. This mechanism was, however, crucial when we designed our RCT because it was precisely the AEs that occurred in between visits that we hoped to capture, preventing them from becoming severe. We also decided that it was up to the patients to react to the alerts triggered by the system when they reported a symptom. There may be an ethical problem in having the patients report their symptoms without anyone monitoring their reports [134]. However, no regulatory bodies require that PRO-data is monitored or demand that alerts to clinicians should be included, even when PROs are used to monitor drug-related symptoms [58]. In this trial, the reports were only reviewed when the patients came to the outpatient clinic, and the alerts only seen by the patients. But what if a patient reported a severe symptom that proved to be fatal and the patient did not contact the clinic? Is that too much responsibility to put on the patients? Stressing the importance of reacting on alerts to the patients was vital so that they were aware that their reports in between visits were not monitored by a health care professional [134]. In our RCT, it was stressed to the patients that when they reported a new symptom or worsening of an existing symptom, and an alert was triggered, they should contact the hospital.

When the patients were interviewed about their experiences with the intervention, none of them had doubts as to when to react. However, the patients sometimes discarded the alert if they did not believe they had to react, which may have resulted in AEs not being detected. This dilemma could, however, have been avoided if an alert was sent to a clinician in case a patient reported a symptom (Fig. 15) as done in several other studies [63, 74, 126, 135, 136]. In a review of electronic patient reporting [69], 85 % of the systems sent real-time alerts that were linked to patient reports to clinicians. We wanted to be able to implement the intervention after the study period in case of a positive outcome. It may be too time- consuming in routine practice if clinicians constantly had to monitor and respond to alerts.

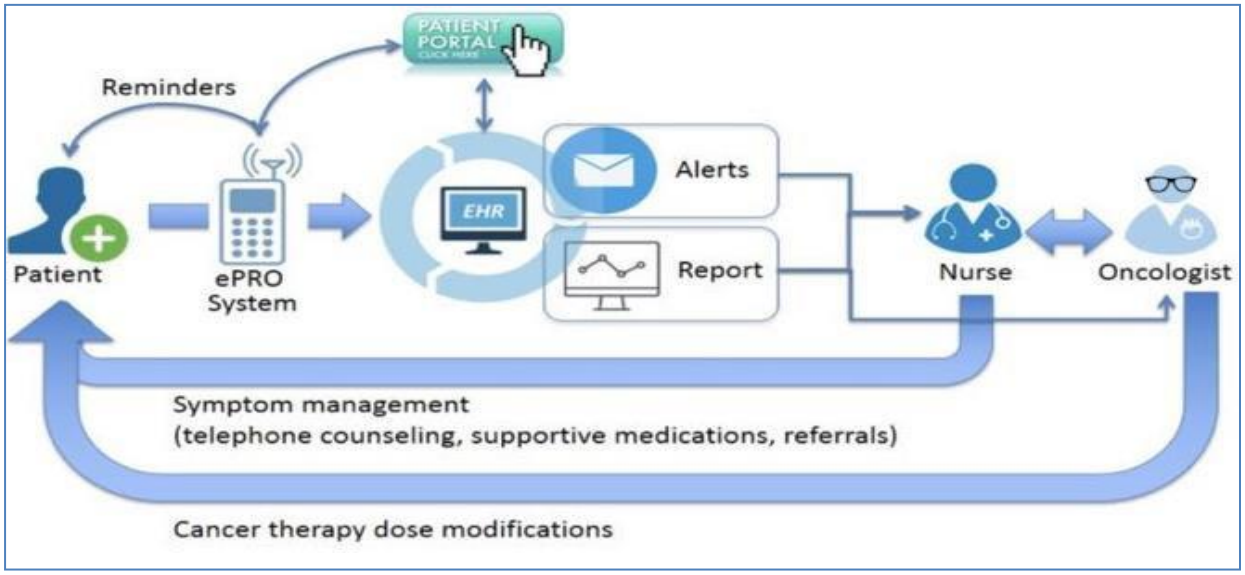


Fig. 15 Reprinted with permission from [137]. Example of a more complex PRO-set-up, where the patient triggers an alert. The alert is sent to an oncology nurse who helps the patient or refers the patient to the oncologist.

We could, however, have included a self-management feature, containing guidance on what to do in case of the emergence of a symptom. This approach would have been more pro-active and empowered the patients even more. The Australian PROMPT-Care study is a good example of how tailored self-management guidance was given to the patients when they reported a symptom or a concern [138]. Patients were also engaged in self-management in the eRAPID-trial where they received personalized feedback on how to manage symptoms and AEs from cancer treatment and when to contact the hospital [139].

Moreover, when the study was designed, patient data needed to be summarized and presented in a visual way for clinicians, for example, by the use of histograms or bar charts, and they should be easy to interpret [64]. In our trial, the patient responses were summarized in a very transparent way. It is displayed above (Fig. 12) what the reporting looked like for the clinician. A bar attached to each symptom appeared green, yellow, or red depending on the frequency and severity of the symptom and how much it affected daily activities. Thus it was easy for the clinician to get an overview of the patient's current condition and the development of symptoms over time. In addition, the reporting could be used to streamline the consultation, prioritizing the toxicities most burdensome to the patients.

Integrating PROs into the electronic health record (EHR) is an advantage [140]. However, clinicians in our study had to log into a separate web-system to view the patient's response. Even though it only took 1-2 minutes, it did add to the workload in an already busy outpatient clinic. Having to access another system may be a barrier for clinicians and result in the patient reports not being viewed [141]. The importance of integration was also expressed by the clinicians in our study when they were interviewed about their experiences.

The study set-up could also have been different when it comes to the time of reporting. The patients were asked to report weekly [79, 85], but more AEs may have been detected if the patients, in addition to the weekly reporting, also had been encouraged to report as soon as they noticed a symptom. The fact that the patients in the intervention of our study did call the hospital more often, however, indicates that attention to AEs was increased due to the reporting.

8.3 Evaluation of the e-Health intervention

We used mixed methods to measure patient acceptability with the e-Health Intervention. As for the survey, the American version was originally developed to evaluate symptom- monitoring [94], but it has also been used to compare various PRO measures with each other. Snyder et al. [101] describe how cancer patients in an RCT were assigned to complete one of three questionnaires: The Quality-of-Life Questionnaire-Core 30 (QLQ-30), the Supportive Care Needs Survey-Short Form-34 (SCNSSF-34) or The Patient-Reported Outcomes Measurement Information System (PROMIS). The Patient Feedback Form was used to elucidate which of the PROs was best suited from a clinical perspective. Thus, we expect the questionnaire to be useful in many settings where PROs are integrated into clinical practice. Further validation should be made, however, to support the initial psychometric testing that we performed, as suggested in paper II [142]. As a result of the publication of the translation and validation process of the American Patient Feedback Form, the Danish version is currently being used by other Danish researchers in four out of five regions, which confirms its relevance.

It may also be relevant to have a questionnaire that measures clinician satisfaction. In connection with our search for a questionnaire, we also came across a Clinician Feedback Form from the same group of researchers that had developed the Patient Feedback Form. The questionnaire sheds light on clinicians' views on PRO-questionnaires [101]. It is a 4-item questionnaire that asks questions about how the questionnaire was used and if it helped identify areas of need (Fig. 16). We translated and cognitively validated the questionnaire using the same rigorous method as with the Patient Feedback Form. We were not, however, able to find a sample size large enough to enable us to make a proper psychometric evaluation. Accordingly, we decided to disregard the form in our project and focus on interviewing clinicians instead. It may, however, be relevant also to make psychometric testing of this questionnaire so that the Clinician Feedback Form can be used to evaluate clinician satisfaction with various PRO-interventions in the future.

		Strongly Agree	Agree	Disagree	Strongly Disagree
1.	The information from the questionnaire was helpful in promoting communication.	1	2	3	4
2.	The information from the questionnaire was helpful in identifying areas of need.	1	2	3	4
3.	The information from the questionnaire improved the quality of care.	1	2	3	4
4.	In what ways did you use the information from the questionnaire? (check all that apply)				

☐ Did not use

☐ Providing overall assessment of the patient

☐ Providing additional information

☐ Confirming knowledge of patient's problems

☐ Identifying issues/problems to be discussed

☐ Contributing to patient management

☐ Other _____

Fig. 16 Clinician Feedback Form

Data from survey, patient interviews, and focus group interviews demonstrated that acceptability of and satisfaction with the intervention was high among participating patients and their treating clinicians. Others have also found high clinician satisfaction. According to Howell at al., most clinicians give positive feedback when PROs are used in cancer routine

practice [68]. Other studies confirm this notion [68, 69, 143], and Fiteni even describes how PROs, among other things, can improve the workflow efficiency and save time, thus enhancing physician well-being [96]. One may argue that carrying out the evaluation study was obsolete because many studies already report that clinicians and patients are keen on using PROs as long as certain requirements are met. We believe, however, that because the PRO-CTCAE has never been used for our patient group (melanoma patients), nor treatment with immunotherapy, uncovering the experience of patients and clinicians was meaningful.

8.4 PROs and quality of life

Albeit our primary endpoint was not met, it is a different matter in the case of the exploratory endpoint. Using interviews and a survey, we have demonstrated that the e-Health intervention resulted in an increased focus on AEs, improved patient-clinician communication, and provided the patients with a feeling of being more in control of treatment and care. In this connection, it would be interesting to explore if the high level of satisfaction is reflected in the patients' QoL. A study by Basch et al. published in 2016, suggests that cancer patients who reported the most common toxicities during chemo-therapy at the hospital and/or in-between visits followed by a clinician response had a higher QoL compared to patients who received standard care, where symptoms were only addressed at the clinical encounter [63]. Other studies also suggest that using PROs actively results in an improvement of patients' QoL [74, 96]. Inspired by these studies, we found it relevant to compare the QoL of the patients randomized to the intervention to that of the patients in the control group. In the abovementioned studies [63, 74], the change in QoL was measured at six months from baseline using the EuroQol EQ-5D Index questionnaire [144] and the FACT-L, respectively. We decided to use both the disease-specific questionnaire FACT-M and the generic EuroQol EQ- 5D because the cancer-specific questionnaire can detect the minimal change in disease. In contrast, the generic can be used to compare different disease populations [145, 146]. By including both kinds, we believed that we were adequately covered to detect any changes in the patient group and compare the results with other patient groups. We also chose to administer the questionnaires at baseline and after six months. In addition, we also have an additional follow-up at 12 months. At this point, we have not reached the final collection date, and the QoL data will not be included in this thesis, but will be analyzed and published in 2020. It was important to mention, however, that this study is being conducted because it is in line with other PRO-research that evaluates QoL in connection with PRO instruments dealing with, for example, symptomatic toxicities.

9. Strengths and Limitations

- Study I
    - Strengths: Careful item selection process resulting in a questionnaire designed specifically for melanoma patients receiving immunotherapy, the number of items made the questionnaire acceptable to the patients
    - Limitations: A few symptoms were left out because they were not present in the PRO-CTCAE library, rare toxicities were not included even though they can become severe

- Study II
    - Strengths: The translation and adaption process was in accordance with existing guidelines, validation of the translated version included some psychometric testing
    - Limitations: More psychometric test could have been performed, only a minority of the patients were able to answer all the questions and data had to be imputed, testing was performed in a prostate cancer population

- Study III
    - Strengths: Randomized controlled trial, few exclusion criteria yielded a representation of a typical melanoma patient, the trial was conducted in routine care, and it was easy to recruit patients, most patients adhered to weekly reporting, most of the times clinicians viewed the patient reports
    - Limitations: Small sample size, pilot study, one center-study, blinding not possible, some patients - particularly the elderly - declined to participate because they were not used to electronic devices, patient reports were not monitored continuously by clinicians, the alerts may have been triggered too often, the design could have been more complex

- Study IV
    - Strengths: Mixed methods study was used to evaluate patients' and clinicians' perspectives, the used Patient Feedback Form is a valid tool for measuring patient satisfaction, variation in gender and age for the participants, interviewing continued until data saturation was reached
    - Limitations: Small sample size in the survey, only one focus group interview with clinicians

10. Conclusion and Perspectives

In a randomized controlled trial, the use of patient-reported outcomes, in the form of an electronic questionnaire designed on the PRO-CTCAE library specifically for melanoma patients receiving immunotherapy was investigated. The primary aim was to examine if the number of severe (grade 3 and 4) AEs could be reduced by 50% for the patients who received the e-Health intervention compared to patients who received usual symptom-monitoring. We did not find a difference in the number of severe adverse events between the two groups, which was also true for the overall number of AEs. However, patients in the intervention group called more frequently, suggesting that the attention to AEs was increased. Concerning the number of days in the hospital, days in steroid treatment, the number of extra visits to the outpatient clinic, and the duration of grade 2 or higher toxicity, there were no improvements either.

Acceptance and satisfaction with the intervention were high among patients and clinicians. They believed that the e-Health intervention was useful, helped set an agenda for the consultation and that patients became more aware of their symptoms, which corresponds to the extra number of phone calls to the hospital. Based on these results in terms of clinical outcome, it will not make sense to carry out a larger trial with this design and in this patient population. If the work should be continued in the future, it may be considered changing the design, for example, by having clinicians respond to the alerts triggered by the patients in real-time or including self-management advice. Also, instead of just reporting on a fixed weekday, patients in a future study could be asked to make a report as soon as a new symptom occurred.

More and more consultations in the outpatient clinic, where a physician is assessing the patients, for example, before treatment or as follow up, are being replaced by telephone calls from specialist nurses [147, 148]. In this connection, the tool that we developed can be extremely useful. Before calling the patient, the nurse can get a quick overview of the patient's condition during the last 3-4 weeks (or longer) by using this system. This situation may help to focus on the symptoms that are most burdensome to the patient and/or get an idea of whether or not the patient is up for treatment or should be seen by a physician before treatment. Such a set-up can help prioritize the resources in the healthcare system because fewer patients will require a scheduled appointment with a physician. More importantly, it will also make a change for the group of patients who tolerate treatment well and find it burdensome having

many visits to the hospital. It is important to stress, however, that if PROs are used in future studies or routine care, the patient reports must be integrated into the EHR, making it easy for clinicians to access.

11. English summary

This thesis is on the self-reporting of symptoms by melanoma patients receiving immunotherapy. In a randomized pilot study, it has been examined if melanoma patients who report their adverse events (AEs) weekly by the use of an e-Health intervention as a supplement to routine assessment carried out by a clinician, experience an overall reduction of severe (grade 3/4) AEs by 50% compared to patients who receive standard toxicity- monitoring. One hundred forty-six patients were recruited from January 2017 till May 2019. The tool applied for patient reporting was designed on the PRO-CTCAE library, which is a web-based tool intended for patients to report the AEs they experience with cancer treatment.

The AEs which the patients reported in the trial were carefully selected after the completion of a literature review uncovering the AEs reported in international trials, a chart audit performed at the Department of Oncology at Odense University Hospital, and an examination of product information for the relevant drugs. Following this, the equivalent PRO-questions to include from the PRO-CTCAE library were identified.

Furthermore, we translated, validated, and carried out initial psychometric testing of the American Patient Feedback Form. We wished to use the questionnaire to measure patient satisfaction with the e-Health intervention. Fifty-seven patients in the intervention arm filled out the questionnaire. In addition to the survey, 14 individual interviews with patients and one focus group interview with clinicians were carried out to investigate their experiences with the intervention qualitatively. Patients and clinicians agreed that the attention to symptoms was increased and that the patients were better prepared for the consultation. Furthermore, patients believed that the electronic PRO was easy to access and fill out.

Although acceptance and satisfaction were high among patients and their treating clinicians, and patients in the intervention arm called more often as a result of the reporting. We did not, however, find a difference between the two groups in the number of severe AEs. About the number of days in the hospital, days in steroid treatment, the number of extra visits to the outpatient clinic, and the duration of grade 2 or higher toxicity, there were no improvements either. Thus, in terms of clinical outcome, nothing suggests that it will make sense to carry out a larger trial with this design and in this patient population.

12. Danish summary/Dansk resumé

Denne afhandling omhandler melanompatienters egenrapportering af bivirkninger i forbindelse med behandling med immunterapi. I et randomiseret forsøg har vi undersøgt, om melanompatienter, som rapporterer immunrelaterede bivirkninger ugentligt vha. en "e-Health" intervention som et supplement til standard bivirkningsregistrering foretaget af en læge, får nedsat antallet af alvorlige bivirkninger med 50 % sammenlignet med patienter, som udelukkende får foretaget standard bivirkningsregistrering. 146 patienter blevet inkluderet fra januar 2017 til maj 2019. Redskabet, som blev anvendt til patientrapportering er PRO- CTCAE-biblioteket; et web-baseret redskab, som gør det muligt for patienter elektronisk at rapportere de bivirkninger, de oplever i forbindelse med kræftbehandling.

De bivirkninger, som patienterne i interventionsarmen rapporterede var omhyggeligt udvalgt efter at have udført en litteratursøgning, som afdækkede de bivirkninger, som er rapporteret i internationale forsøg og en journalaudit på Kræftafdelingen på Odense Universitetshospital. Derudover blev produktinformationerne for de forskellige immunterapier gennemgået. Herefter blev de ækvivalente PRO-spørgsmål udvalgt fra PRO-CTCAE-biblioteket.

Derudover oversatte og validerede vi det amerikanske spørgeskema "Patient Feedback Form" til dansk samt udførte psykometriske tests. Vi ønskede at anvende spørgeskemaet til at måle patienternes tilfredshed med interventionen. I tillæg til spørgeskemaet, som blev udfyldt af 57 patienter, udførte vi 14 interviews med patienter og et fokusgruppeinterview med klinikerne for kvalitativt at afdække deres oplevelser. Overordnet set var patienter og klinikere enige om, at opmærksomheden på bivirkninger var blevet øget som følge af interventionen og at patienterne var bedre forberedt, når de kom til kontrol i ambulatoriet. Ydermere mente patienterne, at det var nemt at tilgå og udfylde det elektroniske spørgeskema.

På trods af at både patienter og klinikere var meget tilfredse med interventionen og patienterne i interventionsgruppen ringede hyppigere som følge af rapporteringerne, var det imidlertid ikke muligt at se en forskel i antallet af alvorlige bivirkninger mellem de 2 grupper. Ift. indlæggelsesdage, dage i steroidbehandling, antallet af ekstrabesøg samt længden af grad 2 og højere toksicitet fandt vi heller ikke forbedringer. Der er således ikke noget, der indikerer, at det giver mening at udføre en større randomiseret undersøgelse med dette design og denne patientgruppe.

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14. Papers and Appendices

1: Tolstrup LK, Bastholt L, Zwisler AD, Dieperink KB, Pappot H. Selection of patient-reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. *Journal of patient-reported outcomes. 2019 Mar 21;3(1):19.*

2: Tolstrup LK, Pappot H, Zangger G, Bastholt L, Zwisler A-D, Dieperink KB. Danish translation, cultural adaption, and initial psychometric evaluation of the patient feedback form. *Health and quality of life outcomes. 2018 April 27;16(1):77.*

3: Tolstrup LK, Bastholt L, Möller S, Zwisler, AD, Dieperink KB, Pappot H.
The use patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: A randomized controlled trial
Manuscript

4: Tolstrup LK, Pappot H, Bastholt L, Zwisler, AD, Dieperink KB.
Patient-reported outcomes during immunotherapy for metastatic melanoma: Mixed methods study of patients' and clinicians' experiences
In review*, Journal of Medical Internet Research*

Paper I

Tolstrup LK, Bastholt L, Zwisler AD, Dieperink KB, Pappot H. Selection of patient-reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy. *Journal of patient-reported outcomes. 2019 Mar 21;3(1):19.*

Journal of Patient-Reported Outcomes

SHORT REPORT Open Access

Selection of patient reported outcomes questions reflecting symptoms for patients with metastatic melanoma receiving immunotherapy

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Abstract

Context: Toxicity-monitoring plays an important role in all cancer treatment, however, early recognition is vital for detecting and treating immune-related symptoms. Preparing a Patient Reported Outcomes tool and including melanoma patients receiving immunotherapy in the reporting of symptoms, may optimize toxicity-monitoring.

Objectives: The objective of this study was to identify the symptoms and their equivalent questions to include from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) library for melanoma patients, receiving immunotherapy and, further, to evaluate if all relevant symptoms are covered by this tool.

Methods: To establish the relevant symptoms, three measures were taken. First, a literature search was carried out in three databases. Second, a chart audit was performed including medical records from melanoma patients receiving immunotherapy. Finally, the product information for the relevant immunotherapies was studied.

Results: Ten articles were included as a result of the literature search. As for the chart audit, a total of 37 patients (48 treatments with immunotherapy) were included. Overall, the reported symptoms from the literature review aligned with those identified in the chart audit. The examination of the product information supported the findings from review and chart audit, revealing only one additional symptom. In total, 28 PRO-CTCAE symptoms were selected comprising of 56 PRO-questions plus an additional question on blood in stool.

Conclusion: When preparing a Patient Reported Outcomes tool it is important that the preparatory work of selecting questions is done properly. By going through the literature, performing a chart audit, and examining the product information, the most important and relevant symptoms have been uncovered, facilitating the design of a PROquestionnaire, based on PRO-CTCAE, that fits the patient population under investigation.

Keywords: Patient-reported outcomes, PRO-CTCAE, Item-selection, Symptomatic toxicity, Adverse events, Melanoma, Immunotherapy

Introduction

The number of Danes who are diagnosed with malignant melanoma have increased significantly during the last 50 years. Approximately 2200 new cases are reported every year. Malignant melanoma is the most common cancer form in the 15–34 year old and more than 400 persons are diagnosed with metastatic disease each year [1]. This development aligns with the development worldwide [2]. When metastatic, the majority of patients are treated with immunotherapy, using checkpoint inhibitors either as monotherapy or in combination [3]. Survival has improved significantly with these new treatment strategies. However, the adverse events (AEs) that patients may experience can be severe and potentially life-threatening [4–7]. Studies report that 16% of patients treated with immunotherapy targeting PD-1 experience CTC > = grade 3 AEs measured by the Common Criteria

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for Adverse Events (CTCAE). With immunotherapy targeting CTLA-4, the number is 27%, and when the drugs are combined, the frequency is 55% [6]. With all cancer drugs, toxicity-monitoring plays an important role, however, early recognition is vital for detecting and treating immune-related AEs. If symptoms are dis- covered early, relevant treatment can be initiated in time, and major complications avoided [8].

CTCAE is widely used when it comes to toxicity-monitoring in oncological, clinical trials and in routine cancer care. The CTCAE consists of 790 AEs and is divided into three categories: laboratory-based events, physical examination findings and symptomatic adverse events [9]. Physicians perform a systematic evaluation using the CTCAE to describe the severity of organ toxicity for patients receiving cancer therapy. In Denmark, a melanoma patient who receives immunotherapy will be clinically evaluated every third week prior to treatment. Consequently, there is a risk that a symptom may go from mild to severe in the time span. Moreover, evidence suggests that clinicians may underestimate symptom onset and severity compared to patient report [10]. It may be hypothesized that includ- ing patients in the reporting of symptoms - and more frequently [11] - can optimize symptom monitoring.

One way to increase patient involvement is to use patient reported outcomes (PROs). Applying a PRO-tool which resembles the well-known CTCAE grading scale seems advantageous. For this purpose, the National Cancer Institute has developed a tool appropriate for patient self-reporting. A total of 78 symptoms, approxi- mately 10%, in the CTCAE guidelines have been found appropriate for self-monitoring and now constitute what has been labeled as the PRO-CTCAE [10, 12]. As each adverse event is elicited using between one to three questions on frequency, severity and interference with daily activities, there are 124 individual questions repre- senting the 78 symptoms. From this question library and its attached form builder, it is possible for researchers and oncologists to choose relevant symptoms and create a questionnaire [13]. The PRO-CTCAE is translated and validated in a Danish version [14], and a Danish feasibility study has recently been carried out [15], demonstrating that the tool is feasible in a prostate cancer population receiving chemotherapy. However, no guidelines exist on how to select the relevant PRO-items representing expected symp- toms in different disease and treatment situations.

The advantages of using PROs in cancer treatment and care are debated [16, 17]. Current data suggests that physical symptoms are more likely to improve after PRO interventions compared to quality of life (QoL), supportive care needs or psychological symptoms [16]. More evidence is needed, however, to determine if the implementation of PROs in relation to, for example, symptom reporting is worthwhile. So far, research involving PRO-CTCAE has focused on toxicity monitoring associated with other cancer therapies [10]. The tool has not been reported as used by patients receiving immunotherapy. The pattern of symp- toms with this treatment modality differs considerably from the one patients experience when they receive chemother- apy [8]. Thus, it is highly relevant to select the symptoms that fit the toxicity-profile and provide and an unbiased presentation when designing a PRO-tool for melanoma patients receiving immunotherapy [18].

The objective of this study was to identify the symptoms appropriate for patient self-reporting and their equivalent PRO-questions to include from the PRO-CTCAE library for melanoma patients receiving immunotherapy and, further, to evaluate if all relevant symptoms can be covered by the tool.

Material and methods

To establish the relevant symptoms to include in a subsequent randomized trial, a project group was formed. Besides the project manager, the group consisted of two physicians who were experts in handling immune-related symptoms. Moreover, one had experience with selecting relevant PRO-CTCAE-items. It was decided in advance that due to the purpose of the study i.e. to identify symptoms appropriate for self-reporting, labatory based events and physical examination findings would be excluded during the selection process. Only symptomatic AEs that the patients would meaningfully be able to report were to be included.

Literature search

A literature search was performed in the three literature databases Pubmed, Embase, and Cinahl in June 2016 using the Boolean logical operators AND/OR to com- bine the search terms. A combination of keywords for *cancer*, *immunotherapy*, *adverse events* and *melanoma* was combined. Before doing the final search, the search terms were monitored by an expert on literature searches which resulted in minor changes. Articles were included if the studies described were randomized clin- ical trials that [i)] compared immunotherapy with chemo- therapy or placebo, [ii)] compared immunotherapy in different doses, [iii)] compared different immunotherapies, or [iv)] compared immunotherapy with other cancer ther- apies. Articles not written in English were excluded. Articles were eligible if indexed between January 1, 1996 and June 22, 2016.

First, one reviewer screened the titles and abstracts to eliminate all irrelevant references. Second, another reviewer took part in determining the references relevant for full text review. Hereafter, both reviewers jointly de- cided which articles should be included.

Chart audit

In addition to the literature review, a chart audit was performed to examine if the AEs found in the inter- national literature were consistent with symptoms melanoma patients treated with immunotherapy experi- enced in daily practice. The chart audit was performed at the Department of Oncology at Odense University Hospital in the Region of Southern Denmark. Permis- sion was granted from the head of department. Thirty-seven medical records were examined with oral and written informed consent from patients between June and August 2016. No selection criteria was applied and all melanoma patients treated with immunotherapy were asked to participate. No patients refused, however, due to administrative errors, a few patients were not re- cruited. The patients included in the chart audit had re- ceived either anti-PD-1 or anti-CTLA-4. The AEs identified in the medical records were primarily found in a prespecified toxicity-monitoring form build upon the CTCAE grading scale v4 for physicians to register the severity of AEs. In addition, the free text notes in the medical records were included. If a health professional had noted, for example, that a patient suffered from taste changes, the term was translated into the CTCAE term dysgeusia, making it possible to align all the pa- tients´ AEs.

Product information

Finally, the product information from the European Medicines Agency (EMA) for Yervoy (Ipilimumab), Keytruda (Pembrolizumab) and Opdivo (Nivolumab) [19] were studied to ensure that no adverse events had been overlooked. If an AE was reported in one of the EMA sources - and not already identified by the two other data souces - it was included if it affected more than 10% of the patients.

After the construction of the PRO-CTCAE question- naire, the instrument was pilot-tested by four patients and five healthcare professionals to ensure face validity.

Results

Literature search

Initial literature searches retrieved 3.165 titles from the databases. After title and abstract screening and full text screening had been performed, ten articles fulfilled the inclusion criteria and were extracted (Fig. 1). The articles were randomized, clinical trials including a total of 5.706 patients (Table 1). Thus, the number of trial participants were judged sufficient to satisfy the trial objective of identifying relevant AEs. Only two trials had a sample size of less than 400 patients and were not multi-center trials. The immunotherapy in the trials was either com- pared to placebo, other immunotherapy, or other anti-can- cer drugs. The studies tested Ipilimumab [4–6, 20, 21],

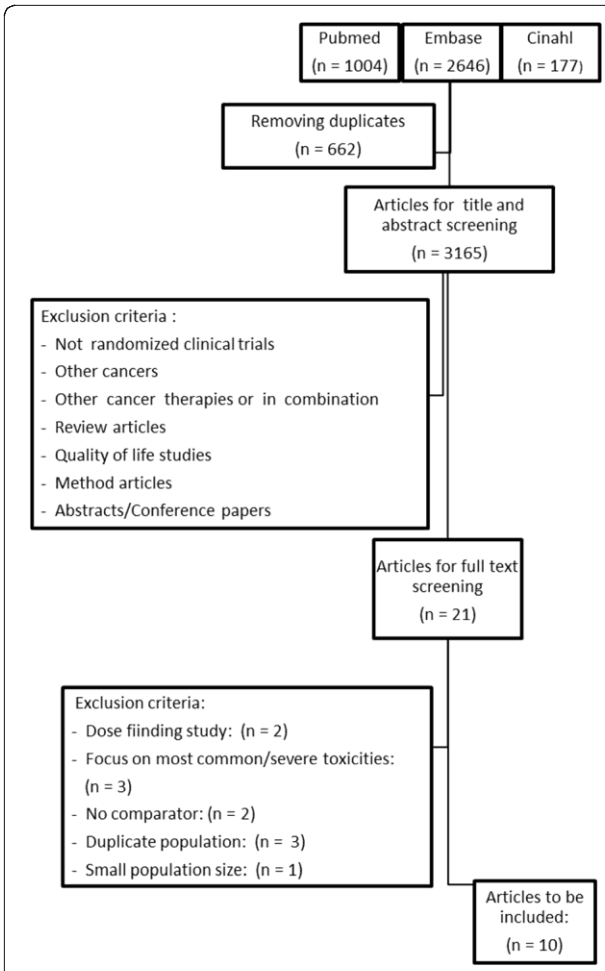

Fig. 1 Article selection flowchart. Articles on immune-related adverse events identified in melanoma patients treated with immunotherapy

Pembrolizumab [7, 21, 22] or Nivolumab [6, 23, 24] as monotherapy or a combination [6, 20] of two of the drugs. One study [25] evaluated sequential single-drug therapy with Ipilimumab followed by Nivolumab (or the reverse sequence). One article evaluated Ipilimumab given as adju- vant therapy, whereas the remaining nine were all con- cerned with treatment of metastatic disease. Some of the articles, including supplementary material, decribed the most common AEs, occurring in at least 5–10% of patients, while others also reported AEs that occurred in as few as 1–2% of the patients.

Chart audit

Among the 37 patients, 23 received Pembrolizumab, three Ipilimumab and 11 received both immunother- apies in sequence. All patients received at least one dose of immunotherapy. In total, the 37 patients re- ceived 48 treatments which were included in evaluation of AEs. None of the patients received combination immunotherapy.

Table 1 Characteristics of studies included to determine which AEs to include in the PRO-CTCAE for melanoma patients

Trial	Design	Enrollment size *N*=	Study drug	Dose (mg/kg)
Eggermont et al. [3]	Adjuvant, Randomized phase 3	951	Ipilimumab	10
Hodi et al. [2]	Phase 3 Randomized	676	Ipilimumab	3
Larkin et al. [4]	Phase 3 randomized	945	Nivolumab Nivolumab/Ipilimumab Ipilimumab	3; 1+ 3; 3
Postow et al. [17]	Double-blind Phase 2 – dose ranging	142	Ipilimumab or Ipilimumab/Nivolumab	3; 3+ 1
Ribas et al. [19]	Phase 1b	655	Pembrolizumab Pembrolizumab	10; 2
Ribas et al. [5]	Phase 2	540	Pembrolizumab Pembrolizumab	2; 10
Robert et al. [20]	Randomized, phase 2	418	Nivolumab	3
Robert et al. [18]	Phase 3	834	Pembrolizumab ipilimunab	10; 3
Weber et al. [21]	Randomized, open-label phase 3	405	Nivolumab	3
Weber et al. [22]	Randomized, open label, phase 2	140	Nivolumab Ipilimumab	3; 3

Product information

One additional AE, injection site reaction, was identified as being very common from the European Medicines Agency (EMA) product information on the three drugs. The AE had also occurred in one of the articles, however, since it was only identified in one data source and not being very common, it had not been initially included.

Adverse events to be included in the PRO-CTCA for melanoma patients

After thorough investigation of the literature, patients´ medical records and the product information 28 AEs were identified as relevant to include from the PRO-CTCAE-library (Table 2). Overall, there was great conformity between the three data sources.

Fifteen AEs were very common (may affect at least 10% of the patients). Eight of these *(nausea, anorexia, diarrhea, abdominal pain, rash, pruritus, arthralgia, fatigue)* were found common in all three data sources. The remaining seven (*vomiting, constipation, dyspnea, myalgia, injection site reaction, headache and chills*) were found very common in at least one or two of the data sources. The AE *asthenia* was also very common in both scientific papers and product information, however, since it was not found in the CTCAE or the PRO- CTCAE library, it was not included. This did not consti- tute a problem since the symptom was covered by the term fatigue which was found in the PRO-CTCAE-li- brary. *Fatigue* is preferentially used in NCI's toxicity grading scale that covers fatigue, asthenia, and malaise [26].

Eleven toxicities were found to be common (may affect up to 10% of patients) in two or three of the three data sources and were therefore included (Table 2). Other AEs which were also common such as *flu-like symptoms, pain in extremity,* and *back pain* were not included since they were not items in the PRO-CTCAE library. These terms seem adequately covered by muscle pain, joint pain, chills and the more general AE pain and thus, it was justifiable to exclude them.

Although the AE *depression* was uncommon [19] it was included as it was the only symptom dealing with mental health. Albeit rare, these symptoms can become very severe. Accordingly, two items from the PRO-CTCAE library concerning depression were selected. Despite the fact that the toxicity *blood in stool* was neither present in the PRO-CTCAE nor common, it was included as it may be a sign of colitis, a severe immune-related AE [27]. The question was placed at the end of the questionnaire as it was not a PRO-CTCAE item.

At face value, the questionnaire appeared to be a good instrument that adequately covered the relevant adverse events. Moreover, filling it out seemed to be uncomplicated and quick.

Discussion

It was found that the AEs identified in the chart audit were consistent with the ones found in the literature search and the product information. This indicates that the information collected from these three sources was representative for melanoma patients receiving immunotherapy and usable when selecting relevant symptoms

Table 2 Adverse events included in the PRO-CTCAE for melanoma patients receiving immunotherapy based on findings in medical records, literature review and product information

Frequency of Adverse Events	CTCAE terms	Literature review	Medical records	Product information	PRO-CTCAE symptom terms
Very common (may affect more than 1 in 10 people)	*Vomiting*	X		x	*Vomiting*
	Nausea	X	x	x	*Nausea*
	Anorexia	X	x	x	*Decreased appetite*
	Diarrhea	X	x	x	*Diarrhea/Loose or watery stool*
	Abdominal pain	X	x	x	*Abdominal pain*
	Constipation	X		x	*Constipation*
	Rash	X	x	x	*Rash*
	Pruritus	X	x	x	*Itching*
	Dyspnea	X			*Shortness of breath*
	Myalgia	X	x		*Muscle pain*
	Arthralgia	X	x	x	*Joint pain*
	Fatigue	X	x	x	*Fatigue*
	Injection site reaction			x	*Pain and swelling at injection site*
	Headache	X	x		*Headache*
	Chills	X	x		*Chills*
	Asthenia	X		x	
Common (may effect up to 1 in 10 people	*Mucositis (oral)*	X	x	x	*Mouth/throat sores*
	Dry skin	X	x	x	*Skin dryness*
	Alopecia	X		x	*Hair loss*
	Blurred vision	X	x	x	*Blurred vision*
	Cough	X	x	x	*Cough*
	Dysgeusia	X	x	x	*Taste changes*
	Dizziness	X	x	x	*Dizziness*
	Edema	X		x	*Swelling*
	Pain	X		x	*General pain*
	Peripheral sensory neuropathy		x	x	*Numbness & tingling*
	Hot Flashes	X		x	*Hot flashes*
	Flu –like symptoms		x	x	
	Pain in extremity	X		x	
	Back pain	X		x	
Uncommon/not present	*Depression (2 items)*		x		*Discouraged Sad*
	Blood in stool				

from the PRO-CTCAE library. The three information sources provided a clear picture of which symptoms to include in a questionnaire. Based on these findings, 28 PRO-CTCAE symptoms have been selected comprising of 56 PRO-questions plus an additional question on *blood in stool*.

It may be argued that having to leave a few symptoms out because they are not present in the PRO-CTCAE-library is a limitation. On the other hand, it is our belief that as long as these items are adequately covered by other items, the decision is justifiable. As the two PRO-CTCAE items deal- ing with depression can become very severe and may be hard to detect in a consultation at the outpatient clinic, it is vital that they are discovered as they arise. Increased attention, for example through frequent patient reporting, may be the way forward. When the study was designed, it was discussed whether or not to carry out focus group interviews with patients to further qualify the selection of items. We decided against it due to the fact it would not be possible to include all the experienced AEs anyway, however releveant to the individual patient. The same experience has been reported in other cancer poulations [28].

A special challenge in AE registration within immunotherapy may be that some symptoms occur rarely but

can be life-threatening if detected too late. This may be an argument for including less frequent symptoms. On the other hand, a subtle balance exists between including the relevant symptoms while at the same time not exhausting the patients with too many questions [29]. In a previous study, it has been shown that a questionnaire containing a similar number of PRO-CTCAE questions (41 questions reflecting 22 symptomatic toxicities) has proven feasible in a Danish prostate cancer population receiving chemotherapy [15]. The patients found the questionnaire easy to fill out and not too time consuming (mean < 7 min.). In addition, 40% reported that it in- creased their focus on side effects. Others have demon- strated similar results [12] which supports the clinical feasibility of our suggested questionnaire for melanoma patients. Moreover, the fact that patients have the oppor- tunity of adding other symptoms decreases the risk of in- frequent AEs not being reported. When designing the study, it could have been considered to include a generic questionnaire that also deals with patients´ health related QoL such as the EORTC QLC-30 or the EQ-5D − used in most melanoma studies [30]. However, the present study focuses on detecting AEs early, and the PRO-CTCAE is specifically developed to enable patients to report on ex- perienced AEs. Based on findings from Basch et al. [31] demonstrating improvement of QoL following PRO as intervention future studies should be designed with the in- clusion of Qol measurement.

Furthermore, the material included in our analysis could be perceived as too comprehensive. Additional re- search has been warranted, however, to qualify the selec- tion ofPRO-CTCAE items for given populations and contexts [32]. It was the purpose of this study to develop a PRO-CTCAE questionnaire for use in patients with metastatic melanoma who are treated with immunother- apy in the future. Consequently, three of the ten articles included described studies using the combination of two immunotherapies. This treatment was not standard treatment at the time of the review, however, it was introduced in Denmark in 2017, justifying the inclusion of studies testing the combination. Additionally, an article dealing with Ipilimumab as adjuvant treatment was included because the toxicity profile was evaluated as being identical to the profile seen in metastatic dis- ease. Thus, the questionnaire can also be used for mel- anoma patients who receive adjuvant therapy.

Conclusion

When melanoma patients receive immunotherapy, close monitoring of symptoms is crucial. One of the ways to detect AEs early may be to have the patients self-report the symptoms they experience, using PRO-questions. In this regard, it is important that the preparatory work to select questions is done properly. By going through the literature, examining the product information, and per- forming a chart audit, the most important and relevant symptoms have been uncovered, making it possible to design a PRO-questionnaire based on PRO-CTCAE that fits the patient population under investigation. This questionnaire is applied in an ongoing randomized clin- ical trial (ClinicalTrials.gov. NCT03073031) where mel- anoma patients treated with immunotherapy self-report the symptoms they experience.

Abbreviations

AEs: Adverse events; CTCAE: Common Terminology Criteria for Adverse Events; EMA: European Medicines Agency; PROs: Patient-reported Outcomes; QoL: Quality of life

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Availability of data and materials

Literature search string and notes from chart audit and are stored at the Department of Oncology, Odense University Hospital, DK and are available from the corresponding author on reasonable request.

Authors´ contributions

Design of the study: LKT, LB, HP Literature search, chart audit and selection of articles: LKT, LB, HP Item selection: LKT, LB, HP. Manuscript writing: LKT, LB, KBD, ADZ, HP. Final approval: LKT, LB, KBD, ADZ, HP. Our manuscript has not been published elsewhere, and is not under consideration by another journal.

Ethics approval and consent to participate

According to Danish law, approval from the ethical committee was not required, but the study was registered with the Danish Data Protection Agency (16/13968).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Paper II

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Health and Quality of Life Outcomes

SHORT REPORT Open Access

Danish translation, cultural adaption and initial psychometric evaluation of the patient feedback form

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Abstract

Aim: No suitable Danish questionnaire exists to evaluate patient satisfaction with various patient reported outcome measures. Thus, the aim of this research project was to conduct a study on the translation and cultural adaption of an American patient reported experience measures questionnaire, "Patient Feedback Form", among Danish patients, and to examine selected psychometric properties within reliability.

Material and methods: In the first phase of the study, the Patient Feedback Form was forward and backward translated following the methodology of existing guidelines. Subsequently, cognitive interviewing was performed with seven cancer patients and seven healthy persons (19–86 years old/6 men and 8 women) to ensure that questions were easy to understand and made sense to Danish interviewees.
In the second phase, phone interviews were carried out with 95 prostate cancer patients after they had responded to the same Patient Feedback Form. Missing data was imputed using the Expectation-Maximization technique. To examine the structure of the questionnaire, an exploratory factor analysis was conducted. Cronbach's alpha was calculated to investigate internal consistency.

Results: There were only minor disagreements in the translation process, and the reconciliation went smoothly (phase 1). With regard to one item, however, it was difficult to reach a consensus. Through the qualitative validation process, the right solution was found. The results from the psychometric testing (phase 2) showed that four factors had an Eigen value > 1, but only one factor was extracted as the Scree plot had a clear "elbow", showing a one factor structure that explained 46.1% of the variance. The internal consistency was high as Cronbach's alpha was 0.89.

Conclusion: The translated, culturally adapted, and validated version of the Patient Feedback Form seems to be suitable for measuring satisfaction with patient reported outcome measures in a Danish setting. While the results should be treated with caution due to the small sample size, psychometric testing indicates that the questionnaire is a valid instrument. However, additional psychometric testing such as hypotheses testing, responsiveness, and test-retest on a larger and more diverse sample size is required to further verify the validity of the instrument.

Keywords: Questionnaire, Translation, Validation, Psychometric testing, Patients reported experience measures, PREM, Patients reported outcome measures, PROM

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Introduction

Several questionnaires to measure patient reported outcome measures (PROMs) exist and have become an increasingly popular source for collecting information on patient conditions, e.g. physical symptoms, toxicities, or psychosocial problems [1]. Some instruments are generic, dealing with issues such as quality of life(QoL), anxiety, depression, and pain, while others are disease- specific [2]. In the past, PROMS have mainly been used in clinical trials to determine safety, efficacy and cost effectiveness of, for example, a new drug [3, 4]. Thus, the data collected in research settings has generally not been available to clinicians [5]. In many cases, the ques- tionnaires have been independent tools that have helped the health care system gain knowledge of, for example, patients´ symptoms and QoL on a general level. Fortunately, PROMs have also moved into the world of routine care – probably eased by electronic data collection – where they are integrated into the patient trajectory with the purpose of influencing treatment and care. In some circumstances, the results are provided to clinicians to improve patient care and focus on patient concerns [4, 5]. Little is known, however, about the value of this integration from a patient perspective or how patients experience filling out the questionnaires. Thus, it is important to explore if the patients found the questionnaire easy to complete, if it improved patient-clinician communication and/or enhanced quality of care. These are relevant issues to examine at a time when focus on patient reported experiences and attention to patient involvement and satisfaction have increased and are mandatory in many health care settings. More research is needed on the effects of PROM interventions in different settings [6–8] and to establish what realistic benefits can be gained from using PROMs in routine care [9]. Using a Patient Reported Experience Measures questionnaire (PREM-questionnaire) to evaluate if a given PROM is worthwhile [5], and/or to identify which PROM(s) to use [4, 10], may be one method to select feasible and patient-acceptable PROMs.

Since no suitable PREM-questionnaire was available in Danish, an American questionnaire entitled "Patient Feedback Form" was chosen [4, 5, 11]. The Patient Feedback Form was selected because it evaluates the usefulness and value of a given PROM from the patient perspective. Thus, the Patient Feedback Form is relevant in situations where the health care system wishes to examine patient satisfaction with PROMs that are inte- grated into clinical practice. Furthermore, the Patient Feedback Form is short and, due to its generic nature, we expected it to be adaptable to a Danish setting and useful in many different areas within the health care sys- tem. To our knowledge, the form has not been trans- lated into other languages. The questionnaire consists of 13 items (Fig. 1). Respondents evaluate their level of agreement/disagreement on a scale with four options to eliminate the neutral response [12]. Two questions have a 3-point option. The Patient Feedback Form has not undergone any traditional psychometric testing in the original language.

Firstly, the aim of this study was to translate and culturally adapt the questionnaire into Danish following existing guidelines [13, 14] and, secondly, to carry out initial psychometric evaluation.

Materials and methods

Phase 1 – The translation and cultural adaption process

Preparation and approvals

An expert group was formed to oversee the translation process. The group consisted of a senior oncologist [15] and a senior nurse who both had experience with translations and cross-cultural adaptions and the project manager.

Permission to translate the Patient Feedback Form was granted from the developer, Ethan Basch [11], and Claire Snyder [4, 5], who had adapted the questionnaire. According to Danish law, approval from the ethics committee was not required, but the study was registered with the Danish Data Protection Agency.

Forward translation and reconciliation

The Patient Feedback Form was translated into Danish by two independent, experienced translators, who had Danish as their mother tongue, were fluent in English [13], and had been residents in an English speaking country for more than two years. They did not have a medical background, which was acceptable because the questionnaire does not contain medical language, health care terminology, or require any particular knowledge. Focus was kept on the natural, spoken language with its cultural nuances addressing a common audience [16].

Comparisons were made between the independent translations regarding ambiguity and discrepancies of words, sentences, or meaning for each item in the questionnaire in order to create a consensus version.

Backward translation and review

The Danish consensus version was back-translated by two independent bilingual translators blind to the ori- ginal. The translators had English as their mother tongue but had resided in Denmark for several years. As with the forward translations, the translators were asked to take a conceptual approach due to the subjective nature of the construct (patient experience and satis- faction) [13].

The two translations were then compared to the original to ensure that the translated versions reflected the same item content.

PATIENT FEEDBACK FORM **SUBJECT #:** _____

Date: _____

We are interested in your opinion of the questionnaires you have been asked to complete. Please answer all of the questions yourself by circling the number that best applies. There are no "right" or "wrong" answers to the questions. The information that you provide here will remain strictly confidential.

		Too short	Just right	Too long
1.	The amount of time it took me to complete the computerized questionnaire was:	1	2	3
		Not often enough	**Just right**	**Too often**
2.	The number of times I was asked to complete the computerized questionnaire was:	1	2	3

		Strongly Agree	Agree	Disagree	Strongly Disagree
3.	The questionnaire was easy to complete.	1	2	3	4
4.	Completing the questionnaire was useful.	1	2	3	4
5.	The questionnaire was easy to understand.	1	2	3	4
6.	Completing the questionnaire made it easier for me to remember my symptoms and side effects when I met with my doctor.	1	2	3	4
7.	Completing the questionnaire improved discussions with my doctor.	1	2	3	4
8.	My doctor used information from the questionnaire for my care.	1	2	3	4
9.	The quality of my care was improved because of the questionnaire.	1	2	3	4
10.	Communication with my doctor was improved because of the questionnaire.	1	2	3	4
11.	Completing the questionnaire made me feel more in control of my own care.	1	2	3	4
12.	I would recommend completing the questionnaire to other patients.	1	2	3	4
13.	I would like to continue responding to the questionnaire in the future.	1	2	3	4

Fig. 1 Patient Feedback Form: Developed by Ethan Basch: Adapted by Claire Snyder

Pre-testing/pilot testing

Cognitive interviewing was performed with 7 cancer patients receiving immunotherapy for malignant melan- oma and 7 healthy persons (19–86 years/6 men and 8 women). The respondents were selected to ensure an equal distribution across age and gender. A combination of the "think aloud" method and "probing" was applied [14] to ensure that the items were easy to understand and made sense to a Danish population. Proofreading was performed and a report sent to the developer and adaptor [13].

Phase 2 – Psychometric testing

There are no general criteria for calculating sample size when assessing internal consistency and factor analysis. The Cosmin guideline, however, contains standards for evaluating the methodological quality of studies on measurement properties [17]. According to the Cosmin checklist, a sample size of minimum 100 respondents or seven respondents times the number of items is recommended [17]. A convenience sample of 102 men with prostate cancer in post-treatment control (54–73 years old) were chosen as respondents because they all had filled out the same PROM-questionnaire concerning sat- isfaction with treatment and care, and were available as respondents. In total, 95 (93%) accepted the invitation to respond. Not all of the patients had experienced any problems during their post-treatment control and as a consequence, they had not been in contact with a health care professional. Accordingly, they were not able to an- swer the items in the Patient Feedback Form which deal with this interaction.

In the original version, the Patient Feedback Form was used in connection with cancer patients [4, 5, 11], which explains why we selected this group of patients for psychometric evaluation. The respondents were interviewed over the phone. Phone interviews were chosen to motivate respondents to answer and to facilitate conducting the survey within a short period of time. An expert on questionnaire technique was consulted to make sure that the questionnaire was adapted to the chosen survey format. Consequently, I, me and my were exchanged with you and yours during the interviews. Moreover, a guideline was designed [18] to make the interaction as smooth as possible. The interviews were carried out by the same interviewer to ensure uniformity.

The structure (i.e. the number of factors) of the Patient Feedback Form was unknown, and it was not possible to make a confirmatory factor analysis because no psychometric testing of the original version had been carried out. Thus, the psychometric evaluation comprised of an exploratory factor analysis (EFA) if the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was > 0.6 and if the Bartlett's test of sphericity was significant ($p < 0.05$) [19]. The number of latent factors were decided by evaluating the scree plot and the number of factors with Eigenvalues > 1. The EFA method and rotation of the factors were chosen depending on the number of factors in the initial EFA. If one factor (as expected) was extracted, the maximum likelihood extraction method without rotation was applied [19]. Further, to assess internal consistency, Cronbach's Alpha (α) was evaluated. The level of α was considered: fair = 0.70–75; moderate = > 0.75–0.80; good
= > 0.80–0.85; excellent > 0.85–0.90 [20]. Missing data was assessed by Little's Missing Completely at Random (MCAR) test [21]. If participants had > 3 missing items (aside from the five items concerning interaction with healthcare professionals), they were excluded from the analysis. In the case of missing data and a non-significant ($p > 0.05$) MCAR test, the Expectation-Maximization (EM) technique was used to impute data [21]. A significant level of 0.05 was chosen and all analyses were executed using SPSS version 23.

Results

Phase 1 – The translation and cultural adaption process

Overall, consensus was easy to achieve and neither the translators nor the experts felt that they had to compromise. As for the forward translation, minor discrepancies such as the use of synonyms – digital vs. electronic – and different word order were detected. One of the translators, for example, suggested, "Completing the questionnaire improved discussions with my doctor" whereas the other suggested, "Discussions with my doctor were improved because I had completed the questionnaire." Also, the back-translated versions were close to the original. In the original version, the word "completed" was used for filling out the questionnaire whereas the two backward translators had chosen "answer" and "respond to". However, it was not possible to reach a consensus on whether or not the English loanword "feedback" should be translated into Danish. The expert group decided to leave it up to the pilot testing, resulting in the word being translated into a Danish word. Also, the respondents found two items (Fig. 1, items 7 and 10) to be almost identical. However, in order to be true to the original, nothing was changed. With regard to item 11, the semantics was changed somewhat. The phrase "Control of"´ did not sit well with the Danish patients, who did not feel it was in their power to be in control – nor did they want to be. "That is the doctor's job," as one respondent put it. Instead of control, the Danish respondents suggested the word "involved", which they found more appropriate. The Danish version was adapted accordingly. Furthermore, the word doctor was changed to healthcare professional to broaden the scope of the questionnaire. All changes were approved by the developer.

Phase 2 - psychometric testing

Of the 95 respondents, 56 respondents (58.9%) were not able to answer all 13 items since they had not been in contact with a healthcare professional; five of the items (Fig. 1, items 6–10) deal with this interaction. Moreover, two respondents had > 3 items missing (when the items about interaction with a healthcare professional where not included) and, therefore, they were excluded (Table 1). The MCAR test showed that data was missing completely at random ($p = 0.307$). The missing data was replaced by the EM method. The EFA was conducted as the KMO was 0.731 and Bartlett's test significant ($p < 0.001$). Four factors had an Eigen value > 1, but only one factor was extracted as the Scree plot had a clear "elbow", showing one factor explaining 46.1% of the variance. Three items had a factor load < 0.4, (Table 2). The internal consistency was high as Cronbach's α was 0.89. The inter-item correlations ranged widely between – 0.001-0.773, with items 2 and 5 showing the lowest correlation and items 10 and 11 the highest (Table 3).

Discussion

Overall, the translated version was equivalent to the original version with only minor changes. However, one item had to be changed due to cultural differences. The results from the psychometric testing supported a one factor-structure and showed a high internal consistency (0.89) in the final Danish version.

In the forward translation, both translators had chosen not to translate the English word "feedback" in the title.

Table 1 Item statistics and percentage of missings per item of the Patient Feedback Form

Item	N	Mean	SD	Missing	
				Count	Percent
1: Time it took completing	93	2.12	0.357	2	2.1
2: Number of time completing	92	1.97	0.346	3	3.2
3: Easy to complete	94	1.74	0.671	1	1.1
4: Completion was useful	95	1.69	0.745	0	0.0
5: Easy to understand	95	1.67	0.643	0	0.0
6: Easier to recall symptoms and side effects	38	2.00	0.805	57	60.0
7: Improved discussions with clinician	37	1.95	0.780	58	61.1
8: Clinician used information for care	33	1.85	0.870	62	65.3
9: Care quality improved	31	2.26	0.815	64	67.4
10: Communication with clinician improved	35	2.09	0.919	60	63.2
11: Made me more in control of care	94	1.79	0.760	1	1.1
12: Recommend to other patients	93	1.30	0.484	2	2.1
13: Want to continue using	90	1.28	0.450	5	5.3

N, numbers; SD, Standard deviation

The word is a loanword in Danish and the translators believed that the word was so integrated into the Danish language that everyone would understand the meaning. The respondents disagreed on whether or not it was appropriate in the Danish version since there was a risk that older patients in particular would not understand it. Consequently, we decided to choose the Danish word "tilbagemelding" – the best possible translation of feedback – which was also suggested by some of the respondents. Concerning items 7 and 10, which were found to be similar, it might be argued that future respondents may find it annoying that two items are almost identical. However, there are some nuances. The word "discussions" may, for example, be more of an active exchange of opinions between patient and physician whereas "communication" may also be one-sided with the physician setting the agenda. Moreover, the importance of staying true to the original was prioritized. An inter-item correlation of 0.728 supports the argument that, despite the similarity, the items are not redundant. As for the phrase "control of", which the Danish respondents disapproved of, we decided that cultural adaption was more important than sticking to the original phrase. Due to cultural differences, it may be more natural for Ameri- can patients to feel in control of treatment and care [22], whereas the cognitive interviewing suggests that Danish patients prefer to be actively engaged in the process, which is also supported by the patient organization Danish Patients [23]. Accordingly, the wording was chan- ged. Similar cultural adaptions are found in other ques- tionnaire translations [15].

Table 2 Factor matrix and item statistics with no missings from the Patient Feedback Form

Item	Factor	Mean	SD
1: Time it took completing	0.333	2.12	0.358
2: Number of time completing	0.132	1.97	0.345
3: Easy to complete	0.307	1.75	0.670
4: Completion was useful	0.568	1.70	0.749
5: Easy to understand	0.594	1.67	0.631
6: Easier to recall symptoms and side effects	0.573	1.95	0.669
7: Improved discussions with clinician	0.922	1.86	0.598
8: Clinician used information for care	0.836	1.79	0.627
9: Care quality improved	0.807	2.12	0.576
10: Communication with clinician improved	0.746	2.01	0.750
11: Made me more in control of care	0.858	1.78	0.764
12: Recommend to other patients	0.656	1.32	0.511
13: Want to continue using	0.568	1.29	0.463

SD, Standard deviation

Far from all patient satisfaction questionnaires have undergone psychometric testing [2], which is also the case for the original version of this questionnaire. However, initial psychometric testing of the translated version shows satisfactory results. The EFA reveals a one factor latent structure. As less than half of the variance (46.1%) is explained by one factor, the pres- ence of two factors could be discussed. One factor fo- cused on the feasibility of completing the PROM and the other focused on the clinical utility of the ques- tionnaire in the process of health care. Internal consistency is defined as the degree of relation be- tween items [12], and the high Cronbach's α (0.89) supports the results of a one factor structure. However, the possibility of an artificially increased Cronbach's α is present as the test is sensitive to the small number of items within the scale [24], as well as the

Table 3 Inter-item correlation matrix of the Danish version of the Patient Feedback Form

Item	1	2	3	4	5	6	7	8	9	10	11	12	13
1: Time it took completing	1.000	0.302	0.268	0.439	0.180	0.166	0.302	0.095	0.264	0.137	0.295	0.454	0.392
2: Number of time completing		1.000	0.169	0.141	*−0.001*	0.223	0.058	0.044	0.150	0.116	0.054	0.246	0.313
3: Easy to complete			1.000	0.413	0.466	0.166	0.229	0.237	0.329	0.009	0.210	0.289	0.319
4: Completion was useful				1.000	0.406	−0.024	0.479	0.462	0.704	0.103	0.475	0.506	0.580
5: Easy to understand					1.000	0.595	0.616	0.415	0.398	0.423	0.413	0.396	0.308
6: Easier to recall symptoms and side effects						1.000	0.587	0.476	0.250	0.637	0.448	0.441	0.215
7: Improved discussions with clinician							1.000	0.768	0.747	0.728	0.770	0.573	0.513
8: Clinician used information for care								1.000	0.772	0.651	0.742	0.509	0.334
9: Care quality improved									1.000	0.473	0.695	0.482	0.454
10: Communication with clinician improved										1.000	*0.773*	0.413	0.253
11: Made me more in control of care											1.000	0.536	0.510
12: Recommend to other patients												1.000	0.750
13: Want to continue using													1.000

Bold and italic for highest and lowest correlation

imputation of data. Only a slightly higher Cronbach's α of 0.90 could be reached if items 2 or 3 were deleted, suggesting a high degree of item-interrelatedness.

It is a limitation that data had to be imputed to complete the dataset. In future research, a study sample where the respondents are able to answer all the items, including the ones dealing with contact between patient and health care professional (items 6–10), should be considered. Also, the generalizability of the results may be reduced by the fact that all the respondents were male, prostate cancer patients and limited to those between the ages of 54–73. Furthermore, it has to be taken into consideration that even though the sample size is accurate to test the EFA, a larger sample size is preferable.

Psychometric testing is often left out when a questionnaire is being used, and the fact that some initial testing has been performed is an obvious strength. Furthermore, the questionnaire may be a valuable tool to assess whether or not a given PROM-questionnaire should be implemented in the clinic or to assist clinicians in choosing which questionnaire to use in a given context. There is a need to "capture patient's experience of treat- ment and care as a major indicator of health service quality and treatment effectiveness" [25]. Using the Pa- tient Feedback Form may be a possibility. Moreover, fu- ture studies including PROMs can be improved by using the present PREM-instrument, which is now available in Danish, allowing researchers and clinicians to measure patient satisfaction parallel to PROMs [4] and compare results nationally and internationally.

Conclusion

The translated, culturally adapted, and validated Danish version of the Patient Feedback Form seems to be suitable for measuring satisfaction with PROMs in this prostate cancer population. To further verify the validity of the instrument, the next step should be psychometric testing such as hypotheses testing, responsiveness, and test-retest on a larger and more diverse sample size.

Abbreviations

EFA: Exploratory factor analysis; EM: Expectation-maximization; KMO: Kaiser-Meyer-Olkin; MCAR: Missing Completely at Random; PREM: Patient-reported Experience Measures; PROM: Patient-reported Outcome Measures; QoL: Quality of life

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Availability of data and materials

Permissions from the original developer and adaptor, questionnaires, notes and reports are stored at the Department of Oncology, Odense University Hospital. Please contact corresponding author for more information.

Authors' contributions

Design of the study: LKT, HP, KBD. Collection and assembly of data: LKT. Data analysis and interpretation: All authors. Manuscript writing: All authors. Final approval: All authors. The manuscript has not been published elsewhere, and is not under consideration by another journal.

Ethics approval and consent to participate

According to Danish law, approval from the ethical committee was not required, but the study was registered with the Danish Data Protection Agency. All respondents have agreed to participate.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Paper III

Tolstrup LK, Bastholt L, Möller S, Zwisler, AD, Dieperink KB, Pappot H.

The use patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: A randomized controlled trial

Manuscript

The use of patient-reported outcomes to detect adverse events in metastatic melanoma patients receiving immunotherapy: A randomized controlled pilot trial

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Purpose
A randomized controlled trial was conducted to preliminary assess if melanoma patients treated with immunotherapy had the number of grade 3 or 4 adverse events during treatment reduced by 50% using a tailored electronic patient-reported outcomes tool in addition to standard toxicity monitoring compared to standard monitoring alone. Secondary endpoints were: if more AEs were reported in the intervention group, if there was a difference between the two groups in the number of telephone consultations, extra out-patient visits, number of days in the hospital, days in steroid treatment and the time patients experienced grade 2 or higher toxicity.

Patients and methods
Melanoma patients receiving immunotherapy at the Department of Oncology, Odense University Hospital, Denmark participated. In standard care, patients had AEs assessed by a clinician before each treatment cycle. In addition, patients randomized to the intervention reported their AEs weekly. The electronic questionnaire used for patient reporting was designed on the PRO-CTCAE platform.

Results
One hundred forty-six melanoma patients were randomized. In this study, we did not detect a difference between the two groups in the number of severe AEs (P = 0.983), and we did not see a difference in the overall number of AEs either (P = 0.560). The number of phone contacts was significantly higher in the intervention group as these patients called the hospital more frequently (P = 0.009).

Conclusion
Even though attention to AEs was increased for patients in the intervention, resulting in a significant increase in number of phone calls, we did not find a difference between the control group and the intervention group when it comes to the number of severe AEs, and a larger trial will have little chance of showing a significant difference by using this electronic platform in this patient population.

INTRODUCTION

The number of people diagnosed with malignant melanoma worldwide has increased significantly during the last 50 years[1], which is in keeping with the development in Denmark[2,3]. Approximately 2300 new cases of melanoma are reported annually in Denmark, and more than 400 Danes are diagnosed with metastatic disease[4]. Despite the increase in incidence, survival has improved significantly due to new treatment modalities such as immune checkpoint inhibitors (CPIs)[5]. Furthermore, CPIs have resulted in significantly longer recurrence-free survival in the adjuvant setting[6]. It is well established that the toxicity profile of CPIs differs considerably from other cancer therapy strategies such as chemotherapy[7] and that immune-related adverse events (AEs) can be severe and, in some cases, life-threatening[8]. Since the introduction of CPIs, many trials have been carried out, which has not only improved survival significantly but also elucidated the adverse AEs related to CPIs[9-18]. Dealing with these AEs requires specific training of the caring physician and specialized nurses[5], and international guidelines to manage these toxicities have been developed[19]. It is well-known that early recognition may limit severity and duration[8]. Thus it would be interesting to explore if it is possible to develop a clinical setup using an electronic solution including patient-reported outcomes to detect AEs at an earlier time-point before they turn into grade 3 or 4 AEs requiring hospitalizations, treatment with steroids and/or treatment discontinuation. In many oncology settings, toxicity-monitoring is carried out by a physician who assesses the patient before each treatment using the Common Terminology Criteria of Adverse Events (CTCAE)[20]. Apart from these scheduled visits, the patient usually may not have any contact with the hospital between treatments, i.e., typically for three to four weeks. The patients are informed about the specific toxicities which may arise. They were encouraged to contact the hospital in case of the occurrence of a symptom. However, some patients may still be reluctant to do so[21] either because they neglect their symptoms, worry that treatment may be stopped, or has not understood the importance of early detection. Accordingly, there is a risk that a symptom may go from mild to moderate/severe in this period. If patients become engaged in the reporting of symptoms on a more frequent basis, there is a presumption that AEs are discovered at an earlier time-point, enabling relevant treatment to be initiated and thereby avoiding major complications[22]. Studies suggest that using patient-reported outcomes (PROs) may result in improved communication, early relapse detection, optimized symptom monitoring, improved

survival, and better quality of life[23-25], particularly by the use of electronic devices[26]. However, it has not been examined if PROs in relation to symptom management for melanoma patients treated with immunotherapy may lead to earlier detection of symptoms resulting in a reduction in the number of severe AEs. Thus, based on current knowledge on AEs in melanoma patients receiving immunotherapy and PROs used in connection with symptom management, we hypothesized that self-reporting of AEs weekly direct from patients using a digital PRO system would be able to reduce the number of severe AEs during treatment compared to patients who get standard monitoring. To explore the above hypothesis, we designed a questionnaire from the PRO-CTCAE item library specifically tailored for melanoma patients receiving immunotherapy[27]. Following the development of the PRO tool, an open, randomized controlled trial was conducted to preliminary assess if the number of grade 3 or 4 AEs during treatment could be reduced by 50% at 24 weeks follow up using the designed electronic PRO tool on patient self-reporting, in addition to standard toxicity monitoring compared to standard monitoring alone.

PATIENTS AND METHODS

Setting

At the Department of Oncology, Odense University Hospital (OUH), approximately 100 patients with metastatic melanoma are treated each year. Recruitment took place at OUH between January 2017 and May 2019. Patients were introduced to the study when they were informed about treatment with a CPI. Before the first treatment, the patients were contacted by telephone and asked to give oral and written informed consent.

Design

This study cites an open, randomized controlled trial, PROMelanoma (*ClinicalTrials.gov NCT03073031).* The consort checklist for the Reporting of Patient-Reported Outcomes in Randomized Trials was followed[28]. Patients were randomly assigned in a 1:1 ratio using the Open Patient data Explorative Network[29] to one of the following groups: standard toxicity assessment performed by a physician before each treatment cycle or standard toxicity assessment performed by a physician before treatment supplemented by weekly web-based electronic reporting at home. Randomization was stratified according to treatment (anti-CTLA-4 vs. anti-PD1 or anti-CTLA-

4/anti-PD1 in combination) and disease status (treatment for metastatic disease vs. adjuvant therapy after surgery for metastatic disease).

Standard Care

Patients had their adverse events assessed by a clinician before each treatment cycle. The patients were informed orally and in writing about the treatment and the toxicities, which may occur. The importance of contacting the hospital in cases of the occurrence of new symptoms was also emphasized to the patients. In Denmark, an algorithm exists, in alignment with international guidelines, which describes in detail how specific AEs should be handled[30].

Intervention

In addition to standard care, patients in the intervention group received a tablet computer with a sim-card to ensure all patients could participate in the web-based evaluation. Moreover, they were trained in the self-reporting of symptoms. Baseline registration was made at the clinic. The software platform AmbuFlex[31] was used for patient reporting. Studies demonstrate that the vast majority of AEs occur within 24 weeks of treatment[32,33]. Accordingly, the patients reported weekly for a maximum of 24 weeks. If the patients stopped treatment due to toxicity or disease progression before this time-point, toxicity-monitoring would take place for 30 days after the last dose of immunotherapy or until the initiation of other anti-neoplastic therapy. As soon as the patients reported a mild or higher AE, an alert was triggered for the majority of AEs telling the patient to contact the hospital. The alert was triggered for 24 out of the 29 items included in the questionnaire. No alerts were triggered for *fatigue, skin dryness, hair loss, decreased appetite,* and *taste changes* because these symptoms were not at risk of becoming severe overnight. A clinician did not routinely monitor the patient reports. When the patients came for their scheduled appointment in the out-patient clinic, the physician would log into the system to see the patient reporting and discuss it with the patient. Figure 1 shows what the reporting looked like for the clinician. A bar attached to each symptom appeared green, yellow, or red depending on the frequency and severity of the symptom and how much it affected daily activities.

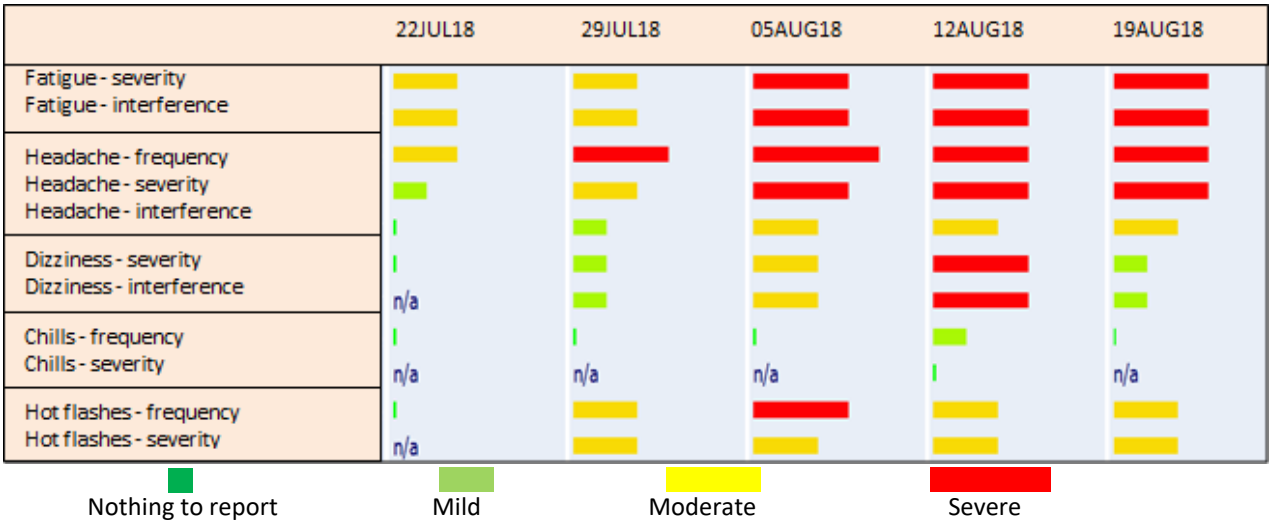


Fig. 1 example of part of a patient reporting available to clinicians

Participants

Eligible patients had unresectable stage III or stage IV disease and were scheduled to receive a CPI either as monotherapy or in combination as first, second or third line therapy. Patients treated with a CPI as monotherapy in adjuvant settings could also be included. Other eligibility criteria included the age of at least 18 years; be able to read and understand Danish; be willing and able to comply with the completion of an electronic PRO-questionnaire on symptoms and required quality of life (QoL) questionnaires. Baseline characteristics such as age, gender, performance status, disease stage, and experiences with electronic devices, were collected.

Method for patient reporting

The American National Cancer Institute (NCI) has developed standardized definitions for AEs – The Common Criteria for adverse events (CTCAE) to describe the severity of organ toxicity for patients receiving cancer therapy[20]. The system consists of 780 adverse events, and in the beginning, it was primarily used in clinical trials. Today, however, it is also used in routine cancer treatment. In order to enhance patient involvement, the NCI has developed the CTCAE scoring system for toxicity-monitoring into a tool appropriate for patient self-reporting [34]. An item-library of 78 items have been found appropriate for self-monitoring and constitutes now the PRO-CTCAE[35]. The PRO-CTCAE item library has been translated and validated in a Danish context[36]. Because existing

questionnaires may not adequately capture the toxicities unique to CPIs[37], this item bank was chosen for this study, making it possible to design a questionnaire fitted for melanoma patients receiving immunotherapy. A thorough item-selection process was carried out, which has resulted in a questionnaire consisting of 29 items[27]. Weekly reporting was chosen since this is the preferred recall period in PRO-CTCAE questionnaires[38].

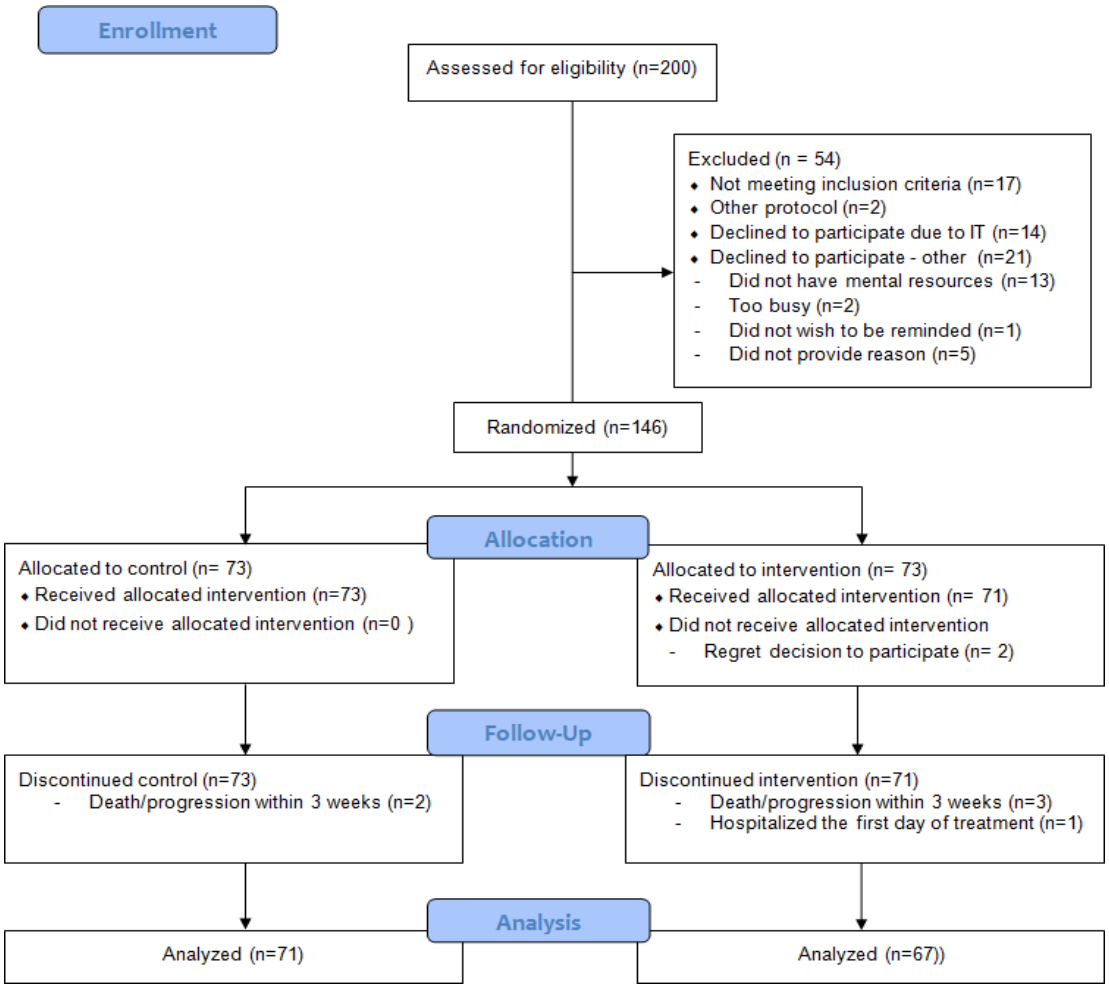


Fig. 2 Consort diagram of inclusion process

Statistical considerations

As the trial was a pilot study evaluating a new health technology, a significance level of 0.2 and a power of 0.64 was accepted [39] to preliminary evaluate the endpoints. Baseline characteristics and AEs by randomization groups were reported as counts and proportions. Moreover, we compare the number of AEs, phone contacts, and extra visits to the outpatient clinic by Poisson regression,

respectively, negative binomial regression, in case of detected overdispersion. We compare the total duration of grade 2 or higher AEs, duration of hospital stay and duration of steroid treatment by Wilcoxon rank-sum test, and display the total length of grade 2 or higher AEs a Kaplan-Meier curve. All analyses were carried out in Stata 15.0[40].

Primary outcome

To explore if the number of grade 3 or 4 AEs assessed by the CTCAE could be reduced by 50% by having patients more actively involved in the reporting of symptoms.

Secondary endpoints

To explore if more AEs were reported in the intervention group, if there was a difference between the two groups when it comes to number of telephone consultations and extra out-patient visits, if the time patients experience grade 2 or higher toxicity differs in the two groups and if there is a difference in the number of days in hospital and if the number of days in steroid treatment differs.

RESULTS

Patients and treatments

Two hundred patients were screened for the trial, and 181 patients were considered eligible. Among these patients, 146 were randomized to the trial. Thirty-five patients declined to participate (Fig. 2). Among the 35 patients who declined randomization, 14 patients gave IT- related reasons, whereas 13 patients did not have the mental resources. The median age of the patients who declined to participate due to IT was 78 years, compared to 66 years in the randomized group. Two patients withdrew their consent to participate, and six patients were excluded within the first three weeks after randomization due to rapid disease progression.

The majority of patients (51%) received Pembrolizumab as monotherapy (Table 1). Only seven patients (5%) received Ipilimumab. The 24 patients who received adjuvant therapy were all treated with Nivolumab. The last recruited patient made the final report in ultimo October 2019. Comparisons of baseline characteristics in the two groups show that there are no significant differences between the intervention and the control group. Baseline characteristics are shown in Table 1. The median age in both groups was 66 years (range: 32-87). 53% of the participants were

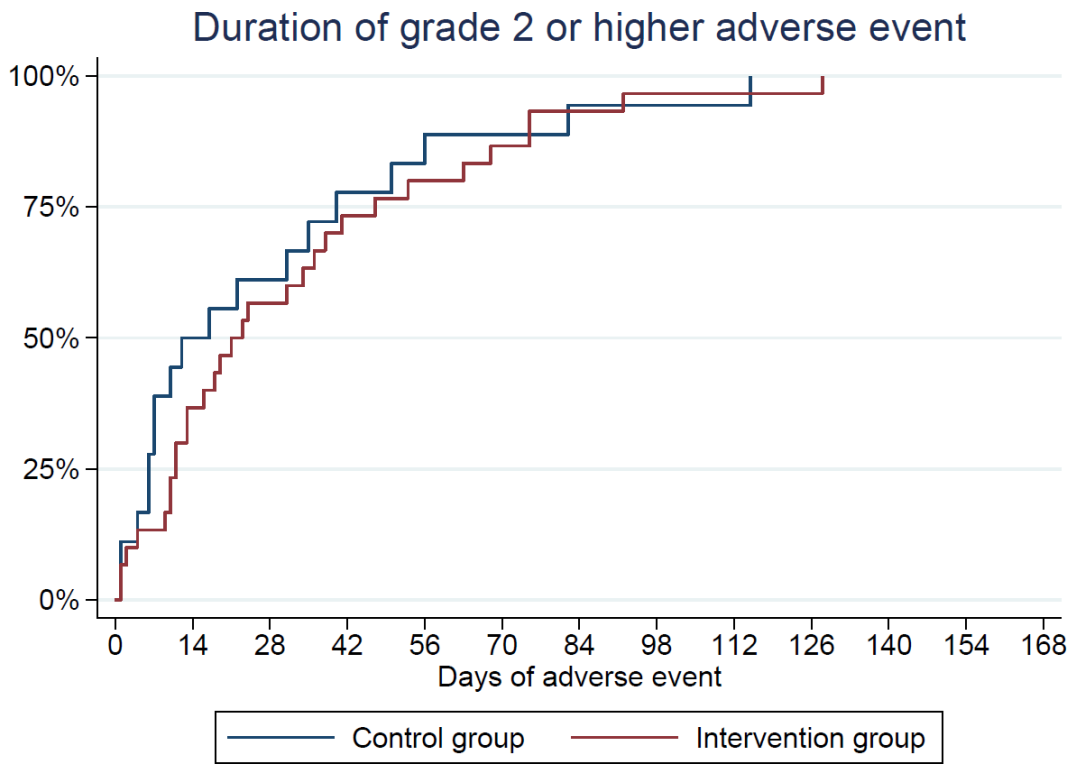
male, and 47% female. The majority of patients (69%) had performance status 0. Three of the included patients (6%) reported that they had no computer experience.

	Control N = 73 (%)	Intervention N=73 (%)
Random assignment		
Ipilimunab	3 (4)	4 (6)
Pembrolizumab	36 (49)	38 (52)
Nivolumab	13 (18)	11 (15)
Ipilimumab+Nivolumab	21 (29)	20 (28)
Age		
Median (range)	66 (32; 83)	66 (34; 87)
Sex		
Male	43 (59)	35 (48)
Female	30 (41)	38 (52)
ECOG Performance status		
0	52 (72)	49 (69)
1	19 (26)	19 (27)
2	1 (1)	3 (4)
Disease stage		
Stage III	12 (16)	10 (14)
Stage IV	61 (84)	63 (86)
Line of therapy		
Adjuvant	13 (18)	11 (15)
1st line	52 (71)	52 (71)
2nd line	6 (8)	6 (8)
3rd line	2 (3)	4 (5)
Lactate dehydrogenase		
Normal	51 (76)	46 (69)
Elevated	16 (24)	21 (31)
BRAF status		
Mutated	31 (42)	32 (44)
Wild type	30 (41)	27 (37)
Unknown	12 (16)	14 (19)
Experience with electronic devices		
None	0 (0)	3 (6)
A little	16 (38)	15 (32)
A lot	26 (62)	29 (62)

Table 1 Patient characteristics at baseline in the randomized trial

Primary and secondary outcomes

As for the number of severe AEs (grades 3 and 4), there was no significant difference between the two groups (P = 0.983), which is also the fact for the overall number of reported AEs (P = 0.560). A sub-analysis comparing the number of grade 3 and 4 AEs corresponding to the PRO items showed no difference either (Table 2). Thus, approximately one-third of the AEs that occurred were the same as the symptoms that the patients were asked about in the PRO-CTCAE questionnaire. More than one-third of the AEs were elevated liver enzymes, creating few symptoms for the patients to report upon. The overall number of patients who experienced a grade 3 or 4 event was 58% for the combination therapy and 13% for patients who received anti-PD1 as monotherapy. There was not a significant difference in the time the patients in the two groups experienced grade 2 or higher toxicity (0.516) either.



There was a significant difference in the number of phone calls to the hospital, as patients in the intervention group called more frequently (P = 0.009). However, 13 patients (19%) represent almost half of the phone calls (47%) in the intervention group, which means that a minority of patients called frequently. There was also a tendency towards patients in the intervention group having more extra visits (P = 0.156), which correlates to the higher number of extra phone calls.

	Kontrol n	Intervention n
All treatment-related events		
Any grade	202	202
Grade 3 or 4	20	19
Events related to PRO-items		
Any grade	129	124
Grade 3 or 4	8	6
Treatment-related contacts		
Phone calls	102	163
Extra visits	31	44
Days in hospital		
Accumulated	131	221
Days in steroid treatment		
Accumulated	714	1133

Table 2 Overview of treatment-related events, contacts, days in hospital and days in steroid treatment.

A significant difference was found in the number of days patients received steroid treatment. Patients in the intervention group had more days on steroid treatment (P= 0.004). When it comes to the number of days in the hospital, there was a tendency (P = 0.101) that patients in the intervention group had more days in the hospital compared to patients in the control group. However, in total, only a small number of patients received steroids or were admitted to the hospital.

DISCUSSION

This randomized trial aimed to compare the number of severe (grade 3 and 4) AEs developed during standard toxicity monitoring versus standard toxicity-monitoring plus weekly patient reporting for melanoma patients receiving immunotherapy. In this study, we did not detect a difference between the two groups, and we did not see a difference in the overall number of AEs either. Patients in the intervention group called significantly more often, indicating that they reacted on the triggered alerts and were thus more aware of their symptoms compared to patients in the control group. Also, the fact that patients had significantly more days in steroid treatment may suggest that symptoms were detected early, initiating relevant treatment.

There may be several explanations as to why we did not detect a difference in the number of grade de 3 and 4 AEs. Although the need for early detection is underlined again and again in the literature, our study demonstrates that a relatively large group of AEs cannot be detected early point, using patient self-reporting systems. For example, elevated liver enzymes, which constituted approximately one-third of the severe AEs in this trial, are usually asymptomatic[41]. They can only be detected by blood samples which are carried out before each treatment cycle according to existing guidelines[30]-Another reason may be that the overall attention to AEs was increased based on the information all patients received about the clinical trial, perhaps leading to an unanticipated reduction in the number of severe AEs in the control group resulting in the two groups experiencing similar improvements[42]. Patients in the control group had been introduced to the study before randomization, which might have increased their desire to contact the hospital unscheduled. No design of a clinical trial could have avoided this. However, the number of patients who developed severe AEs aligns with the numbers found in the literature [6,11,12,14,16,43], which indicates that the risk of bias is negligible. Furthermore, because immunotherapy is still relatively new as a cancer treatment strategy, there may also be a general tendency to be more aware of the toxicity profile. Oncologists and oncology nurses in Denmark specialized in treating melanoma patients receiving CPIs are very attuned to potential severe AEs which may occur.

Consequently, patients are well informed on how to react in case new symptoms occur, and there may not be much to improve because of the high standard of routine care. Bruin et al. argue in a

non-cancer study that the level of routine care to a great extent determines how much improvement in behavior change can be acheived[44]. Had the study been carried out in another setting with a poorer quality of care, results may have been different.

Regarding the patient population we have examined, there was also a built-in risk that the least resourceful patients may also be the ones who declined to participate. More than 75% of the patients who declined to participate did so either due to lack of computer skills or due to lack of mental resources. The median age of the patients who declined due to IT-related reasons was 78 years compared to 66 years for the patients who were included. Only three of the patients included in the study reported that they had no computer experience beforehand. These numbers indicate that technology was a barrier when trying to recruit older/computer-naive patients to our RCT. This result is in line with Fiteni et al., who argue that patients who are computer-naive may be excluded from this kind of intervention[26]. These patients may also be the ones who would benefit the most from the intervention because they may be less likely to contact the hospital unscheduled. According to Basch et al., patients with no IT skills may have weaker communication skills and therefore benefit more from a structured set-up [24]. If our study had had a more complex set-up with an oncology nurse contacting the patients when the alert was triggered, the weaker patients might have been reached, and AEs might have been detected at an earlier time point. Other studies suggest that this pro-active approach may be the way forward[23,24,45].

We did see a significant difference in the number of phone calls between the two groups, which demonstrates that the attention to AEs was increased, as was the intention of the study. The threshold (when an alert was triggered as a result of patient reporting) for contacting the hospital may have been set too low. Too many alerts may have been triggered, resulting in too many irrelevant phone calls/extra visits to the hospital. Moreover, the patients who were already inclined to call the hospital (maybe the most resourceful) may call even more. The fact that 13 patients represented almost half of the phone calls supports this argument. Patients who were already reluctant to call the hospital (maybe the least resourceful) may, on the other hand, continue to be hesitant and disregard the alert. To what extent the patients actually did react on alerts will be examined in a future study. There was also a tendency towards patients in the intervention group having more days in the hospital. In relation to steroid treatment, a significantly higher number of patients in the intervention arm received steroids due to an AE.

Possibly there may be a tendency towards attending physicians to add treatment with steroids to be sure not to overlook an important AE. This context may explain why patients in the intervention group received more steroids. The number of patients who had received steroids, or had been admitted to the hospital, however, was low, and the results should therefore be interpreted with caution. Moreover, it does seem highly unlikely that the electronic reporting AEs would put patients in the intervention group in a poorer position compared to the control group.

Patients and clinicians were also asked about their experiences with the intervention through a survey[46] and interviews. Overall, patients and clinicians agreed that the attention to side effects was increased and that the patients were better prepared for the consultation when they came to the out-patient clinic. Moreover, the patients believed that the electronic questionnaire was easy to access and fill out[47]. Thus in terms of clinician and patient satisfaction, the study did make a difference for the included patients. If this is reflected in an improved QoL will be elucidated when the collected QoL-data is analyzed.

Strengths and limitations

It is an obvious strength that an RCT was carried out to evaluate the primary endpoint. Furthermore, the chosen PRO-questionnaire was specifically designed for patients receiving immunotherapy. It may be a limitation that it was a single-center study and a pilot study with small sample size. Moreover, less resourceful patients may have declined to participate, and the set-up may have been too simple as patient reports were not monitored in real-time by a clinician.

Conclusion

In this RCT it was examined if the number of grade 3 and 4 AEs for melanoma patients receiving immunotherapy with CPIs could be reduced by including the patients in the reporting of symptoms. We did not find a difference. However, a significant difference in the number of phone call was found as patients in the intervention group called for frequently, indicating that attention to AEs was increased. Even though the use of an electronic PRO could not reduce the number of grade 3 or 4 AEs in this melanoma population, the positive impact of the electronic PRO on other endpoints such as QoL, communication, or treatment-planning, cannot be excluded.

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Paper IV

Tolstrup LK, Pappot H, Bastholt L, Zwisler, AD, Dieperink KB.

Patient-reported outcomes during immunotherapy for metastatic melanoma: Mixed methods study of patients' and clinicians' experiences

In review, *Journal of Medical Internet Research*

Patient-reported outcomes during immunotherapy for metastatic melanoma: Mixed methods study of patients' and clinicians' experiences

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Background

Using electronic patient-reported outcomes questionnaires has proven in many settings – in hospitals and patient homes. It remains to be investigated, however, how melanoma patients and their treating clinicians experience the electronic self-reporting of side effects and the derived communication.

Objective

The primary objective of the study was to examine patients´ and clinicians´ experiences with an e-Health intervention to weekly monitor side effects during treatment with immunotherapy.

Methods

An e-Health intervention based on questions from the PRO-CTCAE library was used and tested in a randomized clinical trial with patients receiving immunotherapy for malignant melanoma and clinicians at a university hospital in Denmark. On a weekly basis, patients reported their symptoms from home during treatment via a tablet provided to them. The electronic patient reports were available to clinicians in the out-patient clinic. A mixed methods approach was applied to investigate the patients´ and clinicians´ experiences with the intervention. Data from patients' experiences was collected in a short survey, the Patient Feedback Form. Moreover, a subset of the patients participating in the survey was interviewed about their experience. Furthermore, one focus group interview with clinicians was carried out to elucidate their views.

Results

A total of 57 patients completed the Patient Feedback Form, and 14 patients were interviewed. The focus group interview included five clinicians. Overall, patients and clinicians were satisfied with the tool. They believed it enhanced patients´ awareness of side effects and increased their feeling of involvement. The patients reported that it was easy to fill out the questionnaire and that it made sense to do so. However, a minority of the patients expressed in the interviews that they did not believe that the health care professionals had seen their reports when they came to the clinic and that the reporting did not lead to increased contact with the department.

Conclusion

Overall, the satisfaction with the e-Health intervention was high among patients and their treating clinicians. The tool was easy to use and contributed to greater symptom awareness and patient involvement. Thus, in terms of patient and clinician satisfaction with the tool, it makes sense to continue using the tool beyond the project period.

Introduction

Underreporting of symptoms by clinicians in connection with cancer therapy, particularly when it comes to chemo and radiotherapy, is well accounted for in the literature [1-4]. However, over the last decades, new therapies have been developed and various kinds of immunotherapy now play an important role in fighting cancer [5]. Particularly in connection with melanoma, immunotherapy plays an important role and survival has improved significantly [6]. The side effects that patients experience when treated with immunotherapy can be severe and unpredictable [5], and they differ immensely from the side effects experienced by patients who receive chemotherapy [5]. Furthermore, untreated toxicities may progress and become potentially life-threatening [7]. Thus, toxicity-monitoring may advantageously be optimized to meet the need for early detection of symptoms. Studies have demonstrated that using Patients Reported Outcomes (PROs) to detect and monitor symptoms and improve communication in routine care may be useful [8] and should be encouraged [9, 10]. Moreover, including the patients more has become a priority in many health care settings across the world [11]. Similarly, there has been an increasing awareness within the Danish health care system of patients not being sufficiently involved when it comes to treatment and care, [12] despite the fact that the Danish regions recommend that efforts are to be planned *with* the patient rather than *for* the patient [13].

Using electronic PRO-questions (ePROs) to monitor symptoms has proven feasible in connection with scheduled consultations, i.e. in the waiting area in various oncology settings [14], and new evidence suggests that the method is also useful at home, i.e. via a link to a web page [15]. Studies also demonstrate that including cancer patients in the reporting of symptoms may increase their quality of life [16] and that the general acceptability of routine data collection is high [8]. With regard to immunotherapy, studies have examined the quality of life during treatment [17, 18], but it has not been examined whether patient reporting of side effects also results in improved toxicity monitoring. Therefore, we decided to design a randomized clinical trial, PROMelanoma (*ClinicalTrials.gov NCT03073031),* with the primary aim of investigating whether the severity and frequency of severe side effects can be reduced by including the patients in the reporting of symptoms on a frequent basis. Enrollment has just finished.

An exploratory endpoint of PROMelanoma was to examine whether our set-up of including an e-Health intervention on symptom management is implementable in clinical practice and makes the

patients feel more involved in treatment and care. Patient and clinician satisfaction with various e-Health interventions has been measured in other studies within the oncology setting to support clinical decision making and improve patient self-management [19, 20]. Many outcome measures are not sufficiently tested in clinical practice, however, which is imperative before implementation. In order for PRO-interventions to be successful, it is vital that they are approved by the patients [21]. Thus, there is a need for more precise measures [22] that fit the patient population under investigation [23] to make sure that the PRO-intervention is feasible and easy for the patient to adopt. In this connection, studies that elucidate the usefulness of a given PRO from the perspectives of patients and their treating clinicians must be carried out. To our knowledge, no study has explored how melanoma patients treated with immunotherapy experience the electronic self-reporting of symptoms using an e-Health intervention specifically designed for this patient group [24], which makes this study highly relevant. However, there is no recipe for measuring the patient experience, and measurement is not routinely conducted in a standardized way [25]. Thus, the patient experience can be captured in different ways. However, in order to acquire a broad perspective on the topic in question, a mixed methods approach may be the way forward. For example, a short survey can help provide feedback about the general trends, whereas in-depth interviews may provide a more detailed understanding of both the patient and clinician perspective [26]. Similarly, Hudak et al. suggest that it is preferable to combine a standardized quantitative measure with a qualitative method when measuring patient satisfaction [27]. Girgis et al. used a similar method when they evaluated feasibility and acceptability of real- time reporting in a cancer population [19]. Thus, the primary objective of this study was to examine, using both qualitative and quantitative data, patients´ and clinicians´ experiences with an e-Health intervention to monitor side effects during treatment with immunotherapy in routine clinical practice (*ClinicalTrials.gov NCT03073031).*

Material and methods

A mixed methods approach was applied to gain a deeper insight into the topic. For the quantitative part of the study, a questionnaire to measure patient satisfaction – the Patient Feedback Form [20, 28] – was provided to patients who experienced the PROMelanoma e-Health intervention. In addition to the questionnaire, qualitative interviews with a subsample of these patients and one focus group interview with clinicians were conducted using a deductive approach

[29] in order to evaluate the intervention. The COREQ Checklist [30] was applied to ensure that important aspects were included. A convergent design was selected [31], where survey data and interview data were collected in parallel over the same period of time (February 2017 – March 2019). Data was analyzed separately and compared to determine similarities and differences. By using the triangulation technique, cross verification of data from interviews and survey was achieved, Fig. 1.

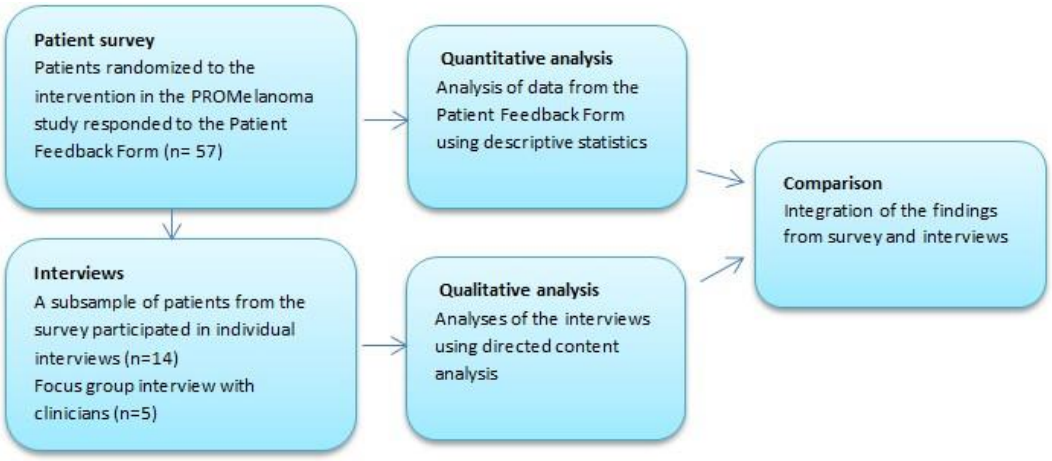

Fig. 1 Overview of the mixed methods study design, including a survey, individual interviews and one focus group interview with clinicians

Setting

The survey and interviews took place at the Department of Oncology, Odense University Hospital, Denmark. The patients completed the Patient Feedback Form when they came to the out-patient clinic to receive their treatment for metastatic melanoma. The interviews also took place in the out-patient clinic in a separate room.

The e-Health intervention

The National Cancer Institute´s PRO-CTCAE developed for patient self-reporting [32] was chosen as PRO tool since the CTCAE grading scale [33] is well known within oncology [34] and used by oncologists all over the world. Through a careful selection process, the relevant items were selected from the PRO-CTCAE library [35]. The software platform AmbuFlex, which is especially developed for electronic PROs, was used [36]. The patients received a tablet with SIM card to ensure internet access. The reporting would take place on the tablet, at home, once a week, which

is the preferred recall period for PRO-CTCAE items [37], and continue for 24 weeks to ensure that the majority of symptoms were detected. The patients did not receive a weekly reminder in the form of a text message or a phone call, but they were asked, when introduced to the intervention, to report their symptoms on a fixed weekday, making reporting easier to remember. If the patients experienced a symptom, an alert would tell them to contact the department. The alert function was triggered for side effects that could potentially become severe. Accordingly, side effects such as alopecia or fatigue did not trigger an alert. As soon as the patients had responded to the questionnaire, the report was visible to the healthcare professionals at the hospital. However, clinicians did not receive a notification when an alert was triggered by a patient report. It was left up to the patients to react on the alert. Not until the patients came to the out-patient clinic, did the clinicians log into the electronic system to see the patient´s report. A bar attached to each symptom appeared green, yellow or red depending on the severity of the symptom, fig. 2.

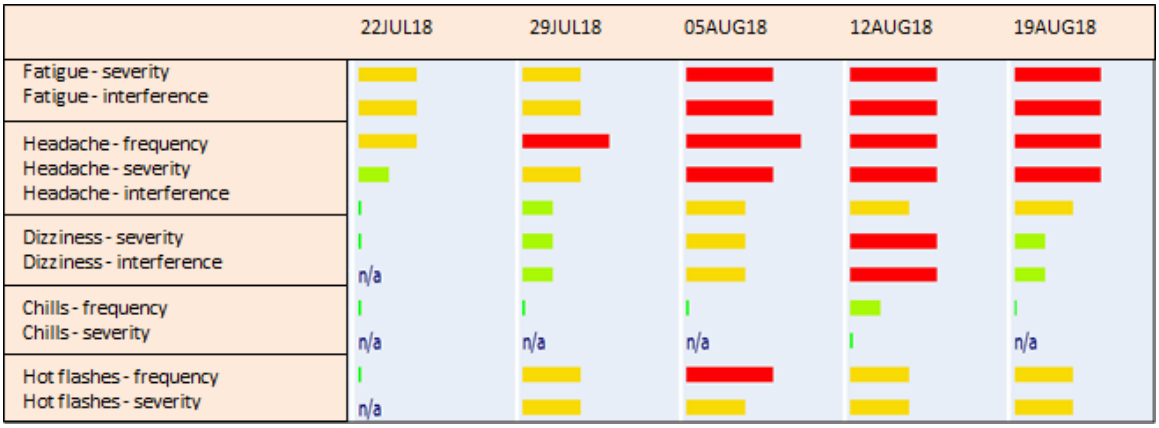

Fig. 2 Example of part of a patient report available to clinicians

Patients

Patients were eligible for the qualitative part of the study if they had been enrolled in the randomized study PROMelanoma. Inclusion criteria: Melanoma patients, >18 years old, randomized to the intervention in PROMelanoma and had received at least one cycle of immunotherapy. Exclusion criteria: Not able or willing to comply with the study procedure, e.g. fill out the electronic questionnaire, or if they did not speak Danish.

Survey

All patients in the PROMelanoma intervention were asked to fill out the Patient Feedback Form between January 2017 and April 2019, dealing with patient satisfaction relating to the e-Health

intervention. The Feedback Form was developed by Basch et al. in order to measure patient satisfaction with online self-reporting of toxicity symptoms [28]. Later it was adapted by Snyder et al. who also used it to measure patient satisfaction with PRO-interventions [20]. Thus it is an established tool to measure quantitative feedback and it was found appropriate for evaluating the usefulness and acceptability of our e-Health intervention. The adapted version consists of 13 items [20]. Respondents evaluate their level of agreement/disagreement on a scale with four options. Questions included were, e.g.: Was it easy to use? Did the questions make sense? And were the patient reports included in the patient-clinician consultation? In order to use the questionnaire for evaluating the e-Health intervention, we had translated it into Danish and validated it in a Danish setting according to existing guidelines, including psychometric testing [38]. The patients had carried out the weekly PROMelanoma reporting at least three times and had had the opportunity to discuss their report at least once with a physician before filling out the Feedback Form. Data was analyzed using descriptive statistics when enrollment in the PROMelanoma study closed in April 2019, and 70 patients had been enrolled in the intervention group.

Interviews with patients

Patients enrolled in the PROMelanoma study were contacted over the phone by the project manager and informed about this study between November 2017 and June 2018. The patients gave verbal consent and signed the written consent form in connection with the interview. It was decided to use a convenience sample at the same time, taking into account the patients´ gender and age to ensure that the group was representative. The patients already had several visits scheduled in the out-patient clinic, and in order not to burden them further, the interviews were planned to take place on days when they were already at the hospital. If the patients were accompanied by relatives, the relatives were invited to participate in the interview. A semi- structured interview guide was prepared, based on the research questions, in collaboration with an expert. The interviews were carried out by the same interviewer (LKT) who also carried out audio taping and transcription. The interviewer had talked to the majority of the patients during inclusion in the PROMelanoma study, but apart from that one time there had been no contact between the interviewer and the informants. In light of the fact that we had some knowledge about the research area in question – the interviewer had worked with this patient group for more than 10 years – there were four major categories that we wished to explore: the usefulness of the

IT solution, the questionnaire, physician-patient communication and involvement of relatives. Thus, having an idea of which categories were to be explored, a directed content analysis as suggested by Hsieh and Shannon [39] was applied, using a deductive approach [40]. The fact that the level of interpretive complexity was expected to be relatively low contributed to our choice of content analysis as the preferred method [41]. Any text that could not be categorized within the initial categories would be given a new code during the analysis [39]. Recruitment continued until data saturation was reached.

Focus group interview with clinicians

A focus group interview was chosen as the preferred method for clinicians, because the number of physicians and nurses caring for these patients was limited to a selected group, which made a questionnaire pointless. For the same reason, only one interview was conducted. The physicians and nurses who had the most experience with the intervention were chosen for the interviews. A co-author (KD) carried out the interview. The interviewer is a qualified researcher experienced in conducting focus group interviews. The interview was conducted in a semi-structured way [42]. Data was to be generated through group interaction about the specific topic predetermined by the research group. The purpose of the focus group was to explore the perspectives of the clinicians regarding the implementation and acceptability of the e-Health intervention in routine cancer care. The interview was transcribed by LKT. The same approach – content analysis – was applied in relation to the group interview as described above [39].

Results

Survey

Patients who were randomized to the intervention arm in the PROMelanoma study (n=70, median age 65 years old, 33 men/37 women) were expected to evaluate the eHealth intervention by filling out the Patient Feedback Form, Table 1. However, two patients who had been randomized to the intervention did not wish to do the electronic reporting anyway, and two patients were hospitalized due to side effects and never received the second series. In nine patients, the melanoma progressed quickly and they deteriorated, making it unethical to ask them to participate. Thus, 57 patients evaluated the intervention. None of the patients found the e-Health

intervention too time-consuming (item 1). In fact, one patient thought that it was too short. Similarly, almost all the patients found the frequency with which the eHealth intervention was administered (item 2) to be just right (94%). The general satisfaction was high. The lowest in satisfaction were items eight, nine and ten, dealing with the inclusion of the patient response in treatment and care. 84% agreed/strongly agreed that the doctor used information for their care, 75% that the questionnaire improved the quality of care (item nine) and 80% that the questionnaire improved communication with the doctor (item ten). The proportion of patients who responded "strongly agree", "agree" or "just right" was over 90% for 8/13 questions. All the patients (100%) recommended filling out the questionnaire to other patients and they would like to continue responding to the questionnaire (items 12 and 13).

Patient Feedback Form	**Too short**		**Just right**		**Too long**		**Missing**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
1: Time it took completing	1	2	54	94	0	0	2	4
	Not often enough		**Just right**		**Too often**		**Missing**	
2: Number of 1:times completing:	1	2	54	94	1	2	1	2

	Strongly agree/ agree		**Disagree/strongly Disagree**		**Missing**	
	N	**%**	**N**	**%**	**N**	**%**
3: Easy to complete	56	98	1	2	0	0
4: Completing was useful	55	96	2	4	0	0
5: Easy to understand	53	93	4	7	0	0
6: Easier to remember symptoms and side effects	52	91	4	7	1	2
7: Improved discussions with clinician	51	89	4	7	2	4
8: Clinician used information for my care	48	84	6	11	3	5
9: The quality of care improved because of the questionnaire	43	75	8	14	6	11
10: Communication with clinician improved	45	78	6	11	6	11
11: Made me more in control of care	50	87	6	11	1	2
12: Recommend to other patients	57	100	0	0	0	0
13: Would like to continue responding	57	100	0	0	0	0

Table 1 Evaluation of the e-Health intervention PROMelanoma in a Danish study with melanoma cancer patients

Patient interviews

In addition to filling out the Patient Feedback Form, 16 of the patients were invited to participate in an in-depth interview about their experience. One patient declined and one patient, who had agreed to participate, was hospitalized due to deteriorating disease before the interview was conducted. Thus, 14 interviews were conducted. Median age of the patients was 67 years, range 41-79 – six men and eight women. Apart from one patient, who had only self-reported symptoms three times, the patients had reported between 6-24 times (weeks), the majority (ten) more than 15 times. Relatives were present during ten of the interviews. The interviews lasted on average 20 minutes (9 – 33 minutes). Nine interviews lasted more than 20 minutes. A total of 280 minutes of interview data was available for analysis. The three themes that were identified from the transcripts aligned with three of the predetermined categories. A fourth theme, however (involvement of relatives), did not become a theme when the final analysis was carried out.

- *Usefulness of the IT solution*

Overall, the patients reported that accessing and filling out the e-Health questionnaire was easy. Only two patients were not used to electronic devices upon entering the study: "*I´m pleasantly surprised. I think it is really easy to deal with",* one of them said *(man, 79 years old)*. "*I did not think he could do it because he is a clown when it comes to computers… (wife, man 73 years old)*. Some of the patients, particularly the elderly, had a hard time using the touch screen function with their fingers because they either pressed too hard or too long. However, when they were given a touch screen pen, which is more accurate than the fingertip, they did not have any problems. Only one patient could not do it and asked his wife to do the reporting following his instructions. Almost all the patients experienced that they were asked to update the operating system of the tablet while using it, but they closed the message easily and continued their reporting. Otherwise there were only minor technical challenges and the patients were very compliant and contacted the department in case of technical problems. The majority of patients were pleased with the tablet. Only a few patients would have preferred a link instead of having to take home the tablet. As mentioned, it was not possible to send a text message reminding the patient to fill out the questionnaire on the relevant days. This did not constitute a problem for the patients, who found

it easy to remember because they were doing it on a fixed weekday. Two patients mentioned that a reminder text message would be advantageous.

- *The questionnaire*

The patients reported that the number of items and the length of the questionnaire were appropriate and that reporting on a weekly basis was fitting. A few of the patients missed a free text field where they could write a comment or elaborate if the questionnaire did not adequately cover existing symptoms: *"It is as if you (health care professionals) don´t get enough information"* (woman, 71 years old) 3). The patients were divided when asked if responding to the PROMelanoma questionnaire was reassuring. Half of the patients confirmed that this was the case, while the other half rejected this notion: *"I feel reassured enough as it is" (woman, 52 years old).* The majority reported that their attention to side effects was heightened due to the intervention: *"Your focus is increased because you have to remember to write it" (woman, 62 years old)*, and that responding to the questionnaire was useful. More of the patients also found that filling out the questionnaire made it easier to remember symptoms when they came to the clinic. One patient reported that she was reminded of her disease every time she responded. A majority of the patients reported that the alert reminding them to contact the department popped up too frequently. As one interviewee put it: *"If I were to call every time it pops up, I would have to call very often" (woman, 67 years old*). However, if the patients decided that it was not a new symptom or a worsening of an already existing symptom, they were able to reject the alert.

- *Patient-physician communication*

When the patients came to the out-patient clinic, two out of three of the patients who were interviewed experienced that the health care professionals had in fact seen their reports and included them in the talk: "*It is like having an agenda for a meeting" (man, 66 years old). "It makes you feel as if you are not just a number in the system,* another interviewee said *(informant no. 6)*. A minority did not know if their reports had been seen by the clinician: *"I think they have seen it (the report), but it is not something we have discussed" (woman, 69 years old)*. A few believed that the clinician had in fact not seen it at all which was of course frustrating due to the fact that the they had spent time filling out the questionnaire. One third had the feeling that they contacted the department more as a result of the reporting. Thus, the majority of patients did not think that

they were more in touch with the hospital due to the reporting. Overall, the reporting made the patients feel more involved in their treatment and care: "*It is nice that we have something common to talk about" (man, 66 years old).*

- *Other themes*

Many of the patients explained that a strong incitement for entering the study was that they would be able to help future patients. Of course, they believed that they themselves would benefit, but being able to help others was also important. Including relatives in the reporting was not a theme. The patients did it alone, apart from one patient, and it did not prompt any discussions within the family.

Focus group interview with clinicians

The participants in the focus group consisted of three doctors and two nurses. They were all women with a median age of 43 years. All of them had broad experience working with cancer patients and dealing with symptoms/side effects (6-11 years). They were also used to caring for melanoma patients receiving immunotherapy. They had all seen the patient reports several times and had included them in the clinician-patient communication.

There was sometimes a discrepancy between how the patient and the clinician graded a given symptom. In some cases, the clinician did not find the symptom to be as severe as the patient. In other instances, the clinician experienced that the patient had in fact neglected a symptom that they believed should have been reported: "*sometimes there's a discrepancy between what you find out when you talk to the patient and what has been reported … the two things supplement each other*" (physician).

Furthermore, the inclusion of patient reporting was seen as being more time-consuming than a 'normal' consultation, due to the fact that the clinicians had to log into another system to see the report. Having the reports integrated in the electronic health records (EHRs) was stated not only to save time but also make it much easier to remember to include them in the consultation.

The clinicians agreed that the patients were better prepared when they came to the out-patient clinic and that the patients had an increased focus on their symptoms and were more alert: *"I think it is an advantage that the patients become more aware of the side effects that can occur"*

(nurse). Moreover, the information on toxicity that had been given to the patients prior to treatment start was repeated when the patients responded to the electronic questionnaire at home. Accordingly, there was a better chance that the patients would react appropriately by contacting the department in time instead of waiting for the next scheduled consultation, which might be days or weeks ahead. Thus having the patients call more often was seen as an advantage because it might enable earlier detection. Moreover, it was an advantage to be able to use the patient reporting as the basis of the consultation by starting with the symptoms that had bothered the patient the most. *"…then I scroll down to see where it is red or yellow and that is typically where we start…" (physician).* In this way, the patients took part in setting the agenda. However, according to the health care professionals, the patient reporting should be seen as a supplement and not something that could replace the clinician-patient consultation. Also, the clinicians reported that the eHealth intervention was a valuable tool, particularly for the group of patients who was normally a bit reluctant to contact the department unscheduled: "…*it may be precisely the group of* patients *who are not good at self-care or at least some of them … the weakest patients who … will benefit most from self-reporting by being guided into becoming more aware of when to react on symptoms" (physician).* Because the patients were encouraged to make contact if they experienced a new or worsened symptom, they might feel that it was more legitimate to call the out-patient clinic. Everyone believed that the patients with the best social resources would benefit least from the intervention because they were sure to contact the department in agreement with the given instructions.

Overall, the clinicians had a positive attitude towards the intervention using an eHealth tool, even though there was also room for improvement in some areas.

Comparison between survey and patient interviews and focus group interview

The clinicians believed that the reporting would make the patients call the hospitals more, whereas the majority of patients did not think that they called more frequently. Some of the patients thought that their reports did not provide the clinicians with enough information. None of the clinicians stated this to be the case. Patients and clinicians agreed that the attention to side effects was increased and that the patients were better prepared for the consultation when they came to the out-patient clinic. The patient reports also established a shared agenda for the

consultation at the out-patient clinic. Overall, the findings from the survey confirmed what had been established in the patient interviews. The patients reported that it was easy to fill out the questionnaire and that it made sense to do so. Moreover, it increased symptom awareness. Both patients and clinicians agreed that when the report was in fact included, it helped to prioritize the problems that were most acute.

Discussion

This study aimed at elucidating malignant melanoma patients´ and their treating clinicians´ experiences with an eHealth intervention. Overall, acceptance was high for both clinicians and patients and both groups believed that it improved communication during the consultation. This is in line with the literature which reports that using PROs prompt patient-clinician dialog, streamlines consultations and increases focus on side effects [10, 43]. Also, the finding that there can be discrepancies between the degree of severity when clinicians and patients grade a given symptom confirms what has previously been established in the literature [1-4].

A minority of the patients in this study, however, did not believe that the clinician had actually seen their reports when they came to the clinic. This point was primarily expressed by patients who were enrolled in the beginning of the study, when monitoring the patient reports had not yet become routine in the out-patient clinic. This improved over time as clinicians got used to taking the reports into consideration. This is in keeping with Mooney et al. [44], who argue that when the advantages of systematic PRO collection in clinical care become visible, adoption will rapidly occur. Although the use of PRO in the clinic can improve communication, it does not necessarily result in intensified symptom treatment and improved symptom management [45]. Thus, it remains to be seen if patient and clinician satisfaction with the eHealth intervention equals a reduction in symptom severity; this is being investigated in the ongoing RCT PROMelanoma.

As for the survey, patient satisfaction was extremely high for many of the questions. The three items lowest in satisfaction (items eight, nine and ten) deal with the inclusion of patient response in the clinic. The response is comparable with the results found in other studies using the Patient Feedback Form [20]. This suggests that one of the challenges when using PROs may be to ensure that the patient responses from questionnaires are included in treatment and care. For many years, PROs have been collected in clinical trials, but not used routinely in clinics. It will probably

be a while before implementing PROs in clinical practice becomes as natural as other procedures within the health care system.

The clinicians participating in the focus group interview agreed that the least resourceful patients would benefit most from the e-Health intervention, because they were usually less inclined to contact the clinic in case of any symptoms. This notion has been confirmed in other studies, which have shown that the level of patient-involvement is dependent on the degree of health literacy. Patients with a high level of education, for example, are more inclined to be involved in medical decision-making compared to patients with a low level of education [46]. Basch et al. also suggest that patients who do not have any computer experience may have weaker communication skills and therefore benefit more from a structured set-up [47]. It may be argued that if this patient group becomes involved in the reporting of side effects, they may be encouraged to react appropriately when an alert is triggered, thereby potentially improving toxicity management. When data from the RCT on the number of phone contacts is analyzed, it will be revealed if patients in the intervention arm actually did call more frequently. In this connection it may be relevant to mention that preliminary findings reveal that 78% of the patients actually did adhere to the intervention by reporting their symptoms on a weekly basis.

Some of the patients also argued that the eHealth intervention was very box-like and they missed a space where they could write more about their symptoms instead of just checking a box. The patients in the PROMelanoma study can add other symptoms as adviced by the NCI, but the patients also wish to be able to elaborate on some of the symptoms. Although this is understandable from a patient point of view, one must keep in mind that the primary aim of introducing the intervention was to increase patient awareness, hoping to reduce the number of severe side effects and improve clinical outcome. Also, it was important that it was fairly easy and not too time-consuming for the clinicians to acquire a quick outline of the reporting if it were to be implementable in the clinic. Moreover, patients had the opportunity to elaborate on the various symptoms that they experienced when they came to the clinic.

Limitations

It might be viewed as a limitation to the study that a deductive approach was used by having the coding framework decided in advance, which may limit the development of new themes [29]. By

using a deductive approach, and thus imposing our own structure on the data, the analysis may become biased. However, the fact that we had some knowledge about the subject made the deductive approach an obvious choice. The fact that one of the predetermined categories – involvement of relatives – did not develop into a theme, and was removed during the analysis, indicates that we were not too locked in our preconception.

It is an obvious limitation that we were only able to conduct one focus group interviews with clinicians. We aimed, however, at selecting participants with a vast knowledge and expertise of the subject [48], which made the number of potential informants limited. Of course other physicians and nurses had treated these patients, but the fact that they did not do so on a routine basis made them unsuitable as participants. Consequently, we settled for one focus group although it would have been preferable to have more. As for the number of interviewed patients, it was our judgement that data saturation was reached with patient number 14, as data were replicated which is why we stopped including patients in the study at this point. According to Francis et al. data saturation may very well be reached after 14 interviews when diversity sampling is appropriate [49]. We believed this was the case in this study.

It may also be viewed as a limitation that the alert function was triggered too frequently according to the majority of patients. This may be changed when designing future studies or implementing the intervention beyond the study period to avoid alert fatigue. Having an alert function, though, is a good idea as studies show that patients value advice on when it is appropriate to contact the hospital [50]. Also, it is vital that the clinicians log into the system and see the patients´ report every time prior to the consultation. Otherwise patients may lose the incentive to make the reporting. PROs must be implemented in such a way that it is embedded as part of routine care [22] so that clinicians do not have to be reminded to view the patient report by for example project managers or study coordinators. In this relation, it is important that PROs are easily accessible to clinicians i.e. integrated in the electronic health record in order to be successful, as recommended by the clinicians in the focus group interview. Recommendations on how to integrate PROs into the electronic health record (EHR) have been developed by the PRO-EHR Users' Guide Steering and Working Groups [51].

Conclusion

We found a high acceptance of the e-Health intervention tool among clinicians and melanoma patients being treated with immunotherapy. The tool was easy to use and contributed to greater symptom awareness and patient involvement. Thus, in terms of patient and clinician satisfaction, it makes sense to continue using the tool beyond the project period. It remains to be investigated, however, if the predominantly positive perceptions of the intervention by patients and clinicians will also be followed by a reduction in the number of severe side effects. Our RCT PROMelanoma will shed light on this.

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Appendices

A Search string (PubMed)

B Included PRO-CTCAE items

C Patient Feedback Form

D Patienttilbagemelding

E Interviewguide - patienter i interventionsarmen

F Interviewguide - læger og sygeplejersker

Example of Search String (Pubmed)

Search ((((((((((((cancer) OR cancers) OR neoplasm) OR neoplasms) OR neoplasia) OR tumor) OR tumors) OR tumour) OR tumours)) AND ((checkpoint inhibitor) OR checkpoint inhibitors) OR immune checkpoint blockade) OR immune checkpoint antibodies) OR programmed cell death 1 receptor) OR pd1) OR pd-1) OR anti-pd1) OR anti-pd-1) OR pd1-inhibition) OR pd-1-inhibition) OR pembrolizumab) OR lambrolizumab) OR keytruda) OR mk-3475) OR pidilizumab) OR tremelimumab) OR immune checkpoint therapy) OR immune checkpoint therapies) OR nivolumab) OR mdx-1106) OR ono-4538) OR bms-936558) OR opdivo) OR pd1-receptor) OR pd-1-receptor) OR anti-pd1-antibody) OR anti-pd-1-antibodies) OR ctla4) OR ctla-4) OR anti-ctla4) OR anti-ctla-4) OR ctla4-antigen) OR ctla-4-antigen) OR cytotoxic t lymphocyte antigen 4) OR ipilimumab) OR mdx-ctla4) OR mdx-ctla-4) OR yervoy) OR mdx 010) OR mdx-010) OR checkpoint inhibition) OR anti-pd1-antibody therapy) OR anti-pd-1-antibody therapy) OR anti-ctla4 antibody) OR anti-ctla-4 antibody)) AND ((((((((((((((((((((((((((((((adverse event) OR adverse events) OR side effect) OR side effects) OR toxicity) OR toxicities) OR drug toxicity) OR drug toxicities) OR pharmaco toxicity) OR pharmacol toxicities) OR side reaction) OR side reactions) OR pharmacological toxicity) OR pharmacological toxicities) OR safety profile) OR adverse reaction) OR adverse reactions) OR drug-related side effect) OR drug-related side effects) OR adverse drug event) OR adverse drug events) OR drug side effect) OR drug side effects) OR adverse drug reaction) OR adverse drug reactions) OR safety) OR adverse effect) OR adverse effects) OR ae) OR aes) OR medication side effect) OR medication side effects)) AND ("1996/01/01"[PDat] : "2016/06/10"[PDat]))) AND (((melanoma)OR lung cancer) AND ("1996/01/01"[PDat] : "2016/06/10"[PDat])) Filters: Publication date from 1996/01/01 to 2016/06/10

Pubmed 21. juni 2016 **Items found: 1004**

PRO-CTCAE EMNE	PRO-CTCAE SPØRGSMÅL	SVAR

Almene symptomer

Udmattelse, træthed eller manglende energi	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **UDMATTELSE, TRÆTHED ELLER MANGLENDE ENERGI** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Udmattelse, træthed eller manglende energi	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **UDMATTELSEN, TRÆTHEDEN ELLER DEN MANGLENDE ENERGI** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Hovedpine	Inden for de seneste 7 dage, hvor OFTE havde du **HOVEDPINE**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Hovedpine	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **HOVEDPINEN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Hovedpine	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **HOVEDPINEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Svimmelhed	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **SVIMMELHED** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Svimmelhed	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **SVIMMELHEDEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Kuldegysninger eller kulderystelser	Inden for de seneste 7 dage, hvor OFTE havde du **KULDEGYSNINGER ELLER KULDERYSTELSER**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Kuldegysninger eller kulderystelser	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **KULDEGYSNINGERNE ELLER KULDERYSTELSERNE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Hedeture	Inden for de seneste 7 dage, hvor OFTE havde du **HEDETURE:**	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Hedeture	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **HEDETURENE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Hævede arme eller ben	Inden for de seneste 7 dage, hvor OFTE havde du **HÆVEDE ARME ELLER BEN:**	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Hævede arme eller ben	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af de **HÆVEDE ARME ELLER BEN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig

Hævede arme eller ben	Inden for de seneste 7 dage, hvor meget FORSTYRREDE de **HÆVEDE ARME ELLER BEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Psykiske symptomer

Følelse af, at intet kunne muntre dig op	Inden for de seneste 7 dage, hvor OFTE **FØLTE DU, AT INTET KUNNE MUNTRE DIG OP:**	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Følelse af, at intet kunne muntre dig op	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af**, AT INTET KUNNE MUNTRE DIG OP** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Følelse af, at intet kunne muntre dig op	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **DET, AT INTET KUNNE MUNTRE DIG OP** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Triste eller ulykkelige følelser	Inden for de seneste 7 dage, hvor OFTE havde du **TRISTE ELLER ULYKKELIGE FØLELSER**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Triste eller ulykkelige følelser	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af de **TRISTE ELLER ULYKKELIGE FØLELSER** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Triste eller ulykkelige følelser	Inden for de seneste 7 dage, hvor meget FORSTYRREDE de **TRISTE ELLER ULYKKELIGE FØLELSER** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Hud og hår

Tør hud	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **TØR HUD** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Udslæt	Inden for de seneste 7 dage, havde du noget **UDSLÆT:**	Nej / Ja
Kløende hud	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **KLØENDE HUD** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Hårtab	Inden for de seneste 7 dage, havde du noget **HÅRTAB**:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Smerter & ømhed

Smerte, hævelse eller rødme ved stik fra indsprøjtning eller drop	Inden for de seneste 7 dage, havde du nogen **SMERTER, HÆVELSE ELLER RØDME VED STIK FRA INDSPRØJTNING ELLER DROP:**	Nej / Ja / Ikke relevant
Smerter	Inden for de seneste 7 dage, hvor OFTE havde du **SMERTER**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Smerter	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **SMERTERNE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Smerter	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **SMERTERNE** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Ømme led (såsom albuer, knæ, skuldre)	Inden for de seneste 7 dage, hvor OFTE havde du **ØMME LED (SÅSOM ALBUER, KNÆ, SKULDRE):**	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Ømme led (såsom albuer, knæ, skuldre)	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af de **ØMME LED (SÅSOM ALBUER, KNÆ, SKULDRE)** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Ømme led (såsom albuer, knæ, skuldre)	Inden for de seneste 7 dage, hvor meget FORSTYRREDE de **ØMME LED (SÅSOM ALBUER, KNÆ, SKULDRE)** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Ømme muskler	Inden for de seneste 7 dage, hvor OFTE havde du **ØMME MUSKLER**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Ømme muskler	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af de **ØMME MUSKLER** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Ømme muskler	Inden for de seneste 7 dage, hvor meget FORSTYRREDE de **ØMME MUSKLER** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Nervesystemet

Følelsesløshed eller prikken i dine hænder eller fødder	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **FØLELSESLØSHED ELLER PRIKKEN I HÆNDER ELLER FØDDER** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Følelsesløshed eller prikken i hænder eller fødder	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **FØLELSESLØSHEDEN ELLER PRIKKEN I HÆNDER ELLER FØDDER** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Lunge

Åndenød	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **ÅNDENØD** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Åndenød	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **ÅNDENØDEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Hoste	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **HOSTE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Hoste	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **HOSTEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Øjne

Sløret syn	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **SLØRET SYN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Sløret syn	Inden for de seneste 7 dage, hvor meget FORSTYRREDE det **SLØREDE SYN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget

Mave og tarm

Opkast	Inden for de seneste 7 dage, hvor OFTE havde du **OPKAST**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Opkast	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **OPKASTNINGEN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Kvalme	Inden for de seneste 7 dage, hvor OFTE havde du **KVALME**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant

Kvalme	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **KVALMEN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Nedsat appetit	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **NEDSAT APPETIT** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Nedsat appetit	Inden for de seneste 7 dage, hvor meget FORSTYRREDE den **NEDSATTE APPETIT** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Problemer med at smage mad eller drikke	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **PROBLEMER MED AT SMAGE MAD ELLER DRIKKE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Sår eller læsioner i slimhinden i mund eller svælg	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **SÅR ELLER LÆSIONER I SLIMHINDEN I MUND ELLER SVÆLG** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Sår eller læsioner i slimhinden i mund eller svælg	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **SÅRENE ELLER LÆSIONERNE I SLIMHINDEN I MUND ELLER SVÆLG** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Smerter i maveregionen	Inden for de seneste 7 dage, hvor OFTE havde du **SMERTER I MAVEREGIONEN**:	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant
Smerter i maveregionen	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **SMERTERNE I MAVEREGIONEN** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Smerter i maveregionen	Inden for de seneste 7 dage, hvor meget FORSTYRREDE **SMERTERNE I MAVEREGIONEN** dine sædvanlige eller daglige aktiviteter:	Slet ikke / Lidt / Noget / En hel del / Rigtig meget
Forstoppelse	Inden for de seneste 7 dage, hvad var SVÆRHEDSGRADEN af **FORSTOPPELSE** da det var VÆRST:	Ingen / Mild / Moderat / Kraftig / Meget Kraftig
Tynd eller vandig afføring (diarre)	Inden for de seneste 7 dage, hvor OFTE havde du **TYND ELLER VANDIG AFFØRING (DIARRE):**	Aldrig / Sjældent / Af og til / Ofte / Næsten konstant / Ikke relevant

Tillægsspørgsmål til Mave og Tarm

Blod i afføringen	Inden for de sidste 7 i hvilket omfang havde du **BLOD I AFFØRINGEN**	Slet ikke / Lidt / En del / Meget

PATIENT FEEDBACK FORM

SUBJECT:_____
DATE: _____

We are interested in your opinion of the questionnaires you have been asked to complete. Please answer all of the questions yourself by circling the number that best applies. There are no "right" or "wrong" answers to the questions. The information that you provide here will remain strictly confidential.

		Too short	**Just right**	**Too long**
1.	The amount of time it took me to complete the computerized questionnaire was:	1	2	3

		Not often enough	**Just right**	**Too often**
2.	The number of times I was asked to complete the computerized questionnaire was:	1	2	3

		Strongly Agree	**Agree**	**Disagree**	**Strongly Disagree**
3.	The questionnaire was easy to complete.	1	2	3	4
4.	Completing the questionnaire was useful.	1	2	3	4
5.	The questionnaire was easy to understand.	1	2	3	4
6.	Completing the questionnaire made it easier for me to remember my symptoms and side effects when I met with my doctor.	1	2	3	4
7.	Completing the questionnaire improved discussions with my doctor.	1	2	3	4
8.	My doctor used information from the questionnaire for my care.	1	2	3	4
9.	The quality of my care was improved because of the questionnaire.	1	2	3	4
10.	Communication with my doctor was improved because of the questionnaire.	1	2	3	4
11.	Completing the questionnaire made me feel more in control of my own care.	1	2	3	4
12.	I would recommend completing the questionnaire to other patients.	1	2	3	4
13.	I would like to continue responding to the questionnaire in the future.	1	2	3	4

PATIENTTILBAGEMELDING

Patientnr.: _____
Dato: _____

Vi er interesseret i din mening om de spørgeskemaer, som du har besvaret. Vi beder dig besvare alle spørgsmålene selv ved at sætte en ring om det tal, som passer bedst. Der er ingen "rigtige" eller "forkerte" svar på spørgsmålene. Dine svar vil blive behandlet fuldt fortroligt.

		For kort	**Passende**	**For lang**
1.	Længden på spørgeskemaet var	1	2	3
		For få	**Passende**	**For mange**
2.	Det antal gange, jeg blev bedt om at besvare spørgeskemaet var	1	2	3

		Meget enig	**Enig**	**Uenig**	**Meget uenig**
3.	Det var nemt at besvare spørgeskemaet	1	2	3	4
4.	Det gav mening at besvare spørgeskemaet	1	2	3	4
5.	Det var nemt at forstå spørgsmålene	1	2	3	4
6.	At besvare spørgeskemaet gjorde det nemmere for mig at huske mine symptomer og bivirkninger, når jeg talte med personalet	1	2	3	4
7.	At besvare spørgeskemaet forbedrede samtalen med personalet	1	2	3	4
8.	Personalet anvendte oplysninger fra spørgeskemaet i forbindelse med min behandling	1	2	3	4
9.	Jeg oplever, at kvaliteten af min behandling blev forbedret, fordi jeg havde besvaret spørgeskemaet	1	2	3	4
10.	Jeg oplever, at kommunikationen med personalet blev forbedret, fordi jeg havde besvaret spørgeskemaet	1	2	3	4
11.	At besvare spørgeskemaet fik mig til at føle, at jeg blev inddraget i min behandling	1	2	3	4
12.	Jeg vil anbefale andre patienter at besvare spørgeskemaet	1	2	3	4
13.	Jeg vil gerne fortsætte med at besvare spørgeskemaet fremover	1	2	3	4

For anvendelse af spørgeskemaet se: Danish translation, cultural adaption and initial psychometric evaluation of the patient feedback form. Lærke K. Tolstrup, Helle Pappot, Graziella Zangger, Lars Bastholt, Ann-Dorthe Zwisler and Karin B. Dieperink *Health and Quality of Life Outcomes* 2018 https://doi.org/10.1186/s12955-018-0900-4

Interviewguide – Patienter i Interventionsarmen

1. **Hvordan har dit forløb været?**

2. **Teknikken (It- systemet)? Problemer?**
   - Nemt at tilgå/udfylde
   - Tablet eller link
   - Pop-up feltet
   - Nemt at huske uden reminder

3. **Selve spørgeskemaet**
   - Længde
   - Forståelse
   - Nyttigt
   - Mindede det dig om sygdommen
   - Øget tryghed/mere fokus
   - Mere kontakt til afd.

4. **Samarbejde med afdelingen**
   - Havde lægen set besvarelsen?
   - Anvendt?
   - Inddraget?
   - Hjælp til at huske symptomer?
   -

5. **Pårørendeinvolvering**
   - Hvad synes de?
   - Var de med i processen/lægesamtalen?
   - Medførte rapporteringen at I talte mere om bivirkninger?

6. **Hvad kunne have været anderledes? Noget at tilføje?**

Interviewguide – Læger/sygeplejersker

1) Har du benyttet Ambuflex til at se patienternes egne bivirkningsregistreringer?
- Hvis nej, hvorfor?
- Hvis ja, hvor mange (ca.) og hvordan brugte du informationerne i Ambuflex?

2) Hvad ser du af fordele og ulemper ved, at patienten selv har registreret sine bivirkninger forud for jeres samtale?

3) Hvordan synes du, at Ambuflex værktøjet fungerer (papir-elektronisk)?

4) Hvordan påvirker AmbuFlex den daglige arbejdsgang? (tidsforbrug m.m.)

5) Har det givet dig et andet billede af patientens bivirkninger? Er der nogle barrierer?

6) Gør det noget ved din faglighed at anvende Ambuflex?

7) Kunne du forestille dig, at bivirkningsregistrering kunne overgå til patienterne? Hvad tænker du? Hvorfor/hvorfor ikke?
(nogle lægesamtaler er allerede blevet erstattet af telefonsamtaler – kan Ambuflex anvender her?)

8) Andre kommentarer?