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Development and testing of an eHealth-enhanced model of care for patients treated with immune-checkpoint inhibitors

da Silva Lopes André Manuel

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Development and testing of an eHealth-enhanced model of care for patients treated with immune-checkpoint inhibitors

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par
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Development and testing of a model of care in the detection and monitoring of symptomatic immune-related adverse events in oncology patients treated with immune checkpoint inhibitors

Lausanne, le 22 avril 2024

Pour le Doyen
De la Faculté de Biologie et de Médecine

Directrice de l'IUFRS

Vice-Directeur de l'Ecole Doctorale

Dissertation Abstract

Introduction: Patients treated with immune checkpoint inhibitors (ICIs) have substantial support needs to manage symptomatic immune-related adverse events (IrAEs). These events typically manifest outside the clinical setting, and though the majority are mild, they can become chronic and life-threatening. Modern interventions targeting cancer treatment toxicities have been shown to improve outcomes related to symptom burden, health-related quality of life and overall survival**.** However**,** few have targeted patients treated with immune checkpoint blockade. These interventions often fail to describe the underlying mechanisms to achieve these beneficial outcomes. This dissertation reports on the development of the IePRO study, where a patient-reported outcomes-based model is tested in the monitoring and management of IrAEs. The goals of this thesis were to (i) develop a patient-reported outcomes measure (PROM) to monitor symptomatic immune-related adverse events in patients treated with ICIs, (ii) to describe the development of a nurse-led model of care that enables remote management of symptoms of patients treated with ICIs and (iii) provide preliminary evidence from the testing of the model of care within a bicentric phase II randomised controlled trial, taking place from November 2021 to October 2023.
Methods: This thesis was part of a larger study, the IePRO Study, which was composed of five phases. The present thesis covers the first three phases: the development of an ePROM, the development of an ePROM-based model of care, and the development of the research protocol of the IePRO Study. An expert Delphi was conducted to develop the ePROM from the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) for patients treated with ICIs. A panel of 11 experts participated in a four-round iterative process with consensus set at 75% agreement. Development of the model of care took place in four stages, including identifying an underlying theoretical framework, selecting an electronic PROM and adapting it to collect PROs data with a description of an ePRO-oriented workflow. Finally, a randomised controlled trial was designed to test the model of care to monitor and manage symptomatic IrAEs remotely. Given the active status of the study as of writing, we report on a single descriptive case study to demonstrate the nature of the data collected and its potential uses.
Analysis: Descriptive statistical and qualitative methods were used to analyse and disseminate the expert Delphi results. Preliminary data analysis on the case study included descriptive methods covering self-reported patient data and telephone triage data.
Results: The final electronic PROM is comprised of 30 priority PRO-CTCAE items obtained through expert consensus. The model of care is based on the eHealth-enhanced Chronic Care Model. It describes a complete feedback loop between patients and healthcare staff, such as leveraging PRO-CTCAE symptom data and a standardized triage process. A research protocol targeting relevant outcomes was designed. The descriptive case study demonstrates the large volume of ePRO data and potential uses to describe nursing activities to promote symptom self-management.
Conclusion: The resulting PROM is among the first to target this patient population, though future studies should assess the coverage of the symptomatic IrAE spectrum. Broader international agreement and patient involvement are needed to further validate initial findings on additional symptoms to supplement the PRO-CTCAE. The model of care describes the workflow sustaining ePRO-based interventions, though its strengths and limitations still need to be tested. Analysis of the recently completed randomised controlled trial data should provide greater insight and opportunities for improvement.

Résumé de la thèse

Introduction : : Les patients traités par des inhibiteurs de points de contrôle immunitaire (IPCI) présentent des besoins en soins de support importants pour gérer les effets indésirables symptomatiques liés à l'immunité (Immune-related Adverse Events, IrAEs). Ces événements se manifestent généralement en dehors du cadre clinique et, bien que la majorité d'entre eux soient bénins, ils peuvent devenir chroniques et menacer le pronostic vital. Les interventions basées sur les données rapportées par les patients (PROs), ciblant les toxicités des traitements anticancéreux, améliorent les résultats liés à la charge des symptômes, à la qualité de vie liée à la santé et à la survie globale. Cependant, peu d'entre elles ont ciblé les patients traités par blocage des points de contrôle immunitaires. Ces interventions ne décrivent souvent pas les mécanismes sous-jacents qui permettent d'obtenir ces résultats bénéfiques. Cette thèse rend compte du développement de l'étude IePRO, dans laquelle un modèle basé sur les résultats rapportés par les patients est testé dans le cadre du suivi et de la prise en charge des IrAEs. Les objectifs de cette thèse étaient de (i) développer une mesure des résultats rapportés par les patients (ePROM) pour surveiller les effets indésirables symptomatiques liés à l'immunité chez les patients traités par ICIs, (ii) décrire le développement d'un modèle de soins dirigé par une infirmière qui permet la gestion à distance des symptômes des patients traités par ICIs et (iii) fournir des preuves préliminaires de l'essai du modèle de soins dans le cadre d'un essai contrôlé randomisé de phase II bicentrique, qui se déroulera de novembre 2021 à octobre 2023.

Méthodes : Cette thèse s'inscrit dans le cadre d'une étude plus vaste, l'étude IePRO, composée de cinq phases. La présente thèse couvre les trois premières phases : le développement d'une ePROM, le développement d'un modèle de soins basé sur l'ePROM et le développement du protocole de recherche de l'étude IePRO. Lors de la première phase, un Delphi d'experts a été réalisé pour développer l'ePROM à partir de la *patient-reported outcomes version of the common criteria for adverse events* (PRO-CTCAE) pour les patients traités avec des IPCIs. Un panel de 11 experts a participé à un processus itératif en quatre tours, le consensus étant fixé à 75 %. Le développement du modèle de soins s'est déroulé en quatre étapes, comprenant l'identification d'un cadre théorique sous-jacent, la sélection d'un PROM électronique et son adaptation pour collecter des données PRO avec une description d'un flux de travail orienté vers l'ePRO. Enfin, un essai contrôlé randomisé a été conçu pour tester le modèle de soins afin de surveiller et de gérer à distance les IrAEs symptomatiques. Étant donné le statut actif de l'étude au moment de la rédaction, nous rapportons une seule étude de cas descriptive pour démontrer la nature des données collectées et leurs utilisations potentielles.

Analyse : Des méthodes descriptives ont été utilisées pour analyser et diffuser les résultats du Delphi d'experts. L'analyse préliminaire des données de l'étude de cas comprenait l'utilisation de méthodes descriptives couvrant les données autodéclarées par les patients et les données de triage téléphonique.

Résultats : Le PROM électronique final comprend 30 éléments PRO-CTCAE prioritaires obtenus par consensus d'experts. Le modèle de soins est basé sur le E-Health Enchanced Chronic Care Model de Gee et al (2015). Il décrit une boucle de rétroaction complète entre les patients et le personnel soignant, notamment en s'appuyant sur les données PRO-CTCAE relatives aux symptômes et sur un processus de triage normalisé. Un protocole de recherche ciblant des résultats pertinents a été conçu. L'étude de cas descriptive démontre le grand volume de données ePRO et les utilisations potentielles pour décrire les activités infirmières visant à promouvoir l'autogestion des symptômes.

Conclusions : Le PROM qui en résulte est l'un des premiers à cibler cette population de patients, bien que les études futures devraient évaluer la couverture du spectre symptomatique de l'IrAE. Un accord international plus large et la participation des patients sont nécessaires pour valider davantage les résultats initiaux sur les symptômes supplémentaires pour compléter le PRO-CTCAE. Le modèle de soins décrit le flux de travail qui soutient les interventions basées sur les ePRO, bien que ses forces et ses limites n'aient pas encore été testées. L'analyse des données de l'essai contrôlé randomisé récemment achevé devrait permettre d'identifier les possibilités d'amélioration pour l'implémentation de l'intervention.

Preface

This thesis is inserted in the IePRO study, which tests a model of care to remotely monitor and manage symptomatic toxicities in patients with cancer treated with immune checkpoint inhibitors. The study contains several work packages that overlap with some of this thesis' goals, each addressed by one publication.

This thesis begins with a background chapter providing an overview of symptomatic immune-checkpoint inhibitor (ICI) toxicity, followed by the use of patient-reported outcomes in oncology to describe treatment toxicity, and the development of a patient-reported outcomes measure to monitoring symptomatic toxicities in cancer patients treated with ICIs.

A second chapter highlights interventions to remotely monitor and manage symptoms using patient-reported outcomes data collected electronically. A third chapter presents the research protocol of the IePRO study, and a fourth chapter discusses preliminary evidence from a case study from one of the research sites.

List of Integrated Articles

Article 1 (published)
Da Silva Lopes AM, Colomer-Lahiguera S, Mederos Alfonso N, Aedo-Lopez V, Spurrier-Bernard G, Tolstrup LK, et al. Patient-reported outcomes for monitoring symptomatic toxicities in cancer patients treated with immune-checkpoint inhibitors: A Delphi study. European Journal of Cancer 2021;157:225–37. https://doi.org/10.1016/j.ejca.2021.08.026.

Article 2 (published)
da Silva Lopes AM, Colomer-Lahiguera S, Darnac C, Giacomini S, Bugeia S, Gutknecht G, et al. Development of an eHealth-enhanced model of care for the monitoring and management of immune-related adverse events in patients treated with immune checkpoint inhibitors. Support Care Cancer. 2023 Aug;31(8):484

Article 3 (published)
da Silva Lopes AM, Colomer-Lahiguera S, Darnac C, Giacomini S, Bugeia S, Gutknecht G, Spurrier-Bernard G, Cudendet M, Muet F, Aedo-Lopez V, Mederos N, Michielin O, Addedo A, Latifyan S, Eicher M. Testing a model of care for patients on immune-checkpoint inhibitors based on electronic patient-reported outcomes: Protocol for a randomized phase II controlled trial. JMIR Res Protoc 2023 Sept 29.

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Abbreviations

CAT	Computer adaptive testing
CCM	Chronic Care Model
CDS	Clinical Decision Support
CE	Conformité Européenne
CHUV	Lausanne University Hospital
CIS	Clinical Information Systems
CROs	Clinician-reported outcomes
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DSD	Delivery System Design
eCCM	eHealth Enhanced Chronic Care Model
eHE	eHealth Education
EHR	Electronic health record
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer's core quality of life questionnaire
ePRO	Electronic patient-reported outcomes
ePROM	Electronic patient-reported outcomes measure
EQ-5D	EuroQol 5 Dimension Scale
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-ICM	Functional Assessment of Cancer Therapy – Immune Checkpoint Modulator
HRQoL	Health-related quality of life
HUG	Geneva University Hospital
ICIs	Immune-checkpoint inhibitors
IFS	Institute for Higher Education and Research in Healthcare
IrAEs	Immune-related adverse events
ISREC	Swiss Institute for Experimental Cancer Research
PD-1	Programmed death receptor-1
PD-L1	Programmed death ligand-1
PIs	Principal investigators
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PROMIS	Patient-reported outcomes measurement information system
PROs	Patient-reported outcomes
QoL	Quality of life
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture
SMS	Self-Management Support
UKONS	United Kingdom Oncology Nursing Society
UNIL	University of Lausanne

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Introduction

Novel cancer treatments can represent hope for patients in different stages of their disease, yet they can also be a source of uncertainty. The toxicities associated with emerging treatment are new grounds for both patients and healthcare professionals. Clinical research is often tasked with deeply understanding these new challenges so that once those new treatments are widespread in routine practice, the tools to manage those side-effects are readily available. After a decade and a half of immune checkpoint inhibitors (ICIs) being part of the growing strategies against multiple cancer and particularly some advanced metastatic tumours, the challenge of immune-related adverse events (IrAEs) remains significant. The spectrum of potential symptoms is considerably wide and their pathophysiology is not completely understood (1). Although progress had been made in identifying the most frequent IrAEs and their underlying patterns of time to onset and resolution (2), new studies point to long-lasting IrAEs that extend beyond the active treatment period, with symptoms that can quickly vary in severity in a matter of days, and that are subjective and difficult to describe (3–5). As patients experience side-effects outside of the clinical setting, supportive care strategies that target symptom self-management and can be delivered remotely have emerged as potential alternatives to traditional periodical and in-person follow-up (6,7). An increasing number of these strategies involve the use of patient-reported outcomes (PROs), that add to the description of symptomatic toxicities and complete the healthcare provider's understanding of patients' needs and challenges (8). Recent studies targeting symptom management have leveraged PROs to monitor patients' symptoms remotely, and in most studies, nurses were the interface through which self-reported data informed or influenced the care practised by healthcare institutions (9). This is also evident in interventions using electronic systems that convey real-time patient information, to enable remote follow-up and management (8). Nurses are typically tasked with interpreting self-reported data and providing feedback to patients via an electronic platform or via telephone call (10). These exchanges are usually at the core of more complex and encompassing interventions to provide more effective care that meets the patient's needs and values (11). These interventions have the potential to decrease symptom severity by facilitating early intervention, thus maintaining or improving health-related quality of life (HRQoL), enabling patients to remain longer in treatment and therefore contributing to superior overall survival rates (11). However, these beneficial outcomes are not universal, and in addition to different electronic platforms with varying feature sets, the factors that condition these outcomes are influenced by varying and often incomplete implementation strategies (10,12). For patients treated with immune checkpoint inhibitors, the PROs measures used to assess symptomatic IrAEs capture only a fraction of the full spectrum of IrAEs (13). Most symptomatic toxicities related to ICIs are mild, and electronic systems to monitor them remotely often use instruments that only assess a limited number of toxicities and are guided by algorithms that only alert healthcare professionals of severe symptoms at specific points in time (14). How nurses make use of the data that is collected, how they influence symptom management and how they communicate within healthcare teams are seldom described. Yet, these underlying processes are crucial components of implementation strategies aiming to implement PROs in routine care and are, therefore, likely to play a role in obtaining the benefits described previously.

Patients treated in the ambulatory oncology care units of the largest university hospitals in French-speaking Switzerland typically attend clinical visits on the same days as their treatment schedule. As such, clinical follow-up can occur every two to every four weeks. Remote monitoring can be provided by physicians and advanced practice nurses, but its frequency and related procedures are not standardised, no formal criteria exist to determine when it should be put in place, and its use is highly dependent on each patient's clinical condition. Outside of clinical visits, patients are encouraged to contact the ambulatory care unit when faced with new or concerning symptoms.

The overall aim of the present thesis was to, within a larger study, describe the development and preliminary evaluation of an eHealth-enhanced model of care to monitor and manage symptoms of patients treated with ICIs remotely. Its objectives were to (i) develop a patient-reported outcomes measure (PROM) to monitor symptomatic immune-related adverse events in patients treated with ICIs, (ii) to describe the development of a nurse-led model of care that enables remote management of symptoms of patients treated with ICIs and (iii) provide preliminary evidence from the testing of the model of care within a bicentric phase II randomised controlled trial, taking place from November 2021 to October 2023. Each objective is the subject of one of three publications included in this thesis.

Chapter 1: Thesis background

Patients with cancer continue to face the challenge of symptoms related to their condition and to their treatment despite the successes in improving overall survival and progression-free survival with emerging therapies. In the past decade, patients with cancer have had access to new treatment modalities that include ICIs, which have transformed the therapeutic pathway of multiple cancers (15–17). This class of anti-cancer agents typically target the programmed death receptor-1 (PD-1), its ligand (PD-L1), and the cytotoxic T lymphocyte antigen-4 (CTLA-4). By blocking these molecules, the amplitude and duration of the immune response are magnified, disrupting its normal modulation. As a result, patients might benefit from improved overall survival and undergo longer periods of disease stability, with initial studies suggesting a lower incidence of side effects impacting HRQoL compared to other systemic treatments (18).

Despite this, subsequent trials highlighted frequent and sometimes recurring symptomatic IrAEs, that could persist throughout and beyond the treatment cycle (15,18–20). IrAEs are the inflammatory damage to self-tissues incurred by disrupting normal immune function (15,16). Patients can face a wide variety of symptoms that are not strictly conditioned by the cancer type alone but are also closely associated with the affected tissue and treatment modality (19,21). The temporal kinetics of these symptomatic IrAEs appear to be less predictable than other toxicities related to cancer treatments (e.g. chemotherapy), while also ranging from mild to severe and potentially life-threatening (2,15,19). Importantly, many of these symptoms are experienced outside the clinical setting, where patients are often the first to notice them (22). While professionals educate and prepare patients to identify and manage potential treatment side-effects, it is not feasible to cover all potential symptoms. As a result, patients treated with ICIs express feelings of uncertainty regarding their ability to feel in control of their health, and report difficulties in identifying and self-managing symptomatic IrAEs (23–25). To ensure that patients receive adequate support in the short and long-term, enabling healthcare professionals to monitor their status more closely has become part of IrAE management recommendations (26).
Patient-reported outcomes measures (PROMs) have become a standard recommendation to improve the description of symptoms related to cancer and cancer treatments (27). The measured PROs are patient self-reports on their health status, without interpretation from any third party (28). Studies using these measures have highlighted the wide spectrum of short and long-term effects of ICIs (29). PROMs assessing HRQoL and symptoms have provided insight into the significant impact of aforementioned persistent symptomatic IrAEs, such as fatigue, distress and other psychological symptoms associated with neurocognitive dysfunction (23,29,30). In this chapter, we will expand on the IrAEs experienced by patients treated with ICIs, the use of PROs to describe symptoms of patients with cancer and highlight how existing PROMs may only portray a fraction of symptomatic IrAEs experienced by patients.

Symptomatic immune-checkpoint inhibitor toxicity

Patients treated with ICIs may experience a particularly large spectrum of symptoms. ICI class, treatment modality, cancer type and the underlying health status of the patient are the most significant determinants of the incidence and severity of IrAEs (15,19). Single-agent ICI treatments (monotherapy) are associated with lower incidence (10 to 60% of patients) and lower grade (<3) adverse events (up to 80% of all IrAEs) (15,19). A 2021 systematic review by Ouyang et al. (31) noted that CTLA-4 inhibitors trigger significantly more grade≥3 events (34.2% of patients) than PD-1 and PD-L1 inhibitors (15.1 and 13.6% of patients, respectively). Combining ICI agents, particularly anti-PD-1/PD-L1 with CTLA-4 inhibitors, further increases any-grade IrAE incidences to up to 90% of patients, with 40 to 55% of patients suffering severe (grade≥3) events (15,19). It is posited that solid tumours that exhibit high mutational burden may trigger more IrAEs due to a stronger immune response (16,18). Skin and respiratory IrAEs also appear to correlate with melanoma ($p<0.01$) and lung cancer ($p=0.03$), respectively, suggesting different tumour types may increase the likelihood of specific IrAEs (32). Patients with pre-existing autoimmune diseases may also be at greater risk of severe IrAEs ($p=0.01$), although evidence is still limited (33).

Detecting and diagnosing IrAEs can be challenging due to their aforementioned temporal progression and the heterogeneity of their presentation. The onset time is highly variable, ranging from days to multiple months after treatment has started (17). A systematic review and meta-analysis of fatal IrAEs by Wang et al (34) has shown median time to onset is significantly ($p<0.001$) shorter for combined ICI (14.5 days) than for monotherapy (40 days). Tang and colleagues (2) have also noted that time to resolution is, on average, longer for anti-PD-1 monotherapy (10.1 weeks) over anti-CTLA-4 (4 weeks) and combined treatments (5.1 weeks). ICI classes also differ in the spectrum of organ involvement, with PD-1 inhibitors typically triggering a wider variety of IrAEs (34,35). Endocrine adverse events are among the longest to resolve (pooled-median time of 54.3 weeks), and infusion reactions are the shortest (0.1 weeks) (2). Furthermore, while most IrAEs develop within the first four to six months of immunotherapy, an increasing number of studies have reported new-onset IrAEs with a delay beyond two years after treatment discontinuation (2,3).
In addition to physical symptoms, psychological and neurocognitive symptoms have been identified among cancer survivors treated with ICIs, including anxiety, fatigue and depression (36,37). Rogiers et al (36) reported limited evidence on how these symptoms correlated with impairment in subjective cognition, despite no correlation with neurocognitive function impairment. In their limited sample, patients developing neuroendocrine IrAEs such as hypophysitis were particularly at greater risk, with symptoms like suicidal ideation being present in patients with no recent history of depression. Anxiety persisted in all survivors a year after treatment.

The challenge of detecting IrAEs mirrors that of portraying an accurate view of HRQoL. Recent systematic reviews (38,39) found HRQoL to be improved in patients treated with ICIs, when compared to chemotherapy agents, particularly in patients with advanced malignancies such as non-small cell lung cancer and melanoma. The author noted that because symptomatic degradation can occur later in patients treated with ICIs (3). This, in turn, delayed HRQoL degradation in physical, emotional, cognitive and social functions, as assessed withT the European Organisation for the Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30) (39). However, higher HRQoL correlated with generally improved overall survival (OS) rates of this cancer population compared to patients receiving chemotherapy (39).

While mild-to-moderate IrAEs can often be managed through close monitoring and supportive care, including self-management, more severe IrAEs demand timely medical interventions, often involving immunosuppressive agents, and may necessitate reducing or withholding ICI

treatment (40,41). Strategies to limit severity progression highlight the importance of understanding of typical occurrence patterns to anticipating IrAEs, and initiate countermeasures as soon as possible (2,40,42). Current guidelines also underline the need for active monitoring, particularly for grade ≥2 events, within 72 hours to adapt treatment (40). The need for close follow-up extends beyond the resolution of an adverse event, as the likelihood of additional severe IrAEs increases, particularly upon resuming or re-challenging ICI treatment (40). Contrastingly, medical visits are often tied to treatment infusions, which can be scheduled multiple weeks apart, particularly when treatment toxicity is anticipated and a major cause for concern (43). The gaps between patient visits underline the need for patients to engage in self-monitoring activities, as well as for facilitated access to acute care services to manage toxicities and symptoms and to prevent and manage further complications (5). To further explore the challenges presented by treatment toxicity and its potentially chronic symptoms, understanding how the symptom experience is defined can be useful.

Symptom experience and symptom management

As demonstrated, symptoms associated with ICI toxicity are diverse in nature, but the experience of those symptoms by each patient is unique, as it is influenced by other individual factors such as age, gender, the presence of other chronic diseases and previous lived experiences (44). As symptoms interact with the patient's environment and circumstances, they become deeply personal experiences that require personalised interventions to be managed effectively (45).
Conceptual frameworks like the Symptom Management Theory (SMT) [OBJ] can be useful in guiding the interpretation of the concepts involved in symptom management (Figure 1). The SMT describes three main concepts: (i) symptom experience, (ii) symptom management strategies and (iii) outcomes. The concepts are encircled within the domains of nursing science: the Person, the Health and Illness and Environment domains. These provide contextual variables that influence the main concepts. The three concepts are in constant, bi-directional interaction, each one further contextualizing their neighboring concepts.

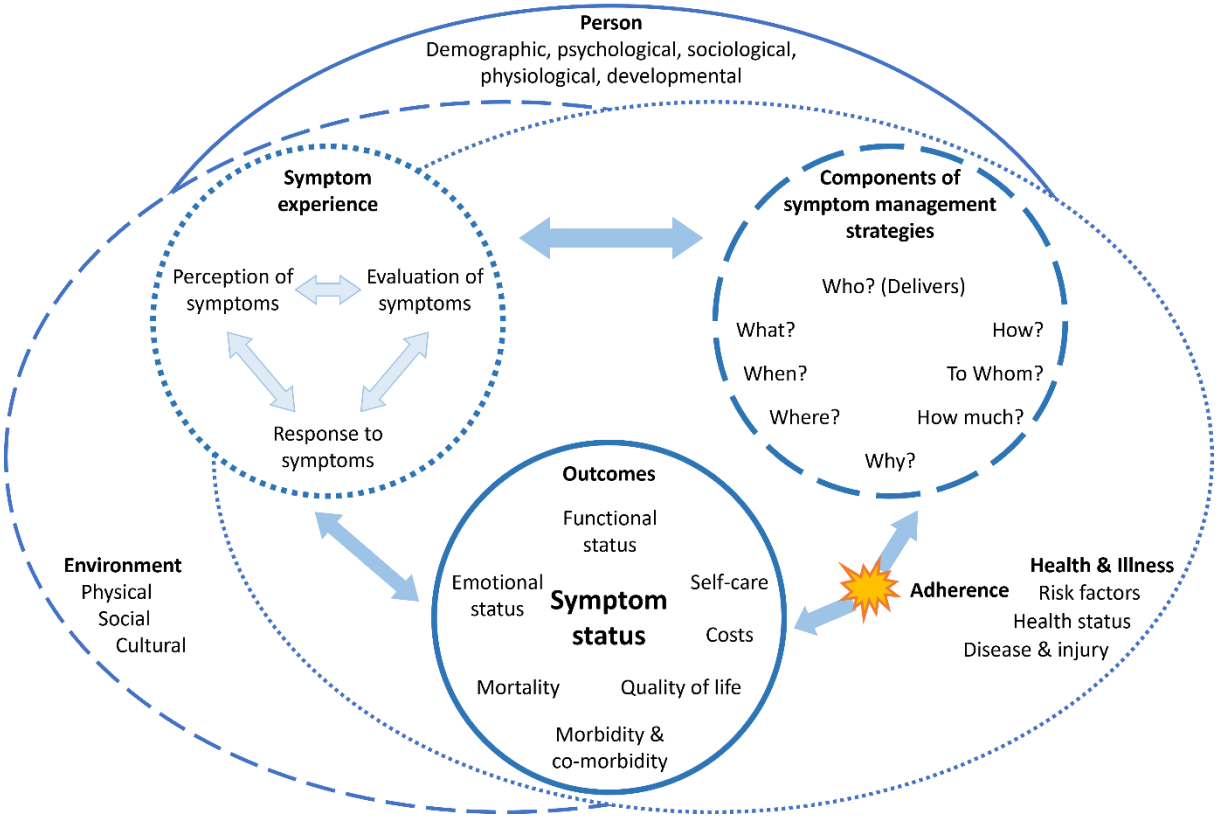

Figure 1 - Symptom Management Theory (SMT) by Dodd et al., 2001 (adapted)

Symptom experience represents the interaction of perception, evaluation and response to a symptom or change in health status. Perception of a symptom describes how the person notices a symptom as a change in their status compared to how they usually feel. The emergence of multiple simultaneous symptoms can also be perceived as a single change. A symptom is typically self-assessed by the patient by judging its severity, cause, interference on their daily lives and treatability. This self-assessment usually helps patients determine how to respond to a given symptom, which may affect how the symptom is perceived and re-assessed. Responses that draw positive outcomes such as improved symptom control, may help patients perceive the symptom as less severe than before, and vice-versa.
Symptom management strategies are efforts to attenuate, avert or delay negative outcomes of the symptom experience. When a management strategy decreases a symptom's frequency, severity and distress-inducing interference, the latter is considered effective. A strategy can target a single or multiple components of the symptom experience. Designing a strategy implies describing who, how, when, where and what each intervention in the symptom experience entails. This concept guided the development of the remote interventions provided in the model of care to support patients through the creation of roles and the flow of communication between providers and patients.
The symptom outcomes derived from the symptom experience and the symptom management strategies are multifaceted: while the main measurable outcome is a change in symptom status, other outcomes can refer to functional status, emotional status, self-care, costs, quality of life, morbidity and co-morbidity, and mortality.
The relationship between symptom management strategies and outcomes is mediated by adherence. Its absence leads to the breakdown of the process of managing symptoms. If interventions are too demanding, inconsistently administered of administered in the wrong dose or amount, adherence is negatively impacted. This underlines the need for standardised and tailored interventions resulting from transparent communication between the healthcare providers and the patient, whose impact is closely monitored.
Dodd et al. (46) describe self-reporting as the gold standard for assessing the symptom experience, which can be facilitated through patient-reported outcome measures (PROMs). These instruments contribute to a more personalised approach to managing their unique, individual experience (46,47). In the following section, we explore the concept of patient-reported outcomes and how they are used in cancer care.

Use of patient-reported outcomes in oncology

PROs directly convey the patient's perception of their health status without the interpretation of a third party, including the healthcare provider (27). Efforts in the past decades to include PROs as data points in clinical trials emerge from their potential to complement clinician-reported outcomes (CROs), such as grading with the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) (27,48,49). Quinten et al (50) have previously shown how the accuracy of predictive models of overall survival can be improved by considering both PRO and CRO data, including when the patient's self-assessment significantly contrasts with the clinician's assessment. Patients tend to report symptoms more frequently and earlier, of higher incidence and intensity, better portraying symptom burden than CROs (51–53). Despite the differences in nature between PRO and CRO data, the latter is also vulnerable to some subjectivity, as evidenced by differences between physicians' and nurses' assessments (54). Nurses' reports appear to more closely align with patients' self-reports than those of physicians (54). Cirillo and colleagues note that beyond subjective, personal and professional experiences, the tools used to collect self-reported data can contribute to closing this gap (54). A clear example of this challenge can be noted in standardised tools like the CTCAE, which attributes a symptom grade of 3 ("severe") or higher when a medical intervention is required or when the symptom creates clear functional interference. As a result, symptoms that patients perceive as severe for the burden and

suffering they experience daily, may be attributed a low CTCAE grade (<3), as they may not yet require clinical intervention (55). While certain treatments may be safe, CROs may fail to portray if they are tolerable from the patient's point of view (55). The realisation that patients' self-reports better reflect the underlying health status than CROs creates the argument for adopting PROMs such as the patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE) in routine care (56).

As patients with cancer navigate a multidisciplinary environment with several specialists involved to manage their condition, the opportunities for misrepresentations of the patient's condition by healthcare professionals increase through the occurrence of omissions, inclusion of biases and errors (56). PROMs enable patient-centred care by ensuring the patient's perspective is explicitly and accurately communicated in a standardised way, maximising the visibility of their physical and psychological symptoms and their needs, particularly in supportive care (11). They are used to facilitate shared decision making, by increasing clinician and patient awareness of symptoms, by facilitating care that aligns with patients' preferences and values, and by revealing the outcomes of interventions that were put in place from the patient's point of view (11). Their use has been shown to improve the efficacy of clinical encounters, and by helping determine what and how resources are allocated to fit patients' needs and values, PROMs are a driver for value-based healthcare (57). PROMs may also help prevent complications by conveying early symptom data that may signal developing complications, particularly when delivered electronically, facilitating timely interventions, potentially reducing the need for hospital admissions and overall cost of care (11,57–59).

Patient-reported outcomes measures for patients treated with immune-checkpoint inhibitors

Clinical trials using PROs to monitor symptoms in patients treated with ICIs, usually combine two or more PROMs (13). The majority of these trials rely on quality of life measures like the EORTC QLQ-C30, and some on more general-purpose instruments like the EuroQol 5 Dimension Scale (EQ-5D) (13,60,61). The broad range of symptoms related to ICIs eludes existing PROMs, as the majority of the most common IrAEs are not captured through these instruments (13). Quality of life measures often include similar sets of symptom items, which were conceived around frequent chemotherapy-related toxicities (60). This appears to be at odds with the aforementioned variability of IrAEs, while also explaining some of the discrepancies identified by Hall et al (60), where HRQoL scores remained relatively stable throughout treatment, despite the occurrence of severe and consequential adverse events.
Partial coverage of adverse events can also motivate the use of multiple PROMs, as the majority of clinical trials complement measures with disease, tumour or cancer-specific instruments (13). A minority of clinical trials have used selected items from PRO item libraries, including the PRO-CTCAE and the Patient Reported Outcomes Measurement Information System (PROMIS), to complement other PROMs (13). Such complementary measures seem all the more necessary, as existing PROMs may underestimate categories of ICI-related symptoms – notably, frequently-reported dermatologic IrAEs are seldom included in PROMs used in clinical trials (13,61). A recent trial by Zhang and colleagues (62) relied on a custom questionnaire to identify and follow-up on symptoms potentially related to IrAEs, with favourable results in improving follow-up of patients treated with ICIs. However, the questionnaire is integrated within an algorithm that took into consideration results from periodical blood tests, complementing the collected PROs, and enabling the system to autonomously issue standardized recommendations directly to patients. Results from the custom PROM lack clear guidelines and scoring methods for interpretation on their own.
Proposed solutions to the lack of ICI-related symptom PROMs include the creation of new, specific measures like the FACT-ICM, and the use of large item libraries like the aforementioned PRO-CTCAE and PROMIS (13,60,61,63). Tailoring these solutions to the specific needs of the target population or of the clinical trial is advised (56). Adapting these

PROMs is challenged by the lack of guidelines to select items to meet specific populations and specific needs (64,65). Colomer-Lahiguera et al (13) have suggested that, in the case of ICIs, PROM development should target therapy rather than tumour types present in the population. Describing IrAEs is a pervasive, current challenge, that is mirrored in the development of appropriate PROMs. As knowledge on ICI-related symptoms is still maturing, PROMs need to accommodate yet unknown symptoms. The possibility of unanticipated symptoms is already addressed by the PRO-CTCAE, which enables the use of free-text to add and describe symptoms that may not be covered by the item library (56).
The reliance on quality of life-oriented instruments to assess symptoms appears to be a significant setback in PRO research in cancer patients treated with ICIs. Item libraries overcome some of the limitations of the small scope of symptom item subsets in existing PROMs. Nevertheless, some of these solutions may present inherent limitations of their own in this context. The PRO-CTCAE was created to address symptomatic toxicities associated with chemotherapy, radiotherapy and targeted therapy, with surgery and ICI-related outcomes being notably absent (56). While updates to include ICI-related toxicity are ongoing, in its current form, the PRO-CTCAE presents some limitations when addressing the more complex symptomatic toxicities of ICIs. This is all the more likely as the CTCAE has been criticized for limitations in describing IrAEs from the clinician perspective (26). Despite the aforementioned limitations and challenges, item libraries like the PRO-CTCAE to address ICI-related symptomatic toxicity remain a promising approach, given their flexibility.

eHealth interventions using patient-reported outcomes for remote symptom monitoring

As cancer treatments became more effective, the understanding of cancer as a complex chronic disease unravelled the need for interventions that support patients beyond the confines of hospitals and cancer clinics (66). To address this need, an increasing number of electronic systems designed to monitor patients remotely using PRO data have been developed (6,10). In contrast to their analogue equivalent, these systems enable real-time collection of PRO data electronically (ePROs) rather than retrospectively (10). As electronic health records (EHRs) became standard, the ability to directly capture and integrate that data improved the accessibility of ePROs to healthcare professionals, encouraging their use in the continuum of care (6,10). Their usefulness for symptom monitoring is also greatly increased through real-time data collection, enhancing the timeliness of the interventions put in place by healthcare professionals (67). Tools such as personal computers and smartphones have become ubiquitous, and they have been leveraged to further drive the creation of systems that rely on the patient's own electronic devices to deliver electronic PROMs (ePROMs). Through computerized adaptive testing (CAT), ePROMs can be tailored further than traditional paper-based PROMs, unlocking new opportunities for more personalized care interventions (6,68).

A seminal study by Basch and colleagues (69) proposed collecting symptom data through a web-based interface system for patients of the Memorial Sloan Kettering Cancer Center. Patients were enrolled into one of two groups, including a control group receiving usual care and an intervention group where patients used the web-interface to self-report symptoms. The intervention group was in turn split into two subgroups, one with computer-experienced patients able to access the system from home, and another accessing the system during in-clinic appointments. The researchers used a symptom questionnaire based on the CTCAE, with the system issuing e-mail alters to nurses when symptoms were of grade≥3 or worsened by at least 2 points. Patients were encouraged to contact the medical office directly outside business hours, instead of relying on the ePROM system. The system output was printed out for physicians during each clinic visit, for nurses and the treating oncologist. This trial included 766 participants of which 539 were computer-experienced patients in the intervention group. The authors demonstrated improved HRQoL at 6 months for more patients in the intervention group compared to usual care ($p<.001$) using the EQ5D. Patients in the intervention group also underwent less emergency room (ER) visits, less hospitalizations and remained in treatment for longer, with superior quality-adjusted survival. A minority of 1.7% of symptoms were severe

or disabling (grade 3 or 4). Nurses responding to the e-mail alerts were able to take immediate action, including making telephone calls for symptom management, managing and starting medication, changing chemotherapy dose, ordering imaging and tests, making referrals to the ER and admitting patients to the hospital.

Similar studies have reported comparable benefits when using ePROMs as a starting point for remote symptom management, including smaller declines in HRQoL scores and improved symptom control (10,11,70,71). Improvements in patient satisfaction, self-efficacy and self-management have also been observed in several clinical trials (10,11,71). A minority of studies also reported decreases in ER admissions (12,70). Not all studies consistently reported these benefits, though meaningful methodological and setting differences exist, and the variability of the features of the ePROM applications is also likely to be related with these differences (10,14,72). Differences in implementation strategies can also be considerable and may explain such variability (12). The significant variability of these outcomes across clinical trials is partially explained by differences in the PROMs used and by inconsistencies on how these findings are assessed and reported (9,11).

Electronic patient-reported-outcomes-based applications in eHealth Interventions

Understanding what features of eHealth platforms enable safe, reliable, and valuable follow-up care, is challenging. A 2019 systematic review by Warrington et al (10) concludes that electronic platforms to collect ePROs vary greatly in their feature set. Fewer than half of the reviewed ePRO applications allowed patients to review the data they submitted to healthcare providers. Most (59%) did not send alerts to healthcare professionals when symptoms hit a predefined severity threshold, nor did they provide patients with any type of automated tailored feedback (71%). A small subset of applications (15%) allowed patients to contact healthcare providers. Patients, however, do favour applications that allow communication with other patients and healthcare professionals (10). They also value tailored feedback they get via the electronic application, which can include automated and non-automated feedback (68). More recent studies have increasingly met the aforementioned desirable set of features, with applications allowing patients to review symptom reports, receive tailored telephone-based feedback or automated feedback, and allowing to communicate with healthcare professionals (7,62,73–77).

The platform used in the aforementioned seminal study included automated self-management advice for mild symptoms (grade<3), only notifying nurses of more severe symptoms (69). One significant advantage of this approach is that patients immediately receive feedback, with steps they can take autonomously, which can be empowering. For nurses, this represents a method to mitigate the significant burden for professionals, with educational materials being automatically shared with the patient without the need for their intervention. The drawback is the possibility of professionals missing persistent symptoms that interfere with the patient's activities of daily living, despite not hitting severity targets to merit a grade≥3. It is also unclear what materials were shared, and how they were tailored to the patient. The study also enabled nurses to enact consequential interventions without high levels of friction but provided no details of the resources and decision mechanisms nurses used to make those decisions.
In the eRAPID study (72), the authors note the use of a clinical algorithm to tailor advice for patients that is implemented in their electronic patient record platform. The symptom questions underwent a participatory design process involving with patients and healthcare professionals (78). These questions and the classification of each item according to the CTCAE version 4.0 were aligned with the UKONS's triage tool grading system (78). This contributes to the transparency of the underlying algorithm. Though the study did not result in fewer treatment interruptions and ER admissions, this is likely related to the small number of patients in a palliative setting as opposed to a curative setting and the time during which the trial took place.

The system created low levels of alerts without impacting chemotherapy delivery and patient burden, hinting towards a potentially cost-effective solution.

To date, only a small number of studies involving ePROMs and targeting patients treated with immune checkpoint inhibitors specifically have been completed (62,73–75,79,80). These interventions have been shown to be feasible and acceptable, with some potential to lower symptom severity, decrease emergency department admissions related to ICI toxicity, and improve patient-provider communication and the HRQoL (62,73,75). It is important to consider that these findings are not universal, as some trials (79) did not detect any difference in IrAE severity and led to more frequent admissions initiated by remote follow-up, though methodological differences between trials are significant, particularly from an implementation point of view (24).
Tolstrup et al (74,79) described an intervention where patients are notified by the web application if a symptom requires contacting the hospital if symptoms worsened, with the minimal threshold being a mild symptom. This in turn resulted in more telephone contacts and ER visits in the intervention group, with patients being slightly more likely to be hospitalized. Nevertheless, a positive effect in HRQoL and in patient-healthcare professional communication was demonstrated. Zhang et al (62)also demonstrated improvements in HRQoL, with decreases in the number of ER visits and shorter in-person clinic visits. In this study, the threshold to alert the clinical team was higher, from grade≥3. In addition, a specific follow-up team was tasked with managing patients remotely, This team was comprised of an oncology physician and trow nurses, with at least 2 years of experience with ICI therapy. The study by Msaouel et al (73) has not published comparable data, yet it contains a web application that notifies patients to contact clinical oncology team and simultaneously informing the staff via e-mail. Similar to the previously cited studies, the ePROM application only generates clinical alerts under specific conditions. Symptom thresholds that activate an alert have been subjected to a panel of experts' assessment and were linked to specific interventions based on current toxicity management guidelines. The approach is innovative and may hold promise to decrease the potential burden on care team.
With the growing amount of available data, it becomes apparent that benefits of these interventions do not strictly relate to the electronic applications, but to how they are implemented and how they further support clinical activities beyond symptom monitoring, such as improving self-efficacy and quality of life.

Self-efficacy in eHealth Interventions

For patients, one of the benefits of these eHealth interventions is the self-management support they enable. Self-management of a chronic condition refers to the set of tasks individuals put in place to preserve their well-being (81). The ability to perform these tasks is associated with the individual's perceived self-efficacy, which in itself is the individual's confidence in performing a particular task or behaviour (82).
As a target of ehealth interventions, self-efficacy is a facilitator for patients to acquire self-management skills (66). Because of its close relationship with the task to be performed, when measured, self-efficacy is contextualized towards a specific goal or task (83,84). If an eHealth intervention aims to support patients in managing symptoms, self-efficacy should be assessed with that goal in mind. Perceived self-efficacy to manage symptoms consists in the patient's confidence in being able to perform the actions and behaviours required to achieve that goal, and is associated with lower symptom occurrence and lower distress (85,86). In the context of ePRO-based interventions, improved self-efficacy and self-management skills are likely associated with specific features or the software applications used, including the ability to communicate with healthcare professionals and to track the patient's own health status (10). Nurses are often the point of interaction between patients and healthcare teams, through face-to-face and telephone interactions (87). They implement specific strategies to leverage different sources of self-efficacy, including vicarious experiences, verbal persuasion and

motivational interviewing, while maintaining close collaboration and communication between patients and the oncology teams (86) Their interventions include educational, monitoring and feedback components meant to increase the patient's knowledge on their condition and engage them in self-management, developing skills such as self-monitoring, more effective communication with the healthcare team, goal setting and action planning, among others (66,86).

Health-related quality of life in eHealth Interventions

Self-efficacy is a facilitator or HRQoL through self-management (84). Some PROM-based eHealth interventions (69–71,79) have shown improvements in overall HRQoL, although the majority of studies have not found statistically significant benefits (88). Improvements can be particularly significant in some subscales of the instruments used, rather than overall scores, though the reasons for this are challenging to clarify (88). Assessment of the effects on HRQoL are difficulted by the methodological variability across studies that use a PROM as part of their intervention. Nevertheless, it is suggested that benefits on HRQoL are associated with more frequent discussion with clinicians on the objective and subjective symptoms and challenges that those measures assess (39,89).
In the context of treatments with ICIs, HRQoL has been noted to be positively correlated with overall survival (39). It should be noted that a statistically significant positive correlation between overall survival and the occurrence of IrAEs has also been found in multiple studies (90). Some insights in patient perceptions on the occurrence of IrAEs have revealed that some see their occurrence as a positive, which may in turn affect the perception of their own quality of life, even in the presence of potentially limiting IrAEs (39). Critically, given how IrAEs may manifest over time, it can be questioned if HRQoL PROMs should be applied more often to detect variability during treatment.

Integrating patient-reported outcomes measures in routine care

Although the adoption of PROMs in clinical trials is longstanding, use of these measures in routine cancer care has only recently gained traction, as clinical studies reported on their use as essential elements to guide the provision of care (7,56,71,74,91). Despite ongoing efforts to tailor PROM-based interventions to different cancer populations, the body of work on the implementation of PROs in a "real-world" setting is limited, with studies frequently failing to clarify how these interventions interfere with or enhance normal workflow. Clinical studies typically describe procedures that complement established care routines or introduce new procedures in parallel (62,69,73,75,92,93).
The integration in routine care remains highly desirable given the potential benefits. Integrating PROMs into routine can lead to improved communication between patients and healthcare providers: patients tend to discuss symptoms more often, including those of an emotional and intimate nature, and report higher levels of satisfaction when communicating with the care team (11). While most studies (9,94) have reported little to no impact on the length of conversations between physicians and patients Zhang et al (62) have reported a decrease in the time expended for follow-up tasks in patients treated with ICIs, with an average of 8.2 minutes (3.9 [95% CI, 5.0-10.6]) when using an ePRO-based model of care, against 36.1 minutes (15.3 [95% CI, 33.6-38.8] in standard care ($p<.001$). This aligns with reports from nurses who noted that the availability of PROMs allowed for more efficient patient interactions, by tailoring consultations to the self-reported needs of patients (11). However, findings on the direct contributions of PROMs as a support for clinical decision-making are mixed (9,11). Healthcare provider's perceptions suggest PROMs bring valuable information to inform clinical decisions, identify patient concerns, and increase their awareness of patients' symptoms (9,11). Clinical trials using electronic PROMs to track symptoms remotely and in real-time report lower symptom severity and comparatively fewer admissions to the emergency department (62,69,70). However, follow-up interventions are difficult to trace back to PROM data, and the reported increased awareness has failed to translate into a higher number of

interventions or referrals to other specialists (9,11). It is, to date, unclear if and how the decision-making process is significantly impacted by the use of PROMs.

In a recent systematic review, Lai-Kwon et al. (14) described the feasibility, acceptability and effectiveness of ePROM-based interventions for patients treated with ICIs, with favourable preliminary results for both patients and clinicians. Acceptability for patients ranged from 54% to 100%, corroborated by qualitative feedback. In one example (74), patients highlighted how the use of ePROMs facilitated symptom recall during in-person visits, thus improving patient-healthcare provider communication, which are benefits that have been previously identified in other cancer populations (11).
In their review, Lai-Kwon et al. (14) also note the considerable variability in features of the different ePROM platforms, which Warrington et al. [OBJ] have identified as detrimental to establish comparisons between interventions. Significant differences in implementation strategies and level of patient and healthcare provider engagement across interventions compound this difficulty. One of the reviewed studies, a feasibility study by Taarnhøj et al (80) reported that while patient compliance was high and comparable to other trials, physician compliance in reviewing PROMs data was remarkably low, with only 35% of questionnaires reviewed at the first outpatient consultation, and hitting a peak of 52% after the third treatment cycle, and a sharp decrease to 0% until the sixth and last cycle. These declining compliance rates are not unique to the context of ICIs, as noted by Howell et al (47), who have underlined the need for short and long-term strategies to ensure PROMs data is used consistently in a real-world setting. This once again confirms that successful interventions require engagement at multiple levels by all stakeholders, with short-term and long-term strategies to maintain adherence and compliance.
In their quality improvement collaborative project, Howell et al (47) used the Knowledge-to-Action framework (95) to drive the implementation of ePROs in multiple sites in oncology practice. Readiness and barriers were assessed in a pre-implementation phase, where multiple interventions to drive engagement and identify implementation champions are put in place. Nguyen et al (96) have described barriers to PROs and PROMs implementation on the patient-level, the healthcare provider-level and the service-level. Their findings are summarized in table 1.

The perceived value of PROs data is a common challenge to acceptability across patients and healthcare providers (8,47,96). Current guidelines highlight the need for visibility of how PROs data can inform and support clinical decision-making, for both healthcare providers and patients. This shared perception can trigger a positive feedback loop, where patients understand how the PROs data they provide can enhance the care they receive, and healthcare providers make use of this data to improve patient interactions and inform the provision of patient-centred care (47). Realising the value of PROs data is facilitated by training healthcare providers in their interpretation and use, and educating patients in self-assessment and self-monitoring by including PROs in educational material (47).
Introducing PROs data into clinical routine requires significant time investment at an initial stage, as established workflows need to be intently modified to include collecting and reviewing the data. For healthcare providers, having PROs data passively collected and automatically integrated within the patient's EHR is highly desirable and favours their continued use in a real-world setting (8,10). By improving data accessibility and decreasing friction, providers can bring PRO data to consultations with the patient and refer to that data when communicating with other team members to plan care across the continuum. Current guidelines also call for dedicated resources to be allocated to collecting and interpreting PROs data (8). For patients, extensive PROMs may prove burdensome if they are lengthy, thus interfering significantly with day-to-day activities (47,96).

Table 1: Barriers to PROs and PROMs in routine cancer care, adapted from Nguyen et al (96)

Barrier category	Patient-level barriers	Healthcare provider-level barriers	Service-level barriers
Knowledge	Perceived irrelevance and perceived lack of value of PROs data	Perceived uselessness of PRO data	Difficulty identifying actionable PROs data
	Concerns around privacy	Lack of knowledge to interpret and use PROs data in routine practice	
Time and Infrastructure	Time required to complete PROMs	Insufficient time to interpret, action and discuss PRO data with patients during clinics	Insufficient resources (physical, human, hardware and software) to implement PROs data collection in routine practice
Accessibility	Limiting physical or cognitive conditions; declining or severe health status.	Difficulty using the electronic platform to view and assess PROs data	Lack of integration of PROs into clinical workflows
	Difficulty using electronic devices (software and hardware ergonomics, accessory requirements)		
Patient-Provider relationship	Concerns that PROMs may compromise the patient-healthcare provider relationship	N/A	N/A

While electronic platforms have introduced features that increase the accessibility of PROMs, such as facilitating the use of questionnaires in multiple languages and interactive feedback features, they may prove a challenge to some patients. Remote and automated feedback to patients improves PROs data value and decreases the burden on healthcare teams (8). Simultaneously, they may lead patients to question if such features result in less in-person assessments and direct interactions, thus decreasing the perceived quality of care (96). This once again underlines the need for transparency in how the data is used. Such transparency is also crucial when patients express concerns over their data privacy, and how their data is shared across providers.

Technological literacy, physical limitations, and accessory requirements such as the need for a persistent internet connection, can constrain the value and benefits of ePROs data at a population level. Older patients stand to gain the most when ehealth interventions are built with accessibility concerns in mind, specifically with alternatives to strictly electronic-based interactions, such as telephone calls (97). Telephone interaction is often used in the context of acute care as the medium for remote patient triage, including in patients treated with ICIs (22).

The long-term viability of PROs data in routine care is tightly related to the creation of self-sustaining cycles where patient participation is rewarded with reactive action from healthcare providers, who in turn continue to encourage and educate patients in making use of that data to engage other stakeholders and communicate their health-related needs and preferences. Among healthcare providers, audit and feedback systems and internal meetings that re-engage professionals to value and use PROs data, while being attentive to the changing needs and challenges of the real-world setting are crucial for sustainability.

Chapter 3: Methods

To address the previously mentioned gaps in knowledge, we defined a strategy comprised of five distinct phases (Figure 2). The first four phases were developed as part of this thesis. This project began in September 2019 and is currently in the data analysis stage (phase 5).

Figure 2 - Phases of the IePRO Project

The first phase aimed to develop a PROM to assess symptomatic adverse events of patients treated with ICIs. As previously noted, item libraries allow for tailored PROMs to a given population's needs. In previous research conducted by our research group, we relied on the PRO-CTCAE to enable patients treated with immunotherapy to self-report symptoms. Construct validity of the PRO-CTCAE has been demonstrated in a large (n=975) and diverse sample, with high convergent validity with the QLQ-C30, which is the most widely used PROM in studies involving patients treated with ICIs (98). When testing for reliability, the median intraclass correlation coefficient (ICC) was of 0.76 (0.53 to 0.96), and for thirty-six of the 49 tested PRO-CTCAE items were found to have an ICC of at least 0.7. Notably, the sample included patients with impaired performance status and high symptom burden. To our knowledge, translation of the PRO-CTCAE in French has been internally validated through cognitive interviews, but no published data is available. These factors led us to conduct a Delphi study where we describe the selection process of PRO-CTCAE items that could be useful in monitoring and managing symptomatic ICI-related toxicity.

Most studies reporting on their selection of symptoms to monitor through ePROs, report on those more often related to hospitalizations or that may present vital danger to patients, as well as those outlined by published guidelines (69,70,99). In discussion with the core study team, it was agreed with members of the medical team that several symptoms may not present significant vital or hospitalisation risk to patients, but that are nevertheless frequent and could be of consequence to their quality of life and activities of daily living, such as fatigue. As previously argued in this thesis, ICIs are associated with symptomatic IrAEs that can be underestimated by healthcare professionals. In addition, at the time of planning there were no published guidelines on the selection of PRO symptom items for this patient population. We thus considered that the Delphi method would allow us to take guidance from a diverse panel of experts in this emerging field and create an environment of discussion and continuous revision of our approach.

This Delphi study was designed in accordance to the proposed key methodologic criteria to report in Delphi publications (Table 2) of Diamond et al (100). We recruited an international panel of clinical experts and one patient-representative through convenience sampling. Experts evaluated the relevance and importance of each PRO-CTCAE item for patients treated with ICIs. The Delphi took place over four rounds in 6 months. The first round concerned the relevance of the PRO-CTCAE items, and the second to fourth rounds addressed their importance for remote symptom monitoring. Consensus was defined as a minimum of 75% agreement among experts. Importance of the items was combined in three levels, with level

one being the most important items, and a level three the lowest. While experts were blinded during the first three rounds, the final round included a remote live discussion in which experts were unblinded. Further details of this process are covered in the first article of this thesis in its fourth chapter.

Table 2. Key methodologic criteria to report in publications of Delphi studies - Diamond et al, 2013 (100)

Study objective
• Does the Delphi study aim to address consensus?
○ Is the objective of the Delphi study to present results (eg, a list or statement) reflecting the consensus of the group, or does the study aim to merely quantify the level of agreement?
Participants
• How will participants be selected or excluded?
Consensus definition
• How will the consensus be defined?
• If applicable, what threshold value will be required for the Delphi to be stopped based on the achievement of consensus?
○ What criteria will be used to determine when to stop the Delphi in the absence of consensus?
Delphi process
• Were items dropped?
○ What criteria will be used to determine which items to drop?
• What criteria will be used to determine to stop the Delphi process or will the Delphi be run for a specific number of rounds only?

The second phase of this project aimed to address how ePRO-based ehealth applications are used in the context of more complex interventions, by defining a care model that used PRO data collected remotely to enhance existing symptom management strategies.

The need for a new model of care emerged from multiple exchanges between the IePRO project team and multiple healthcare professionals of the participating sites, including nurses, physicians and administrators. The initial aim was to describe a workflow that could be inserted in existing care processes and that ensured patient engagement in the act of self-reporting symptoms. As the ultimate goal of the intervention was to provide patients with remote self-management support, with a focus on symptom management, we aimed to include an algorithm that would guide the delivery of that support. The development of this model of care is described in the second article included in this thesis.

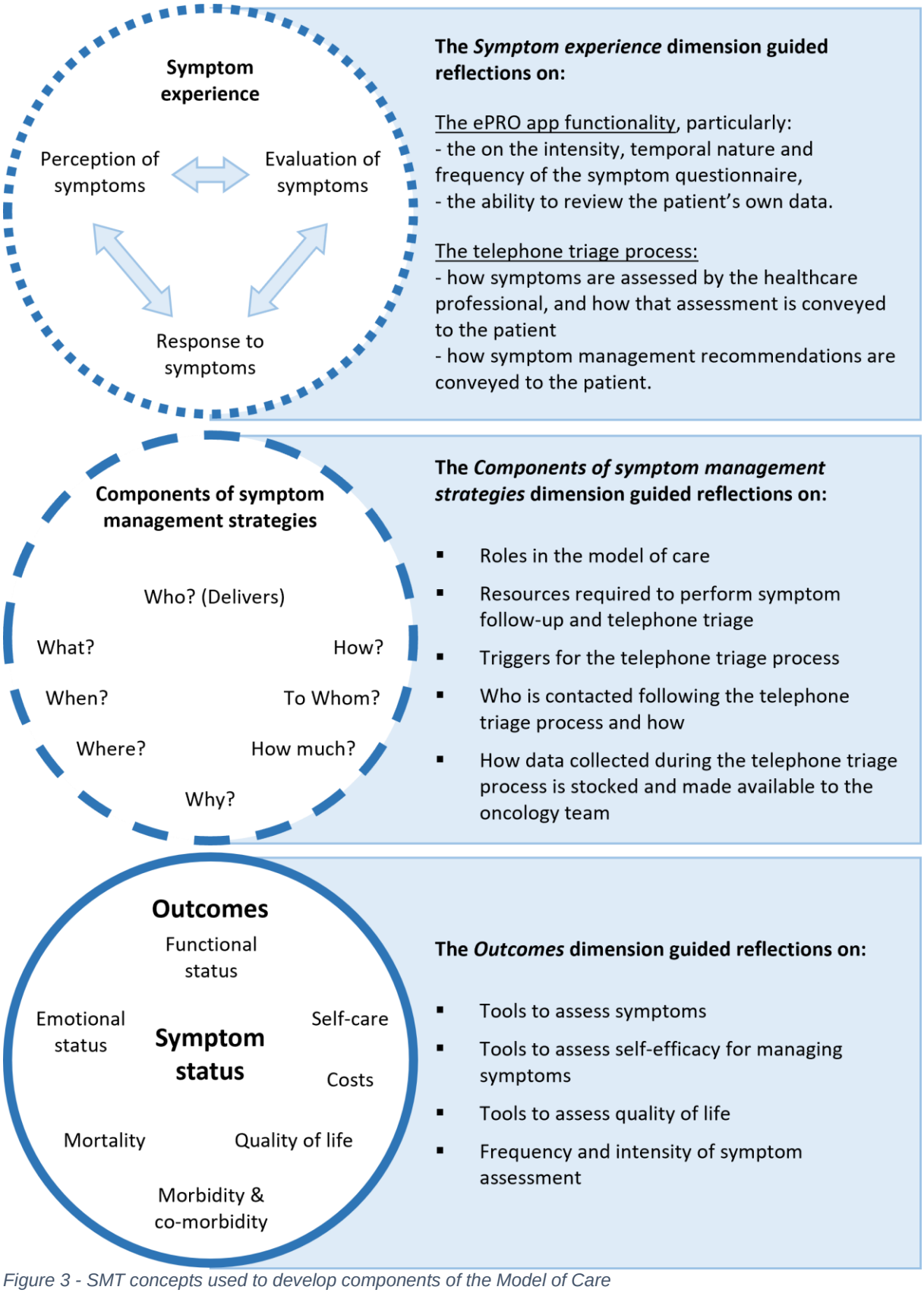

Figure 3 - SMT concepts used to develop components of the Model of Care

Following the development of the model of care, the next phase of this project was the development of a phase II randomized controlled trial aiming to test the model of care. This study would also provide data on the efficacy of the model of care through the number of

detected symptomatic IrAEs, as well as safety data by highlighting missed triggers for triage calls, missed IrAEs, and deviations from the triage algorithm. As this was the first iteration of the model of care, we also aimed to provide data on recruitment and attrition, suitability of the outcome measures and acceptability of the model of care among patients and healthcare providers. The randomized controlled trial took place in the ambulatory units of the oncology departments of two university hospitals. Initially, the trial aimed to include patients diagnosed with melanoma or lung cancer, treated with ICIs exclusively. New standards of care established between 2019 and 2020 significantly decreased the number of patients meeting that criterion, resulting in significant challenges for recruiting the target sample size. The recruitment process was thus revised, and the criterion was modified to include any cancer type treated exclusively with ICIs. Certain factors outside of our control limited the scope of some of the goals of this thesis. The nurse-led model of care was initially conceived as an advanced practice nurse-led model of care, but due to personnel restrictions during the SARS-CoV-2 2019 pandemic, this was not possible to put in practice. The pandemic also limited access to research sites, limiting deployment of implementation strategies and access to patients. Although a more comprehensive analysis of the results of the trial was planned, new cancer treatment guidelines phased out the exclusive use of ICIs to treat certain cancers, recommending combination with chemotherapy in most cases, limiting the projected recruitment rates, and leading to the early termination of the study by 6 months. We thus present evidence from a case analysis that describes how the model of care was put in place, and briefly discusses the nature and volume of data collected throughout the study, as well as its potential implications for future research and nursing practice.

The case study includes descriptive data collected during phase four, on an intervention group participant's health status during treatment, and their interaction with the model of care tested in the randomized controlled trial. The objective of this case study was to exemplify in greater detail the behaviour and challenges of the model of care in real-world practice. To select this particular case study, we exchanged with the triage nurses on participants that they had found to be representative of most patients in the trial, while also challenging the limits of the model of care. In this case study, we report the secondary outcomes described in the protocol, and add the number of completed questionnaires, the number of triage calls and their triggering symptoms, and the actions nurses took following each triage call. We also elaborate on situations where the patient deviated from the expected behaviour in the study, as well as on actions undertaken by the oncology care team to manage non-treatment-related and non-cancer-related symptoms.

Chapter 4: Results

Phase 1: Symptomatic IrAE PROM Delphi

As previously covered in this thesis, ICIs are associated with a wide spectrum of symptomatic IrAEs, which are challenging to assess by both clinicians and patients. In the absence of ICI-specific PROMs, the adequacy of existing instruments for this patient population was still unproven. Until 2019, most clinical trials used a combination of PROMs to cover the symptoms associated with ICI, with the more popular being HRQoL instruments (102–105). In previous work developed within the clinical-academical partnership between the department of oncology of the CHUV and the IUFRS, a systematic review of PROMs used in clinical trials with patients treated with ICIs was conducted by Colomer-Lahiguera et al (13). In their review, PROMs were found to fully cover only 45% of the most frequent IrAEs, while 23% were partially covered and 29% not covered at all. In their discussion, the authors underline the fact that given how ICI-related toxicities are more independent of the underlying cancer diagnosis than other cancer treatments, the choice of a PRO instrument should be made based on the target population rather than the type of treatment. As such, the use of item libraries such as the PRO-CTCAE, that could be tailored to the population, could be a viable choice to encompass

a broader range of symptoms associated with ICI toxicity. With this consideration in mind, we conducted a Delphi study with an international panel of experts, which we describe in the first article (Article 1) of this thesis. The method and results analysis of this study were performed in collaboration with Dr. Sandra A. Mitchell, Program Director in the Outcomes Research Branch in the Healthcare Delivery Research Program, of the National Cancer Institute (United Sates of America), who was involved in the development of the PRO-CTCAE (56).

Article 1: Patient-reported outcomes for monitoring symptomatic toxicities in cancer patients treated with immune-checkpoint inhibitors: a Delphi study

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HIGHLIGHTS

- This study suggests existing PRO-CTCAE™ symptom terms do no cover the full spectrum of immune-related adverse events (IrAEs).
- This Delphi produced a set of prioritized PRO-CTCAE™ items to address symptomatic toxicities of ICIs.
- The study adds 56 new symptom terms suggested by experts to inform the expansion of the current PRO-CTCAE™ item library.
- Further studies on patients' symptoms are needed to guide how ICI toxicity can be approached with patient-reported outcomes.

ABSTRACT[1]

Background: Immune-related adverse events (IrAEs) associated with the use of immune checkpoint inhibitors (ICIs), may not be fully covered by existing measures like the PRO-

[1]Abbreviations :

CTCAE™. Selecting PRO-CTCAE™ items for monitoring symptomatic adverse events is hindered by the heterogeneity and complexity of IrAEs, and no standardized selection process exists. We aimed to reach expert consensus on the PRO-CTCAE™ symptom terms relevant for cancer patients receiving ICIs and to gather preliminary expert opinion about additional symptom terms reflecting ICI symptomatic toxicities. Additionally, we gathered expert consensus about a core set of priority symptom terms for prospective surveillance and monitoring.
Design: This Delphi study involved an international panel of experts (n=6 physicians; n=3 nurses, n=1 psychiatrist and n=1 patient advocates). Experts prioritized the relevance and importance of symptom terms to monitor in patients treated with ICIs.
Results: Experts reached consensus on the relevance of all (n=80) PRO-CTCAE™ Symptom Terms. Consensus on the importance of these symptom terms for prospective monitoring in patients receiving ICIs was reached for 81% (n=65) of these terms. Additional symptoms terms (n=56) were identified, with consensus that 84% (47/56) of these additional symptom terms should also be considered when monitoring symptomatic IrAEs.
Conclusion: This study identified a prioritized list of symptom terms for prospective surveillance for symptomatic IrAEs in patients receiving ICI treatment. Our results indicate the need to strengthen the validity of PRO measures used to monitor patients receiving ICIs. While these results provide some support for the content validity of the PRO CTCAE™ and resulted in a preliminary set of salient symptomatic adverse events related to the use of ICIs, broader international agreement and patient involvement is needed to further validate our initial findings.

KEYWORDS

Patient-reported outcomes; Immune checkpoint inhibitors; Symptomatic immune-related adverse events; Delphi consensus; PRO-CTCAE™

Introduction

The growing complexity of cancer care motivates efforts to improve the safety, effectiveness, and tolerability of cancer treatments. With the recent widespread adoption of immune checkpoint inhibitors (ICIs) for an expanding number of disease indications, a wide range of new immune-related adverse events (IrAEs) has been reported (5). While detection and monitoring of treatment toxicity is a priority across cancer care, it is particularly important during immunotherapy treatment. IrAEs are thought to be effects of an over-activated immune system, that can affect almost any organ (“off-target” effects), varying in frequency and severity, with the most severe leading to hospitalization, treatment discontinuation, long-term or permanent conditions or even death (15,18,106–108). Despite frequent patient follow-up visits while on treatment, IrAEs can rapidly progress in severity (15), underlining the need to empower patients with the means to self-monitor and self-report their symptoms (5).
The Common Terminology Criteria for Adverse Events (CTCAE) are standardized criteria used by clinicians to identify, grade, and report adverse events (AEs) experienced by patients receiving cancer therapies, including ICIs (109). However, accurately and reliably reporting AEs can be challenging, prompting the United States Food and Drug Administration (FDA) to call for the inclusion of the patient’s own perspective when describing symptomatic AEs through the collection of patient-reported outcomes (PROs) (28,53,110,111). PROs are

CTCAE	Common Terminology Criteria for Adverse Events
ICIs	Immune-checkpoint inhibitors
IrAEs	Immune-related adverse events
PRO(s)	Patient-reported outcome(s)
PROM(s)	Patient-reported outcome measure(s)1
PRO-CTCAE™	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events™

defined as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” (28). Their use in clinical trials to track symptomatic toxicities of cancer treatments can improve the management of those symptoms, thereby preserving health-related quality of life, and allowing patients to remain in treatment for longer, and decreasing emergency department visits (9,69). Moreover, using PROs can enhance patient-clinician communication, allowing for more complete discussion of therapy side effects during office visits (9,11).
The PRO version of the CTCAE (PRO-CTCAE™) was developed by the US National Cancer Institute to address the need to capture through self-reporting the symptomatic toxicities experienced by patients participating in cancer clinical trials (56). The PRO-CTCAE™ Item Library is comprised of 124 items representing 78 symptomatic adverse events drawn from the CTCAE (112). For each of these symptomatic AEs, PRO items were created to evaluate attributes of presence or absence, amount, frequency, severity, and interference with usual activities. For a given AE, one to three attributes were selected depending on the content of the CTCAE criteria and the nature of the symptom. The PRO-CTCAE™ has demonstrated favourable validity, reliability, and responsiveness in a large, heterogeneous sample of United States patients undergoing cancer treatment (56) . Researchers elect the relevant symptom terms for prospective surveillance, considering the agent under study, trial goals, and the patient population (56). Regarding the use of the PRO-CTCAE™ items to declare symptomatic adverse events, FDA recommends selecting a set of the most important symptomatic AEs that are expected to occur (27). However, research on methods to select appropriate symptom-related PROs is still limited (64,65).
Using the PRO-CTCAE™ to describe symptomatic toxicities of ICIs poses some challenges. PRO-CTCAE™ development, like that of other PRO measures (PROMs), has to date focused on the symptomatic toxicities of chemotherapy, radiotherapy and targeted therapy, across multiple tumour types (56). As such, the anticipated symptomatic toxicities associated with the use of ICIs, like vitiligo and xerophthalmia, may not be fully addressed by the current version of the PRO-CTCAE™ Item Library. The uniqueness of IrAEs associated with ICIs raises questions about the suitability of existing PROMs to capture ICI- related symptomatic toxicities, and a recent review has identified gaps in the content validity of existing PROMs, including the PRO-CTCAE™ (13,60,113). Consequentially, several clinical trials have reported the use of multiple PROMs, combining cancer-specific and disease specific instruments, to address the large spectrum of IrAEs (13). The highly variable and heterogeneous profile of symptomatic IrAEs experienced by patients receiving ICI treatment also presents a challenge in defining a parsimonious and acceptable PRO strategy that both limits patient burden and is sufficiently comprehensive (64). This underscores the need to systematically appraise the content validity of the symptom terms included in the PRO-CTCAE™ Item Library with respect to the toxicities commonly associated with ICIs, identify candidate symptom terms for expansion of the library, and derive consensus among experts on core domains to be addressed when monitoring for symptomatic IrAEs.
The aim of this study was to reach consensus on the PRO-CTCAE™ Symptom Terms relevant for cancer patients treated with ICIs and gather preliminary expert opinion on additional PRO symptom terms that could be related to symptomatic ICI toxicity. Additionally, we gathered expert consensus on the importance of each symptom term when monitoring patients receiving ICI therapy, thereby identifying a core set of symptoms to be evaluated in that population.

Material and methods

We applied a Delphi technique (100,114) as part of a larger study on the use of electronic patient-reported outcomes monitoring of melanoma and lung cancer patients treated with ICIs.

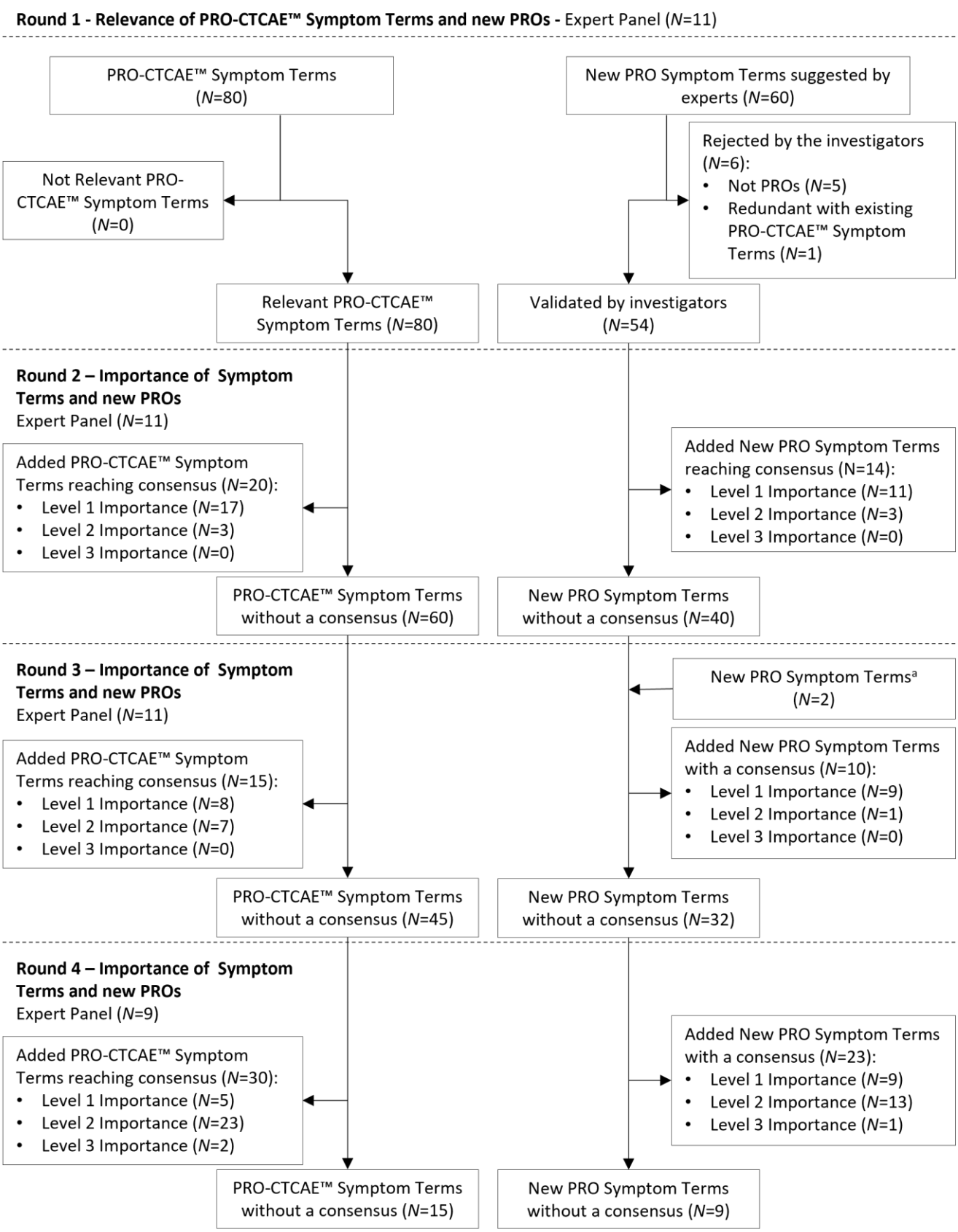
Expert recruitment:

When recruiting an expert panel, we aimed to represent European physicians, nurses and patients, experienced in at least two of four fields of expertise: immuno-oncology, lung cancer, melanoma and PROs. For physicians and nurses, we reviewed relevant publications and

presentations in the medical field across these domains and contacted the experts directly. In particular we aimed to recruit clinically active staff in university hospitals, with at least two years of experience and renowned researchers in their field. We identified patient advocates serving in leadership roles of national and international patient advocacy groups related to the aforementioned fields of expertise, and with experience in dealing with ICIs and their side-effects.
A total of 15 experts (N=8 physicians; N=6 nurses; N=2 patient advocates) were identified through convenience sampling and contacted by e-mail. Experts were sent a plan of the Delphi study that included its background and goals, the number or rounds planned, and how the data would be used.

Delphi planning
This Delphi included four rounds during which experts replied to an online questionnaire. They were e-mailed a secure link and required to log in to a personal account in order to view and reply to the questionnaires. Google Forms and LimeSurvey were used to develop the online questionnaires. STATA® 14 and Microsoft Excel 2016 were used to analyse the data. Through the duration of the Delphi, experts were able to contact the investigators for any questions regarding the online questionnaires, including technical support.
Four investigators collected, reviewed and anonymized expert's answers before sharing them with the other experts that were blinded. Results from each round were presented in a word document and shared via e-mail with all experts. The four investigators were not blinded as they were required to contact the experts to follow-up on replies needing further clarification. The overall process is illustrated in Figure A1.

Figure A1 – Number of PRO symptom terms validated by Delphi round



This flowchart depicts the number of Symptom Terms where a consensus was reached for each round. Only terms where a consensus was not reached were repeated in the following round.

[a] New PRO Symptom Terms - two new symptom terms were developed by experts in Round 2 after revising the terms rejected by the investigators. These were added in Round 3 for importance assessment.

Delphi Round 1

The first round of the Delphi aimed to identify relevant PRO-CTCAE™ Symptom Terms, and collect experts' suggestions on additional symptoms to monitor in the aforementioned population. The 80 symptom terms were grouped according to the categories defined in the PRO-CTCAE™ Item Library Quick Guide (115).

Experts were asked to classify each term as "Relevant", "Not relevant" or "Do not know". A free-text option to add comments to their answers was provided. Consensus was set at 75% agreement, in accordance to the European Society of Medical Oncology's consensus meeting guidelines (116) . If a term was considered not relevant to monitor in patients receiving ICIs by 75% of all experts, it was excluded from the following round.

Experts were also asked to add any additional symptoms not covered by the PRO-CTCAE™ that they deemed relevant for monitoring adverse events in this patient population. Suggested additional symptom terms were assessed by the investigators according to predefined requirements (evidence that the symptom had been observed in the patient population and that it was likely related to ICIs; no redundancy with existing PRO-CTCAE™ terms; clear description of the symptom; and amenable to self-reporting) and submitted to the following round. If a Symptom Term did not meet these criteria, the suggesting expert was approached by e-mail or by phone to clarify what was intended to be addressed. Investigators would draft an assessment to be reviewed separately by the remaining experts in the following round.

Delphi Round 2

In the second round, experts were asked to assess the importance of monitoring symptoms represented by the PRO-CTCAE™ items found relevant in the previous round and new suggested ones. To assess their importance, experts were advised to consider: i) the likelihood that the symptom can be meaningfully self-reported by the patient; ii) the likelihood that the symptom is related to an IrAE and iii) how consequential the resulting IrAE would be to the patient. Importance was rated on a 5-point Likert scale ranging from 1- "not important" to 5 "very important").

Three levels of importance were defined by grouping ratings together: level 1 included ratings 4 ("rather important") and 5 ("very important"); level 2 included rating 2 ("slightly important") and 3 ("moderately important"); and the remainder ("not important") were level 3. Consensus was defined as 75% agreement in one of the three levels of importance.

Furthermore, as part of this second round, experts were asked to review and validate the investigators' decision of rejection or validation of for each of the new symptoms proposed in the previous round. Experts could choose "Agree", "Disagree" or "Undecided". If experts expressed disagreement or were undecided, they were encouraged to provide a rationale for their opinion using a free text field.

Delphi Round 3

The third round of the Delphi shared the same goal and was structurally similar to the second round, featuring the same 5-point Likert scale with an added ability to comment on each of the answers. Experts were able to see the overall results of the previous round as they replied to each question, and were encouraged to express their views on the previous results. The intent was to understand why there was no consensus in certain PRO terms.

Delphi Round 4

The fourth round of the Delphi featured a questionnaire with the same structure as that of round 2 and 3. Experts were invited to a real-time online discussion after they consented to being unmasked to other experts. Experts who were unavailable for the online discussion were given the option to reply to the questionnaire, with the written comments of the live discussion, at a later date.

The live discussion was moderated by the investigators. Each of the participating experts was able to access the same questionnaire, and reply to it at the same time. In addition to expressing their opinions verbally during the live discussion, experts were encouraged to write them down in the questionnaire.

Ethical considerations

Since no medical data were collected, this study is not covered by the Human Research Act and did not require an ethics approval. All experts consented to participate to all expert rounds in written form.

Results

Expert panel

The Delphi process took place between July 2019 to and May 2020. Eleven experts were available and consented to participating in the Delphi by e-mail. All experts participated in rounds one to three and nine experts participated in the final round (n=1 physician and n=1 nurse were unavailable), due to decreased availability during the SARS-CoV-2 pandemic. All experts had training and experience relevant to at least two fields of expertise, as described in Table A1.

Table A1 – Delphi experts' field of expertise

Expert	Fields of expertise			
	Immuno-oncology	Lung cancer	Melanoma	Patient-Reported Outcomes
Oncology Physician 1	✓	✓		
Oncology Physician 2	✓	✓		
Oncology Physician 3	✓		✓	
Oncology Physician 4	✓			✓
Oncology Physician 5	✓		✓	
Oncology Physician 6	✓		✓	✓
Oncology Psychiatrist	✓		✓	✓
Oncology Nurse 1	✓		✓	✓
Oncology Nurse 2	✓	✓	✓	✓
Oncology Nurse 3	✓		✓	
Patient Expert	✓		✓	✓

PRO-CTCAE™ Symptom Terms

In round one, all (n=80) PRO-CTCAE™ Symptom Terms were considered relevant to the target population. With respect to importance to monitor, consensus was reached for 65/80 (81%) of the PRO-CTCAE™ Symptom Terms. Among the Symptom Terms considered rather or very important (n=30), 23% belonged to the gastro-intestinal subgroup, followed by pain (13%), respiratory (10%), cutaneous terms (10%). In the slightly or moderately important category (n=33), 24% of the terms were cutaneous symptoms, followed by gynaecologic/urinary, sexual and miscellaneous terms at 15% each. Two terms were considered "not important". The percentage of agreement by level of importance for each symptom term is presented in Table A2. An infographic listing the terms ordered by level of importance is available for PRO-CTCAE™ Symptom Terms (Figure A2) and for the terms suggested by experts (Figure A3).

Table A2 – Expert agreement (%) on the importance level of PRO-CTCAE™ Symptom Terms (1/2)

Symptom Term	Importance level[a] 1	2	3	Symptom Term	Importance level[a] 1	2	3	Symptom Term	Importance level[a] 1	2	3
Oral Terms											
Dry mouth	56	44	0	Mouth/throat sores	44	56	0	Voice quality changes	0	82	18
Difficulty swallowing	91	0	9	Cracking at the corners of the mouth (cheilosis/cheilitis)	0	56	44	Hoarseness	0	100	0
Gastrointestinal Terms											
Taste changes	9	82	9	Heartburn	44	44	12	Constipation	91	9	0
Decreased appetite	90	0	10	Gas	0	89	11	Diarrhoea	100	0	0
Nausea	90	0	10	Bloating	0	89	11	Abdominal Pain	100	0	0
Vomiting	91	0	9	Hiccups	0	78	22	Faecal incontinence	82	9	9
Respiratory Terms											
Shortness of Breath	100	0	0	Cough	82	18	0	Wheezing	100	0	0
Cardio-circulatory Terms											
Swelling	91	9	0	Heart palpitations	91	9	0				
Cutaneous Terms											
Rash	90	10	0	Hand-foot syndrome	67	33	0	Radiation skin reaction	0	100	0
Skin dryness	0	100	0	Nail loss	0	100	0	Skin darkening	9	82	9
Acne	0	89	11	Nail ridging	0	82	18	Stretch marks	0	56	44
Hair loss	11	78	11	Nail discoloration	0	56	44				
Itching	82	9	9	Sensitivity to sunlight	0	100	0	Hives	82	18	0
Bed/pressure sores	0	22	78								
Neurological Terms											
Numbness & tingling	91	9	0	Dizziness	91	10	0				
Visual/Perceptual Terms											
Blurred vision	91	9	0	Visual floaters	67	33	0	Ringing in ears	44	56	0
Flashing lights	100	0	0	Watery eyes	22	78	0				
Attention/Memory Terms											
Concentration	91	9	0	Memory	82	18	0				
Pain Terms											
General Pain	91	9	0	Muscle pain	91	9	0	Headache	91	9	0
Joint pain	100	0	0								
Sleep/Wake Terms											
Insomnia	56	44	0	Fatigue	82	18	0				
Mood Terms											
Anxious	0	89	11	Discouraged	0	100	0	Sad	0	100	0

Table A2 – Expert agreement (%) on the importance level of PRO-CTCAE™ Symptom Term (2/2)

Symptom Term	Importance level[a] 1	2	3	Symptom Term	Importance level[a] 1	2	3	Symptom Term	Importance level[a] 1	2	3
Gynaecologic/Urinary Terms											
Irregular periods/vaginal bleeding	9	82	9	Vaginal dryness	0	100	0	Urinary frequency	78	22	0
Missed expected menstrual period	11	89	0	Painful urination	22	78	0	Change in usual urine colour	0	33	67
Vaginal discharge	10	80	10	Urinary urgency	56	44	0	Urinary incontinence	11	33	56
Sexual Terms											
Achieve and maintain erection	11	78	11	Decreased libido	0	89	11	Unable to have orgasm	0	82	18
Ejaculation	0	89	11	Delayed orgasm	0	80	20	Pain with sexual intercourse	22	11	67
Miscellaneous Terms											
Breast swelling and tenderness	0	100	0	Increased sweating	18	82	0	Nosebleed	67	33	0
Bruising	0	100	0	Decreased sweating	9	82	9	Pain and swelling at injection site	0	78	22
Chills	89	11	0	Hot flashes	89	0	11	Body odour	0	11	89

[a] Importance Level:

- Level 1 – includes Symptom Terms considered “rather important” or “very important”
- Level 2 – includes Symptom Terms considered “slightly important” or “moderately important”
- Level 3 – includes Symptom Terms considered “not important”

Oral, cutaneous and gynaecologic/urinary terms, each make up 20% of the 15 PRO-CTCAE™ Symptom Terms where no consensus on importance was achieved. For the gynaecologic/urinary terms in particular, experts expressed difficulty in relating the occurrence of these symptoms to immune-checkpoint blockade. They also noted that several terms in this subgroup and in the sexual terms subgroup were likely underreported in the literature, as they may not often be discussed with patients.

New PRO symptom terms

In round one, experts suggested 60 new symptom terms of which six were rejected by the investigators for the following round, with unanimous agreement from the experts. These included five symptom terms that could not be meaningfully captured by patient self-report ("Arrythmia", "Arthritis", "Asthenia", "Cellulitis" and "Sudden increase in caries") and one ("Symptom-related Fatigue") that was considered difficult to differentiate from the existing PRO-CTCAE™ Symptom Term "Fatigue". To address "Arthritis" and "Cellulitis", experts suggested and validated two new terms: "Swelling of the joints" and "Heat or burning sensation in an area of the body", respectively. Thus, 56 new symptom terms were rated on importance to monitor.

Expert consensus was reached in 47 of the 56 new symptom terms. Of these, 62% (n=29) were considered "rather" or "very important", 36% (n=17) were classed as "slightly" or "moderately important", and one term "not important". The number of items per Delphi round is illustrated in Figure A1. Expert consensus for each term is described in Table A3.

Consensus on importance was not achieved in nine (14%) of the new terms. These were among the most discussed. Abdominal cramps was among the terms where experts considered that complete contextual information was crucial to determine its importance. Specifically, it would be considered increasingly important as other symptoms were manifested, like diarrhoea or abdominal pain, or if confounding variables like menstrual pain were present.

Other terms like "Infusion-related reaction" were considered either too broad to be meaningfully assessed by patient self-report or were more amenable to direct observation by clinicians during infusion. Experts also noted that some of the suggested PRO terms, like "over-alertness", were more likely related to the corticosteroid treatment for the IrAEs than a symptom of ICI toxicity. Additional comments from experts on symptom terms can be found in Appendix 1.

Figure A2 - Priority PRO-CTCAE™ Symptom Terms to monitor In cancer patients treated with ICIs

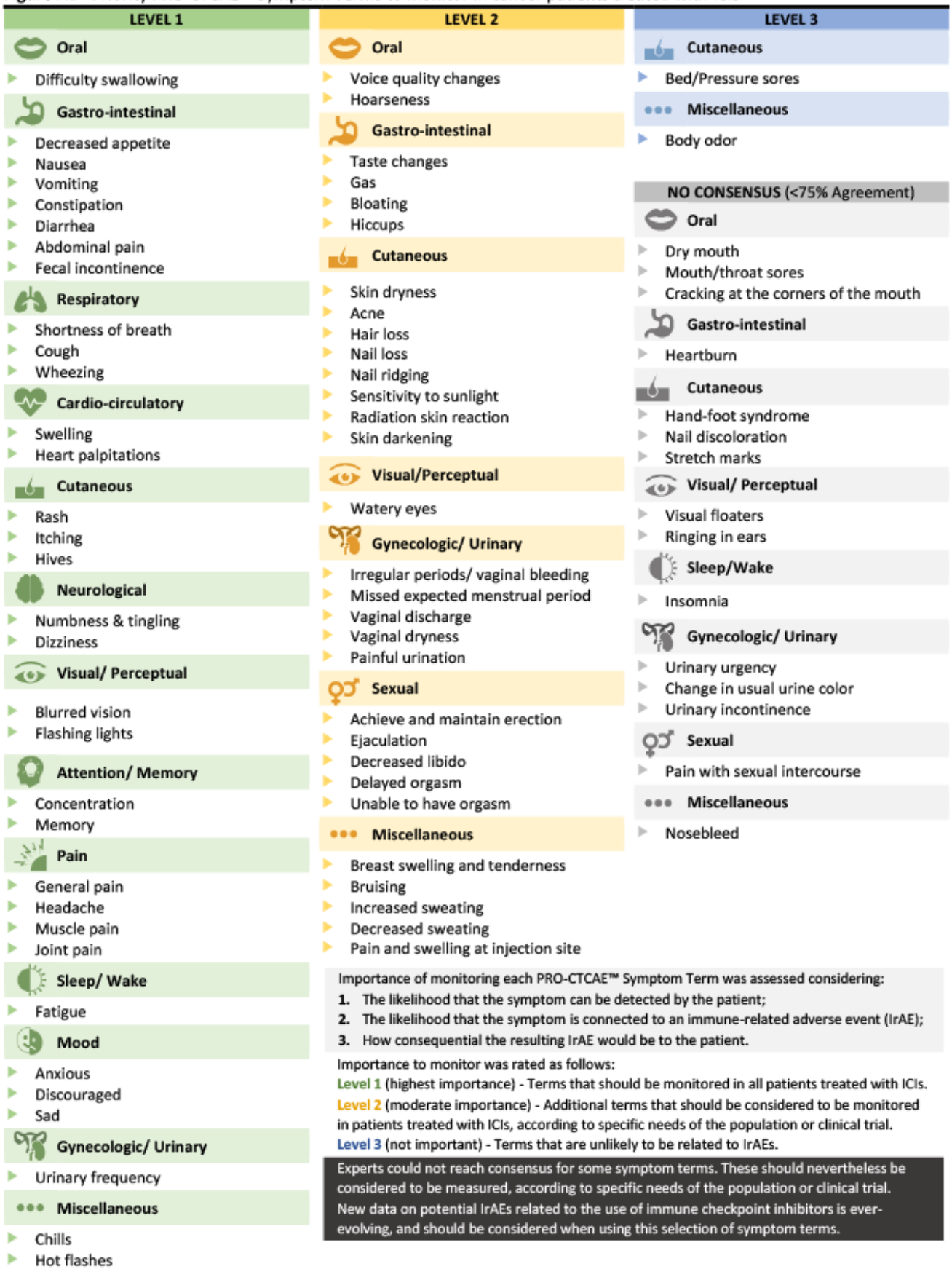
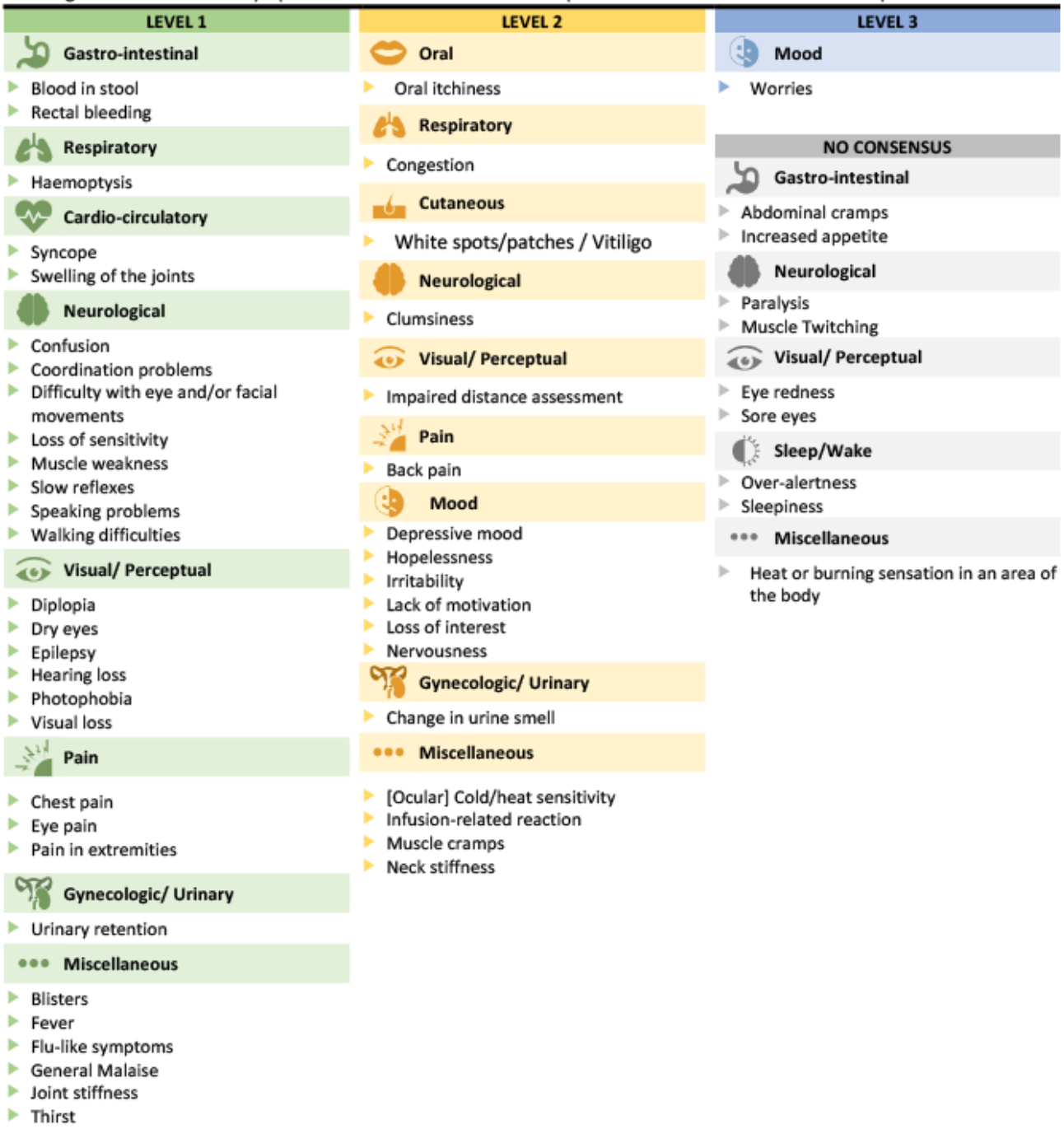


Figure A3 - Additional symptom terms to monitor in cancer patients treated with immune checkpoint inhibitors



The Symptom Terms listed above were suggested by the group of experts and require further development before being formulated as items in patient-reported outcomes measures, and used in clinical research and clinical practice. Importance of monitoring each symptom term was assessed considering:

1. The likelihood that the symptom can be detected by the patient;
2. The likelihood that the symptom is connected to an immune-related adverse event (IrAE);
3. How consequential the resulting IrAE would be to the patient.

Importance to monitor was rated as follows:

Level 1 (highest importance) - Terms that should be monitored in all patients treated with ICIs.

Level 2 (moderate importance) - Additional terms that should be considered to be monitored in patients treated with ICIs, according to specific needs of the population or clinical trial.

Level 3 (not important) - Terms that are unlikely to be related to IrAEs.

Experts could not reach consensus for some symptom terms. These should nevertheless be considered to be measured, according to specific needs of the population or clinical trial. New data on potential IrAEs related to the use of immune checkpoint inhibitors is ever-evolving, and should be considered when using this selection of symptom terms.

Table A3 – Agreement (%) on the importance level of PRO symptom terms suggest by experts

Symptom Term	Importance level[a] 1	2	3	Symptom Term	Importance level[a] 1	2	3
Abdominal cramps	67	33	0	Irritability	0	89	11
Back pain	0	100	0	Joint stiffness	82	18	0
Blisters	78	22	0	Lack of motivation	0	89	11
Blood in stool	82	18	0	Photophobia	100	0	0
Change in urine smell	0	80	20	Loss of interest	10	80	10
Chest pain	82	18	0	Loss of sensitivity	80	20	0
Clumsiness	0	100	0	Muscle weakness	91	9	0
[Ocular] Cold/heat sensitivity	11	78	11	Neck stiffness	18	82	0
Confusion	90	10	0	Nervousness	0	100	0
Congestion	0	89	11	Oral itchiness	0	100	0
Coordination problems	91	9	0	Over-alertness	44	22	33
Muscle cramps	0	89	11	Pain in extremities	78	22	0
Depressive mood	11	89	0	Paralysis	50	50	0
Difficulty with eye and/or facial movements	80	10	10	Rectal bleeding	80	10	10
Diplopia	80	10	10	Sleepiness	44	56	0
Dry eyes	89	11	0	Slow reflexes	82	18	0
Epilepsy	82	0	18	Sore eyes	56	44	0
Eye pain	82	18	0	Speaking problems	91	9	0
Eye redness	33	67	0	Syncope	100	0	0
Fever	90	9	0	Thirst	100	0	0
Flu-like symptoms	78	22	0	Muscle Twitching	44	33	22
General Malaise	91	9	0	Walking difficulties	80	10	10
Hearing loss	82	18	0	Urinary retention	100	0	0
Hemoptysis	91	9	0	Visual loss	80	20	0
Hopelessness	11	89	0	Worries	0	22	78
Impaired distance assessment	11	89	0	Swelling of the joints	100	0	0
Increased appetite	20	80	0	Heat or burning sensation in an area of the body	67	22	11
Infusion-related reaction	0	67	33	White spots/patches / Vitiligo	11	89	0

[a] Importance Level:
Level 1 – includes Symptom Terms considered “rather important” or “very important”
Level 2 – includes Symptom Terms considered “slightly important” or “moderately important”
Level 3 – includes Symptom Terms considered “not important”
Experts’ comments on these symptom terms can be found in Appendix 1.

Discussion

Experts reached consensus on the salience of all (n=80) terms in the PRO-CTCAE™ Item Library for surveillance for symptomatic adverse events in cancer patients being treated with ICIs. A consensus was also reached on the importance of these terms, with 30 terms endorsed as very important by 75% or more of the Delphi panellists. Among the new terms suggested by experts, 56 new PRO terms were proposed as potentially salient in capturing side effects of ICIs, and consensus was reached that 45 of these terms are candidates for item development to expand the PRO-CTCAE™ Item Library for patients treated with ICI therapy.
Several caveats should be considered in interpreting these study findings. While the international expert panel reflected diversity of professional experiences and disciplinary perspectives, the panel was small and drawn predominantly from Switzerland (five out of 11 experts). Expert roles were not equally represented, with only one patient advocate participating. While differences in expertise may increase the challenge of reaching consensus, there were no clear associations between expert background and deviation from consensus, though this can be due to the small sample size. Our findings should be replicated

and extended with a larger, more balanced and more geographically diverse panel, including patients that are receiving or have received immune checkpoint inhibitors. We nevertheless maintain that diversity in expertise enriched the discussion, bringing together multiple perspectives and decreasing the likelihood of an authority bias.

The number of additional symptom terms experts identified for inclusion extends results of a prior systematic review (13) and provides preliminary evidence that the current PRO-CTCAE™ Item Library should be expanded in order to capture the full spectrum of symptomatic toxicities associated with ICIs. The toxicity profile of ICIs has been described as heterogeneous, pleomorphic, and more variable than that of radiotherapy, chemotherapy, molecularly targeted and combination regimens (15). This challenged experts in the interpretation of what existing PROs represent - symptomatic adverse events experienced in association with ICI treatment can be indicators of off-target effects, rather than being related to anti-tumour immunity. The current PRO-CTCAE™ version was conceived with symptoms related to chemotherapy, radiotherapy, and targeted-therapies in mind, which may explain how more complex IrAEs elude existing symptom terms (56). It is important to consider how the PRO-CTCAE™ is derived from the constantly evolving CTCAE, which has been updated to reflect some IrAEs. Some of the newly suggested PRO items do in fact reflect CTCAE terms included in version 5.0, such as photophobia. While updates to the current PRO-CTCAE™ item library are inbound, use of some of the existing symptom terms will remain challenging in the context of ICIs. This is illustrated by some unexpected results on specific symptoms, such as the unanimous assessment of “radiation skin reaction” as level 2 importance. Experts argued such a symptom could signal a broader autoimmune reaction. While there have been reports of ICI-induced radiation recall dermatitis (117–119), it can be questioned if this item would retain its original meaning to patients who were not treated with radiotherapy. Experts mentioned that this effect could be potentially captured by other existing PRO-CTCAE™ cutaneous symptom terms. This argues for the need of further qualitative research on PRO-CTCAE™ Symptom Terms in patients treated with ICIs, not only to further characterize them in different contexts, but also to guide item selection. Another issue evoked by experts is the development of symptom clusters that can alter the significance of individual symptoms, such as hoarseness within the context of ICI-triggered myasthenia gravis. Understanding of symptom clusters in ICI therapy is still developing, rendering the individual interpretation of some items ambiguous. This may have contributed to the unanimous agreement on level 2 importance to monitor hoarseness, as experts require more data to form a more complete opinion. Selection processes of PRO-CTCAE™ items should consider symptom-clusters, as more data on this phenomenon becomes available.

A large item library can pose important feasibility challenges, as patient burden is increased. The defined levels of importance may inform new ways to present patients with a large library of symptom terms, particularly when paired with computer adaptive questionnaires and artificial intelligence. Level 1 terms could be used as a standard starting point, and terms from other levels could be called upon according to potential symptom associations or clusters. As item libraries are expanded to account for the diversity of ICI-related symptomatic IrAEs, these tools will become essential to balance patient burden and the exhaustiveness of symptom-related PROMs.

The heterogeneity of the adverse effects that may be experienced by patients receiving ICI therapy makes self-reporting of symptomatic IrAEs complex, as illustrated by new terms such as “depressive mood”, “impaired distance assessment” and “walking difficulties”. Experts’ comments on these and other terms can be found in Appendix 1. While these examples require further refinement to better clarify what they intend to assess, they raise questions perpetrating to the use of highly specific symptom terms as the most comprehensive approach to best reflect the patient experience regarding IrAEs. Experts were challenged to identify symptomatic components of clinical syndromes (e.g. pneumonitis, myasthenia gravis, iritis) that may have aspects that can be captured through a PRO (e.g. cough, changes in voice quality, visual disturbance) but which can only be identified precisely by inclusion of clinician adverse event reports or information derived from diagnostic or laboratory testing.

Some new suggested PRO terms could be interpreted as redundant when considering existing PRO-CTCAE™ Symptom Terms, as is the case between “Sad” (PRO-CTCAE™) and the expert suggestion “Depressive mood”, or “anxious” (PRO-CTCAE™) and “worries” (expert suggestion). This further illustrates the complexity of symptoms, as experts appeared to have different representations of the same term. While these results provide some support for the content validity of the PRO CTCAE™ and resulted in a preliminary set of salient symptomatic adverse events related to the use of ICIs, broader international agreement and further validation, including patient involvement is needed to continue to validate our initial findings. Further mixed methods studies examining the experiences of adverse effects of ICI are needed to develop and test additional PRO-CTCAE™ items and to identify efficient, interpretable, and meaningful approaches to profile symptomatic adverse effects of ICI therapies.

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COMPETING INTERESTS

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Phase 2: Development of an ePRO-based Model of Care

Following the creation of the PROM, the next phase of the project aimed to insert the PROM within a nurse-led model of care to monitor and manage symptoms related to ICIs, remotely. During development, few studies had reported on the use of ePROs specifically to follow-up patients treated with ICIs. Iivanainen and colleagues (75) used an electronic platform from Kaiku Health Inc, which included a web-based application used by patients to reply to symptom and HRQoL questionnaires. In their review, patients with cancer treated with immunotherapy were followed-up for up to 24 weeks since treatment began. Compliance with the ePRO-based follow-up was demonstrated to be high, with most patients having replied to at least one questionnaire within the first 12 weeks. The questionnaire would automatically grade symptoms according to a severity algorithm, which in itself graded the symptom according to the NCI-CTAE v. 4.03. The system was reportedly attached to an urgency algorithm that activated the medical team, but data concerning that algorithm was not analyzed. It is the gap between what ePRO applications assess and the means through which the healthcare system provides a response that remains unclear in most studies to date (69,70,75). The second article of this thesis details the creation of the model of care that would be used in the IePRO randomized controlled trial, detailing the mechanisms through which symptom trigger a response from the clinical team, and how their feedback is conveyed to the patient.

Article 2: Development of an ehealth-enhanced model of care for the monitoring and management of immune-related adverse events in patients treated with immune-checkpoint inhibitors

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Abstract:

Purpose: The use of electronic patient-reported outcomes (ePRO) data in routine care have been tied to direct patient benefits such as improved quality of care and symptom control and even overall survival. The modes of action behind such benefits are seldom described in detail. Here we describe the development of a model of care leveraging ePRO data to monitor and manage symptoms of patients treated with immune checkpoint inhibitors.
Methods: Development was split into four stages: 1) identification of an underlying theoretical framework, (2) the selection of an ePRO measure (ePROM) (3), the adaptation of an electronic application to collect ePRO data, and (4) the description of an ePRO-oriented workflow. The model of care is currently evaluated in a bicentric longitudinal randomized controlled phase II trial, the IePRO study.
Results: The IePRO model of care is grounded in the eHealth-enhanced Chronic Care Model. Patients are prompted to report symptoms using an electronic mobile application. Triage nurses are alerted, review the reported symptoms, and contact patients in case of a new or worsening symptom. Nurses use the UKONS 24-hour telephone triage tool to issue patient management recommendations to the oncology team. Adapted care coordinating procedures facilitate team collaboration and provide patients with timely feedback.
Conclusion: This report clarifies how components of care are created and modified to leverage ePRO to enhance care. The model describes a workflow that enables care teams to be proactive and provide patients with timely, multidisciplinary support to manage symptoms.

Keywords: patient-reported outcomes, model of care, immune-related adverse events, remote symptom management, self-management support
Funding: The present study was funded by the ISREC Foundation and Kaiku Health Ltd.

Introduction

Immune checkpoint inhibitors (ICI) have become part of the standard of treatment for an expanding range of cancer types (120). Despite having shown a lower toxicity profile compared to other treatments, immune-related adverse events (IrAE) caused by ICI can nevertheless be severe and potentially fatal (17,121). The likelihood of experiencing an IrAE is influenced by treatment modality: between 40 and 75% of patients treated with a single ICI experience an IrAE (any grade), with 10 to 30% experiencing severe events (grade≥3) (19,121). About 95% of patients experience at least one IrAE when treated with combined ICI, and nearly 60% of patients experience at least one severe IrAE (122).
These IrAE are notably heterogeneous, occasionally resembling disease progression and mimicking auto-immune conditions (19). Severe IrAE can be persistent or occur several months into and beyond treatment (2,3,29), thus adding on to the already considerable acute and chronic symptom burden patients experience.
Patient education and symptom self-management, particularly self-monitoring, contribute to more timely detection of IrAEs, better short-term outcomes for patients, andlower incidence of chronic symptoms (123,124). However, patients treated with ICI may not be sufficiently

supported in that domain (5,26). Mild symptoms are often under-recognized and under-reported by patients and clinicians, though they may be indicative of more serious developing conditions impacting quality of life (8,125). Close and frequent communication between patients and healthcare providers is thus essential in preventing severe IrAE. Information flyers and telephone follow-up targeting symptoms related to ICI treatment have been used to support patients and anticipate the delivery of care (22). However, evidence-based procedures to monitor and manage them in a real-world setting are still lacking (15,126).

The use of patient-reported outcomes measures (PROM) has been shown to improve symptom detection, monitoring and management by empowering patients to convey their perception of symptoms to healthcare providers, while also providing valuable treatment safety and tolerability data (8,26,48,62). Electronic PROM (ePROM) can play a role in shared clinical decision support by influencing treatment decisions and improving the scope and efficiency of patient-provider communication (72,127,128). Remote real-time symptom reporting, and monitoring facilitated by the use of ePROM may lead to more accurate insights into patients' health status than delayed self-reports (67).

Studies involving the use of electronic PRO (ePRO) data in oncology reported a decrease in hospitalization rates and emergency department visits, with favourable outcomes on quality of life, perceived self-efficacy and overall survival (8,11). How these studies' interventions mobilized and interacted with existing care structures and procedures to produce beneficial outcomes is seldom described in detail (129). Some interventions used ePRO to assess symptoms remotely as complementary clinical decision support to modify treatment or to refer patients to emergency or acute care services, among others (8). To our knowledge, no studies targeting the remote management of symptoms of patients treated with ICI have detailed the conception and integration of ePRO-based care models, within existing care delivery structures.

In this report, we describe the development of a model of care, that leverages ePRO data to monitor and manage symptoms in patients treated with ICI, in an outpatient care setting. This model is currently being tested in a randomized controlled phase II trial, the IePRO trial, at two Swiss university hospitals (ClinicalTrials.gov Identifier: NCT05530187).

Towards the development of an ePRO-based model of care

Development of the IePRO model of care took place between November 2020 and November 2021. A team of four physicians and five nurses of the participating institutions' oncology departments, and one patient-representative collaborated in the creation of its core components and their integration in the existing workflows of each hospital. All members had previous experience in collecting and interpreting PRO data in clinical oncology trials. Two nurses have published research on PROMs aimed towards patients treated with ICI (13). The patient-representative was identified by screening Swiss and French patient advocacy groups related to oncology. A brief in-person interview allowed to assess their knowledge of ICIs and their side-effects, expertise in using PROs and experience in collaborating in clinical trials.

This ePRO-based model of care was developed in four stages: [1] identification of an underlying theoretical framework, [2] selection of an ePROM, [3] adaptation of an electronic mobile application to collect ePRO data, and [4] ePRO-oriented workflow and clinical roles.

1. Theoretical framework

As ICI-related symptoms may add to the symptom burden of patients, effective management of these symptoms requires a holistic approach. To reflect upon and address the complexity and resources required for symptom management, we grounded the development of this intervention in the eHealth Enhanced Chronic Care Model (eCCM) (101), which is itself an extension of the Chronic Care Model (CCM) (130,131).

The major components of the CCM, community resources and health systems, are complemented by eCommunity and eHealth in the eCCM (101).eHealth includes the digital tools and resources available to patients that complement those provided by the healthcare system. Online communities and health-related social networks constitute the eCommunity, which supports patient engagement and activation for self-management.

The major components of the eCCM encapsulate five smaller interdependent components: Self-Management Support (SMS), Clinical Decision Support (CDS), Delivery System Design (DSD), Clinical Information Systems (CIS) and eHealth Education (eHE). These are brought together to ensure informed and activated patients interact with prepared and proactive practice teams, leading to satisfying encounters and improved outcomes (101). They are described in further detail in Figure B1.

We address each of these smaller components and clarify their role in achieving productive interactions between patients and care providers as we describe the following development phases of the IePRO model.

2. Selection of an ePROM

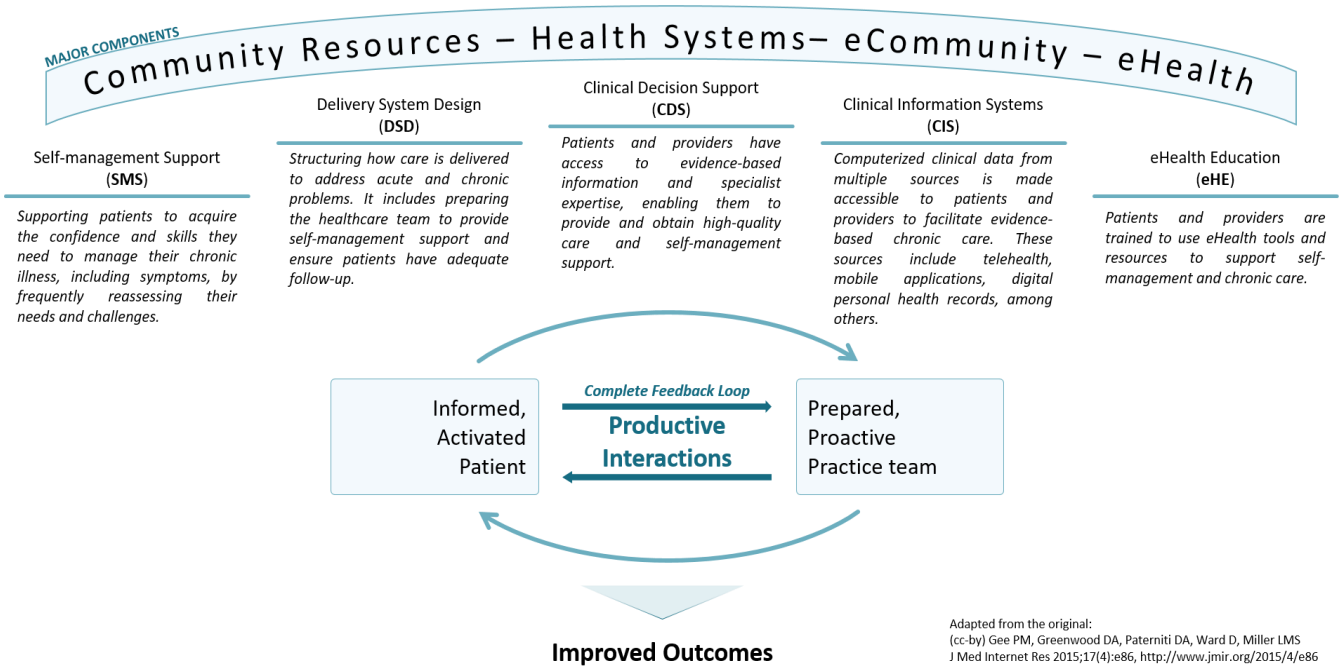

Figure B1 *The eHealth-enhanced Chronic Care Model (eCCM), adapted from: Gee PM, Greenwood DA, Paterniti DA, Ward D, Miller LMS. The eHealth Enhanced Chronic Care Model: A Theory Derivation Approach. Journal of Medical Internet Research 2015;17:e86. https://doi.org/10.2196/jmir.4067. The original is licensed under a Creative Commons Attribution license (CC-BY)*

Active discussions between the model development team allowed to identify an ePROM of particular interest, to both clinicians and patients. The patient-representative mobilized her patient-advocacy network to collect and convey general perceptions on existing PROMs, such as their perceived advantages and disadvantages to assess symptomatic ICI-related toxicity, via e-mail. The PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) item library was considered comprehensive and suitably flexible, measuring a broad spectrum of symptoms (13,56). Using the results of a previous Delphi study, we identified a set of 37 priority PRO-CTCAE™ items for routine symptom monitoring in this patient population, which compose the IePRO trial's weekly symptom questionnaire (132).

Patients participate in the IePRO trial for the first six months of their ICI treatment. Because the majority of IrAEs occur within the first three to four months of treatment (2), active symptoms are re-assessed daily for the first three months, using a modified recall period of 24 hours, between weekly questionnaires. In addition, patients can add any of the 80 PRO-CTCAE™ items to the daily and weekly assessments.

3. Adaptation of an electronic mobile application

The main goal in using an ePRO application is to enhance *self-management support* (SMS). As an eCCM component, SMS includes the provision of tools and resources for patients to acquire the skills and confidence to manage and monitor their health condition (133). We adapted an application developed by Kaiku Health Ltd, where the developed ePROM was

integrated. Studies using similar iterations versions of the Kaiku Health App have reported high agreement across patients and providers on its ease of use, high levels of satisfaction and relevance for clinical practice (75,76).
The application sends patients reminders to fill out the ePROM at the previously mentioned time points, to facilitate data collection (10). It displays all previous replies to any questionnaire, facilitating self-care and self-monitoring tasks (10). In addition, at the end of each symptom questionnaire, a summary portraying symptom evolution is displayed (Figure B2).

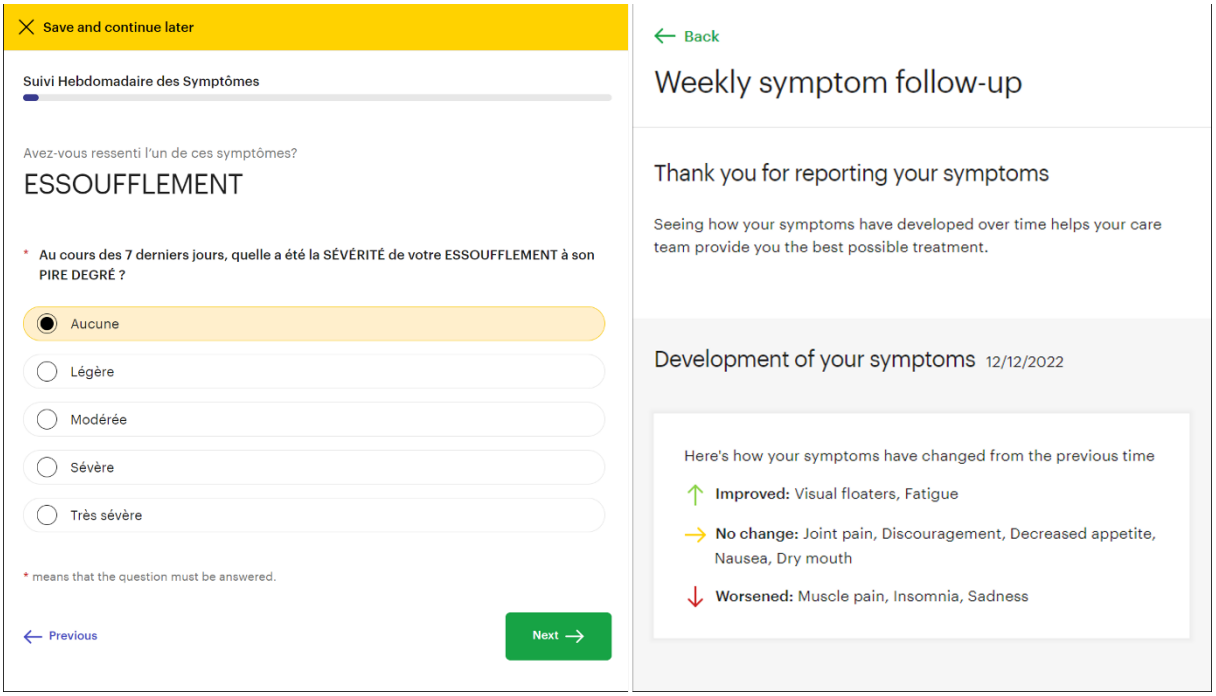

Figure B2 *ePRO application – Questionnaire interface (left) and Patient Feedback View (right)*

Since these features may increase symptom awareness, guidance to perceive their detection as empowering to manage and prevent complications is required, as they can also be perceived as signs of deterioration or disease progression, decreasing perceived self-efficacy (134).
To enable patients to navigate the complete item bank of the PRO-CTCAE™, a symptom selection screen was developed in collaboration with patients from the oncology department and the patient-representative, through a card-sorting exercise. Results were used to adapt the screen presented to patients allowing adding symptoms to be monitored.
Integration of ePRO data into *Clinical Information Systems* (CIS) like the patient's electronic health record (EHR) is a desired outcome, as it can decrease the technological burden and enhance accessibility of data (6,8,133). The IePRO trial is conducted in two university hospitals operating different EHR platforms. An initial assessment for readiness to implement PRO data, concluded that the CIS could not be modified to directly integrate ePRO data in similar ways. Nurses are thus prompted to access the application directly via e-mail when patients report new symptoms.

4. <u>Development of an ePRO-oriented workflow and clinical roles</u>

In the eCCM, delivery system design (DSD) relates to how care is coordinated and delivered across the network of health resources. The participating oncology departments treat a similar range of tumor types and number of patients, with similar provider team compositions. Physicians and nurses involved in direct patient care revealed service-level and provider-level barriers such as the time required to navigate, collect and process PRO data, the integration or lack thereof within the EHR, and internal communication pathways to ensure the continuity of care (93,135). These barriers were included in the development of the model of care.

We hereafter describe how patients are engaged, the triage process and the triage nurse role, and the nurse-physician coordination to provide care. An overview of the model is featured in Figure B3, and components of the eCCM represented in the IePRO model are summarized in table B1.

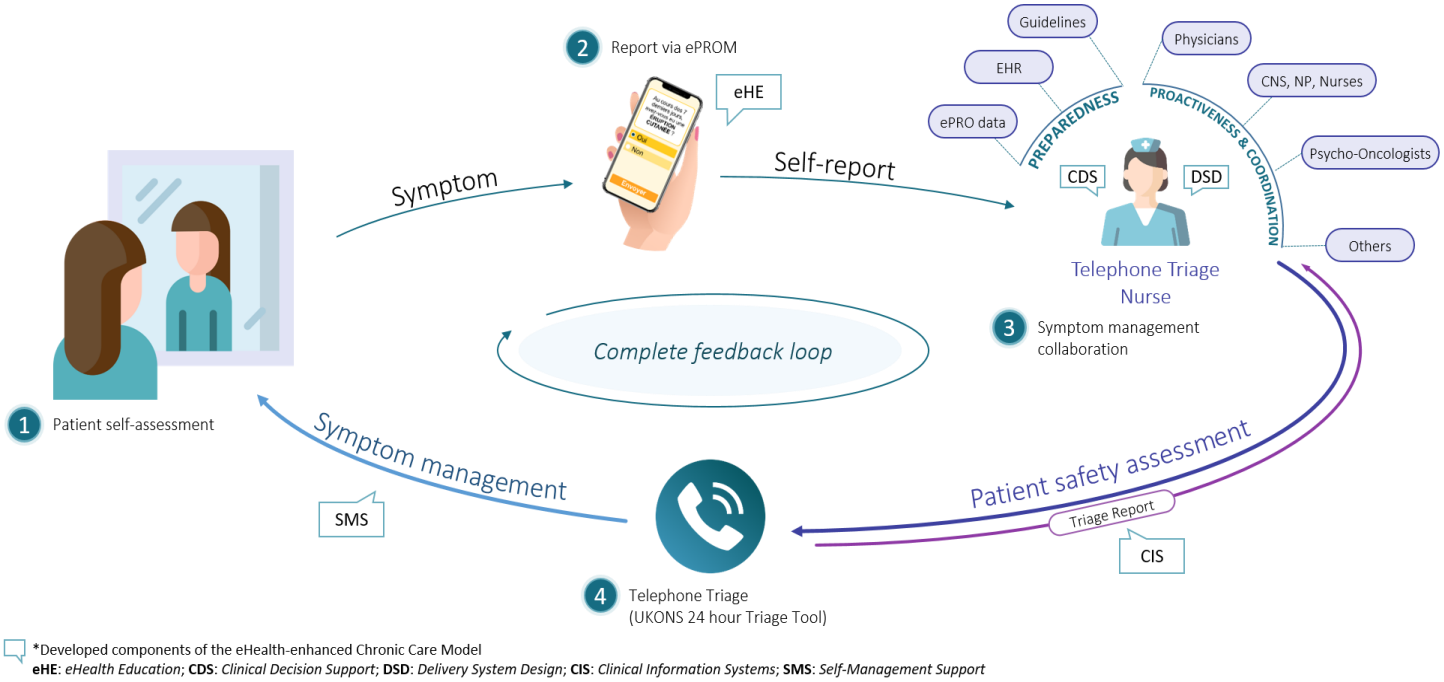

Figure B3 *Overview of the IePRO Model of Care: patients perform self-assessment (1) and declare potential symptoms using the symptom ePROM in the electronic application (2). Telephone triage nurses review PRO data and coordinate with the oncology team preemptively when necessary (3), and contact patients by telephone using a standardized triage process (4)*

Patient engagement:

As in the eCCM, informed and activated patients are key to create productive interactions with the healthcare providers (101). Patients receive information on treatment side effects from clinical nurse specialists (CNS), physicians and nurses. Triage nurses present the electronic application to the patient, provide a set up guide (Appendix 2) and assist in its configuration.
Patients fill-out the 37-item ePROM within the first week of ICI treatment by logging in to the online or mobile (smartphone) version of the application. They are prompted to complete subsequent daily and/or weekly questionnaires via an e-mail reminder or push notifications. Patients are made aware their answers in the ePROM will be reviewed by a team of triage nurses on weekdays between 8 and 12 pm. As part of the standard of care, patients are nevertheless encouraged to contact their oncology team directly in case any of any symptoms self-perceived as a cause of immediate concern.

Telephone triage nurses and triage process:

Telephone triage nurses are the main vector of communication between the patient and the clinical oncology team in the IePRO model. This role was developed and reviewed with oncology physicians, nurses and CNS. For some oncology subspecialties, the CNS provide sporadic telephone consultations for the most vulnerable patients, therefore clarifying the role of triage nurses was essential to avoid confusion among providers and patients. While triage nurses work as gatekeepers, helping patients access and appropriate level of care, CNS are

a resource to ensure evidence-based symptom management, and provide highly standardized care.

Table B1. Components of the eCCM in the IePRO model of care

Components of the eCCM	Related element of the IePRO model of care	Description
Self-Management Support (SMS)	Electronic mobile application	The electronic mobile application containing the ePROM: • communicates patient-reported data in real time; • engages patients with automated reminders to encourage self-assessment of symptoms; • provides patients with a chart portraying the evolution of their symptoms over time.
	Telephone Triage process	SMS is provided to patients by the triage nurses using the French translation of the UKONS 24-hour Triage Tool, and available internal and international guidelines in symptom and IrAE management.
Delivery System Design (DSD)	Redesigned care coordination	• Triage nurses call patients in the event of a new or worsening symptom and administer self-care and self-management support via telephone call. • Symptoms are relayed to the oncology care team via e-mail or telephone call, according to UKONS 24-hour triage tool recommendations. • The triage process is documented in the patient's EHR. • Follow-up measures put in place are communicated with the broader team using e-mail.
Clinical Decision Support (CDS)	Telephone triage algorithm	The UKONS 24-hour Triage Tool algorithm outputs actionable recommendations for self-care and self-monitoring of symptoms, with clear clinical management guidance including if an in-person assessment is recommended.
	Internal symptom management guidelines	Both sites have internal evidence-based symptom management guidelines, based on international guidelines that support clinicians when reviewing the recommendations issued from the triage algorithm.
Clinical Information Systems (CIS)	Telephone triage report	EHR notes are standardized according to the contents of the triage log form of the UKONS 24-hour triage tool, enabling access to triage reports by all healthcare providers.
eHealth Education (eHE)	Patient eHealth education	Patients are guided in the use of the electronic application and the extent of its functionality. And introductory information flyer is provided, and further education is provided in-person or over the phone by nurses.
	Provider eHealth education	Providers were trained in the use of the UKONS 24-hour telephone triage tool and on the use of the ePROM application to monitor patient-reported symptoms.

Triage nurses were trained to use the United Kingdom Oncology Nursing Society (UKONS) 24-hour Triage Tool (136). It was translated and validated in French, in collaboration with the

UKONS, for use in the IePRO trial. Two members of the nursing team in one hospital received online training directly from UKONS, who trained the remaining three nurses.
The tool standardizes remote symptom assessment and provides clear guidance on remote symptom management. Triage procedures are triggered when triage nurses detect a new or worsening symptom in the ePRO application. The triage algorithm outputs three types of alerts according to symptom severity: [1] green alerts are issued for mild and stable symptoms where self-management support is recommended, [2] amber alerts represent symptoms that may increase or decrease in severity and thus require a new assessment within 24 hours, and [3] red alerts that are issued when symptoms are moderate-to-severe, and in-person assessment is recommended. Nurses log triage procedures in the EHR using an electronic version of the tool's triage log form. Since CIS integration was not possible, triage nurses alert physicians, CNS and nurse practitioners of triaged symptoms and of their recommendations by sending a daily summary of all calls.
In the event of a green alert, triage nurses provide self-care guidance, and the oncology team is notified via the e-mail summary. When an amber alert is issued, the oncology team is immediately contacted via e-mail to validate the triage nurses' assessment and determine if any additional care should be provided. More than one amber alert or at least one red alert triggers triage nurses to call the patient's oncology physician to seek their specific recommendations and call the patient back to convey the latter. As this model of care is complementary to the standard of care, outside of the triage nurses' operating schedule, standard procedures apply.
As part of the *eHealth education* (eHE) component in the IePRO model, triage nurses were trained extensively with the ePROM application between April and November 2021. It presents nurses with a visual and numerical representation of the reported symptoms (Figure B4) that reflect a combination of PRO-CTCAE™ attributes (frequency, severity, interference, amount, presence/absence). As outlined in the eCCM, access to this type of remote patient-reported symptom data, enables the care team to be proactive and prepared for triage calls in advance (101).

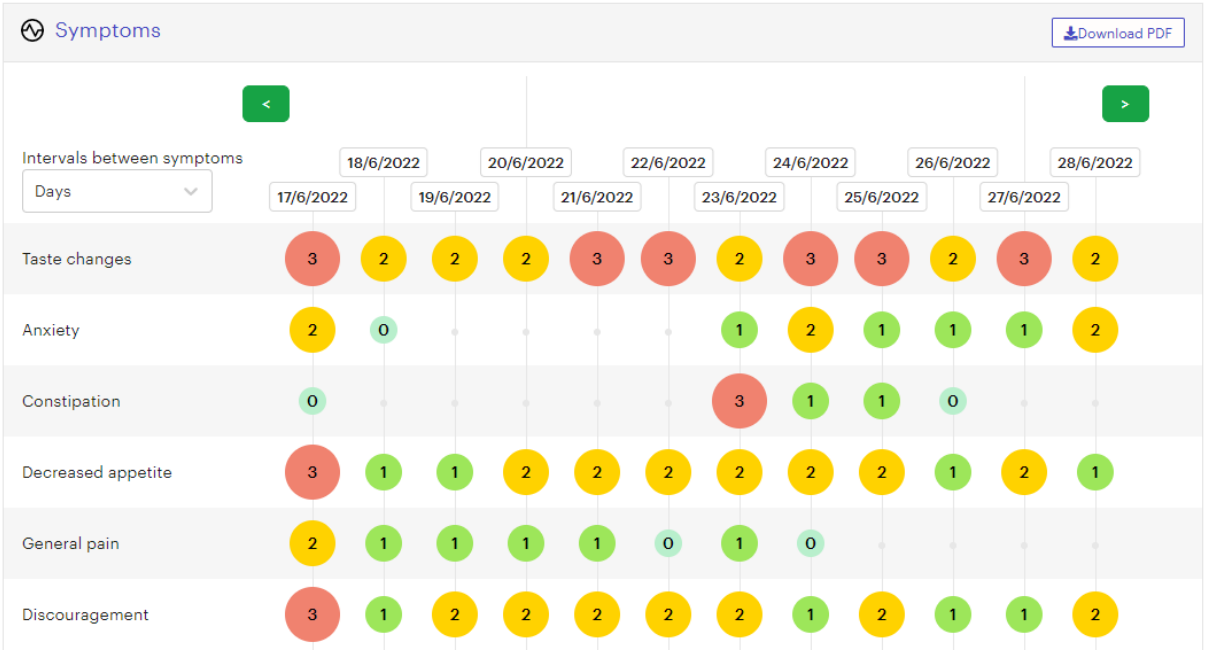

Figure B4 *ePRO app – Triage Nurse's View*

Role of physicians and other healthcare professionals:
Physicians are the primary collaborators with the triage nurses and are responsible for reviewing triage reports. When their assessment differs from the nurse's, the physician is to contact them and the patient to provide their recommendation. Triage nurses and physicians may also forward requests to other professionals, such as psycho-oncologists and

physiotherapists. An automated e-mail reminder to follow-up on and assess previously reported symptoms is sent in the morning of each in-person patient visit.

Assessing usability of the ePRO application and acceptability of the model of care

Assessment of the usability of the ePRO application and the acceptability of the model of care from the patient's perspective takes place up to two weeks after study discontinuation. The mobile application's usability and the model of care's acceptability is assessed through semi-structured interviews with patients. Based on the mHealth App Usability Questionnaire (MAUQ) by Zhou et al. (137), interviews guides have been developed. Items were grouped by their scope and nine open-ended questions were formulated by the research team, available as an online supplement (Appendix 3).
A semi-structured patient interview guide to assess the acceptability of the model of care was created by the research team, using the definition of acceptability by Sekhon et al (138). Questions were derived from the seven constructs of acceptability: "affective attitude", "burden", "ethicality", "intervention coherence", "opportunity costs", "perceived effectiveness" and "self-efficacy" (Appendix 4).
To assess the intervention's acceptability from the healthcare provider's perspective, an interview guide was developed based on the Consolidated Framework for Implementation Research (CFIR) (139). It includes questions addressing the model of care's characteristics, the outer and inner settings, the characteristics of the individuals using the model, and the process of implementation (Appendix 5). Acceptability of the model of care will be assessed up to two weeks after the end of the trial.

Discussion

The IePRO model of care supports the detection and timely management of symptoms of patients treated with ICI. It represents a pragmatic research approach to the use of ePRO data in the context of two university hospitals that retain minor differences in resources and infrastructure, standard operating procedures, and care culture. It describes workflow changes that exist in parallel to usual care, complementing clinical activity and outlining a closed feedback loop between patients and care providers based on electronic monitoring of PRO data.
We consider this model of care to have notable strengths. Due to the potential of symptomatic IrAEs to become chronic conditions, there is a need for forward-looking transformations in care delivery that focus on both short and long-term care (29). The model ensures that pre-existing and new symptoms are equally taken into account, and that the full range of resources are mobilized to manage them. Contrasting with other trials using PRO-CTCAE™ items (69,140), it accommodates the use of the full item library, lending itself to the heterogeneous toxicity of ICI. Alternating weekly fixed-length and adaptive daily questionnaires enables the detection of quick and sudden fluctuations in symptom severity, while potentially 49tandardiz patient burden. Guided by the eCCM, the model aligns with recommendations from previous studies and with recent guidelines for implementing PRO in routine care, despite preceding them (8,77,91,129). As part of a clinical trial, some of the eCCM's components were not developed in this iteration, namely the Community and eCommunity. Integration of these components in the future should be considered to broaden the support for patient self-management.
The model ensures patients receive tailored feedback every weekday they complete a questionnaire, without the requirement of a hospital visit. This closed feedback loop attempts to value the time patients invest in symptom reporting and encourage patients to continue self-monitoring.
Some challenges relating to future implementation, patient engagement, the triage nurse role, and the clinical and technological burden remain. There are no CNS and nurse practitioners available in one of the sites, and thus the triage nurses are likely to more often strictly rely on physician collaboration to manage symptoms. In the same site, physician teams are less differentiated across tumour types, which may simplify the flow of information with nurses. E-mail reports for mild to moderate symptoms may not facilitate as timely of an intervention as

direct telephone or face-to-face contact. However, the care teams agreed it would be the most effective way to request multidisciplinary support and update all relevant parties on patient status. This may increase the burden on triage nurses to obtain a timely reply. An integrated system in the EHR could potentially save time and provide a clearer transfer of responsibility across the oncology team.

The allocation of dedicated resources is recommended for successful implementation of PRO data in routine care, as there is the possibility of increased clinical burden (11,128,141). Training in interpreting PRO data was focused on triage nurses, as time and technical constraints prevented deeper integration with the broader oncology team. Universal access to ePRO data would decrease friction, despite being more resource-intensive in its initial deployment [48]. Currently, triage nurses require more time to process data and create an accessible output for the oncology team. There is a clear risk of incomplete or inaccurate information between the triage reports and the self-reported patient data, which constitutes the most significant limitations of this model. Our preliminary experiences in the IePRO trial suggest clear benefits in training all providers to use PRO data, and in integrating it directly in the EHR to minimise the technological burden. Weekly meetings between the nursing triage staff and the PIs of the IePRO trial, who are involved in direct patient care, facilitate discussions on matters related to the workflow and patient and provider burden. These include optimizing how pending issues can be handled more efficiently and derive consensus on how to manage unanticipated situations.

Features of electronic applications clearly play a role in patient engagement and compliance, with integrated communication with care providers and other patients being among the most desirable functionalities, which is included in the Kaiku Health app (10). The development team considered patients could feel compelled to use the messaging service instead of contacting the medical team via telephone. Given the limited activity period of the nursing triage team, there was considerable risk that some messages would not be addressed in a timely manner, prompting the decision to deactivate this functionality. To accommodate those features in the IePRO model, the flow of communication between patient and providers would need to be revised. The impact on the burden of clinical teams would also need to be considered, as it may result in more frequent prompts to intervene than a system where the decision to initiate contact lies with the provider. Other eHealth interventions have used automated written feedback (10), which could be integrated in this model as well. Ongoing data collection from patient interviews may highlight the strengths and limitations of the application in its current version. Patient feedback will be addressed in future publications.

Data collection concerning the acceptability of the model of care from the provider's perspective will take place after the trial and will be analysed and disseminated in a later stage of the project. It is unclear how patients will perceive the novel role of the triage nurse, and how it may interfere in their relationship with other providers like the CNS. International guidelines for managing IrAEs often require skills, such as prescribing medication and diagnostic tests that most nurses in Switzerland cannot autonomously enact. While close collaboration with physicians in symptom management is essential, the lack of autonomy increases the complexity of the workflow and introduces additional points of failure. Further standardization of practice and continued investment in advanced nursing practice roles may further optimize care delivery and improve the model. Because IrAE management guidelines do not primarily focus on self-management support, some variability in what interventions are put in place by triage nurses is likely. More comprehensive self-management support coverage in those guidelines would empower nurses and patients and further clarify how beneficial outcomes can be achieved (126).

The development of this model benefited from the collaboration with a patient-representative to assess the tools and PROMs used in its different components. This triggered deeper discussions with the care team, relating to symptom management and administrative challenges. As patients' acceptability of the model of care is assessed, we believe future iterations also stand to gain significantly from deeper patient and public involvement.

Conclusion

The described based model of care provides insight into the complexity of using ePRO data to facilitate potential benefits for both patients and care providers. It attempts to draw a closed feedback loop between patients and providers, to ensure symptoms related to ICI treatments and beyond are monitored and managed by a proactive, prepared provider team.
The IePRO model is not intended as a blueprint for other institutions with that goal. Rather, it is an example of the complexity of such an endeavor, by reworking several components of care in the attempt to generate beneficial outcomes to patients. Under that light, we believe it furthers the discussion around PRO implementation by exposing some of the pragmatic difficulties and compromises that researcher and clinicians may have to manage.

DECLARATIONS

Ethics approval and consent to participate
Not applicable.

Availability of data and materials
Not applicable.

COMPETING INTERESTS

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AUTHOR CONTRIBUTIONS:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by André Manuel da Silva Lopes, Sara Colomer-Lahiguera and Manuela Eicher. The first draft of the manuscript was written by André Manuel da Silva Lopes and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Phase 3: IePRO Study Protocol

Following the development of the model of care, we developed the IePRO study protocol. This study is a randomized controlled trial, planned to take place between November 2021 and November 2023. Recruitment was halted in April 2023 following recruitment challenges. The most significant challenge was changes in treatment guidelines concerning ICIs, where a combination of ICIs and other cancer treatments became the most frequent recommendation. The SARS-CoV-2 pandemic also contributed to lower availability of participants for the study. As of writing, the study is still concluding, which prevents final data from being included in this study. Following the article detailing the development of the protocol, we present the results of

a case study of one of the participants that concluded the trial, to exemplify and comment on the nature of the data collected.

Article 3: Testing a Model of Care for Patients on Immune Checkpoint Inhibitors Based on Electronic Patient-Reported Outcomes: Protocol for a Randomized Phase II Controlled Trial

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Author Contributions:

M.E. and O.M. conceived the study's original concept and design. A.D.S.L., S.C.-L., C.D., V.A.L., S.L., N.M.A., G.S.-B. and A.A., later contributed to refining the design, instruments and methods. The first draft of the manuscript was written by A.D.S.L. and all authors commented on previous versions of the manuscript. Analyses will be conducted by the study biostatistician M.A.C., and A.D.S.L., C.D., S.G. M.E. is the sponsor-representative of the Lausanne University Hospital for this study. All authors read and approved the final manuscript.

Abstract

Background: Management of severe symptomatic immune-related adverse events (IrAEs) related to immune checkpoint inhibitors (ICIs) can be facilitated by timely detection. As patients face a heterogeneous set of symptoms outside the clinical setting, remotely monitoring and assessing symptoms by using patient-reported outcomes (PROs) may result in shorter delays between symptom onset and clinician detection.

Objective: We assess the effect of a model of care for remote patient monitoring and symptom management based on PRO data on the time to detection of symptomatic IrAEs from symptom onset. The secondary objectives are to assess its effects on the time between symptomatic IrAE detection and intervention, IrAE grade (severity), health-related quality of life, self-efficacy, and overall survival at 6 months.

Methods: For this study, 198 patients with cancer receiving systemic treatment comprising ICIs exclusively will be recruited from 2 Swiss university hospitals. Patients are randomized (1:1) to a digital model of care (intervention) or usual care (control group). Patients are enrolled for 6 months, and they use an electronic app to complete weekly Functional Assessment of Cancer Therapy-General questionnaire and PROMIS (PROs Measurement Information System) Self-Efficacy to Manage Symptoms questionnaires. The intervention patient group completes a standard set of 37 items in a weekly PROs version of the Common Terminology

Criteria for Adverse Events (PRO-CTCAE) questionnaire, and active symptoms are reassessed daily for the first 3 months by using a modified 24-hour recall period. Patients can add items from the full PRO-CTCAE item library to their questionnaire. Nurses call patients in the event of new or worsening symptoms and manage them by using a standardized triage algorithm based on the United Kingdom Oncology Nursing Society 24-hour triage tool. This algorithm provides guidance on deciding if patients should receive in-person care, if monitoring should be increased, or if self-management education should be reinforced.

Results: The Institut Suisse de Recherche Expérimentale sur le Cancer Foundation and Kaiku Health Ltd funded this study. Active recruitment began since November 2021 and is projected to conclude in November 2023. Trial results are expected to be published in the first quarter of 2024 and will be disseminated through publications submitted at international scientific conferences.

Conclusions: This trial is among the first trials to use PRO data to directly influence routine care of patients treated with ICIs and addresses some limitations in previous studies. This trial collects a wider spectrum of self-reported symptom data daily. There are some methodological limitations brought by changes in evolving treatment standards for patients with cancer. This trial's results could entail further academic discussions on the challenges of diagnosing and managing symptoms associated with treatment remotely by providing further insights into the burden symptoms represent to patients and highlight the complexity of care procedures involved in managing symptomatic IrAEs.

Trial Registration:
ClinicalTrials.gov NCT05530187; https://www.clinicaltrials.gov/study/NCT05530187

International Registered Report Identifier (IRRID): DERR1-10.2196/48386

Introduction

Immune checkpoint inhibitors (ICIs) have increasingly become part of the standard treatment for multiple cancer types and stages, with the main benefits including superior overall survival rates (17,90,105,142–152). Although ICIs are generally considered as well-tolerated, they may trigger immune-related adverse events (IrAEs), which can be severe and result in debilitating or fatal outcomes (19,153). Treatment modality, cancer type, and patient characteristics appear to influence the likelihood of symptomatic IrAEs, which generally occur in 40%-80% of patients (17,19). Combinations of ICI agents generally result in a higher incidence and severity of symptoms, with 55% of IrAEs being severe (grade 3 or higher) (19,121). Even though the incidence of IrAEs appears to be positively correlated with superior objective response rates to ICIs, the occurrence of severe events may lower overall survival rates (90,154). It is posited that solid tumors that exhibit high mutational burden elicit a stronger immune response, which may trigger more IrAEs (16,18). Limited evidence suggests that skin, respiratory, renal, and hepatic IrAEs also appear to be correlated with melanoma, lung cancer, kidney cancer, and hepatocellular cancers, respectively, suggesting that different tumor types may increase the likelihood of specific IrAEs (21,32,155). In addition, genetic risk factors such as allelic variations of *HLA-B* and mutations in the *TMEM162* gene are correlated with higher or lower likelihood of IrAEs (156). Recent studies have highlighted that the potential chronicity of IrAEs could further burden patients and contribute to lower overall quality of life (4,29,153,157). The timing of detection and intervention of IrAEs appears to play a key role in limiting their progression and outcome (17,19,123).

Although most IrAEs occur within the first 3-6 months of the start of treatment, some may develop after a year even when treatment has been discontinued (3,5,19). In addition to the uncertainty of when they may manifest, IrAEs are heterogenous in their symptomatic presentation and are usually related to the affected tissue or organ (19). Therefore, patients need to be ready to engage in self-care activities to self-monitor and self-manage symptoms

they confront outside of the clinical environment during the multiple weeks between treatments (26).

As clinicians rely on patient recall to assess symptomatic adverse events, the time between visits and the clinician's own judgement may inadvertently contribute to an underestimation of their severity, frequency, and burden (8,67). Collecting patient-reported outcomes (PROs) has become a standard to accurately describe symptomatic adverse events by avoiding some of the biases of clinician reporting, thus contributing evidence on safety, tolerability, and efficacy of cancer treatments (11,158). Recent studies show that PRO data collected electronically can enable more timely interventions to support patients in managing symptoms, resulting in improvements in overall survival, health-related quality of life (HRQoL), symptom control, and patients' perceived self-efficacy (11,69,71). Improvements and smaller declines in HRQoL have been observed when actionable PRO data are available to clinicians (159). PROs can improve communication between patients and health care professionals by increasing the scope of symptoms addressed and how often they are discussed (11).

Clinical trials using electronic PROs (ePROs) in remote symptom management have noted how these data enable interventions that prevent complications related to cancer treatment, leading to similar or lower rates of hospital admissions and emergency care admissions than the current standard of care (69,71). These models of care generally interpret ePRO symptom data that nurses use to provide personalized remote symptom management support to patients or that activate automated feedback through custom algorithms (10,69,71). These interventions have seldom been detailed on the procedures put in place to monitor and manage ePRO symptom data. We thus hypothesized that a structured and standardized ePRO-based model of care, including remote monitoring and symptom management, using real-time data may reduce the time to detection of symptomatic IrAEs. This would, in turn, facilitate timely intervention and limit worsening of patients' HRQoL and perceived self-efficacy to manage their conditions. This randomized controlled trial (RCT), the IePRO (IrAEs monitoring through electronic PROs) trial, aims to verify the effect of an ePRO-based model of care on the time to detection of symptomatic IrAEs.

Methods

Project Context

The RCT described in this protocol is the third phase of the IePRO project, which began in the year 2020. The first phase focused on the development of a PRO measure based on the PRO version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (56). The development of this measure has been detailed in a previously published Delphi study (132). The second phase was concerned with the development of the ePRO-based model of care being tested in the RCT (160). This is a 2-arm RCT taking place in the ambulatory care oncology units of 2 university hospitals in French-speaking Switzerland since 2 years. Its overall aim is to compare an ePRO-based model of care that enables remote monitoring and management of symptoms to usual care for patients with cancer receiving ICIs exclusively for up to 6 months.

Study Population

Setting

Patients are being recruited in the Department of Oncology of the 2 university hospitals. They receive treatment and have same-day follow-up appointments at the hospitals' outpatient clinics. Both sites include tumor type–oriented clinical oncology teams with treatment strategies dictated by multidisciplinary tumor boards.

Eligibility Criteria

Participants fulfilling all the following inclusion criteria are eligible for this study: [1] patients 18 years old or older, [2] diagnosed with cancer, [3] starting or restarting systemic single- or dual-agent ICI monotherapy in neoadjuvant, adjuvant, consolidation, or palliative settings, and [4]

providing informed consent as documented by the signature on the informed consent form. The presence of any of the following exclusion criteria will lead to participant exclusion: [1] patients self-declaring not being able to use the electronic app and complete the questionnaire in French, [2] patients with any psychological, familial, or sociological condition and linguistic limitation, potentially hampering compliance with the study protocol requirements or follow-up procedures, [3] patients restarting ICI therapy who have previously participated in this study, [4] patients with cognitive impairment, as declared in the patient record, and [5] patients participating in other interventional clinical studies.

Screening and Enrollment

Patients are identified by the local principal investigator and a team of sub investigators. Potentially eligible patients are approached after clinician appointments or during treatment. They are given the informed consent form (Appendix 6), and a telephone call with a subinvestigator is scheduled within the following week to answer any questions or concerns. Patients are given at least 48 hours to consider participating in the study. Figure C1 shows the flowchart for patient enrollment in this study. Informed consent forms are collected during the patients' next hospital appointment. Patients can be enrolled in the study up to a week after ICI treatment has started. When eligible patients refuse to participate, their reason for refusal is anonymously recorded with their consent.

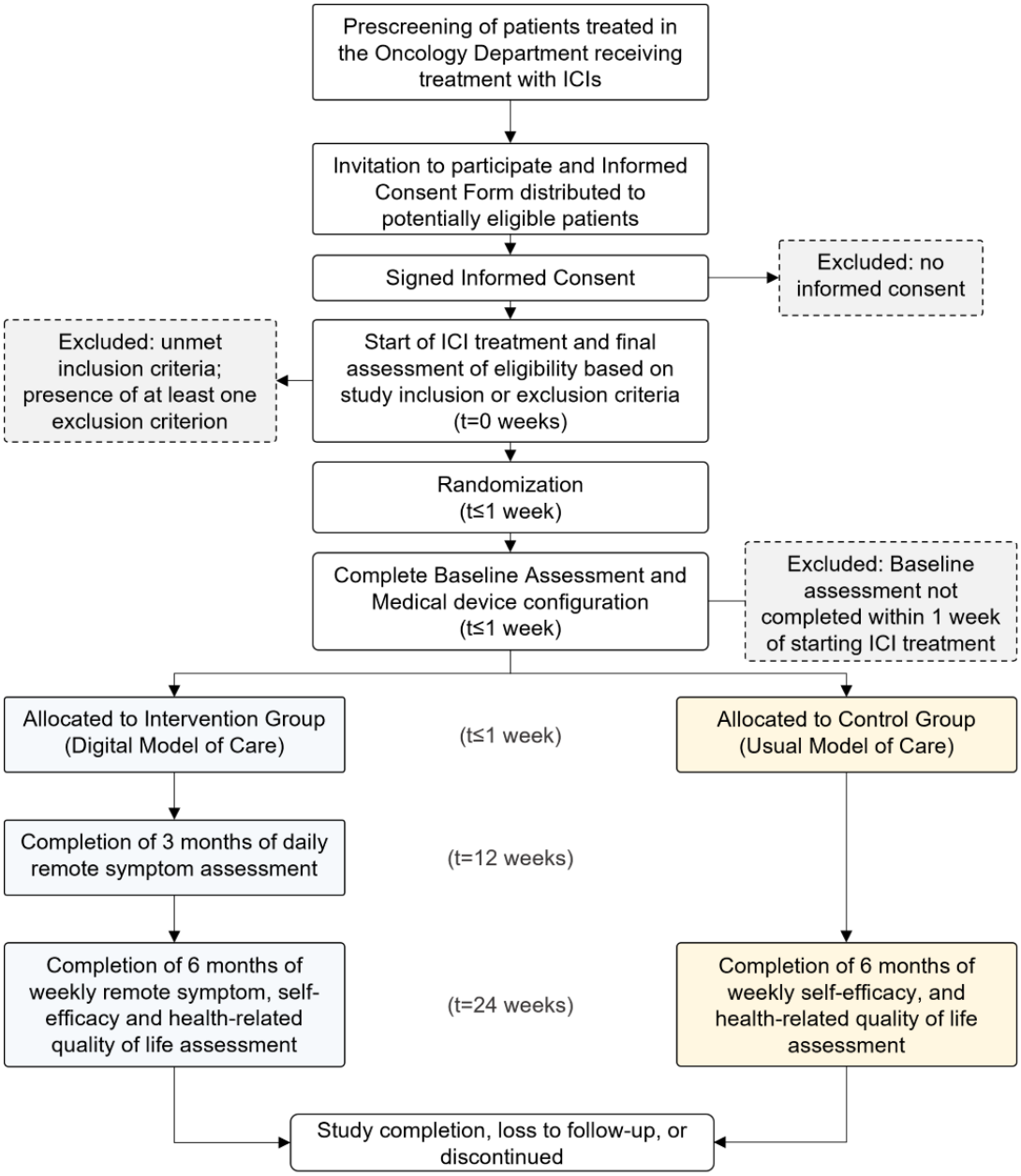

Figure C1*. Flowchart of the enrollment of the patients in this study. ICI: immune checkpoint inhibitor.*

Study Design

Prior to randomization, subinvestigators collect demographic, medical history, and active treatment data from eligible consenting patients. Participants are randomized by subinvestigators using a web-based REDCap (Research Electronic Data Capture) form (version 12.4.21) (161). The form has a randomization table (1 per site) using permuted block 1:1 randomization (block size of 4), independently prepared by the study biostatistician. Initially, the IePRO RCT was open to patients with melanoma and patients with lung cancer exclusively, and randomization was stratified by cancer type. Due to challenges in recruitment and following a protocol amendment in April 2022, this study was open to patients with all cancer types, and the stratification criteria were dropped. Blinding was not possible due to the nature of the intervention. Patients are informed that they will be randomly allocated to 1 of the 2 models of care: the standard model (control group) or the digital model (intervention group).

The informed consent form and support documentation for the electronic app used to deliver the PRO questionnaires include these same conventions to further mitigate the adverse effects of the lack of blinding toward participants. Data collection instructions and reminders sent to clinicians caring for participants do not indicate which group the participant belongs to.
Patients in both groups obtain access to an electronic mobile app, which contains weekly questionnaires for HRQoL and self-efficacy to manage symptoms. An information sheet detailing how to navigate the app is also provided. Nurses and subinvestigators are available to assist patients in installing the app, registering and signing into an account, and replying to the baseline questionnaires in-person or over the phone. Patients in the intervention group have access to a symptoms questionnaire that is part of the intervention being tested. Automated reminders via emails or push notifications are sent to patients when a new questionnaire is available. Patients in both groups have the same number of scheduled clinician appointments—usually the same day and frequency of the ICI treatment—and are followed up for up to 6 months of ICI treatment.

Intervention
The intervention of this RCT consists of a complementary model of care that uses ePROs to facilitate remote symptom management (160). This model is represented in Figure C2. Patients in the intervention arm have access to a weekly PRO-CTCAE questionnaire through an electronic mobile app. Patients receive an email invitation to access the app and an information sheet explaining its interface. Once patients access the app, they are required to complete a questionnaire of predefined symptoms. During the first 3 months of the intervention, active symptoms are reassessed daily. When replying to a questionnaire, patients can add any other item of the full PRO-CTCAE item library, which are automatically added to the following daily or weekly questionnaires as well (see Appendix 7). The rapid and sudden onset of IrAE and ICI's interference with pre-existing conditions and symptoms drove the decision to collect symptom data daily (17,123). Due to the potential burden this sustained frequency could represent to patients, this was restricted to the first 3 months of the intervention. Patient replies are available in real time to the triage nurses. Two triage nurses at each site are notified via email when patients submit new replies or report severe symptoms, and they contact patients

by telephone in the event of new or worsening symptoms. The nurses review patients' answers every working day from 8 AM to noon. Outside of these hours, usual care procedures apply.

Triage nurses perform an assessment of the reported symptoms with the United Kingdom Oncology Nursing Society 24-hour triage tool (136), which are graded on a CTCAE-based scale (162). If patients report symptoms not covered by the PRO-CTCAE questionnaire, they are also addressed during these calls. The combination of symptoms may result in different types of color-coded alerts that tie into different recommendations. Mild symptoms generally result in green alerts, where self-care and self-monitoring instructions are warranted. Moderate symptoms requiring remote follow-up within the next 24 hours correspond to an amber alert. The presence of 2 or more amber alerts or of severe symptoms results in a red alert, where

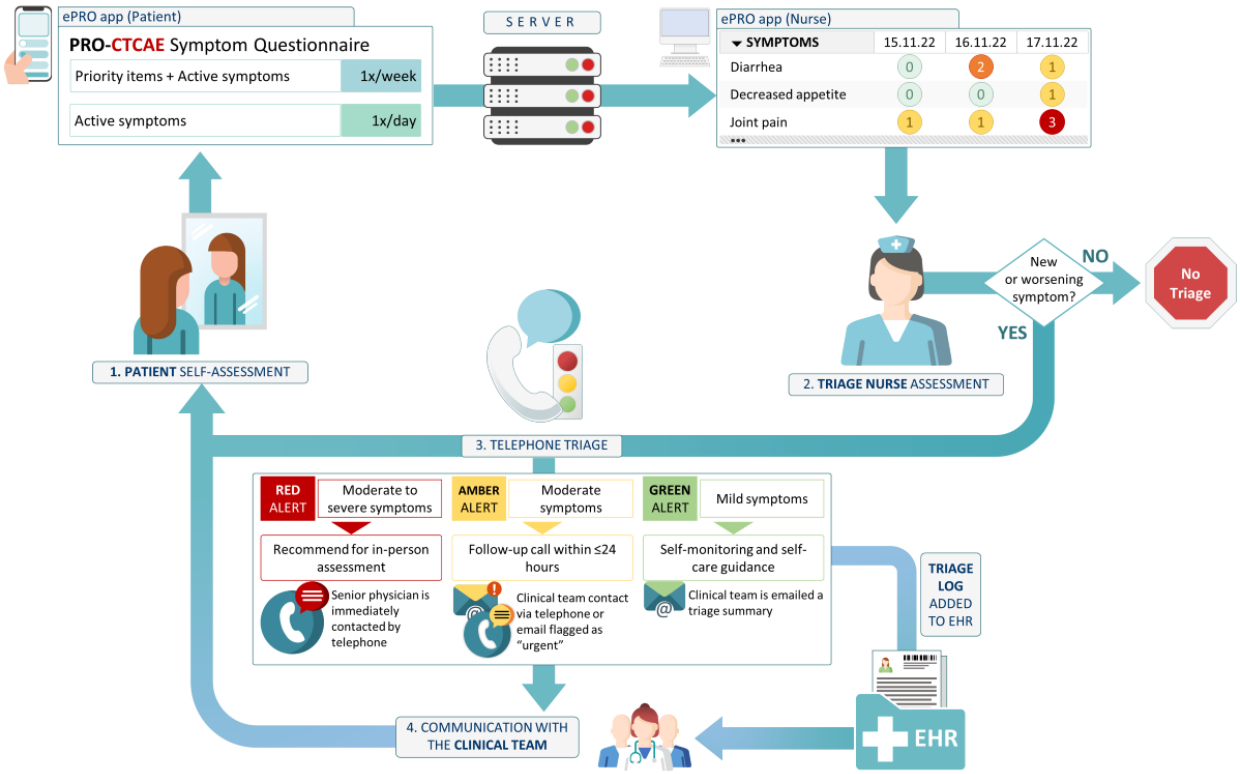

***Figure C2**. IePRO (immune-related adverse events monitoring through electronic patient-reported outcomes) Model of Care: (1) When prompted by the mobile app, patients reply to a Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events symptom questionnaire via their own computer or mobile device. Data collected through the questionnaire are stored in a server controlled by the study sites. (2) Triage nurses are notified when patients have declared symptoms. (3) In the event of new or worsening symptoms, nurses initiate a telephone triage call with the patient. (4) Using the United Kingdom Oncology Nursing Society 24-hour triage tool, nurses determine the adequate course of action according to symptom severity and communicate the outcome of their assessments with the clinical team. The triage nurse's detailed assessment is recorded in a triage log stored in the electronic health record. EHR: electronic health record; ePRO: electronic patient-reported outcome; PRO-CTCAE: Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events.*

urgent in-person assessment is recommended. Triage nurses communicate with physicians via email or telephone according to the type of alert. A triage log detailing the symptom assessment, recommendations to the clinical team, and the actions taken to manage patient care is added to the electronic health record (EHR).

Patients are informed that this model of care is complementary to the usual care model. They are instructed by the triage nurses and subinvestigators in the clinical team that in the event of a symptom that causes them any level of concern and would lead them to seek medical assistance, they must contact their reference clinician or the on-call oncologist as usual. It is also clarified that the likelihood of being called by the triage nurse should never delay them from seeking medical assistance. In this sense, patients are reminded of these procedures at every telephone interaction with the triage nurses.

Electronic App (Medical Device)

This study is categorized as a clinical trial with medical device of risk category A1. It uses a web-based and mobile CE-marked app (Kaiku Health app) containing the PRO measures. The app is classed as a medical device that allows patients to submit their answers and access previous replies. Patients receive a summary of the reported symptoms detailing which of those improved, remained stable, or worsened. The app's security features were assessed and validated by the participating hospitals' information technology departments. Web-based and mobile versions of the app are identical in content and functionality. Patient data collected through the medical device are encrypted at rest and in transit and are subject to regular backups. Security updates are ensured by the app developer (Elekta AB). Two-factor authentication is activated for all patients.

Study Objectives and Outcomes

Primary Objective and Primary Outcome

The primary objective of the IePRO RCT is to compare the effect of an ePRO-based model of care to the current standard model of care on the delay between symptomatic IrAE onset and its detection by health care providers in patients with cancer treated with ICIs. The ePRO-based model of care complements the standard model of care with remote symptom monitoring via ePROs and remote symptom management via telephone triage calls done by oncology nurses. The primary outcome is the time-to-detection of IrAEs, as evidenced by a statistically significantly lower length of time when compared to that in usual care. Time to detection is the difference expressed in days between the IrAE detection date by the clinical team and the associated symptom's onset date according to the patient's self-report.

Secondary Objectives and Secondary Outcomes

The secondary objectives of this trial include assessing the effect of the ePRO-based model of care on the following secondary outcomes: [1] the delay between symptom onset and deployment of pharmacological interventions to manage symptomatic IrAEs by a statistically significant shorter or longer average time delay, [2] the type and amount of pharmacological interventions to manage symptomatic IrAEs by a statistically significant lower average dose, [3] the average maximum symptomatic IrAE grade by a statistically lower or higher average score, [4] the HRQoL through a statistically significant higher or lower overall score of the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire (163), [5] the perceived self-efficacy to manage symptoms through a statistically significant higher or lower score of the PROMIS (PRO Measurement Information System) Self-Efficacy for Managing Chronic Conditions–Managing Symptoms (short form 8a) (164), [6] overall survival at 6 months plotted using Kaplan-Meier estimates, using routine data collected in the EHR, and [7] description of the symptomatic IrAEs experienced by patients by type and grade according to version 5.0 of the National Cancer Institute's CTCAE (109). Remote symptom management processes recorded by nurses will be described using [1] patient-reported symptoms triggering remote symptom management procedures using the composite grading algorithm for the PRO-CTCAE questionnaire (165) and [2] the type of issued triage alerts following triage procedures according to the United Kingdom Oncology Nursing Society 24-hour triage tool (136), and associated symptoms reported using the PRO-CTCAE questionnaire.

Exploratory Objectives

As exploratory objectives, the RCT will also describe the following in the intervention group: [1] symptoms reported via the PRO-CTCAE questionnaire that suggested the need for in-person intervention and patients received the intervention (true positives), [2] symptoms reported via the PRO-CTCAE questionnaire that suggested the need for in-person intervention but patients did not receive the intervention (false positives), [3] type of interventions required and provided for symptoms as reported in the triage log and the EHR, [4] symptoms reported via the PRO-CTCAE questionnaire that require an intervention beyond remote symptom management, [5] usability of the electronic app used to collect PRO symptom data and acceptability of the ePRO-based model of care, assessed through semistructured patient

interviews, and [6] acceptability of the ePRO-based model of care assessed via semistructured individual interviews and focus groups with clinical nurse specialists, nurses, and physicians.

Sample Size Calculation

A sample of 29 health records of previously treated patients with melanoma who experienced IrAEs was used to estimate the required sample size. Patients with lung cancer were not considered for this calculation due to the lack of accessibility to symptomatic IrAE data in that population. Only records where the symptom onset was reported were included for this sample size calculation. In that record sample, the time interval between symptom onset and clinician detection of symptomatic IrAEs was estimated at 4.43 days, with an SD of 3.65 days. A 2-sample *t* test with a statistical power of 90% and significance level set at .05 determined that 138 participants would be required to detect a 2-day difference, assuming the same SD of 3.65 days. Given that similar studies have reported an attrition rate of 30%, the target sample size was adjusted to 198 patients (7,69).

Data Collection Methods

Demographic data and data relating to symptomatic IrAEs and their management for both control and intervention groups are collected through EHR review of the clinical oncologist's follow-up notes at each scheduled appointment with participants. Data from the EHR are recorded in REDCap electronic case report forms hosted in the server of the study sponsor's Clinical Research Center (166). PRO data are collected through the Kaiku Health electronic app, which contains 3 questionnaires. The questionnaires were selected by the study's subinvestigator team, including a patient advocate (GS-B), by discussing matters of burden and of pertinence of the collected data to patients, and what data were actionable for the model of care.

HRQoL data are collected via version 4 of FACT-G questionnaire, translated in French (163,167). The questionnaire targets 4 domains: physical well-being, social or family well-being, emotional well-being, and functional well-being. Recall period, instrument scaling, scoring, and methods to handle missing data do not differ from the official administration and scoring guidelines (168). The self-efficacy for managing symptoms is assessed weekly using the 8-item short-form French version of the PROMIS Self-Efficacy for Managing Chronic Conditions–Manage Symptoms measure (164). Instrument scaling, scoring, and missing data handling also do not differ from the official scoring manual (169).

Symptom data in the intervention group are collected using a weekly PRO-CTCAE that includes symptom terms categorized as of the highest importance to monitor during ICI treatment. Thirty of the 37 symptom terms were identified through the Delphi study conducted in the first phase of the IePRO project (132). The remaining 7 were selected by the IePRO project's clinical team and principal investigators. All PRO-CTCAE items were translated in French. Currently, no official guidelines exist on how to best analyze PRO-CTCAE data longitudinally (170). In this RCT, we will follow guidance provided by Basch et al (165) to calculate a single composite numerical grade for PRO-CTCAE symptom terms to facilitate longitudinal analysis.

As previously stated, active symptoms are reassessed daily during the first 3 months of the RCT. This is done by modifying the standard PRO-CTCAE recall period from 7 days to 24 hours. Although modifications to the recall period of PRO-CTCAE items are not encouraged, this is specifically due to potential considerable measurement errors, as that period is extended (171). Recent studies (172,173) have highlighted how PRO measures using 24-hour recall periods more accurately convey symptom burden and variability over a short period of time, particularly for symptoms such as constipation, diarrhea, nausea, and those related to the patient's emotional state. In patients treated with chemotherapy, shortened recall periods across different symptom PRO measures have enabled detection of clinically meaningful changes and were shown to be capable of detecting severe symptoms earlier (172,173). Because some IrAEs can be fulminant and evolve in severity very quickly, daily reassessment of active symptoms could also support early detection and management. Although there is concern that the inclusion of all PRO-CTCAE items for daily assessment can be burdensome

to patients, this concern addressed static questionnaires. In this intervention, questionnaires are dynamic and only active symptoms are reassessed daily to avoid overburdening patients. To minimize missing data, the app requires respondents to provide a response before they are able to progress within the questionnaire. Patients receive automated reminders to reply to the questionnaires via email. In the event of early study discontinuation or withdrawal, all data collections, including PRO data, are halted. A semistructured interview guide based on the mHealth App Usability Questionnaire by Zhou et al (137) was developed to assess the usability of the ePRO app. Acceptability of the model of care will be assessed using an interview guide developed around the 7 constructs of acceptability of health care interventions as described by Sekhon et al (138). Patient and individual staff interview data will be collected via audio recordings. Recordings will be transferred from the recording device's secure digital card to be stored in the corresponding site's local secured servers. Transcriptions of the recordings will be independently analyzed by 2 subinvestigators by using thematic analysis.

Statistical Methods

In this RCT, the null hypothesis postulates that there is no difference in the primary end point (delay between symptom onset and detection be clinical team) between the intervention and control groups. The primary outcome will be analyzed comparing groups by means of multivariable regressions, adjusting for cancer type, age, and treatment regimen, against a 1-sided hypothesis. Secondary outcomes will be analyzed using multivariate regression analysis, controlled for cancer type, treatment regimen, and age. All statistical analyses will be presented as effect measure plus 95% CI, using a significance level of 5%. Variations in HRQoL and self-efficacy scores will be assessed by adjusting to baseline measure. Overall survival at 6 months will be controlled for cancer type and stage. All data processing and statistical analyses will be performed in R statistical software (v4.2.2; R Core Team 2023) and Microsoft Excel for Microsoft 365 MSO (version 2302, 2023). In-questionnaire data completeness is compulsory, though potential errors in the app may nevertheless occur. In addition, data such as time points may prove difficult to collect. According to the type and amount of missing data, strategies including imputation methods, deletions, or dismissals will be considered. For the HRQoL and self-efficacy for managing symptoms questionnaires, missing data will be handled according to official guidelines (168,169). For exploratory outcomes, descriptive statistics will be applied. Qualitative data of semistructured interviews will be analyzed by the subinvestigators. Interviews will be transcribed verbatim and analyzed through thematic analysis.

Patient and Public Involvement

A patient expert (GS-B) was involved from the initial stages of the design of this study. The patients helped define the outcomes of interest of the study; gave their feedback on its design, choice of instruments for PRO data collection, and choice of medical device; assisted in the creation of documents targeting patients such as the informed consent form and the information sheet for the medical device; and participated in the study's dissemination. Ten patients gave feedback on the medical device interface during its development phase.

Safety Reporting

The university hospitals participating in this study have signed a research agreement detailing each site's responsibilities and data access and management procedures to ensure compliance with the research protocol and data monitoring plan. All information related to the trial will be stored securely at the corresponding study site. Documents containing participant data will be identified by a coded identification number only to maintain patient confidentiality. The sponsor and medical device developer have entered a written data processing agreement that outlines the extent in which data processing can be handled by the developer. Upon trial completion or early withdrawal, patients' login credentials are deactivated, and PRO data are archived. The data archive is stored by the data manager and the sponsor of the study. Accessing encrypted data logs requires prior authorization from the sponsor-investigator. Trial monitoring activities are ensured by a data monitor for each site, following a clinical monitoring plan submitted alongside the research protocol to the competent ethics committee. Monitoring visits are scheduled to occur at 6, 12, 18, and 24 months (end of trial). Any study-related

incidents are reported to the sponsor representative. Serious adverse events are reported to the competent ethics committee of the trial. Patients enrolled in the trial are covered by indemnity for negligent harm through the sponsor.

Ethics Approval

This study has been approved by the ethics committee of the Canton of Vaud, Switzerland (approval 2021-00301) and is conducted according to local regulations and the Declaration of Helsinki (174). This trial is sponsored and led by the Lausanne University Hospital in Switzerland and registered at ClinicalTrials.gov (NCT05530187). Informed consent is obtained from all participants. Due to the nature of the intervention, this study is unblinded. Data are deidentified for data analysis purposes. No compensation was provided to patients participating in this study. In addition to the major amendment to the eligibility criteria, challenges brought by the COVID-19 pandemic (including site-imposed restrictions to conducting research not related to the pandemic) and resulting uncertainty on whether all the components of this trial could be deployed and thus its original outcomes assessed, further prevented this trial from being registered prospectively. Trial registration preceded any interim data analysis, and the original outcomes have been preserved.

Results

The first version of the research protocol of the IePRO RCT was approved in September 2021. In addition to 2 minor amendments, the latest version of the protocol contained a major amendment to the inclusion criteria, which was modified to include patients with any cancer type. This version was submitted and approved by the responsible ethics committee in April 2022. The current version of the protocol includes minor amendments that were approved in March 2023 (version 3.1 on September 22, 2022). All trial documents, including the protocol, site-specific informed consent form, and participant education materials, have been approved by the competent ethics committee. Patients have been actively recruited to this trial since November 2021, and this trial is projected to close by November 2023. The results of this trial will be published through abstracts, posters, presentations, and publications in peer-reviewed journals, when agreed to and reviewed by the principal investigators and the sponsor representative of the trial.

Discussion

The IePRO RCT is, to our knowledge, among the first trials to use PRO data to directly influence the routine care of patients treated with ICIs. Current guidelines argue that PRO measures can guide clinicians in monitoring patients at home, optimize patient interactions when the patients come to the hospital, and highlight symptoms that could improve or resolve through supportive care interventions (8). Crucially, PROs can help identify active treatment-associated toxicities that, if unmanaged, may worsen and require complex care, impact quality of life, lead to treatment interruptions, and thus, ultimately, decrease survival (8,11).

Recent studies have shown the feasibility and acceptability of ePRO symptom monitoring systems to monitor IrAEs but have provided limited evidence of their impact on patient care and clinical outcomes (14). IrAE investigation and management algorithms and the lack of integration and adaptability to routine care are among the key areas requiring improvement for the success of these interventions. The triage process in the IePRO model is a potential strength, as it provides nurses with a standardized procedure to investigate and manage symptoms, potentially decreasing variations in how care and information are provided, facilitating more consistent outcomes. In addition, the model of care was conceived with adaptability in mind, to be able to accommodate 2 tertiary hospitals. The adaptive structure of the PRO-CTCAE questionnaire focuses on active symptoms and enables patients with the choice of adding self-detected symptoms, while limiting the risk of increased burden,

particularly due to more frequent data collection. It is possible that its weekly data collection may more accurately portray changes throughout treatment, as opposed to multiple-month intervals of measures of HRQoL and self-efficacy for managing symptoms.
Other limitations of this study are that the broad triggers for a telephone triage call (new or worsening symptom) may lead to a significant number of calls that may not always result in meaningful changes to how care is provided. A recent publication by Msaouel et al (73) has described adaptive and more granular alert thresholds that could prevent and alleviate clinician burden. Clinicians in similar studies have noted the time-consuming nature of ePRO data review, and these broad triggers may compound that burden further and limit clinician compliance to study procedures (80). Tolstrup et al (74) attempted to empower patients with the decision to contact the hospital, though this may have discouraged computer-naïve patients from doing so even when symptoms were concerning, leading the authors to consider a proactive approach for future iterations of remote PRO monitoring. Integration with the EHR was complicated by the differences in EHR platforms across study sites and the short time interval between the finalized code for the mobile app and the start of the study. EHR integration is a major factor for ensuring successful implementation of ePRO monitoring (14), and it remains unclear if the measures implemented to mitigate the lack thereof will be successful.
Dropping tumor type and excluding ICI agents as stratification criteria constitute a major limitation of this study, as patient groups could present important differences that could influence the type, severity, and frequency of IrAEs. This consideration should guide future analysis of the data, and its impact will be addressed in future publications. More frequent measuring and the reactive nature of the intervention increase the risk of surveillance bias, as clinicians will be more aware of the challenges patients are experiencing. The intervention also does not allow blinding of patients who may alter their usual self-monitoring and self-care behaviors due to their awareness of the triage nurse's monitoring (74). As this study is being deployed in 2 sites, tracking hospitalization and emergency room admissions for patients in the control group was outside the resources available to the study team. As a consequence, they were not included as secondary end points for this study, limiting insight on its efficiency to improved care. Overall survival measures were capped at 6 months due to limited resources to pursue a longer target, which could hinder the visibility of long-term effects of the model of care. Lastly, excluding patients who self-declare unable to use the electronic app and the lack of alternative means to self-report symptoms limit the comparability of this sample to the general population (69,175). Despite these limitations, the IePRO RCT takes a pragmatic approach to symptom monitoring with ePRO data by not insulating its model of care from the existing resources the sites use to assist patients. Importantly, the IePRO RCT may further highlight the challenges patients treated with ICIs face outside the clinical setting, particularly as more data revealing the true burden of treatment-associated toxicities continue to emerge.

Acknowledgments
The authors are grateful to the clinicians, patients, patient-experts, and collaborators in the participating sites who have facilitated the development of this study and to Dr Sandra A Mitchell for her guidance in using the Patient-Reported Outcome version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Data Availability
The data sets generated during or analyzed during this study are not publicly available due to its sensitive nature but are available from the corresponding author on reasonable request.

Authors' Contributions
ME and OM conceived the study's original concept and design. AmdSL, SC-L, CD, VA-L, SL, NM, GS-B, and AA later contributed to refining the design, instruments, and methods. The first draft of the manuscript was written by AmdSL, and all authors commented on the previous versions of the manuscript. Analyses will be conducted by the study biostatistician MC and AmdSL. ME is the sponsor representative of the Lausanne University Hospital for this study. All authors read and approved the final manuscript.

Conflicts of Interest
SC-L reports grants from Institut Suisse de Recherche Expérimentale sur le Cancer Foundation. GS-B reports grants from MSD France, grants from Novartis, and personal fees from Bayer, Melanoma Patient Network Europe, and Working Group of European Cancer Advocacy Networks outside the submitted work. OM reports grants and personal fees from Bristol Myers Squibb (BMS), MSD, Pierre-Fabre, Amgem; personal fees from Roche, Novartis, and Glasgow Smith Kline; and grants from Merck outside the submitted work. ME received institutional research grants from Kaiku Health and reports grants from BMS, Roche, and institutional fees as a scientific advisory board member or consultant from Roche outside the submitted work.

Phase 4: Data collection and preliminary results of the IePRO randomised phase II controlled trial

As of writing, the IePRO RCT is concluding, preventing us from presenting final data from this trial. In this section, we cover a partial extract of unpublished data that will be integrated in a future publication (projected for the year 2024). Only data from site 1 was readily available during the writing of the present thesis, and due to time constraints, we are unable to provide a full characterization of the sample.

As of writing, the IePRO RCT concludes with a total of 67 enrolled patients, across both site. In site 1, a total of 54 patients were screened, with 31 (57%) having been enrolled. Patients who refused enrollment (n=23) provided insight on their motivations not to partake in the study, which are portraied in Figure 4**.** Some patients argued that there were two motivations for skipping participation. A total of nine patients were subject to an early study discontinuation, the majority due to a change in the line of treatment (n=5), two due to a significant status decline, and two were lost to follow-up (non-compliance with study requirements).

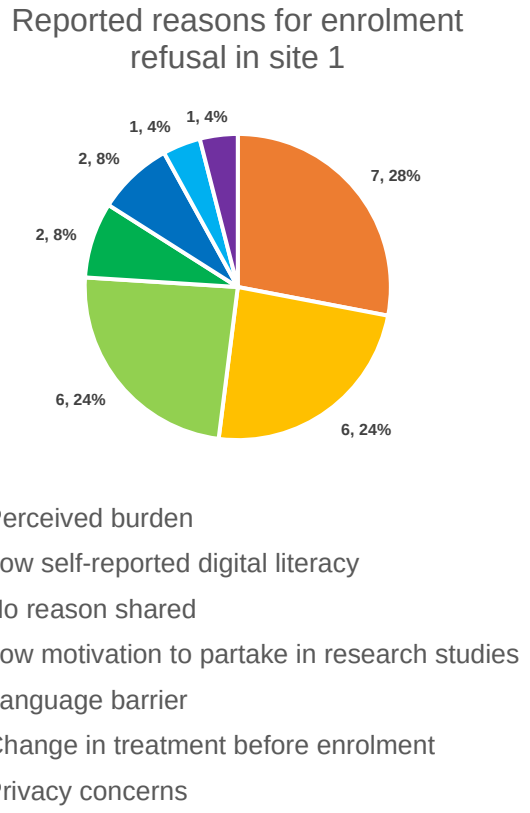

Figure 4 - Motivations of patients (N=25) deciding not to partake in the study.

Seventeen patients from site 1 were enrolled in the intervention group and 14 in the control group. A total of 13 patient interviews on the acceptability of the model of care and the usability of the ePRO application were conducted on site 1. Two triage nurses from site 1 were interviewed at the end of their participation in the study.

Patients in the intervention group were enrolled for a minimum of 42 days and a maximum of 168. For this group, the average length of enrollment was 145.9 (sd 41.6). A total of 222 triage calls were performed to this group during the study, with an average of 13.8 calls (sd 11.3) and a median of 11. The highest number of calls for a single patient was 47 (n=1) and the lowest was 3 (n=1).
To demonstrate the performance of the ePRO-based nurse-led care model, we present data from a single case study, where the patient presented symptoms related to and unrelated to

their cancer disease and treatment, including an IrAE. The present case summary will be the target of a future publication to demonstrate the workings of the model of care. In this thesis, we provide a preliminary analysis of that case study.

Case summary

A male patient in his early fifties presented to the melanoma unit of the outpatient clinic of a university hospital (site 1). For at least one year, the patient presented a pigmented lesion on the left buttock, progressively increasing in size. The patient undergoes a biopsy procedure, revealing a superficial spreading melanoma. A complete excision is performed within the following month. The melanoma is classed as cT4a cN1c (microsatellite) cM0, stage IIIC, with a Breslow of 12.5mm. The patient underwent a second surgery to assess the presence of residual lesions, which were negative. An adjuvant treatment with Pembrolizumab 200mg every 3 weeks is initiated a month later.

In addition to the oncology diagnosis, the patient has been diagnosed for epilepsy, at the time treated with Clonazepam. Despite a history of cancer in immediate relatives, the patient has no family history of melanoma. He is an active smoker with approximately 15 pack-years. Due to the nature of his full-time professional activity, the patient is often exposed to the sun, though rarely wears specific protection such as sunscreen or skin-covering attire.

The patient is enrolled in the intervention arm of the IePRO trial (ClinicalTrials.gov: NCT05530187) the day of his first treatment session, for a total duration of six months. The patient received in-person training with the ePRO application from the triage nurses during his first treatment on 02.12.2021. After completing the baseline symptom questionnaire, the patient completed daily questionnaires for the first 3 months of the study, transitioning to a weekly symptom questionnaire only, in the remaining 3 months. An overview of the patient's replied to the questionnaires is available in Appendix 8.

Out of a total of 96 symptom questionnaires, including daily questionnaires, the patient completed 94 (98%). Full completion was achieved for every questionnaire. Here we report data on a selection of 19 symptoms associated with three major events during the study. All 25 HRQoL and self-efficacy questionnaires were completed in full. At baseline, the patient presented mild constipation, generalised pain with muscle, joint and abdominal pain. Generalized pain, muscle pain and joint pain are for the most part, according to the patient, chronic and related to their professional activity. The patient does concede pain in the surgical site of their biopsy. The patient does describe abdominal pain, and points towards the bladder as they describe it. The patient also reports frequently urinating during the night, limiting the number of hours of uninterrupted sleep per night. The patient described this as the reason for persistent fatigue in the previous days.

Over the six months of participating in the trial, a total of 21 triage telephone calls were placed. The main interventions from nurses are described on table 3. The triage team issued the first red alert within the first week. Initially, triage nurses were unable to contact the patient as they were unavailable during office hours (the patient was professionally active). The patient self-reported fatigue of the highest severity and interference with activities of daily living. The triage team contacted the physician who issued an electronic certificate for a 50% decrease in working hours, sent via e-mail. Fatigue is identified as a CTCAE Grade 2 IrAE, which did not resolve throughout the study, with an onset date of less than two weeks after treatment started. Throughout the remainder of the study, the patient was encouraged to review their activity level with the oncology physician, which was frequently reduced and increased in the following months.

A second major event followed the diagnosis of fatigue as IrAE. In April 2022, fatigue worsened with episodes of vertigo, shortness of breath and one instance of lipothymia over a weekend and holiday break in April 2022, when the triage team was not available. In parallel, the patient also self-reported anxiety, which became more severe in the week leading up to the lipothymia episode. Triage reports suggest the cause for the increased anxiety is the constant fatigue and the persistence of symptoms related to urinary urgency. The patient visits their general practitioner on 20.04.2022, and an antihypotensive agent is prescribed – the patient informs

the triage team on 21.04.2022 The triage team informs the oncologists via e-mail. Following a second episode of vertigo and other signs of general decline, the oncology physician is contacted by telephone and the patient is admitted to the ER. A Grade 2 corticoadrenal insufficiency is detected on 28.04.2022 and confirmed as an IrAE on 02.05.2022. The patient is prescribed hydrocortisone, with symptoms improving, but persisting until the end of the study.

The third major event is related to a suspicion of benign prostatic hyperplasia . The patient declared initial symptoms with the ePRO application on baseline and when informed, the oncology physician instructed the patient to contact his general practitioner or an urologist to follow-up on their symptoms. The patient presents occasional episodes of constipation, and triage nurses highlight hydrating habits throughout the day as a priority. As symptoms worsened in January 2022, the oncology physician formally requests a consultation with an urologist in the local hospital. The patient had their first cystoscopy in the third week of April 2022, nearly four months after symptoms worsened.

Table 3 – Triage alert type, symptoms triggering triage procedures and nurses' actions

Date	Highest alert level	Triggering Symptom Term(s)	Nurses' actions
03.12.21	Amber	Muscle pain; joint pain; fatigue	Follow-up call within 24 hours with self-management education
06.12.21	Red	Abdominal pain ; Urinary frequency	Pain-related and hydration-related self-management education; Follow-up call with physician – no in-person assessment required, pain medication and a stool softener prescribed. Patient oriented towards a surgery consultation due to pain related to a surgical wound.
08.12.21	Green	Muscle pain; joint pain; fatigue	Pain-related self-management and self-monitoring education
13.12.21	Red	Fatigue	Self-management education; Follow-up call with physician – no in-person assessment required. Prescription for reduced workload to 50% due to fatigue.
28.12.21	Amber	Fatigue; Urinary Frequency	Self-monitoring education; Physician contacted - follow-up to be based on ePROM data which revealed symptom improvement the next day.
31.12.21	Amber	Urinary Frequency	Self-monitoring education ; Follow-up based on ePROM data.
06.01.22	Red	Fatigue; Urinary Frequency; Numbness & tingling;	Self-management education; Follow-up call with physician – no in-person assessment required, urologist appointment requested.
12.01.22	Red	General pain ; Muscle pain; joint pain; Urinary Frequency	Self-monitoring education; Patient scheduled for in-person assessment in less than 24 hours
17.01.22	Amber	Fatigue	Self-management education ; patient encouraged to review activity rate with physician. Follow-up based on ePROM data.
25.01.22	Amber	Fatigue	Self-management education ; no follow-up call was placed. Follow-up based on ePROM data.
04.03.22	Red	Fatigue; Urinary Frequency	Self-management education; Given symptom stability, no in-person assessment scheduled. Urologist appointment still pending.
18.03.22	Amber	Fatigue; Urinary Frequency; Anxiety	Self-management education ; no follow-up call was placed. Follow-up based on ePROM data.
25.03.22	Red	Follow-up on previously reported symptoms	Self-management education; Blood in the stool detected during triage call. Physician contacted. Patient received a follow-up call with physician – no in-person assessment required.
31.03.22	Red	General pain ; Muscle pain; joint pain;	Self-management education; Patient self-describes as improving, no in-person assessment scheduled. Follow-up call scheduled.
05.04.22	Red	N/A	Follow-up call confirms patient status is worsening, with signs of a urinary tract infection. Physician contacted, patient admitted to the ER for susprected urinary tract infection.
07.04.22	Red	General pain; Joint pain; Fatigue; Anxious;	Self-management education; Emotional support; Patient is attending scheduled oncology consultation on this day.
14.04.22	Amber	Chills	Self-management education ; no follow-up call was placed. Follow-up based on ePROM data.
21.04.22	Red	N/A	Self-management and self-monitoring education; Patient was assessed in-person by his general practitioner, who prescribes him an antihypotensive agent. Patient encouraged to contact physician If symptoms worse before next scheduled call. Medical team informed.
25.04.22	N/A	Patient-initiated call	Patient contacts the triage team to express general decline, with worsening fatigue, . Physician contacted, patient is admitted to the ER
28.04.22	Red	Urinary frequency	Self-management education; Patient is attending scheduled oncology consultation on this day.
12.05.22	Green	Diarrhea; Concentration	Self-monitoring education
19.05.22	Green	Swelling	Self-monitoring education ; end of study.

Beyond these three events, we can also take note of the quality of life scores and the self-efficacy scores. Regarding quality of life subscores, little variation can be noted in the Physical Well-Being (PWB) subscale throughout the study, despite the emergence and persistence of consequential symptoms like urinary urgency. A slight drop in the PWB score can be noted upon the events that led to the diagnosis of corticoadrenal insufficiency, as well as in the functional well-being (FWB) subscale. Not surprisingly, the lowest total FACT-G score (58) aligns with those events, before returning to comparable scores to that of baseline. A similar trend can be seen for the self-efficacy t-scores, where the lowest (37.7) is simultaneous to that of the FACT-G.

Brief analysis of the case study

Among the arguments behind the selection of this case study is how it portrays real-world challenges that often characterise the journey of cancer patients. Specifically, the fact it includes a recurring and persistent symptom unrelated to the cancer and, as far as assessed during the study, unrelated to the treatment with ICIs. Despite this apparent disconnect, the symptom's influence over the patient's well-being is hard to ignore and remained a source of frustration to the patient as referrals to a urology consultation took nearly 3 months to put in place since symptom onset. Importantly, it is made evident how patients describe other symptoms as consequences of another. In this situation, fatigue was often related to the difficulties sleeping resulting from urinary urgency and nycturia.

By collecting PROs data daily and using the related triage reports, we can clarify how frequently symptoms appear to change on a daily basis for patients treated with ICIs. This is particularly evident in the case of fatigue, which appears to fluctuate between waves of moderate to high severity, that quickly turn into mild symptoms with low interference with activities of daily living. This data set can also show the large spectrum of toxicity experienced by these patients, and could contribute with accurate data for describing time patterns or symptomatic IrAEs. In addition, this level of granularity, together with the triage reports, may enable researchers to portray how symptoms fluctuate when healthcare professionals intervene. Though the data contained in the triage reports requires a significant amount of effort to convert into a usable nomenclature, the color-coded alert classifications (green, amber and red) can also be closely approached to the symptom data and assist in developing algorithms that automate the how symptom reports are managed. Msaouel et al (73) have taken steps towards custom algorithms to decrease potential healthcare provider burden, though they are reportedly informed by expert opinion rather than statistical data. Other studies have used grade≥3 as the threshold that determines when and how the clinical team is informed of a symptom (62,75). This classification is typically derived from the composite algorithm score developed by Basch et al (165), which while certainly useful, is based on a still-limited data set. Furthermore, as the composite score changes the nature of the data from a self-reported outcome to a clinical classification, there is an argument to be made for recreating the algorithm's development in other languages and cultures.
These variations, although small and confined to a single case, do show the potential for variations in the perceived quality of life of patients treated with ICIs, that may go unnoticed when it is measured only occasionally. Although it is unlikely that weekly measurements convey useful information for routine practice, if these variations occur in other patients, there is potential for automated triggers to measure HRQoL according to certain thresholds like the number of active symptoms tracked by the ePRO application.

As we collected data from triage reports for this case study, we noticed how often the presumed courses of action according to alert type were bypassed. In this model, nurses collaborate closely with physicians, who hold the final say in validating or not patient admission. In fours instances, an in-person assessment was avoided. It is important to note that recommendations hailing from the SARS-CoV-2 pandemic still discourage the use of emergency hospital

services when not absolutely required. It is important to review if such situations also occur and frequently in other times of the year and with other patients.
One cause for concern related to the triage process is how often the patient relied on triage nurses to follow up on issues related to their care. This case study includes one instance of this patient directly contacting the triage nursing team despite being informed at multiple moments that they were to contact the physician directly, should they be concerned about their health status. Specific debriefings with patients might clarify the reasoning behind these decisions to interact with the triage team instead.

Finally and of note, the volume of data collected from a single patient is, in this domain and to the best of our knowledge, a first of its kind. Even though patient burden guided some of the decisions around how the electronic questionnaire behaved, the patient completed nearly every single questionnaire issues by the app, which all the most unexpected considering this patient had an active and busy lifestyle, and continued to work throughout the duration of the study. This speaks to the potential of questionnaires with CAT-like characteristics, as we continue to develop future instruments to detect ICI toxicity.

Chapter 5: Discussion

This thesis is part of the IePRO study which aimed to develop a PROM to assess symptoms associated with ICI toxicity, and to develop and test a model of care leveraging the PROM to remotely monitor and manage symptomatic IrAEs. To test the model of care, we developed a research protocol for a trial collecting preliminary evidence on efficacy of the model of care to manage IrAEs, as well as data on self-reported symptoms, health-related quality of life and self-efficacy to manage symptoms.

Development of a patient-reported outcomes measures for patients treated with immune-checkpoint inhibitors

In this Delphi study, 11 experts assessed the relevance and importance of the PRO-CTCAE item library for patients treated with ICIs. Consensus on importance was reached for 65 out of the 80 PRO-CTCAE items. Thirty of these items were considered to be of the highest level of importance, followed by 48 items in the intermediate level of importance, and two of the lowest level. The large number of high-priority items portrays the challenge of the wide spectrum of symptomatic ICI toxicity. While this was not unexpected, as it is one of the main contributors to the observed limitations of non-specific PROMs, it remains a concern for the research and clinical settings, as it may result in high patient burden. This concern led the effort towards defining multiple levels of importance as we reflected on the possibility of taking advantage of electronic systems to tailor the questionnaire to symptoms patients expressed over time.
Furthermore, recent evidence on symptom clustering related to ICIs shows significant differences across PD-1-treated patients with lung cancer(176). Further research is needed to assess whether clustering could provide alternative strategies in how ePROMs are tailored to patients. Artificial intelligence tools may prove pivotal in better understanding underlying patterns and drawing new pathways to make this knowledge actionable (177). Zhang et al note some differences across authors in the selection of what symptom-related PROs to measure, ranging from 18 toxicity-related questions, up to 158. Notably, all studies appeared to cover most of the toxicities listed in current treatment and toxicity management guidelines (176). This underlines the importance of continuing to develop these guidelines in an ever-evolving landscape of new toxicities. Some PROMs have added new subscales that target ICI toxicity, such as the Functional Assessment of Cancer Therapy – Immune Checkpoint Modulator (FACT-ICM) (63), though their use is still not widespread.

The expert panel also identified several new symptoms that patients may express, of which 47 met the consensus threshold, and are mostly neurological and mood-related symptoms. This follows emerging research on this domain of IrAEs (30,36,124). Given the subjective nature of

these symptoms, future studies face the challenge of engaging patients to develop more complete measures while dealing with very recent data.

This study was among the first of its kind, providing transparency on the selection process of PRO items, which few studies have described (14,64). Among the limitations of this Delphi study, we consider the limited number of participating experts to be its most significant, particularly the number of included patient experts. Despite this, the diversity in disciplines involved in the Delphi is notable, which we believe must be preserved in future iterations.
In parallel to this study, updated ICI toxicity management guidelines have been published (17,40), which argue for a repetition and expansion of the Delphi, particularly as we learn from the performance of developed ePROM in the IePRO RCT. A major theme to consider in the development of these instruments, is in how they are implicated into practice. Research and real-world application compete in their goals – while routine practice calls for tailored, personalized measures, research applications require some degree of standardisation to remain comparable across patients. As ePROM systems evolve, and the ergonomics of the applications using them continues to improve, the need for a tiered or limited set of items to assess may disappear completely for real-world applications. New interfaces using artificial intelligence-backed algorithms capable of natural language processing on the same hardware that is readily and widely available to patients, may bypass some of these concerns entirely. Nevertheless, research like the aforementioned Delphi can inform how those algorithms will behave and present options to patients while managing the risk of overwhelming them.

Development of an ePRO-based model of care to monitor and manage symptomatic IrAEs

The model of care we have developed describes the flow of communication between patient, triage nurse and other healthcare professionals. As the eCCM it is based on, it describes the flow of communication between patient and triage nurse, as well as between patient and healthcare institution. The model leverages the previously developed PROM for patients treated with ICIs and described how patient safety is assessed. The description of these modes of action is seldom reported in the literature, and even more so in this patient population.
During the development of the IePRO model of care, we were strained by limited resources and limited availability to conduct pre-implementation activities, particularly due to the SARS-CoV-2 pandemic. A fully realised pre-deployment phase would have allowed more accurate insight on the readiness, barriers and facilitators to ePROM implementation on each site, and to more extensively train nurses and physicians on the value of PROs to monitor and manage symptoms during routine care, a need that other studies have highlighted (12). Future efforts to implement a similar model should take steps to enhance the value proposition of ePROMs as elements of clinical decision support through training, foster leadership support and include measures to enhance accountability within the care team. In a real-world scenario, identifying clinical champions, creating recurring training opportunities and developing an audit and feedback cycle would further improve the long-term reliability of the model of care (178). Initially, this model of care was to be led by clinical nurse specialists tasked with improving the quality and scope of the tool and performing certain tasks independently to decrease friction and ensure potentially higher continuity of care. To directly influence In addition to implementation strategies, implementation outcomes beyond acceptability and feasibility should be considered (178). Patient and provider experiences are crucial to ensure a better understanding of the value of the intervention and would enable the identification of additional facilitators and barriers to the intervention. Assessing intervention fidelity and reach outcomes would further insight into the strengths and weaknesses of the model and complement model acceptability outcomes. Cost-related outcomes should also be assessed as the intervention is refined to estimate the initial investment to deploy the model of care and the potential benefits in cost-reduction of these interventions in the long term, for both healthcare institutions and patients (12,59).

Nurses benefited from standardised education to use the UKONS 24-hour triage tool algorithm, to ensure that recommendations shared with the medical team are preceded by same considerations in patient safety. However, two significant concessions in its implementation were made. The first concession refers to the telephone triage triggers, which in this model are based on ePROM data, unlike in real-world application of the tool where the burden of the decision to call is on the patient side. While patients are encouraged to call in case of any concerns towards their condition or their treatment and side effects, it is possible some patients may delay taking action and interpret the lack of a call from a triage nurse as a reassurance that their concern does not require in-person assessment. Continued reminders and revisiting these themes during patient discussions throughout treatment are crucial to ensure patient safety.

The second concession that deviates from the original triage tool is related to the continuity of the triage process, which in its current iteration is only available during office hours and during weekdays. This introduces breaks in the continuity of care by relying on the on-call physician to make decisions that do not follow the same standardised procedures. This introduces challenges for triage nurses, who aren't systematically notified of patients contacting the on-call physician. Future iterations of this model should seek to minimise the consequences of this gap in continuity, by broadening physician collaboration and ensuring that triage nurses are notified of any out-of-hours contacts between patients and physicians. Clarifying these complementary roles is essential to improve the internal communication flow across care team members (22).

Among the strengths of this model of care is the description of the flow of communication between nurses and physicians according to the type of alerts resulting from the triage tool's algorithm. One potential downside of this model relates to the management of mild symptoms that don't require immediate intervention, where reports to physicians are done exclusively via e-mail and, therefore, risk being dismissed. If these outcomes are overlooked, and the information they provide is not used in the context of in-person assessments, there is potential for frustrating patients and decreasing the perceived value of ePROs. The ePRO application's lack of integration with the EHR is, in part, mitigated by nurses writing triage reports within the EHR. However, the triage report contains the nurse's assessment, and not the patient's self-report. Having the information strictly available through an external portal adds an element of friction that could be significant enough to keep physician engagement low and introduce potential inefficiencies in coordinating care (96).

Given the weaknesses mentioned above of the model, future iterations should broaden the concept of complete feedback loop to professional interactions within the healthcare team. In the eCCM (101), the feedback loop is established between patient and healthcare professional, but ePROM-based interventions often feature nurses or physicians as the gatekeepers between ePROM data and the institution they represent. As gatekeepers, their role may be significantly isolated from the remaining medical team, and this may in turn create the need for clearer and more reliable feedback mechanisms within the team. Similarly, physicians should be trained on the eCCM and the tools created for this ePROM-based model, to ensure that ePROM data is taken into consideration during in-person assessments.

Conclusion

The initial phase involved creating a foundational ePROM using a set of items from the PRO-CTCAE item library, which was considered a valuable starting point despite its limitations in covering all symptoms. The resulting model aimed to serve as a transparent tool for others, shedding light on the positive outcomes of such interventions. Preliminary data highlights its potential to accommodate symptoms beyond those associated with symptomatic IrAEs. The model outlines a workflow for a care team that could serve as a foundational approach for patients and healthcare providers, bringing significance to collecting PROMs data.

Unfortunately, the randomized controlled phase II trial had to be stopped prematurely due to recruitment challenges, highlighting the evolving nature of oncology care. Preliminary data suggests there is potential to nevertheless derive significant contributions to the field given its density. The components of the model appeared to encompass symptoms beyond those related to ICIs, suggesting potential applicability in different environments and settings in the future. Moreover, it highlights how nurses have an essential role to play in bridging the gap between patient-reported symptoms and the resources of healthcare institutions, using a tailored and patient-centred approach, by clarifying their contributions and the type of challenges they face, as they are portrayed in the triage reports. Data from this study could contribute in defining a new nursing role in the remote follow-up of patients with cancer. In parallel, this study can also provide data to improve the eHealth-related skill-set for nurses that are occupying and increasing number of telehealth positions.
Due to the challenges mentioned above in the development of this study and the implementation of its model of care, future research should revise the planning stage of this intervention, using a more structured and implementation framework-guided approach. Nevertheless, the study provides important clues for improving future implementation strategies. Importantly, it may provide data uniquely suited for nurses involved in these types of interventions and address challenges specific to their role, a subject that is commonly omitted in current publications in this domain.

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Appendix 1: Article 1 - Expert comments on PRO-CTCAE™ Symptom Terms and Expert-suggested Terms

The present Appendix reports written comments by experts made during the Delphi rounds one to four (R1 – R4). Comments are transcribed exactly as found in the source text (*sic*), with an identifier code in brackets. Observations made during the live discussion in Round 4 were written by the Investigator Group, and were meant to summarize the discussion around a symptom, especially in the absence of written comments by experts.

PRO-CTCAE items

ORAL SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1–11] and the Investigator Group [IG] by Round		Round 4 discussion observations
OR01	Dry mouth	N/A	--	None	None
OR02	Difficulty swallowing	1	--	None	None
OR03	Mouth/throat sores	N/A	--	None	None
OR04	Cracking at the corners of the mouth (cheliosis/cheilitis)	N/A	R3	"Could be the start of a general Ir tox involving skin and mucosa in general" [1]	None
				"It is a very visible and irritating symptom that should be treatable" [11]	None
				"not a major problem, but irritating for patients. Could be due to too little saliva" [2]	None
				"not very consequential and likelihood is low that its relate to immunotherapy" [3]	None
			R4	"It is not very lileky that the symptom is related to treatment and can easily be treated" [7]	None
OR05	Voice quality changes	2	--	None	None
OR06	Hoarseness	2	--	None	None

GASTROINTESTINAL SYMPTOMS (1/2)

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
GI01	Taste changes	2	R3	"I know this is largely a quality of life issue but can lead to loss of appetite" [11]	None
				"will downgrade this symptom. Not nice for patients. Not typical for an irAE" [2]	
				"When you talk to the patients some of them experience taste changes. It is, however, often only a few food items that they do not tolerate, such as coffee or spicy food. It is not my impression that it impacts their quality of life significantly". [7]	
				"I changed to "slightly important" because I don't see this mentioned often. This probably means there are very few cases, and in most cases nutritional supplements are prescribed. I believe nutritional follow-up is usually already in place, and can be tracked with other PROs". [8]	
				if no associated symptoms its not important to me [3]	None
GI02	Decreased appetite	1	--	None	None
GI03	Nausea	1	--	None	None
GI04	Vomiting	1	--	None	None
GI05	Heartburn	N/A	R4	"Dependent on what other questions covering gastritis are in the first layer" [1]	Expert [11] mentions that if a patient has felt this before, it's easier for them to identify it. If not, it can be confused with other symptoms. It's also difficult to find a direct ICI-relation – in the end, this can be the consequence of a gastric issue.
GI06	Gas	2	--	None	None
GI07	Bloating	2	--	None	None
GI08	Hiccups	2	R3	"again it depends for how long this goes on" [11]	None
				"for the patient an awful experience, extremely tiring but not likely associated with irAE" [2]	
				"Although it can be detected by the patient and annoying to the patient, it is not very conseqquntial" [7]	
				"not potentially a sign of a dangerous irAE and if seriuos, it becomes an objective symptom" [10]	
				"i agree, not important, nevertheless its anoying to the patient" [3]	
			R4	"Depends on the severity of the symptom" [2]	

GASTROINTESTINAL SYMPTOMS (2/2)

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
GI09	Constipation	1	--	None	None
GI10	Diarrhoea	1	--	None	None
GI11	Abdominal Pain	1	--	None	None
GI12	Faecal incontinence	1	--	None	None

RESPIRATORY SYMPTOMS

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
RS01	Shortness of Breath	1	--	None	None
RS02	Cough	1	--	None	None
RS03	Wheezing	1	R4	"I am not sure anout this symptom so I go with the other experts" [7]	None

CARDIO-CIRCULATORY SYMPTOMS

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
CC01	Swelling	1	--	None	None
CC02	Heart palpitations	1	--	None	None

CUTANEOUS SYMPTOMS (1/3)

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
CT01	Rash	1	--	None	None
CT02	Skin dryness	2	--	None	None
CT03	Acne	2	R3	"Needs checking as can be other auto-immune/endocrine issue - has visual impact for patient" [11]	None

				“downgraded to slightly important. Not typical for ir-dermatitis. manageable for pts” [2]	
				“not potentially dangerous » [10]	
				“I confirm, not very important and mostly easy to treat” [3]	
			R4	“I have downgraded in line with comment 2 [7] Comment 2 refers to “downgraded to slightly important. Not typical for ir-dermatitis. manageable for pts”	

CUTANEOUS SYMPTOMS (2/3)

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
CT04	Hair loss	2	R3	“impacts a lot on some patients, link to endocrine deficiency and T cel infiltration should be followed up for better management” [11]	None
				“alopecia areata or totalis. Have seen both as irAE. Serious for patient, but not a severe or dangerous AE” [2]	
				“Even though this AE may be easily detected and that it may be related to the drug, I do not believe that the consequences are severe for the patienets, at the samt time acknowledging that it may impact the QoL for some of the patients” [7].	
				“if hair loss is there, not life treatening and not so much can be done about it if early seen” [3]	
CT05	Itching	1	--	None	None
CT06	Hives	1	--	None	None
CT07	Hand-foot syndrome	N/A	R3	“similar to issues with blistering, indicative of other issues, needs appropriate management” [11]	None
				“same as previous answer” [2] Previous answer [For Hair Loss]: “alopecia areata or totalis. Have seen both as irAE. Serious for patient, but not a severe or dangerous AE”	
				“i agree rather important, especially in the light of combining immunotherapy with anti-VEGF therapy” [3]	
CT08	Nail loss	2	--	None	
CT09	Nail ridging	2	--	None	
CT10	Nail discoloration	N/A	R4	“I have downgraded” [7]	

CT11	Sensitivity to sunlight	2	R3	“skin and eye sensitivity, can make people want to stop therapy, lead to other symptoms blistering/itchiness etc” [11] « downgraded a bit » [2] “maybe not always spontanslously mentioned” [10] “i confirm, I dont see the relationship with immunotherapy if no other associated symptoms” [3]	Experts ask if it only refers to the skin – In the PRO-CTCAE, it is only related to skin: experts suggest naming it “Skin sensitivity to sunlight”

CUTANEOUS SYMPTOMS (3/3)

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
CT12	Bed/pressure sores	3	R3	“may be also indicative of mobility issues/pain/depression” [11] “symptom of poor prognosis and poor PS. serious for patients with risk of infection. Not an ir-AE” [2] “this is important for the patient to be treated, it might indicate that pt is in very bad shape, nevertheless it has not a lot to do with immunotherapy” [3]	Expert [1] says they’ve seen this in practice, but never seen it described in the literature. JH, GSB believe this signifies a larger problem, and would usually be accompanied by other symptoms.
			R4	“Seen but servere, might be another skinreaction” [1]	None
CT13	Radiation skin reaction	2	--	None	Experts argued that it could be the results of a broader autoimmune reaction, though rare, and could potentially be captured by other cutaneous PRO-CTCAE™ terms.
CT14	Skin darkening	2	--	None	None
CT15	Stretch marks	N/A	R3	“link to weight changes” [11] “mostly due to steroid use. In itself not so important. Downgraded this » [2] « not potentially dangerous » [10] “i confirm, not related and not life treatening or sign of other underlying side effect” [3]	None

NEUROLOGICAL SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round	Round 4 discussion observations

NR01	Numbness & tingling	1	--	None	None
NR02	Dizziness	1	--	None	None

VISUAL/PERCEPTUAL SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
VP01	Blurred vision	1	--	None	None
VP02	Flashing lights	1	R3	“can be associated with Brain mets, progression in CNS , high tropism of MM to CNS, Uveal melanoma etc” [11] “Upgraded. Could be sign of epilepsy or other cerebral problem. Not necessarily irAE » [2] “probably not linked but might be a sign of retinal problem which can be severe: immediate examination by oftalmologist is indicated unless visual migraine is suspected” [3]	None
VP03	Visual floaters	N/A	R3	"uveal melanoma treatments, inflammation/effusion/uveitis etc [11] "symptom of uveitis" [10] “i have not enough experience with this, if this might precede uveitis than it is important, otherwise not important” [3]	None
VP04	Watery eyes	2	--	None	None
VP05	Ringing in ears		R3	“commonly reported in people with ICIs , CNS issues, sinus issues, age related and connection to RT treatments also ?” [11] "downgraded to moderately” [2] “might precede hearing loss, nevertheless mostly this is unrelated to immunotherapy” [3]	None

ATTENTION/MEMORY SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
AM01	Concentration	1	--	None	None
AM02	Memory	1	--	None	None

PAIN SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
PN01	General Pain	1	--	None	None
PN02	Headache	1	--	None	None
PN03	Muscle pain	1	--	None	None
PN04	Joint pain	1	--	None	None

SLEEP/WAKE SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
SW01	Insomnia	N/A	R3	"corticosteroid associated, depression, endocrine, apnoea" [11] "problematic for patient, not so likely an irAE" [2] "aspecific symptom" [10] "health care provides should analyse why there is insomnia, according to me not directly related to immunotherapy" [3]	None
SW02	Fatigue	1	--	None	None

MOOD SYMPTOMS

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
MD01	Anxious	2	R3	"Neurological, endocrine, depression" [11] "can have many reasons. Problematic for patients. Not so likely a irAE" [2]	Worries and Anxious are difficult to distinguish, but there is indeed a difference, according to experts [11] and [10]. Most

				“a specific symptom, should be changed in severe anxiety (symptom of GAD,OCD and panic disorder)which could be induced by immune therapy (animal models)” [10]	experts believe that tracing this to ICIs would be very difficult, however.
				“patients should not be anxious, this should be adequatly treated” [3]	
			R4	“ch the wording in severe anxiety would be better” [10]	
				“Important to detect, but not likely to be an irAE” [7]	
MD02	Discouraged	2			None
MD03	Sad	2	R3	"depression/not coping" [11]	A lot of discussion around this item, experts seem to suggest that mood swings/personality changes would be a better symptom to track. Expert [11] suggests “perceived personality change”; Remaining experts agree with this.
				“unlikely irAE.” [2]	
				“but saddness should be changed in depressive mood, sadness is not a symptom of depression” [10]	
				“underlying depression or suicidal ideations should be looked for, probably not related to immunotherapy” [3]	
			R4	“personality change ?” [11]	
				“I have changed my answer. Agree with what has been written under obswervations” [7]	

GYNECOLOGIC/URINARY SYMPTOMS (1/2)

PRO-CTCAE

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
GU01	Irregular periods/vaginal bleeding	2	--	None	None
GU02	Missed expected menstrual period	2	R3	“under-reported endocrine, poor understanding of effects of ICIs on women, fertility” [11]	None
				“can have many reasons. Hypophysitis not most likely” [2]	
				“I am unsure about this question and go with the majority of the experts” [7]	
				“check for pregnancy is important, otherwise only analyse if it persists (might indicate hormonal problems such as hypophysitis,	

				nevertheless these often have other accompanying symptoms as well)" [3]	
			R4	"In line with comment 3 above" [7]	None
GU03	Vaginal discharge	2	--	None	None
GU04	Vaginal dryness	2	--	None	None
GU05	Painful urination	2	--	None	None
GU06	Urinary urgency	N/A	R	"Similar to above" [11] The expert is referring to their comment on symptom [ES56] Urinary retention: "*neurological/CNS, renal tox, metastases*" "probably unrelated unless accompanied with other symtpoms" [3]	None
			4	"I go with the other experts - i´m unsure of this symptoms" [7]	
GU07	Urinary frequency	1	R3	"endocrine, renal tox, non-bacterial cystitis" [11] "can have many reasons (difference between men and women)" [2] "might indicate bladder infection, should be checked, is not life treatening and only very rarely related to immunotherapy" [3]	None

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
GU08	Change in usual urine colour	N/A	R3	"over time and for a long time, hepatic/ renal etc" [11] "It may a sign of inflamation of the liver/hepatitis (due to immunotherapy) and accordingly, I believe that it is rather important" [7] "Hematuria seems to have priority over the elements to be identified" [8] "if not other symptoms, this is not important to me" [3]	Change in urine colour by itself would be hard to qualify from the importance point of view. Experts believe that it should be underlined this change in color is evident/severe or very different from usual. Otherwise, patients may believe that normal

				“traces of blood, kidney or liver problems...” [9]	color variation (due to slight dehydration or overhydration) is a cause for alarm.
				“needs rephrasing please (strong changing in urine colour)” [5]	
			R4	“I have changed my answer. I agree with what has been written under observations though it may be a sign og increased liver parameters” [7]	
				“if specified as strong change in the color” [9]	
GU09	Urinary incontinence	N/A	R3	“non-bac cystitis, endocrine, under-reporting (RT in bladder cancer and ICI) neurological CNS” [11]	None
				“might indicate neurological problems usually related to tumor progression rather than immunotherapy” [3]	
			R4	“If this is a new symptom” [2]	

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
SX01	Achieve and maintain erection	2	R3	“Various cancer agents may impact the ability to achieve and/or maintain erection. It is not, however, well established in the literature that that it is a side effect to immunotherapy. It may be an	None

				underexplored area due to the fact that patients are very often not asked questions about their sexuality.” [7] "probably unrelated to IT" [3]	
SX02	Ejaculation	2	R3	"aspecific symptom [10] important to address, nevertheless probably unrelated unless hormonal problems are present (usually other symptoms as well then) [3]	None
SX03	Decreased libido	2	R3	psych issues and physical [11] "=aspecific symptom (can be related to many other confounding factors)" [10] “important to address, nevertheless probably unrelated unless hormonal problems are present (usually other symptoms as well then)” [3] “unspecific for IrAEs" [9]	None
SX04	Delayed orgasm	2	--	None	None
SX05	Unable to have orgasm	2	R3	“Downgraded” [2] “aspecific symptom” [10] “important to address, nevertheless probably unrelated unless hormonal problems are present (usually other symptoms as well then)” [3] “unspecific for IrAEs” [9]	None
SX06	Pain with sexual intercourse	N/A	R3 R4	"endocrine/mucosae, psy" [11] “can have many reasons. unpleasant for patients. Unlikely irAE” [2] "aspecific symptom" [10] “important to address, nevertheless probably unrelated” [3] “Unlikely irAE as decribed above” [7]	None

Item Code	Item Name	Level	Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
MS01	Breast swelling and tenderness	2	R3	"endocrine under-reported" [11] “important to address, nevertheless probably unrelated unless hormonal problems are present (usually other symptoms as well then)” [3] "hormones, inflammation" [9]	None
MS02	Bruising	2	R3	“corticosteroids/misuse of pain releif due to pain etc” [11] “could point towards platelet problem” [2] “might indicate thrombopenia" [3] "related to bleeding" [9]	None
MS03	Chills	1	--	None	None
MS04	Increased sweating	2	--	None	None
MS05	Decreased sweating	2	--	None	None
MS06	Hot flashes	1	R3	“endocrine under-reported, endocrine mets ??” [11] “Sign of hyperthyroidism” [8] “important to address, nevertheless probably unrelated unless hormonal problems are present (usually other symptoms as well then)” [3] “Hormones” [9]	None
MS07	Nosebleed	N/A	R3	"aplas anaemia ? cytopaenias ?" [1] “might indicate underlying thrombopenia” [3]	None
MS08	Pain and swelling at injection site	2	R3	“Not subcutaneous injection but sign of allergy” [1] “precursor to more serious perfusion related AEs” [11] “might indicate skin infection, should be treated but generally unrelated” [3]	Experts believe this item needs to be more specific – in these patients, it’s likely only related to the ICI infusions, and it could be seen as covered by the other expert-suggested item, “Infusion-related reaction”.
			R4	“Agree with what is written under observations” [7] “To discuss” [9]	
MS09	Body odor	3	--	None	One exerts claimed that in pediatric patients, mothers notice their smell changes significantly, which can be very surprising. Other experts were not familiar with this symptom.

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES01	Abdominal cramps	N/A	R3	“Unspecific sign of many condition: obstipation, ileus, colitis etc” [1]	Experts suggest that this symptom could perhaps be covered by “Abdominal pain” instead of “Abdominal cramps”, but concede the latter is a specific kind of pain that patients may be able to distinguish.
				“It all depends on the time you suffer this symptom, if it is associated with other symptoms like diarrhoea for months and you have to try and work/travel it becomes quite life impacting - also in women this is underreported as assumptions are made about "normal functions" which can be affected by these treatments” [11]	
				“Can have many reasons, one of which is IrAE. Depending on the frequency and intensity it can be moderate or more important.“ [2]	
				“It is well established that abdominal pain is a side effect to immunotherapy. I am not so sure about cramps, however. I believe that the term can be adequately covered by abdominal paim.” [7]	
				“I am switching to “Very important” since it seems to me diarrhoea is often associated to abdominal cramps and can become an emergency that requires further assessment.” [8]	
				“possible symptom of colitis, but at risk not to be considered as important by the patient, thus not reported spontanouesly“ [10]	
				“only important if long lasting or if accompanied by diarrhea” [3]	
				“could be integrated as abdominal pain” [9]	
			R4	“As mentioned by some in the comments, I belive that the symptom can be covered by abdomimal pain” [7]	
ES05	Back pain	2	R3	“bone mets, renal, hepatic pleural etc” [11]	None
				“very common symptom. Not often irAE” [2]	
				“important to treat, in general unrelated unless other symptoms are present” [3]	
				“I find it very important in the sense that it determines the localization of the pain (back)” [9]	
ES06	Blisters	1	R3	“can be painful, indicative of worsening dermatological AEs (cellulitis) , hard to sleep etc associated with photo-tox etc” [11]	None
				“could be a sign of bullous pemphigus or other severe skin disease. In my opinion a very serious sign” [2]	

				“maybe this should be complied with itching: itching and blisters (bullae)” [10] “it might indicate bulleus disease (which might precede steven johnson syndrome)” [3]	

SYMPTOMS SUGGESTED BY EXPERTS (2/7)

EXPERTS

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES07	Blood in stool	1	--	None	None
ES09	Change in urine smell	2	R1	Despite limited evidence in the literature, the **IG** reviewed this item and confirmed it could occur in practice and could be detected by the patient. The item passed to the 2nd Round to be reviewed by experts. **[IG]**	None
ES10	Chest pain	1	--	None	None
ES11	Clumsiness	2	R3	"neurological/CNS mets/bleeds etc" [11] "aspecific symptom "[10] “might indicate underlying neurological problem” [3]	None
ES12	Cold/heat sensitivity	2	R1	When asked to clarify, the expert suggesting this item referred to ocular cold and heat sensitivity, associated with dry eyes. **[IG]**	None
ES13	Confusion	1	--	None	None
ES14	Congestion	2	R3	"impaired sleep/sleep apnea is debilitating again depends on for how long people suffer this and whether can adapt" [11] “i confirm, this might be a rare side effect and associated to dry mouth syndrome” [3]	None
ES15	Coordination problems	1	--	None	None
ES16	Muscle cramps	2	R3	"electrolyte imbalance/endocrine side effects often missed" [11] “Nasty for patient. Could be electrolyte disturbance.” [2] “in general not related” [3]	As requested by all experts, “Cramps” was changed to “Muscle cramps”
ES17	Depressive mood	2	--	None	Experts comment that Hopelessness and Depressive mood are hard to qualify, and that data on them is lacking. Nevertheless, most experts argued existing PRO-CTCAE™ Items do not cover depressive mood.

ES18	Difficulty with eyes/facial movements	1	--	None	None
ES19	Diplopia/double vision	1	--	None	None
ES20	Epilepsy	1	R1	While Epilepsy isn't conceptually a PRO, it was argued patients can identify it when educated. The Investigator Group thus approved the item and passed it to the 2nd Round to be reviewed by experts. **[IG]**	None
ES21	Eye pain	1	--	None	None

SYMPTOMS SUGGESTED BY EXPERTS (3/7) EXPERTS

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES22	Eye redness	N/A	R3	"similar to above* , also retinopathy etc ? [11] Previous answer for Dry eyes: leads on to more serious issues uveitis, infection, other auto-immune" “Could be sign of uveitis and this should be taken serious.” [2] “I have changed my mind on this question. Eye redness may be a sign og uveitis. Eye redness can be detected by the patients, be immune-related and be consequential.” [7] “might be uveitis so ok to change to moderatly important [3] “sign of eye inflammation” [9]	None
ES23	Fever	1		While Fever isn't conceptually a PRO, it was argued patients can identify it when educated. The Investigator Group thus approved the item and passed it to the 2nd Round to be reviewed by experts. **[IG]**	None
ES24	Flu-like symptoms	1	R4	“This symptom is easy to detect for the patients, it is likely to be connected and it is consequential due to the fact that some patients experience it after each infusion” [7]	None
ES25	General Malaise	1	--	None	None
ES26	Hearing loss	1	--	None	None
ES27	Hemoptysis	1	--	None	None
ES28	Hopelessness	2	--	None	Experts comment that Hopelessness and Depressive mood seem hard to qualify, as there isn’t enough data to argue how often they are present

ES29	Impaired distance assessment	2	--	None	None
ES30	Increased appetite	2	--	None	None
ES31	Infusion-related reaction	N/A	R3	“bad if anaphylactic but to monitor” [11] “Perfusion reactions are often visible during their administration, and rarely after (at least I think so).” [8] (Translated from French) « not dangerous » [10] “might be related, can generally be treated with paracetamol, no underlying life treatening condition” [3] "Rare" [9]	Experts suggest the term could perhaps be replaced by more precise symptoms that can come from the infusion of the treatment (ICIs); "reaction" is too broad of a term.
			R4	“It is usually seen during the infusion and more often in the adjuvant setting”. [7] “during administration in the clinics. Could be defined as other symptoms in the list” [9] “we need to clarify what we understanf for "reaction"” [4]	

SYMPTOMS SUGGESTED BY EXPERTS (4/7) EXPERTS

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES32	Irritability	2	R3	“personality changes, stress, sleep loss, endocrine” [11] "downgraded to slightly" [2] « I'll answer with one example of a patient I cared for that did not know of this side-effect. Neither her close ones nor herself understood why she underwent a radical mood change. I believe it would reassure patients if this item is tracked.” [8] “is a symptom of depression, and can be a symptom of neurological irAE” [10] “i agree, if other symptoms accompany then this must be further analysed, if not, I think its not related and can be 'treated' if it lasts chronically” [3]	None
ES33	Joint stiffness	1	--	None	None
ES34	Lack of motivation	2	--	None	None
ES35	Light sensitivity / Photophobia	1	--	None	None
ES36	Loss of interest	2	--	None	None
ES37	Loss of sensitivity	1			None

ES38	Muscle weakness / Paresis	1	--	None	None
ES39	Neck stiffness	2	R3	"bone mets, leptomeningeal mets, neurological complications" [11] “could point towards aseptic meningitis, but if it is only neck stifness that is unlikely” [2] “might indicate aseptic meningitis” [10]	None
ES40	Nervousness	2			None
ES41	Oral itchiness	2			None
ES42	Over-alertness	N/A	R4	"Convinced" [5] “Again I think it should be able to choose but not initially presented” [1] “I have changed my answer” [7] “I change my answer” [4]	A lot of discussion around this item – some experts believe this could be related to endocrinal or neurological changes, while others find this to me more often the result of corticosteroids. HP suggests this symptom could be an option but not show up in the patient questionnaires by default (level 2).

SYMPTOMS SUGGESTED BY EXPERTS (5/7) EXPERTS

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES43	Pain in extremities	1	--	None	None
ES44	Paralysis	1	--	None	None
ES45	Rectal bleeding	1	--	None	None
ES46	Sleepiness	N/A	R3	"endocrine, depression, neuro-inflammatory, CNS functional issues" [11] "Downgraded" [2] "aspecific symptom" [10] “underlying cause should be looked for, the underlying cause might be important and require treatment” [3]	None
ES47	Slow reflexes	1	R3	“Do not see the conection to iR AE” [1] “linked to fatigue, spinal chord issues etc” [11] “Could be a sign of peripheral neuropathy as irAE. For patient not serious.” [2] “can be a sign of neurological irAE” [10]	None

				“i agree, neverheless wil be accompanied in general by other symptoms and one should be able to confirm with earlier clinical examinations” [3]	
ES48	Sore eyes	N/A	R3	“can lead to uveitis/retinopathy, sensitivity to light etc [11] could be uveitis" [2] "symptom of uveitis" [10] “if accompanied by other symptoms this is important, otherwise not” [3] “too unspecific for IrAEs” [9]	None
ES49	Speaking problems	1	--	None	None
ES51	Symptom-related fatigue	N/A	--	None	None
ES52	Syncope	1	R3	“It could be linked with brain metastases, and serious cardio side effects, extremely distressing for patients if not acted upon.” [11] “could point towards arrhythmia and this myocarditis” [2] “in our view this will be spontaneously reported by the patient” [10] “i agree, myocarditis should be excluded” [3]	None
			R4	“I have never seen thsi in the clinic in relation to immunotherapy, but all the other experts agree on this symptom, so I go with that.” [7]	
ES53	Thirst	1	--	None	None

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round	Round 4 discussion observations
ES54	Twitching	N/A	R3	“can be issues of new CNS metastasis, or other neurological issue, CK issues, myositis etc” [11] “downgraded. Not so serious for the patient. could be a sign of neuro-tox” [2] “can be a sign of neurological irAE” [10] “i agree, there shoud be other symptoms as well if problematic” [3] “not specific enough in the context of IrAEs” [9]	None
ES55	Unsteady walk / Walking difficulties	1	--	None	None

ES56	Urinary retention	1	R3	“neurological/CNS, renal tox, metastases” [11] “could be sign of polyneuropathy or other neuro-tox” [2] "might indicate neurological problem" [3]	None
			R4	“Since there seems to be agreement among the other experts, I go with rather important. I have not, however, seen this in the clinic.” [7]	
ES57	Visual loss	1	--	None	None
ES58	Worries	3	R4	“would need improved specification” [9]	Several experts noted that this term was unclear and needs a clearer description. It was commented that worries and anxiety may be difficult to distinguish. Despite agreeing that the distinction was difficult, experts [10] and [11] defended the use of this term, noting that feeling worried may not result in anxiety. Despite most experts agreeing with that assessment, they also believed that tracing this symptom to ICIs would be very difficult.
ES59	Swelling of the joints	1	--	None	None
ES60	Heat or burning sensation in an area of the body	N/A	--	None	None

SYMPTOMS SUGGESTED BY EXPERTS (6/7)

EXPERTS

Item Code	Item Name	Level	Written Comments from Experts [1 – 11] and the Investigator Group [IG] by Round		Round 4 discussion observations
ES61	White spots/patches/Vitiligo	2	R4	“changed my mine [mind] ...though important” [5]	None
VP06	Dry eyes	1	R3	“leads on to more serious issues uveitis, infection, other auto-immune” [11] “could be sign of sicca syndr” [2]	None

				“a symptom of sjorgen” [10]
				“not life threatening, it is generally linked to immunotherapy, symptomatic treatment indicated” [3]
				“One of the four most frequent ocular adverse events together with uveitis, ocular myasthenia and eye inflammation.” [9]

Appendix 2: IePRO app setup guide

IEPRO MODE D'EMPLOI

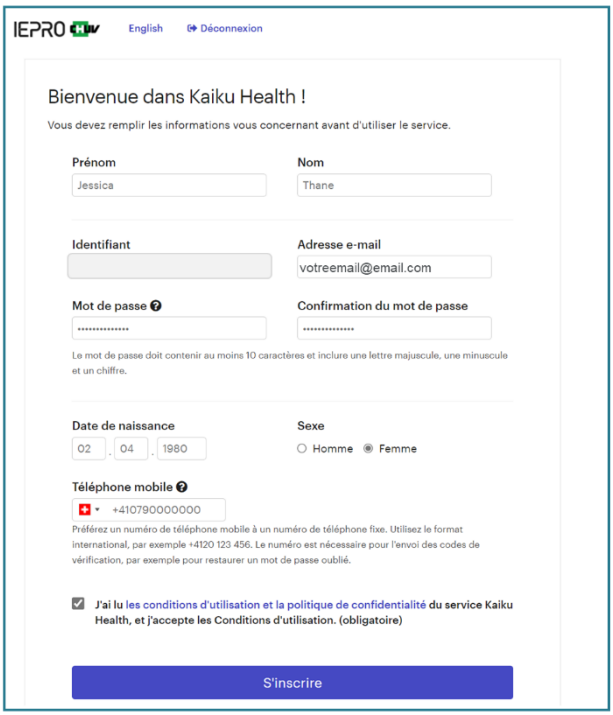
Vous êtes inscrit·e dans le Groupe Numérique.

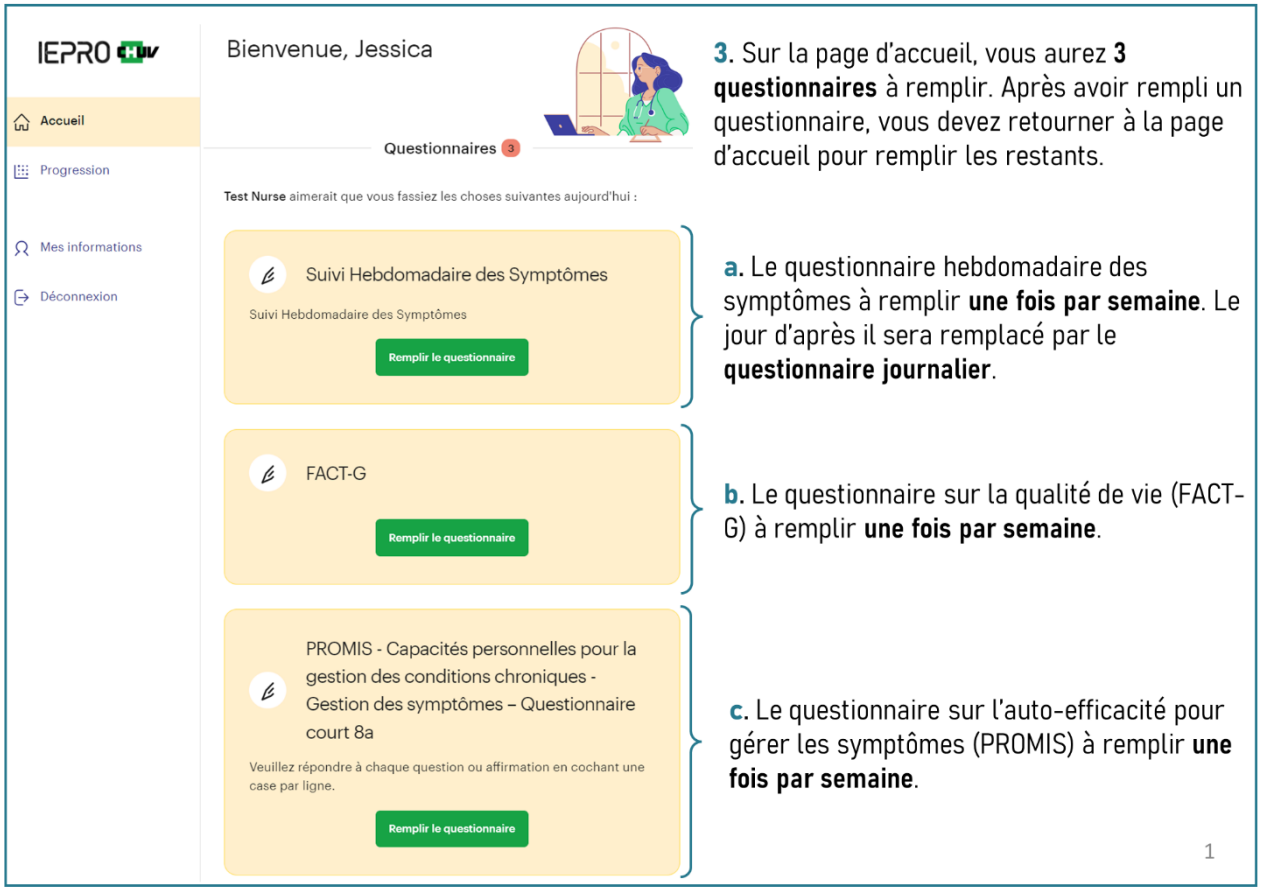
IePRO Information sheet, Version *1 of date 08.03.2022*

A. S'inscrire dans l'application électronique pour remplir les questionnaires

1. Vous recevrez un e-mail avec une invitation à joindre l'application IePRO.

2. Sur la nouvelle page, remplissez toutes les informations nécessaires et cliquez « S'inscrire ».





3. Sur la page d'accueil, vous aurez **3 questionnaires** à remplir. Après avoir rempli un questionnaire, vous devez retourner à la page d'accueil pour remplir les restants.

a. Le questionnaire hebdomadaire des symptômes à remplir **une fois par semaine**. Le jour d'après il sera remplacé par le **questionnaire journalier**.

b. Le questionnaire sur la qualité de vie (FACT-G) à remplir **une fois par semaine**.

c. Le questionnaire sur l'auto-efficacité pour gérer les symptômes (PROMIS) à remplir **une fois par semaine**.

IEPRO MODE D'EMPLOI

Vous êtes inscrit·e dans le Groupe Numérique.

B. Remplir un questionnaire

1. Une fois que vous ouvrez un questionnaire, vous aurez plusieurs options:

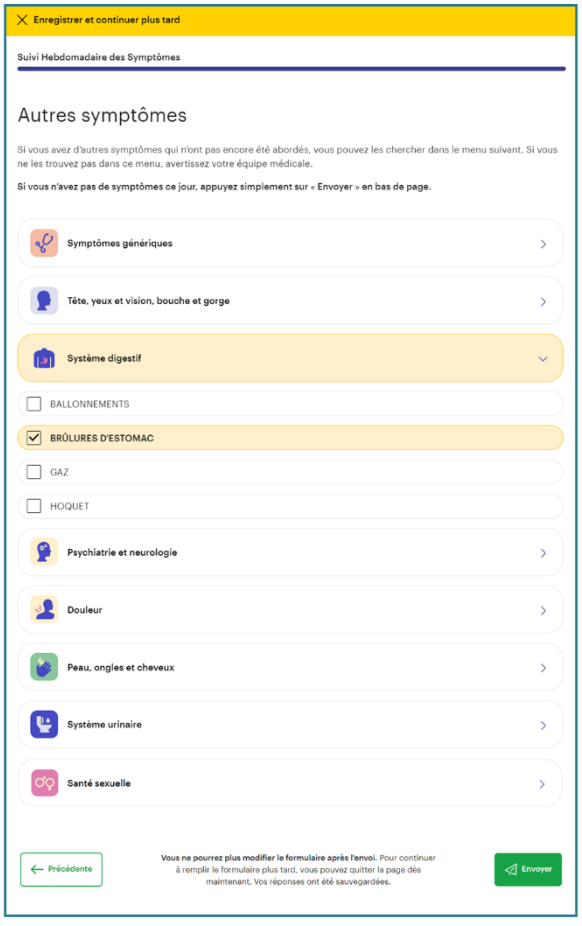
Enregistrer le questionnaire pour le remplir plus tard.

En cliquant ici, vos réponses sont enregistrées **mais ne sont pas envoyées à l'équipe soignante**. Vous êtes ensuite renvoyé à la page d'accueil.

En rouvrant le questionnaire, vous pouvez continuer à le remplir.

C. Ajouter d'autres symptômes au questionnaire des symptômes hebdomadaire et journalier

Après la dernière question du questionnaire des symptômes, vous avez l'option d'en ajouter d'autres:



Cliquez sur une catégorie pour dévoiler les options. Choisissez celles que vous voulez.

En cliquant sur « Suivant → », le questionnaire continuera avec les questions concernant le(s) symptôme(s) choisi(s).

Une fois le questionnaire terminé, vous pouvez cliquer sur le bouton Envoyer

Il vous sera alors possible de consulter un résumé de vos réponses.

Si vous n'avez déclaré aucun symptôme, vous rencontrerez cet écran de sélection lorsque vous ouvrirez le questionnaire journalier sur les symptômes.

- **Installez l'application Kaiku ou allez sur https://chuv.kaiku.ch pour remplir les questionnaires les jours suivants.**
- **Si vous avez un problème avec l'application ou si vous avez déclaré un symptôme par erreur, merci de nous le signaler rapidement à : do.id.iepro@chuv.ch**

Appendix 3: Mobile application usability interview guide

For: Development of an ehealth-enhanced model of care for the monitoring and management of immune-related adverse events in patients treated with immune-checkpoint inhibitors (2022)

Based on the mHealth App Usability Questionnaire (MAUQ) by Zhou L et al (2019) [1]
The original French version of this semi-structured interview guide was translated to English

When interviews will be conducted:	Within 2 weeks after the trial, the same day of a scheduled follow-up consultation.
Where interviews will be conducted:	On site, in a closed, private room.
Who will conduct the interviews	Study investigators

THEMES AND GUIDING QUESTIONS
WELCOME & INTRODUCTION Thank you for your participation - we are all very grateful for your time and cooperation. We would like to record these discussions so that we can listen to them again if necessary, to ensure that we don't miss any of the ideas or issues raised. The details of these discussions will not be shared with anyone else outside this study; your name will be kept confidential and no one else will know what was said during our conversations. Please feel free to express your opinions openly in order to get the best possible representation of reality. We are particularly interested in areas that can be improved. If you are not comfortable with these elements you are not obligated to participate. Are you willing to participate in this interview? This is an open space to discuss your experience.

1. How do you feel about the usability of this application?	
Follow-up questions:	How do you like the navigation of the application?
	How was it to find what you were looking for in the application?
	Can you give examples of easy or difficult things about it?
2. How did you find the information provided by the application?	
Follow-up questions:	What do you think about the clarity of the information provided by the application?
	Did the information seem relevant to you?
3. How do you feel about the time it took you to use the application?	
Follow-up questions:	How long do you think it took you to use it per day?
4. Have you used this application in public? Did you feel comfortable doing so?	
Follow-up questions:	If not, can you explain why?
5. How has this application affected your interactions with healthcare professionals?	
Follow-up questions:	Has it influenced your interactions with healthcare professionals (physicians, nurses,...)?
	Can you give an example?
	Can you explain why?
6. Was there a moment when you questioned if your answers to the questionnaires had reached the nurse?	
Relance	If so, when and why?

Relance	If not, why ?
7. Overall, what did you think of the application? Did it meet your expectations?	
Follow-up questions:	Did the application meet your expectations? (If so/not,) Can you explain why?
	Did you like it or dislike it? Can you point out any reasons for this?
8. Between 0 and 10, how would you rate your overall experience with the application (0 - Poor, 10 - Excellent)?	
9. Would you recommend it to other people with cancer?	
Follow-up questions:	If so, why ?
	If not, why not ?
10. Do you have any other comments or observations about the application that you would like to share?	

[1] Zhou L, Bao J, Setiawan IMA, Saptono A, Parmanto B. The mHealth App Usability Questionnaire (MAUQ): Development and Validation Study. JMIR Mhealth Uhealth 2019;7:e11500. https://doi.org/10.2196/11500.

Appendix 4: Semi-structured interview for patients to assess the acceptability of the IePRO model of care

For: Development of an ehealth-enhanced model of care for the monitoring and management of immune-related adverse events in patients treated with immune-checkpoint inhibitors (2022)

Based on Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework by Sekhon et al, 2017 [1]
The original French version of this semi-structured interview guide was translated to English

When interviews will be conducted:	Within 2 weeks after the trial, the same day of a scheduled follow-up consultation.
Where interviews will be conducted:	On site, in a closed, private room.
Who will conduct the interviews	Study investigators

THEMES AND GUIDING QUESTIONS

WELCOME & INTRODUCTION

- Thank you for your participation - we are all very grateful for your time and cooperation.
- We would like to record these discussions so that we can listen to them again if necessary, to ensure that we don't miss any of the ideas or issues raised. The details of these discussions will not be shared with anyone else outside this study; your name will be kept confidential and no one else will know what was said during our conversations. Please feel free to express your opinions openly in order to get the best possible representation of reality. We are particularly interested in areas that can be improved.
- If you are not comfortable with these elements you are not obligated to participate. Are you willing to participate in this interview?
- This is an open space to discuss your experience.

1. When you think about this model of care, how do you feel?	
Follow-up questions:	Do you feel safe or unsafe, relieved or frustrated about the care?
2. What were your expectations of this model of care at the beginning of this study? To what extent have they been met?	
3. How did you feel when you received a call from the nurse?	
Follow-up questions:	What was your experience with the nurse interactions over the phone?
4. Do you feel like you needed to make a significant effort to participate in this type of care?	
Follow-up questions:	If so, can you give examples of this effort? If not, why?
5. Do you feel that this model of care has impacted the way you manage your symptoms?	
Follow-up questions:	Do you feel that this way of providing care has played a role in how you manage your symptoms?
	Did this type of care work for you or not work for you in managing your symptoms?
	Do you feel that the electronic application played a role in how you manage your symptoms?

[1] Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Services Research 2017;17. *https://doi.org/10.1186/s12913-017-2031-8*.

Appendix 5: Semi-structured interview for nurses to assess the implementation of the IePRO model of care

For: Development of an ehealth-enhanced model of care for the monitoring and management of immune-related adverse events in patients treated with immune-checkpoint inhibitors (2022)
Based on the Consolidated Framework for Implementation Research (CFIR) guide: *https://cfirguide.org/guide/app/guide.html*
The original French version of this semi-structured interview guide was translated to English

When interviews will be conducted:	Within 6 weeks after the trial, individually.
Where interviews will be conducted:	On site, in a closed, private room.
Who will conduct the interviews	Study investigator

Outer Setting
Patient Needs & Resources

1. To what extent were the needs and preferences of the patients considered when deciding to implement the ePRO-based model of care?
    - Can you describe specific examples?
    - Will the ePRO-based model of care be altered to meet their needs and preferences?
2. How well do you think the ePRO-based model of care will meet the needs of patients?
    - In what ways will the model of care meet their needs? E.g. improved access to services? Reduced wait times? Help with self-management? Reduced travel time and expense?
3. How do you think the patients will respond to the ePRO-based model of care?
4. What barriers will the patients face to participating in the ePRO-based model of care?
5. Have you heard stories about the experiences of participants with the intervention?
    - Can you describe a specific event?

Inner Setting
Structural Characteristics

1. What kinds of infrastructure changes will be needed to accommodate the ePRO-based model of care?
    - Changes in scope of practice? Changes in formal policies? Changes in information systems or electronic records systems? Other?
    - What kind of approvals will be needed? Who will need to be involved?
    - Can you describe the process that will be needed to make these changes?

Characteristics of Individuals
Knowledge & Beliefs about the Intervention

1. How do you feel about the ePRO-based model of care being used in your setting?
    - How do you feel about the plan to implement the intervention in your setting?
    - Do you have any feelings of anticipation? Stress? Enthusiasm? Why?

Self-efficacy

1. How confident do you think your colleagues feel about using the intervention?
    - What gives them that level of confidence (or lack of confidence)?

Process
Executing

1. Has the intervention been applied during the study according to the plan?
    - [If Yes] Can you describe this?
    - [If No] Why not?

Other important issues related to the ePRO-based model of care

1. Is there any other theme or issue that you would like to share regarding your experiences with the ePRO-based model of care?

[1] Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Services Research 2017;17. https://doi.org/10.1186/s12913-017-2031-8.

Appendix 6: Model informed consent form for the IePRO RCT (in French)

Test d'un modèle de soins basé sur les symptômes rapportés électroniquement par les patients atteints d'un cancer et traités avec des inhibiteurs du point de contrôle immunitaire: une étude de phase II = IePRO

Cette étude est organisée par : Prof. Manuela Eicher, directrice UNIL-CHUV

Madame, Monsieur,

Nous vous proposons de participer à notre projet de recherche. Cette feuille d'information décrit le projet de recherche, d'abord dans une version courte (résumé), comme s'il s'agissait d'une table des matières, puis dans une version longue (version détaillée).

Résumé

1	Objectifs de l'étude Par la présente, nous vous proposons de participer à notre étude clinique portant sur un modèle de prise en charge complémentaire aux soins standards. Cette étude concerne les patient atteints d'un cancer, traités avec une immunothérapie par inhibiteurs du point de contrôle immunitaire. Nous effectuons cette étude pour vérifier l'efficacité d'un nouveau modèle de soins pour la détection précoce des effets indésirables liés au traitement. Ce modèle de soins utilise les symptômes rapportés par les patients à l'aide d'une application électronique. L'objectif de cette étude est de déterminer si ce modèle pourrait permettre une intervention plus rapide et une meilleure gestion des éventuelles complications liées au traitement.
2	Sélection des personnes Vous souffrez d'un cancer et vous êtes sous un traitement d'immunothérapie par des inhibiteurs du point de contrôle immunitaire. C'est la raison pour laquelle nous vous faisons parvenir cette feuille d'information.
3	Informations générales sur le projet Cette étude se base sur l'utilisation d'une application électronique (disponible sur l'ordinateur, tablette ou smartphone) qui vous permettra de signaler vos symptômes, d'évaluer votre sentiment d'auto-efficacité pour les gérer et la perception de votre qualité de vie, au moyen d'un questionnaire, à distance. Cette application a un marquage CE (conformité européenne). Si vous décidez de participer à cette étude vous serez répartis aléatoirement sur deux groupes, correspondant à deux méthodes de gestion des symptômes : le groupe « soins standards » et le groupe « numérique ». Cette répartition est faite automatiquement sur un ordinateur, une fois que vous aurez donné votre consentement pour l'étude. Vous aurez la même probabilité d'être répartis dans l'un des deux groupes. La durée de participation est de 6 mois et l'étude sera réalisée sur deux sites, dans les départements d'oncologie du Centre Hospitalier Universitaire Vaudois (CHUV) et des Hôpitaux Universitaires de Genève (HUG). Sur l'ensemble des sites, 198 patients participeront à cette étude.
4	Déroulement pour les participants Tous les participants de l'étude auront le même nombre de consultations et le même accès aux soins que les personnes qui ne participent pas à cette étude. Les modalités de prise en charge dans cette étude sont complémentaires à la prise en charge habituelle. Les deux groupes de participants auront accès à une application électronique avec deux questionnaires : un sur leur sentiment d'auto-efficacité (« auto-confiance ») à gérer les

	symptômes et un sur la qualité de vie. Ces questionnaires sont à remplir une fois par semaine et prennent environ 15 minutes. Au-delà des soins normaux, si vous êtes attribués au groupe « soins standards », vous répondrez à ces deux questionnaires une fois par semaine pendant six mois. **Si vous êtes attribué au groupe « numérique »,** vous aurez accès aux mêmes questionnaires que le groupe « soins standards » et à un questionnaire supplémentaire qui vous permettra de déclarer vos symptômes liés au traitement : • Pendant les 3 premiers mois de l'étude, l'application vous demandera de réévaluer vos symptômes actifs tous les jours, avec une version courte du questionnaire (« questionnaire journalier »). • À partir du quatrième mois et jusqu'à la fin de l'étude, vous répondrez uniquement à une version hebdomadaire, une fois par semaine. Une équipe d'infirmier·ère·s relèvera les symptômes déclarés et contactera les participants par téléphone pour les soutenir dans la gestion des symptômes, les jours ouvrables entre 8h et 12h. En dehors de ces horaires, vous devrez contacter le médecin oncologue de garde. En aucun cas ces mesures doivent remplacer un appel à votre médecin oncologue, et vous devrez le contacter directement si vous êtes concerné par un ou plusieurs symptômes, ou si vous avez des questions concernant vos symptômes et votre traitement.
5	Bénéfices pour les participants Si vous participez à l'étude, cela pourra éventuellement vous aider à développer des connaissances plus approfondies sur les méthodes de surveillance et de gestion des effets indésirables liés au traitement avec une immunothérapie par inhibiteurs du point de contrôle immunitaire. Et il se peut que vous tiriez un bénéfice dans la prise en charge de vos symptômes. Les résultats de l'étude pourraient se révéler importants par la suite pour les personnes qui seront touchées par la même maladie que vous.
6	Droits des participants Vous êtes libre d'accepter ou de refuser de participer à l'étude. Si vous décidez de ne pas participer, cela ne changera rien à votre prise en charge médicale. Vous n'avez pas à justifier vos décisions.
7	Obligations des participants Si vous décidez de participer à l'étude, vous devrez observer certaines règles : ▪ Vous devrez informer votre médecin et/ou équipe clinique de tout nouveau symptôme ou nouveau trouble, et de tout changement dans votre état de santé. **L'information que vous rapportez dans cette étude NE SE SUBSTITUE PAS à la communication avec votre médecin / équipe clinique**. ▪ Vous devrez poursuivre les instructions médicales de votre oncologue et de l'équipe clinique. ▪ Vous devrez suivre le plan de l'étude (remplissage des questionnaires, consultations téléphoniques et présentielles, entretiens, aux dates indiquées) pour son bon déroulement.
8	Risques La participation à cette étude ne comporte pas de risques si ce n'est éventuellement des risques mineurs liés à la charge émotionnelle de participer aux entretiens et de compléter les questionnaires. Il se peut que certaines questions, présentes dans les questionnaires ou discutées lors des entretiens, puissent vous affecter émotionnellement. Vous pourriez, en effet, prendre conscience d'éventuelles difficultés ressenties et éprouver une certaine charge émotionnelle à cet égard. Vous pourriez en autre avoir un faux sentiment de sécurité en utilisant l'application ePRO en vous attendant à recevoir une réponse immédiate de l'équipe d'oncologie en cas de survenue de symptômes graves. En cas de

	symptômes perçus comme graves, veuillez contacter directement l'équipe de oncologie. D'autres risques encore inconnus peuvent également exister.
9	**Confidentialité des données et des échantillons** Nous respectons toutes les dispositions légales relatives à la protection des données. Toutes les personnes impliquées sont soumises au secret professionnel. Vos données personnelles et médicales seront protégées et utilisées sous une forme codée. Les données vous concernant pourront être réutilisées dans d'autres projets de recherche si vous y consentez expressément en signant le document prévu à cet effet.
10	Retrait de l'étude Vous pouvez à tout moment vous retirer du projet si vous le souhaitez. Les données médicales recueillies jusque-là seront analysées malgré tout.
11	Compensation des participants Si vous participez à cette étude, vous ne recevrez pour cela aucune compensation.
12	Réparation des dommages subis Le Centre Hospitalier Universitaire Vaudois (CHUV) (promoteur) qui a initié l'étude et est en charge de sa réalisation, est responsable des dommages que vous pourriez subir en relation avec les activités de recherche.
13	Financement de l'étude L'étude est financée par l'Institut Suisse de Recherche Expérimentale sur le Cancer (ISREC) et par Kaiku Health Ltd.
14	Interlocuteur(s) Vous pouvez à tout moment poser toutes vos questions et demander toutes les précisions nécessaires aux personnes suivantes : André Lopes (collaborateur scientifique) [Contact information redacted for publication] Stellio Giacomini (collaborateur scientifique) [Contact information redacted for publication] Célia Darnac (collaboratrice scientifique) [Contact information redacted for publication] Dr. Sofiya Latifyan (Investigatrice Principale): [Contact information redacted for publication] Prof. Manuela Eicher (co-Investigatrice et représentante du Sponsor) [Contact information redacted for publication]

Information détaillée

1. Objectifs de l'étude

Nous vous remercions de votre intérêt et de votre participation à cette étude. Cette étude devrait nous permettre de savoir dans quelle mesure une surveillance à distance complémentaire des symptômes est utile dans la détection précoce des effets indésirables liés du traitement, améliorant la prise en charge des patients traités avec des inhibiteurs de points de contrôle immunitaire.

2. Sélection des personnes pouvant participer à l'étude

La participation est ouverte à toutes les personnes de 18 ans ou plus, et souffrant d'un cancer traité avec des inhibiteurs du point de contrôle immunitaire au département d'oncologie du Centre Hospitalier Universitaire Vaudois (DO-CHUV) ou des Hôpitaux Universitaires de Genève (HUG).

Elle est en revanche fermée aux personnes qui ne se considèrent pas capables d'utiliser un outil électronique (sur un smartphone, tablette ou ordinateur) avec des questionnaires en langue française. Sont également exclues de l'étude les personnes diagnostiquées avec des perturbations cognitives, ainsi que des limitations psychologiques, sociologiques ou linguistiques qui pourraient empêcher les personnes de répondre aux obligations de l'étude. Les personnes inscrites dans d'autres études cliniques interventionnelles sont aussi exclues.

3. Informations générales sur l'étude

- Vous allez recevoir un traitement d'immunothérapie par des inhibiteurs de point de contrôle immunitaire. Ce traitement peut produire des effets indésirables, manifestés par certains symptômes, qui doivent être surveillés et traités.
- Cette étude propose une prise en charge complémentaire aux soins normaux, pour vérifier si les effets indésirables du traitement peuvent être détectés plus rapidement et surveillés d'une manière plus efficace.
- L'étude se base sur l'utilisation d'une application électronique (disponible sur l'ordinateur, tablette ou smartphone) qui vous permettra de signaler vos symptômes, d'évaluer votre sentiment d'auto-efficacité à les gérer et la perception de votre qualité de vie, au travers d'un questionnaire, à distance. Cette application a un Marquage CE (conformité européenne).
- Si vous décidez de participer à cette étude, vous serez répartis aléatoirement dans un des deux groupes, correspondant à deux méthodes distinctes de gestion des symptômes : le groupe « soins standards » et le groupe « numérique ». Cette répartition sera faite automatiquement par un ordinateur, lorsque que vous aurez donné votre consentement pour l'étude. Vous aurez la même probabilité d'être répartis dans l'un des deux groupes.
- La durée de participation est de 6 mois, afin de collecter suffisamment de données pour répondre aux objectifs de l'étude. Une fois terminée, votre prise en charge se maintiendra selon les procédures standards. Cette étude sera réalisée sur deux sites, dans les départements d'oncologie du Centre Hospitalier Universitaire Vaudois (CHUV) et des Hôpitaux Universitaires de Genève (HUG). Sur l'ensemble des sites, 198 patients participeront à cette étude.

- Nous effectuons cette étude dans le respect des prescriptions de la législation Suisse. Nous suivons en outre l'ensemble des directives reconnues au niveau international et de la commission cantonale d'éthique compétente.
- Vous trouverez aussi un descriptif de l'étude sur le site Internet de l'Office Fédéral de la Santé Publique : www.kofam.ch

4. Déroulement pour les participants

Si vous acceptez de participer à l'étude, vous serez aléatoirement attribué à l'un des deux groupes de l'étude (groupe « soins standards » et groupe « numérique »). Vous trouverez à la fin de cette feuille d'information un schéma du déroulement de l'étude.

Pour les participants du groupe « soins standards » :
Vous serez informé par votre oncologue des potentiels effets secondaires du traitement et recevrez des consignes pour la gestion des symptômes. Ensuite, l'investigateur vous donnera accès à deux questionnaires électroniques auxquels vous pourrez accéder à distance, en utilisant votre smartphone, tablette ou un ordinateur connecté à internet. L'investigateur vous aidera à configurer et utiliser ces questionnaires. Les questionnaires sont :

- Questionnaire sur la qualité de vie : composé de 27 questions, qui devrait vous prendre environ 10 minutes à remplir.
- Questionnaire sur l'auto-efficacité à gérer les symptômes : composé de 8 questions, qui devrait vous prendre environ 5 minutes à remplir.

Ces questionnaires seront à remplir une fois par semaine à intervalles réguliers, à distance.
À tout moment, si vous présentez des symptômes qui vous inquiètent, vous devez contacter l'oncologue de garde par téléphone.

Pour les participants du groupe « numérique » :
Comme pour les participants du groupe « soins standard », vous serez informé par votre oncologue des potentiels effets secondaires du traitement, et vous recevrez des consignes pour la gestion des symptômes. Ensuite, l'investigateur vous donnera accès à trois questionnaires électroniques auxquels vous pourrez accéder à distance en utilisant votre smartphone, tablette ou un ordinateur connecté à internet. Les questionnaires sont :

- Questionnaire sur **la qualité de vie** : composé de 27 questions, qui devrait vous prendre environ 10 minutes à remplir, une fois par semaine, à intervalles réguliers.
- Questionnaire sur **l'auto-efficacité pour gérer des symptômes** : composé de 8 questions, qui devrait vous prendre environ 5 minutes à remplir, une fois par semaine, à intervalles réguliers.
- Questionnaire sur **les symptômes** : ce questionnaire a deux versions – une hebdomadaire et une journalière :
    - Version hebdomadaire : composée de 70 questions, qui devrait vous prendre environ 20 minutes à remplir, une fois par semaine, à intervalles réguliers.
    - Version journalière : composée uniquement des symptômes que vous avez signalés dans le questionnaire précédent (nombre de questions variable), à remplir tous les jours. Si vous n'avez pas déclaré des symptômes avant, l'application vous permettra d'en ajouter tous les jours. Cette version est à remplir que pendant les trois premiers mois de l'étude.

Une fois le questionnaire sur les symptômes remplit, une équipe d'infirmier·ère·s du département d'oncologie relèvera les symptômes déclarés. Selon les symptômes déclarés, l'équipe peut vous contacter par téléphone pour vous soutenir dans la gestion des symptômes. Ces appels sont faits uniquement pendant les jours ouvrables, de 8h à 12h. Leurs indications peuvent inclure des conseils pour minimiser les symptômes et aller jusqu'à une demande de vous présenter à l'hôpital pour une évaluation présentielle.
En dehors des horaires mentionnés ci-dessus, vous devez contacter l'oncologue de garde en cas de questions concernant vos symptômes.

En aucun cas ces mesures remplacent un appel à votre médecin oncologue et vous devrez le contacter directement si vous êtes concerné par un ou plusieurs symptômes, ou si vous avez des questions sur vos symptômes et sur votre traitement.

Lors de la visite de fin d'étude nous vous demanderons de participer à un entretien d'environ 1 heure afin d'évaluer l'ergonomie de l'application ePRO et votre expérience de la prise en charge.

Une fois l'étude terminée, votre prise en charge sera assurée par le médecin oncologue. À tout moment de cette étude et après qu'elle soit terminée, si vous présentez des symptômes qui vous inquiètent, vous devrez contacter votre oncologue aux horaires de bureau ou l'oncologue de garde par téléphone en dehors des horaires de bureau.

Il se peut que nous devions vous retirer de l'étude avant le terme prévu. Cette situation peut se produire si votre médecin change de traitement anti-cancéreux ou si vous êtes hospitalisé pour une longue période pendant la durée de l'étude.

En pareil cas, après désactivation de votre compte utilisateur, nous vous proposerons de désinstaller l'application électronique de vos appareils personnels.

5. Bénéfices pour les participants

Si vous participez à l'étude, cela pourra éventuellement vous aider à développer des connaissances plus approfondies sur les méthodes de surveillance et gestion des effets indésirables liées au traitement avec une immunothérapie par inhibiteurs du point de contrôle immunitaire. Et il se peut que vous tiriez un bénéfice dans la prise en charge de vos symptômes. Les résultats de l'étude pourraient se révéler importants par la suite pour les personnes touchées par la même maladie que vous. Nous vous remercions de votre intérêt et de votre participation à cette étude.

6. Droits des participants

Votre participation est entièrement libre. Si vous choisissez de ne pas participer ou si vous choisissez de participer et revenez sur votre décision pendant le déroulement de l'étude, vous n'aurez pas à justifier votre refus. Cela ne changera rien à votre prise en charge médicale habituelle. Vous pouvez à tout moment poser toutes les questions nécessaires au sujet de l'étude. Veuillez-vous adresser pour ce faire à la personne indiquée à la fin de la présente feuille d'information.

7. Obligations des participants

Pour répondre à des critères standards de qualité de l'étude, chaque participant doit correspondre à certaines obligations. En tant que participant à l'étude, vous serez tenu :

- de suivre les instructions médicales de votre oncologue et de vous conformer au plan de l'étude;
- de suivre les indications des infirmier·ère·s si vous intégrez le groupe « numérique » ;
- d'informer votre personne de contact pour l'étude de l'évolution de la maladie et de lui signaler tout nouveau symptôme, tout nouveau trouble et tout changement dans votre état ;
- d'informer votre personne de contact pour l'étude de tout traitement ou thérapie concomitant·e, prescrit·e par un autre médecin ; de l'informer également de tous les médicaments que vous prenez ;
- d'informer votre personne de contact pour l'étude si vous changez l'appareil électronique que vous utilisez habituellement pour remplir le questionnaire (smartphone, tablette, ordinateur).

8. Risques et contraintes pour les participants

La participation à cette étude ne comporte pas de risques, si ce n'est éventuellement des risques mineurs liés à la charge émotionnelle de participer aux entretiens et de compléter les questionnaires. Il se peut que certaines questions, présentes dans les questionnaires ou discutées lors des entretiens, puissent vous affecter émotionnellement. Vous pourriez, en effet, prendre conscience d'éventuelles difficultés ressenties et éprouver une certaine charge émotionnelle à cet égard.
Vous pourriez en autre avoir un faux sentiment de sécurité en utilisant l'application ePRO en vous attendant à recevoir une réponse immédiate de votre infirmière investigatrice en cas de survenue de symptômes graves. En cas de symptômes perçus comme graves, veuillez contacter directement votre médecin oncologue.
D'autres risques encore inconnus peuvent également exister. Si vous avez besoin d'exprimer ces émotions, et que vous n'êtes pas à l'aise pour les partager avec l'équipe de l'étude, vous pouvez prendre contact avec la psycho-oncologue du département d'oncologie :

[Contact information redacted for publication]

9. Découvertes pendant l'étude

L'investigateur vous avisera pendant l'étude de toute nouvelle découverte susceptible d'influer sur les bénéfices de l'étude ou votre sécurité, et donc sur votre consentement à participer. Vous serez informé oralement et par écrit.

10. Confidentialité des données et des échantillons

Pour les besoins de l'étude, nous enregistrerons vos données personnelles et médicales. Seul un nombre limité de personnes pourront consulter vos données sous une forme non codée, et exclusivement afin de pouvoir accomplir des tâches nécessaires au déroulement du projet. Les données recueillies à des fins de recherche sont codées lors de leur collecte. Le codage signifie que toutes les données permettant de vous identifier (p. ex. le nom, la date de naissance, etc.) sont remplacées par un code. Le code reste en permanence au sein de l'institution / de l'hôpital. Les personnes ne connaissant pas ce code ne peuvent pas lier ces données à votre personne. Dans le cas d'une publication, les données agrégées ne vous sont donc pas imputables en tant que personne. Votre nom n'apparaîtra jamais sur Internet ou dans une publication. Parfois, les journaux scientifiques exigent la transmission de données individuelles (données brutes). Si des données individuelles doivent être transmises, elles sont toujours codées et ne permettront donc pas de vous identifier en tant que personne. Toutes les personnes impliquées dans l'étude de quelque manière que ce soit sont tenues au secret professionnel. Toutes les directives relatives à la protection des données seront respectées et vous aurez à tout moment le droit de consulter vos données.

Durant son déroulement, l'étude peut faire l'objet d'inspections. Celles-ci peuvent être effectuées par la commission d'éthique qui s'est chargée de son contrôle initial et l'a autorisé, par l'autorité suisse de contrôle et d'autorisation des produits thérapeutiques Swissmedic ou par l'organisme qui l'a initiée. Il se peut que l'investigateur doive communiquer vos données personnelles et médicales pour les besoins de ces inspections.
Il est possible que le médecin s'occupant de votre suivi médical soit contacté au sujet de votre état de santé.

Pour les patients participants du groupe « numérique », les données personnelles utilisées par l'application électronique seront encryptées et stockées sur un serveur en Allemagne géré par Google, Inc, sous la plateforme Google Cloud. Ces données pourront uniquement être décryptées avec l'autorisation de la personne responsable de l'étude IePRO, Prof. Manuela Eicher. À la fin de l'étude, ces données seront supprimées du serveur.

11. Retrait de d'étude

Vous pouvez à tout moment vous retirer de l'étude si vous le souhaitez. Les données médicales recueillis jusque-là seront tout de même analysées, ceci afin de ne pas compromettre la valeur de l'étude dans son ensemble.
Il est impossible de rendre vos données anonymes, c'est pour cela qu'elles resteront codées. Vous devez donc être d'accord avec cela avant de donner votre consentement.

12. Compensation des participants

Si vous participez à cette étude, vous ne recevrez pour cela aucune compensation financière.
Votre participation n'aura aucune conséquence financière pour vous ou votre assurance maladie.

13. Réparation des dommages subis

Le Centre Hospitalier Universitaire Vaudois (CHUV) (promoteur) qui a initié l'étude et est en charge de sa réalisation, est responsable des dommages que vous pourriez subir en relation avec les activités de recherche. Les conditions et la procédure sont fixées par la loi.
Pour les dommages occasionnés par un dispositif médical approuvé et employé selon les standards médicaux ou qui seraient également survenus lors d'un traitement avec une thérapie conventionnelle, les règles de responsabilité applicables sont celles régissant les traitements en dehors d'une étude.
Si vous avez subi un dommage, veuillez-vous adresser à l'investigateur responsable du projet.

14. Financement de l'étude

L'étude est financée par l'Institut Suisse de Recherche Expérimentale sur le Cancer (ISREC) et par Kaiku Health Ltd.

15. Interlocuteur(s)

En cas de doute, de craintes ou d'urgences pendant ou après l'étude, vous pouvez vous adresser à tout moment à l'un des interlocuteurs suivants :

André Lopes (collaborateur scientifique)
[Contact information redacted for publication]

Stellio Giacomini (collaborateur scientifique)
[Contact information redacted for publication]

Célia Darnac (collaboratrice scientifique)
[Contact information redacted for publication]

Dr. Sofiya Latifyan (Investigatrice Principale):
[Contact information redacted for publication]

Prof. Manuela Eicher (co-Investigatrice et représentante du Sponsor)
[Contact information redacted for publication]

16. Glossaire (termes nécessitant une explication)

- Qu'entend-on par « auto-efficacité » ?

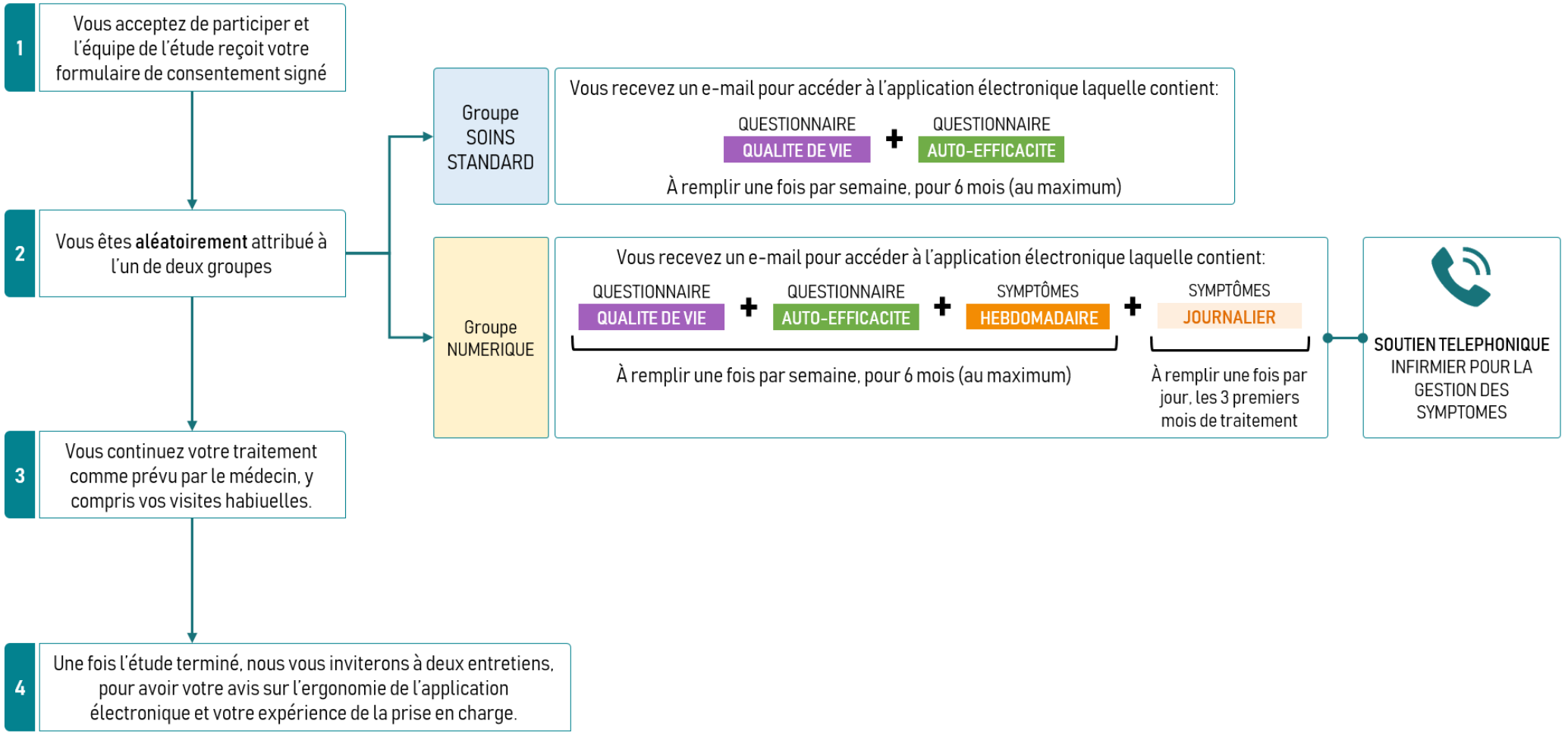
L'auto-efficacité correspond aux croyances d'un individu par rapport à sa capacité de réaliser une tâche, un apprentissage, un défi ou un changement avec succès. Dans le contexte spécifique de cette étude, il s'agit des croyances des participants par rapport à leur capacité de gérer leurs symptômes.

- Qu'entend-on par « immunothérapie par inhibiteurs du point de contrôle immunitaire » ?

L'immunothérapie par inhibiteurs du point de contrôle immunitaire est un type de traitement anti-cancéreux qui augmente la réponse du système immunitaire au cancer. Ce type de traitement est de plus en plus utilisé contre différents types de cancer.
Le rôle des points de contrôle du système immunitaire est de limiter la réponse du système immunitaire afin de ne pas endommager les cellules saines. Malheureusement, les cellules cancéreuses exploitent ce mécanisme au point de désactiver le système immunitaire, permettant au

cancer de progresser. Les inhibiteurs du point de contrôle immunitaire évitent que le cancer puisse profiter de ce mécanisme.

Déroulement de l'étude



Déclaration de consentement

Déclaration de consentement écrite pour la participation à un projet de recherche
Veuillez lire attentivement ce formulaire. N'hésitez pas à poser des questions lorsque vous ne comprenez pas quelque chose ou que vous souhaitez avoir des précisions.

NUMÉRO BASEC DE L'ÉTUDE: (APRÈS SOUMISSION À LA COMMISSION D'ÉTHIQUE COMPÉTENTE) :	2021-00301
TITRE DE L'ÉTUDE : (TITRE SCIENTIFIQUE ET TITRE USUEL)	Test d'un modèle de soins basé sur les symptômes rapportés électroniquement par les patients atteints d'un cancer et traités avec des inhibiteurs du point de contrôle immunitaire: une étude de phase II (IePRO)
Institution responsable : (Promoteur avec adresse complète) :	Centre Hospitalier Universitaire Vaudois, Rue du Bugnon 46, 1011 Lausanne
LIEU DE RÉALISATION DE L'ÉTUDE:	
Médecin responsable du projet sur le site : (nom et prénom en caractères d'imprimerie) :	
Participant / participante : (nom et prénom en caractères d'imprimerie) : Date de naissance :	

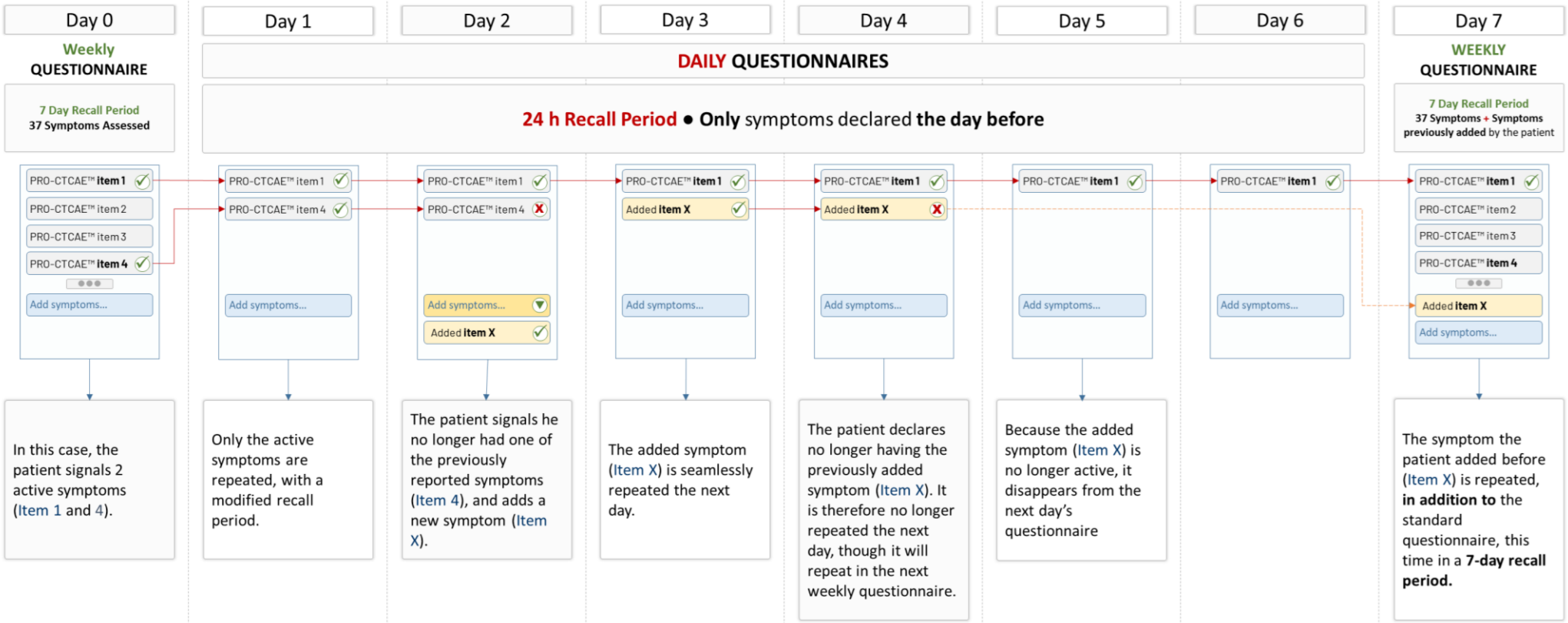
- Je déclare avoir été informé, par l'investigateur responsable de cette étude soussigné, oralement et par écrit, des objectifs et du déroulement de l'étude ainsi que des effets présumés, des avantages, des inconvénients possibles et des risques éventuels.
- Je prends part à cette étude de façon volontaire et j'accepte le contenu de la feuille d'information qui m'a été remise sur l'étude précitée. J'ai eu suffisamment de temps pour prendre ma décision.
- J'ai reçu des réponses satisfaisantes aux questions que j'ai posées en relation avec ma participation à l'étude. Je conserve la feuille d'information et reçois une copie de ma déclaration de consentement écrite.
- J'accepte que les spécialistes compétents du promoteur de l'étude, de la Commission d'éthique compétente et de l'autorité suisse de contrôle et d'autorisation des produits thérapeutiques Swissmedic, puissent consulter mes données brutes afin de procéder à des contrôles, à condition toutefois que la confidentialité de ces données soit strictement assurée.
- Je sais que mes données personnelles peuvent être transmises / transmis à des fins de recherche dans le cadre de ce projet uniquement et sous une forme codée, aussi à l'étranger.
- Je peux, à tout moment et sans avoir à me justifier, révoquer mon consentement à participer à l'étude, sans que cela n'ait de répercussion défavorable sur la suite de ma prise en charge. Les données médicales qui ont été recueillis jusque-là seront cependant analysés.
- Je suis informé que le promoteur couvre les dommages éventuels que je pourrais subir imputables au projet.
- Je suis conscient que les obligations mentionnées dans la feuille d'information destinée aux participants doivent être respectées pendant toute la durée de l'étude. La direction de l'étude peut m'en exclure à tout moment dans l'intérêt de ma santé.

Lieu, date	Signature du participant / de la participante

Attestation de l’investigateur : Par la présente, j’atteste avoir expliqué au participant / à la participante la nature, l’importance et la portée de l’étude. Je déclare satisfaire à toutes les obligations en relation avec ce projet conformément au droit en vigueur. Si je devais prendre connaissance, à quelque moment que ce soit durant la réalisation du projet, d’éléments susceptibles d’influer sur le consentement du participant / de la participante à prendre part au projet, je m’engage à l’en informer immédiatement.

Lieu, date	Nom et prénom de l’investigateur assurant l’information aux participants en caractères d’imprimerie. Signature de l’investigateur

Appendix 7: Electronic symptom questionnaire flow



Appendix 8: Self-reported symptoms table for Case Study

Appendix Table 1 – Patient self-reported symptoms and attributes, health-related quality of life, self-efficacy and triage alert type

Attributes[1] / Date	Decreased appetite			Constipation		Diarrhea		Abdominal pain				Shortness of breath			Anxious				Numbness & Tingling			Ringing in Ears		Concentration			Discouraged				Chills			Increased Sweating		
	S	I	C	S	C	F	C	F	S	I	C	S	I	C	F	S	I	C	S	I	C	S	C	S	I	C	F	S	I	C	F	S	C	F	S	C
02.12.21	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
03.12.21				0	0			2	1	1	1				2	1	1	1																		
04.12.21								2	1	2	1				2	1	1	1																		
05.12.21				2	2			2	2	2	2				2	1	1	1				1	1												
06.12.21				2	2			3	2	2	2				2	1	1	1				0	0												
07.12.21				2	2			2	2	2	2				1	1	1	1																		
08.12.21				1	1			1	1	1	1				0	0	0	0																		
09.12.21	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
10.12.21	0	0	0												0	0	0	0						0	0	0										
11.12.21																																				
12.12.21																																				
13.12.21																																				
14.12.21																																				
15.12.21																																				
16.12.21	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
17.12.21								0	0	0	0				1	1	1	1																		
18.12.21															1	1	1	1																		
19.12.21															0	0	0	0																		
20.12.21																																				
21.12.21																																				
22.12.21																																				
23.12.21	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	1	1	1	1	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
24.12.21															0	0	0	0																		
25.12.21																																				
26.12.21																																				
27.12.21																																				
28.12.21																																				
29.12.21																																				
30.12.21	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
31.12.21								0	0	0	0				0	0	0	0																		
01.01.22																																				
02.01.22																																				
03.01.22																																				
04.01.22																																				
06.01.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Continues in the next page

Attributes[1] / Date	General pain				Muscle pain				Joint pain				Fatigue			Urinary urgency			Urinary frequency			FACT-G[2]					PROMIS Self-Efficacy to Manage Symptoms Short Form 8a[3]				Triage Alert
	F	S	I	C	F	S	I	C	F	S	I	C	S	I	C				F	I	C	PWB	SWB	EWB	FWB	**TOTAL**	Raw Sc.	**t-score**	SE		
02.12.21	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**2**	**2**	**2**				**2**	**0**	**1**	24	20	19	18	**81**	32	**47.7**	1.9		
03.12.21	2	1	1	1	2	1	1	1	2	2	2	2	2	2	2				0	0	0										Amber
04.12.21	2	2	1	2	2	2	2	2	1	1	2	1	2	2	2																
05.12.21	2	2	2	2	2	2	2	2	2	1	2	1	2	2	2				3	1	1										
06.12.21	3	2	2	2	2	1	1	1	2	1	1	1	1	1	1				3	2	2										Red
07.12.21	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1				2	2	1										
08.12.21	2	1	1	1	2	1	1	1	2	1	1	1	2	2	2				1	1	1										Green
09.12.21	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**				**0**	**0**	**0**	21	20	20	15	**76**	30	**47**	2.1		
10.12.21	2	1	1	1	2	1	1	1	1	1	1	1	3	3	3																
11.12.21	1	1	1	1	1	1	1	1	1	1	1	1	4	4	3																
12.12.21	1	1	1	1	1	1	1	1	1	1	1	1	4	3	3																
13.12.21	2	1	1	1	1	1	1	1	1	1	1	1	3	3	3																Red
14.12.21	1	1	1	1	1	1	1	1	1	1	1	1	3	3	3																
15.12.21	2	1	2	1	1	1	1	1	1	1	1	1	3	3	3																
16.12.21	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**				**0**	**0**	**0**	20	25	21	19	**85**	36	**54.2**	2.6		
17.12.21	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2				0	0	0										
18.12.21	1	1	1	1	1	1	1	1	1	1	1	1	3	2	2																
19.12.21	0	0	0	0	0	0	0	0	0	0	0	0	2	2	2																
20.12.21													3	1	2																
21.12.21													1	1	1																
22.12.21													1	1	1																
23.12.21	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2				0	0	0	21	28	20	17	**86**	35	**51.8**	2.3		
24.12.21	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1																
25.12.21	0	0	0	0									1	1	1																
26.12.21													1	1	1																
27.12.21													1	0	1																
28.12.21													3	3	3				3	3	3										Amber
29.12.21													2	2	2				1	1	1										
30.12.21	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**2**	**1**	**1**	**2**	**2**	**1**	22	27	21	20	**90**	35	**51.4**	2.1		
31.12.21	2	1	1	1	0	0	0	0	0	0	0	0	2	2	2	3	2	2	2	1	1										Amber
01.01.22	0	0	0	0									2	2	2	2	2	1	2	2	1										
02.01.22													0	0	0	1	1	1	1	1	1										
03.01.22													2	2	2	2	1	1	0	0	0										
04.01.22													1	1	1	1	1	1													
06.01.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**2**	**2**	**3**	**2**	**2**	26	25	24	20	**95**	36	**52.1**	2.2		Red

Appendix Table 1 (continued) – Patient self-reported symptoms and attributes, health-related quality of life, self-efficacy and triage alert type

Attributes[1] / Date	Decreased appetite			Constip ation		DIarrhea		Abdominal pain				Shortness of breath			Anxious				Numbness & Tingling			Ringing in Ears		Concentration			Discouraged				Chills			Increased Sweating		
	S	I	C	S	C	F	C	F	S	I	C	S	I	C	F	S	I	C	S	I	C	S	C	S	I	C	F	S	I	C	F	S	C	F	S	C
07.01.22															0	0	0	0	0	0	0															
08.01.22																																				
10.01.22																																				
11.01.22																																				
12.01.22																																				
13.01.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
14.01.22															1	0	0	0	0	0	0						0	0	0	0						
15.01.22															0	0	0	0																		
16.01.22																																				
17.01.22																																				
18.01.22																																				
19.01.22																																				
20.01.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
21.01.22																																				
22.01.22																																				
23.01.22																																				
24.01.22																																				
25.01.22																																				
26.01.22																																				
27.01.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**
28.01.22															1	1	0	1									1	1	1	1						
29.01.22															1	1	1	1									0	0	0	0						
30.01.22															0	0	0	0																		
31.01.22																																				
01.02.22																																				
02.02.22																																				
03.02.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
04.02.22															1	1	0	1																		
05.02.22															1	1	1	1																		
06.02.22															1	1	1	1																		
07.02.22															0	0	0	0																		
08.02.22																																				
09.02.22																																				
10.02.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

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Attributes[1] / Date	General pain				Muscle pain				Joint pain				Fatigue			Urinary urgency			Urinary frequency			FACT-G[2]					PROMIS Self-Efficacy to Manage Symptoms Short Form 8a[3]				Triage Alert
	F	S	I	C	F	S	I	C	F	S	I	C	S	I	C	F	I	C	F	I	C	PWB	SWB	EWB	FWB	**TOTAL**	Raw Sc.	**t-score**	SE		
07.01.22	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	2	2	1	3	2	2										
08.01.22	0	0	0	0	1	1	1	1					2	2	2	2	2	1	3	2	2										
10.01.22					1	1	1	1					2	2	2	2	2	1	2	2	1										
11.01.22					0	0	0	0					2	3	2	3	2	2	3	2	2										
12.01.22													2	2	2	3	3	3	3	2	2										Red
13.01.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	3	3	3	**3**	**3**	**3**	22	26	21	18	**87**	33	**48.8**	1.9		
14.01.22	1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	3	3	3	3	3	3										
15.01.22	1	1	1	1	0	0	0	0	1	1	1	1	2	2	2	3	3	3	3	3	3										
16.01.22	0	0	0	0					0	0	0	0	3	4	3	3	3	3	3	3	3										
17.01.22													3	3	3	3	3	3	3	3	3										Amber
18.01.22													1	1	1	3	3	3	3	3	3										
19.01.22													1	2	1	2	2	1	2	2	1										
20.01.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**3**	**2**	3	3	3	**3**	**3**	**3**	23	25	23	21	**92**	35	**50.3**	2		
21.01.22	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	1	2	2	1										
22.01.22	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1	2	1	1	2	1	1										
23.01.22	0	0	0	0									2	3	2	3	4	3	3	3	3										
24.01.22													2	3	2	3	3	3	3	3	3										
25.01.22													1	1	1	3	3	3	3	3	3										Amber
26.01.22													2	2	2	3	3	3	3	3	3										
27.01.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	3	3	3	**3**	**3**	**3**	22	25	22	16	**85**	36	**52.7**	2.3		
28.01.22	1	1	1	1	1	1	1	1	0	0	0	0	1	1	1	3	3	3	3	3	3										
29.01.22	1	1	1	1	0	0	0	0					1	1	1	3	3	3	3	3	3										
30.01.22	0	0	0	0									1	1	1	3	3	3	3	3	3										
31.01.22													1	1	1	3	3	3	3	2	2										
01.02.22													1	1	1	2	2	1	2	2	1										
02.02.22													2	2	2	3	3	3	3	3	3										
03.02.22	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	3	3	3	**3**	**3**	**3**	22	26	22	16	**86**	37	**54.3**	2.6		
04.02.22	1	1	1	1	0	0	0	0					2	2	2	3	3	3	3	3	3										
05.02.22	0	0	0	0									1	1	1	3	3	3	3	3	3										
06.02.22													1	1	1	3	3	3	3	3	3										
07.02.22													1	1	1	3	3	3	3	3	3										
08.02.22													1	2	1	2	2	1	3	2	2										
09.02.22													2	2	2	3	3	3	3	3	3										
10.02.22	**1**	**1**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	3	2	3	**3**	**3**	**3**	23	25	22	20	**90**	37	**52.9**	2.2		

Appendix Table 1 (continued) – Patient self-reported symptoms and attributes, health-related quality of life, self-efficacy and triage alert type

Attributes[1] / Date	Decreased appetite			Constip ation		Dlarrhea		Abdominal pain				Shortness of breath			Anxious				Numbness & Tingling			Ringing in Ears		Concentration			Discouraged				Chills			Increased Sweating			
	S	I	C	S	C	F	C	F	S	I	C	S	I	C	F	S	I	C	S	I	C	S	C	S	I	C	F	S	I	C	F	S	C	F	S	C	
11.02.22															1	1	1	1																			
12.02.22															0	0	0	0																			
13.02.22																																					
14.02.22																																					
15.02.22																																					
16.02.22																																					
17.02.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
18.02.22															1	0	0	0																			
19.02.22															1	1	0	1																			
20.02.22															1	1	1	1																			
21.02.22															0	0	0	0																			
22.02.22																																					
25.02.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
03.03.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
04.03.22																																					
10.03.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
17.03.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
18.03.22																																					
24.03.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
25.03.22																																					
31.03.22	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	
05.04.22																																					
07.04.22	**2**	**2**	**2**	**0**	**0**	**0**	**0**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**2**	**2**	**2**	**1**	**1**	**1**	**0**	**0**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	
14.04.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**2**	**2**	**0**	**0**	**0**	
21.04.22	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
28.04.22	**1**	**1**	**1**	**0**	**0**	**3**	**2**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	
05.05.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	
12.05.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
19.05.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	

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Attributes[1] / Date	General pain				Muscle pain				Joint pain				Fatigue			Urinary urgency			Urinary frequency			FACT-G[2]					PROMIS Self-Efficacy to Manage Symptoms Short Form 8a[3]				Triage Alert
	F	S	I	C	F	S	I	C	F	S	I	C	S	I	C	F	I	C	F	I	C	PWB	SWB	EWB	FWB	TOTAL	Raw Sc.	t-score	SE		
11.02.22	1	1	1	1	0	0	0	0	0	0	0	0	1	1	1	3	3	3	3	3	3										
12.02.22	0	0	0	0	0								1	1	1	2	3	2	2	2	1										
13.02.22													1	0	1	2	1	1	2	2	1										
14.02.22													1	1	1	2	2	1	2	2	1										
15.02.22													1	1	1	2	3	2	2	2	1										
16.02.22													2	2	2	3	3	3	3	3	3										
17.02.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**2**	**3**	**3**	**3**	**3**	26	24	22	23	**95**	36	**52.4**	2.1		
18.02.22	1	1	0	1	1	0	0	0	0	0	0	0	1	1	1	2	2	1	2	2	1										
19.02.22	1	0	0	0	1	1	0	1					1	1	1	2	2	1	2	2	1										
20.02.22	1	1	1	1	1	1	0	1					1	1	1	2	2	1	2	2	1										
21.02.22	1	1	0	1	0	0	0	0					1	1	1	2	2	1	2	2	1										
22.02.22	0	0	0	0	0	0	0	0					2	2	2	3	3	3	3	3	3										
25.02.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	23	26	23	18	**90**	37	**54.3**	2.6		
03.03.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	23	25	23	17	**88**	39	**57.9**	3.3		
04.03.22																															Red
10.03.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**2**	**3**	**3**	**3**	**3**	25	27	23	18	**93**	36	**51.7**	2		
17.03.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	25	26	22	19	**92**	37	**53.4**	2.2		
18.03.22																															Amber
24.03.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**0**	**0**	**0**	**0**	**2**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	24	27	23	24	**98**	35	**51.3**	2.1		
25.03.22																															Red
31.03.22	**2**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**3**	**3**	**3**	**3**	**2**	**3**	**3**	**3**	**3**	21	24	20	16	**81**	32	**47.7**	1.9		Red
05.04.22																															Red
07.04.22	**3**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**1**	**1**	**1**	**1**	**4**	**4**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	9	25	15	9	**58**	20	**37.7**	1.9		Red
14.04.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**2**	**2**	**1**	**1**	**1**	**2**	**1**	**1**	21	26	21	10	**78**	33	**48.7**	2		Amber
21.04.22	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**2**	**2**	**3**	**3**	**3**	**3**	**2**	**2**	20	26	21	11	**78**	30	**46.2**	2.5		Red
28.04.22	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**3**	**3**	**3**	**2**	**2**	**1**	**2**	**1**	**1**	16	26	20	10	**72**	30	**46.4**	1.9		Red
05.05.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	22	26	23	15	**86**	36	**52.4**	2.3		
12.05.22	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	24	25	23	16	**88**	40	**63.5**	5.4		Green
19.05.22	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**1**	**1**	**1**	**0**	**1**	**1**	**1**	**1**	25	26	24	20	**95**	39	**57.9**	3.3		Green

Symptoms reported in weekly questionnaires are in bold. Non-bold replies correspond to daily questionnaires, which use a 24-hour recall period.

[1]PRO-CTCAE Symtpom attributes:

F: Frequency (0 "Never", 1 "Rarely", 2 "Occasionally", 3 "Frequently", 4 "Almost constantly") | S: Severity (0 "None", 1 "Mild", 2 "Moderate", 3 "Severe", 4 "Very severe") | I: Interference (0 "Not at all", 1 "A little bit", 2 "Somewhat", 3 "Quite a bit", 4 "Very much") | C: Composite grading score (0 "None", 1 "Mild", 2 "Moderate", 3 "Severe")

[2]FACT-G:

PWB: Physical well-being subscale | SWB: Social/Family well-being subscale | EWB: Emotional well-being subscale | FWB: Functional well-being subscale

[3]PROMIS Self-Efficacy to Manage Symptoms Short Form 8a

Raw Sc.: Raw score (raw sum of points) |T-score: standardized raw score with a mean of 50, standard deviation of 10 | SE: standard error