Implementation of daily patient-reported outcome measurements to support children with cancer

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Funding information
Kinderkrebshilfe Tirol und Vorarlberg; Kinderkrebshilfe Südtirol-Regenbogen

Abstract
Background: Several stakeholders, including patients and health care providers, suggest symptom self-reporting measurements for a more patient-directed cancer control approach. However, services tailored to measure daily reporting and implementing it in clinical care are lacking. This study aimed to evaluate the feasibility and value of daily patient-reported outcome measures (PROMs) by children receiving chemotherapy for cancer.

Methods: Health status was recorded daily with a web-based child-friendly patient portal (ePROtect). Following aspects of feasibility and usability were assessed: (a) the completion rate and time, (b) user feedback on usability and satisfaction, and (c) the performed interventions if moderate to severe symptom deterioration was noted.

Results: Twelve children (median age: 7.2 years) were included. A total number of 891 daily reports were collected during the study period; the median percentage of ePROtect completion days was 85.3% (interquartile range [IQR] 64.2–100.0) and 55.9% (IQR 51.9–76.9) for inpatient and outpatient stay, respectively. Mean time to complete the questionnaire was 47.6 seconds. Severe symptoms were reported in 14.7% of measurement time points, which led to prompt health care interventions in 57 cases, including extension of supportive care (n = 37) and pre-emptive inpatient admissions (n = 5). Over 80% of the patients (10/12) and their proxies (16/18) provided feedback with high rating for satisfaction (>90%) and usefulness (>80%) of ePROtect.

Conclusion: Our study shows that daily symptom monitoring is feasible for all children with newly diagnosed cancer aged 5–18 years. Monitoring offers the opportunity to identify symptoms early and trigger appropriate clinical action.

KEYWORDS
childhood cancer, daily web based, ePROtect, patient-reported outcome measure, symptoms

Abbreviations: CHES, computer-based health evaluation system; HRQoL, health-related quality of life; IQR, interquartile range; MAUQ, mHealth App Usability Questionnaire; PROM, patient-reported outcome measure.

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Pediatr Blood Cancer. 2021;68:e29279.
https://doi.org/10.1002/pbc.29279
1 | INTRODUCTION

Treatment of cancer in children and adolescents is a true success story: in the 1960s, survival rates for acute lymphoblastic leukemia were in the single digits, today they are higher than 92% in high-income countries.1 Despite these promising numbers, treatment for cancer carries a high potential risk of severe side effects, which have a significant impact on both short- and long-term organ functioning and patient’s health-related quality of life (HRQoL).2 For this reason, health care professionals should not simply limit their resources to improving cancer survival rates, but need to address how cancer treatment influences the patient’s personal life, and develop a more comprehensive and patient-centered cancer control approach.3

In this context, symptom monitoring with patient-reported outcome measures (PROMs) has become the focus of interest in oncology. Research in adult patients has shown that the implementation of PROMs has improved their self-esteem, as well as the efficiency and outcomes of care.4 Despite evidence that use of PROMs in children and adolescents is feasible and that patients, families, clinicians, and political organizations are interested in using them, less than 1% of pediatric clinical cancer trials investigated PROMs as their primary endpoint.5,6 The reason behind this is that PROM has been insufficiently considered in large international clinical trials to date, digital technologies are not yet seamlessly integrated into clinical practice, and most importantly, a culture of integrating child- and family-specific needs is grossly missing.7,8

Based on the great need to conduct such studies and to help overcome obstacles to the routine measurement of PROMs in the treatment of pediatric cancer, we have developed a unique web-based approach for daily child self- and parent-based proxy reporting and evaluated the feasibility and implementation of this tool in daily clinical care.

2 | PATIENTS AND METHODS

2.1 | Study design and ethical approval

To evaluate the feasibility of the ePROtect software, a prospective, single-arm longitudinal study was started on May 1, 2020 at the Division of Childhood Oncology at the Medical University of Innsbruck. We consecutively recruited patients and introduced them to the ePROtect software where they could complete PROMs daily online. The Ethics Committee at the Medical University of Innsbruck approved this study (EC number: 1055/2020); written informed consent was obtained from all children and their parents.

2.2 | Description of ePROtect software

We developed ePROtect based on the computer-based health evaluation system (CHES)9,10 as an easy-to-use application for patients during cancer therapy. Positive findings and previous experience with CHES in adult cancer populations have been incorporated.11,12 The software comprises two components: (a) a web-based patient portal (Figure S1), and (b) a health care professional interface that allows to review the data from all patients and to consequently integrate it into their care (Figure S2). The clinical usage of the ePROtect system has recently been described in a case report.13 This study is focused on the feasibility.

The patient portal can be accessed using a personalized username and password, which is provided by the health care team (https://ches.tirol-kliniken.at/protect-portal). It allows patients to complete daily PROMs online and also provides specific information on the respective disease, its treatment, necessary medical examinations, the ward plan, and the health care team. It was designed to be child-friendly, contained its own animation characters, patient stories of experience during treatment, and a detailed explanation of the need to assess patients’ HRQoL (Figure S1). The questionnaires could be completed with smartphone, tablet, or computer (no installation required).

2.3 | PROMs used in ePROtect system

ePROtect includes eight questions to monitor patients’ symptom burden during and after treatment. Using an eminence-based approach, a team of pediatric oncologists and PRO experts decided to assess seven common symptoms with high relevance for children’s HRQoL: appetite loss, fatigue, nausea, pain, physical functioning, cognitive impairments, and sleep quality. The selection of symptoms was made to include the most relevant symptoms that can be self-reported and to keep the overall item burden low as the symptoms were to be reported daily. The item list is given in Table S1. The items referred to the previous day and were answered on a smiley scale with three faces (<8 years), or a five-point Likert scale (≥ 8 years) ranging from never to almost always, as recommended by a guideline of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).14

This study was designed as a feasibility study, therefore we did not analyze patients’ symptom burden as reported in the item lists (the symptom burden was, however, used for clinical care by health care professionals). Symptom severity was graded from level zero (not at all bothered) to four (severe impairment or disabling). When a symptom severity of level 3 or 4 was reported, an automated alarm for the health care team was triggered by the ePROtect system and interventions were undertaken (Figure S2). Additionally, the patient was contacted by the health care team when combinations of moderate symptom (level 2) resulted in significant symptom burden and had persisted over a period of 48–72 h.

2.4 | Patients

We consecutively included all German-speaking children with cancer, who were 5–18 years of age at enrollment and were treated with chemotherapy. Exclusion criteria were a Karnofsky performance status score <50%, cognitive disability or visual impairment that precluded utilization of the web application. We collected patients’
socio-demographical and clinical data at study inclusion. Additionally, one-way driving distance and travel time from each patient’s home to the medical facility was calculated with Google Maps.

2.5 Study procedure

Patients and their parents were approached at the Division of Childhood Oncology at the Medical University of Innsbruck, briefed about the study and asked to provide informed consent. Patients and their parents were then given access to the ePROtect patient portal and trained in the use of the software with the help of trained study staff. Patients were instructed to complete the symptom monitoring once per day during the study period. If patients or parents did not have a mobile device, an iPad was provided by the primary health care team for the entire observation period. Patients remained on the study until the end of the study period or until their active treatment was completed.

To encourage daily symptom screening, patients were reminded during inpatient treatment to complete the questionnaire each day before the morning round and the results were then immediately discussed at the patient’s bedside with the medical team. During outpatient therapy episodes, the administrator checked daily for any relevant deviations in symptoms. In the case of clinically relevant deviations, the medical team was immediately alerted and the patients or their parents were called by the physicians to confirm the reported symptoms, including the weekends. Subsequently, detailed questions were asked and, if necessary, medical advice or a recommendation for prompt admission to the hospital was given.

2.6 Selection of outcome measures

We assessed several aspects of feasibility and usability of ePROtect. Table 1 gives an overview of the outcomes analyzed in this study. The study procedure and individual outcome measures are explained in the subsequent paragraph.

2.7 PROM completion rate and durations

The PROM completion rate was calculated by dividing the number of days on which PROMs were completed by the number of days that the patient stayed in the study period (N of PROMs completed/N of days in study*100). We analyzed the completion rate for each patient separately and calculated the median of all patients during outpatient care and inpatient treatment. We extracted the mean duration (in seconds) from the system access logs and computed an average for each patient, which was then again averaged across all patients to give equal weight to all patients.

2.8 mHealth app usability questionnaire (MAUQ)

To evaluate the usability of ePROtect, the target users, including both patients and their proxies, were asked for feedback using the “mHealth App Usability Questionnaire.” The MAUQ was recently published and demonstrated to have sufficient reliability and validity. As no German language translation of the questionnaire was available, the English version was independently translated to German by four experts in the PRO outcome research. The translations were then discussed in an expert panel, which consisted of the translators and pediatric oncology experts. In the panel, the most fitting translations of the items were chosen via consensus discussion. Additionally, three questions from the original questionnaire were dropped as they were not applicable to our study design. For instance, the current version of ePROtect did neither provide information about the progress of the therapy, nor about the usage of ePROtect, thus the question “the app adequately acknowledged and provided information to let me know the progress of my action” was removed. Table S2 gives an overview of the translation process. The translated questionnaire comprised 18 items, of which seven assessed “ease of use and satisfaction,” four the “system information arrangement,” and seven the “usefulness” of ePROtect. The items are presented in Table S3. Responses to the statements ranged from 1 (strongly disagree) to 7 (strongly agree) for proxies and patients older than 8 years. Patients between 5 and 8 years responded on a three-face smiley scale. To determine the usability, the total was calculated and the average of the responses to all statements determined. Finally, the values were converted in percentage. The higher the overall average, the higher was the usability of the app.

2.9 Analysis of clinical usage of system

In addition to the feasibility and usability analysis of the ePROtect system, we also descriptively analyzed health care professionals’ usage of
the system. Any clinical action (e.g., telephone call, rescheduling consultation) taken in response to a PROM symptom report was considered an intervention and documented in the system.

### 2.10 Statistical analysis

Sample characteristics were calculated as absolute numbers, percentages, median, and interquartile ranges (IQRs). Intraclass correlation coefficients (ICC) were calculated to evaluate the consistency in the MAUQ between patients and proxies. The chi-square test was applied to analyze the distribution of frequency in the completion rate. Differences were considered statistically significant at a \( p < .05 \). All statistical analyses were performed using SPSS 26.0.

### 3 RESULTS

#### 3.1 Recruitment

Between May 1 and December 31, 2020, 14 potential participants were approached for inclusion in daily ePRO monitoring. One patient was excluded due to the diagnosis of a cerebral tumor and the development of cognitive disability following neurosurgery and another patient declined participation after the first baseline assessment due to deteriorated health condition. The ePROtect system was first used (i.e., a PROM was completed) at a median of 7.0 days (IQR 2.8–15.5) after the diagnosis had been established and at 0.5 median days (IQR 0.0–2.0) after treatment had commenced. At the time of analysis, three patients had already finished ePROtect monitoring at the end of treatment and nine patients were still being recorded. Median observation time was 2.9 months (IQR 1.9–4.9), with 28% of time being spent on inpatient stay.

#### 3.2 Patient characteristics

Patients had a median age of 7.2 years (IQR 6.7–10.1) and 25% were female. The diagnoses included five patients with leukemia and five patients with lymphoma (see Table 2 for detailed report of patient characteristics). The remaining patients had either a central nervous system tumor (\( n = 1 \)) or Langerhans cell histiocytosis (\( n = 1 \)). While chemotherapy was a prerequisite for inclusion in the study, one (8%) patient had previously undergone surgical tumor removal, and one (8%) patient had had both surgery and subsequent radiation therapy.

#### 3.3 Completion rate

During the observation period, patients completed 891 daily questionnaires. This corresponds to an overall median completion rate of 61.3% (IQR 55.0%–85.3%). A trend to less self-reporting was observed during outpatient care as compared to inpatient treatment (median completion rate 55.9% vs. 85.3%; \( p = .2 \); Figure S3). Altogether, a total of 4243 individual symptoms were self-reported to the health care team. Of these, 625 or 14.7% were severe or disabling. Every patient reported a level 3 or 4 symptom at least once. The most common severe or disabling PROMs concerned pain (29.4%), sleep disturbance (16.0%), physical functioning (12.7%), and nausea (11.2%). Symptom reporting was equally distributed over age groups. Mean completion time for the whole questionnaire was 45 and 52 seconds for patients aged 5–7 and 8–18 years, respectively.

#### 3.4 Multiple intervention report

When a symptom severity of level 3 or 4 was reported, an automated alarm for the health care team was triggered by the ePROtect system and interventions were undertaken. They included immediate counseling about symptom management with direct consultation for inpatients and via telephone for patients in home care (\( n = 57 \)), including extension of supportive medication (\( n = 37 \); 64.9%) and recommendation for prompt clinical presentation and/or admission for patients in home care (\( n = 5 \); 8.8%). Figure 1 illustrates a total of four interventions based on PROM use, where the family was first counseled by telephone due to unclear sleep disturbance (Cloud 1 and Cloud 2), followed by the recommendation for prompt admission (Cloud 3), and finally pain management for mucositis was extended during inpatient treatment (Cloud 4).

### Table 2 Demographics of the study cohort

| Characteristics                  | Data                                      |
|----------------------------------|------------------------------------------|
| Patients, total number            | 12                                       |
| Median age, years                 | 7.2 (IQR 6.7; IQR 10.1)                  |
| Sex                              |                                          |
| Male                             | 9 (75%)                                  |
| Female                           | 3 (25%)                                  |
| Underlying diagnosis             |                                          |
| ALL                              | 4 (33%)                                  |
| AML                              | 1 (8%)                                   |
| NHL                              | 3 (25%)                                  |
| Mb Hodgkin                       | 2 (17%)                                  |
| CNS tumor                        | 1 (8%)                                   |
| LCH                              | 1 (8%)                                   |
| Treatment                        |                                          |
| CTX                              | 10 (83%)                                 |
| CTX + surgery                    | 1 (8%)                                   |
| CTX + surgery + radiation        | 1 (8%)                                   |
| Distance to hospital, kilometers (mean) | 84                                          |
| Travel time to hospital, minutes (mean) | 61                                          |

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; CNS, central nervous system; CTX, chemotherapy; LCH, Langerhans cell histiocytosis; NHL, non-Hodgkin’s lymphoma.
FIGURE 1 Frequency of interventions based on patient-reported outcome measures (PROMs). Graph illustrates four areas of PROMs (pain, nausea, malfunctioning, and sleep disturbances) with the respective interventions, including telephone counseling (1+2), recommendation for admission (3), and extension of pain management (4). The x-axis shows the time course in days, the colors designate inpatient (blue), outpatient (green), and unplanned inpatient (red) stay. The y-axis indicates the level of severity for each symptom category. The dotted line is set at mild symptoms (level 2) and the solid line at severe symptoms (levels 3 and 4).

FIGURE 2 Usability evaluation of ePROtect according to the mHealth App Usability Questionnaire (MAUQ). Analysis of usability with the MAUQ questionnaire was assigned to three subscales as indicated by the respective grading "ease of use and satisfaction," "system information arrangement," and "usefulness".

3.5 Evaluation of usability of routine ePRO monitoring

The MAUQ was used to assess the usability of the ePROtect system and for quality assurance. All 12 patients and their respective parents were consecutively enrolled to complete the survey after a median follow-up of 2.8 months after enrollment. Ten (83%) patients and 16 (89%) proxies completed the questionnaire. Figure 2 shows evaluation of the questionnaire, and a detailed breakdown of the individual questions is given in Figure S4. Summarized from the individual questions, a positive rating agreement was reported for "ease of use and satisfaction," "system information arrangement," and "usefulness," namely, 92.9%, 87.1%, and 80.5%, respectively. Comparison of the ratings given by the patients and those of their proxies showed high consistency (ICC 0.75) and no statistical difference (p > .05).

4 DISCUSSION

Many studies have assessed the implementation and benefit of adding daily electronic PROMs for symptoms related to cancer treatment in adults. Children and adolescents are treated with the same drugs, suffer from the same side effects, and are now growing up in an environment that is saturated with digital technologies, but rarely have these studies been conducted in childhood. There is no doubt that accurate communication between pediatric patients and their clinicians about symptoms is crucial for optimal supportive care and can be facilitated by an automated electronic system, such as our ePROtect. ePROtect was developed by a team of pediatric oncologists and PRO experts based on an eminence-based approach to improve clinical care. Therefore, the current version of ePROtect assesses seven common symptoms with high relevance for children's HRQoL: appetite loss, fatigue, nausea, pain, physical functioning, cognitive impairments, and sleep quality (the importance of this symptoms is reviewed by Dupuis et al.).

The value of patients as the best reporters of their symptoms (patient’s voice) is increasingly recognized in drug development and clinical care. However, the integration of the patient voice is more challenging in pediatric oncology. The complexity of PROM assessments in this vulnerable group is hindered by the age, the developmental stage, family relationships, and psychosocial challenges, which...
all impact on the ability to participate on self-reporting. Despite the proven demand, there is no PROM available or in clinical usage for daily symptom monitoring. Therefore, even studies with small numbers of participants (particularly with children) are needed and it has been demonstrated that they can have meaningful impact on refinements of mHealth tool’s development. Current practice in cancer treatment includes administration of chemotherapy in the day clinic or, if necessary, on the ward for several days and discharging the patient whenever possible, so that most of the time can be spent at home. Indeed, as we illustrated in our evaluation, during the first 3 months of therapy, most of the time (65%, data not shown) is spent outside the hospital. This situation can be very challenging, as toxic side effects typically manifest in the between-visit period and real-time monitoring is not in effect. Thus, ePROtect creates a way to empower the patients to have a voice in their care that does not get diluted by recall bias or the chaos of a clinic visit.

In our study, we found that the questionnaires are completed on most days irrespective of age, diagnosis, and therapy, whereby some patients complete the questionnaire daily. Patient completion rates differed between the in/outpatient modalities: the completion rate was highest during inpatient stay, indicating that adherence to monitoring is most easily achieved via close clinical contact. The completion rate was slightly lower during outpatient stay, which may be attributed to less contact with the clinical team that could remind the patient to complete the monitoring. Finally, the completion rate was lowest during unplanned hospitalization, which can mostly be attributed to debilitating conditions such as treatment for sepsis. Nevertheless, patients completed the monitoring on more than 50% of the days, even during unplanned inpatient stays. Of note, all children were able to complete the questionnaire without difficulty and in less than 1 minute. This is important to emphasize, because lengthy questionnaires might be one major reason for nonadherence and handicap the incorporation into daily life of the patients and caregivers. Thus, when the patients were asked for their feedback on ePROtect use, they gave high marks for “ease of use” and “satisfaction,” with no significant differences between patients and their proxies.

As seen from screening, 11.5% and 3.2% of symptoms were severe and were reported in association with levels 3 and 4 of impairment, mostly attributed to pain and/or sleep disturbances. These figures confirm the findings of previous studies that measured symptoms either selectively at only one time point or over a limited period of maximum 5 days. In the follow-up of 245 days, a total of 57 interventions were initiated, all of which included immediate counseling in the form of direct consultation for inpatients and telephone consultation for patients at home care. In selected cases, supportive medicine was extended and/or prompt admission was recommended. A recently published case report highlights the clinical usage of ePROtect and the importance of identifying urgent medical issues reported by the patients. The need for continuous monitoring is particularly crucial for patients, who live a long distance from the hospital, which is common in the state of Tyrol (Table 2). In fact, ePROtect has strong potential in getting patients to the emergency room when necessary, but also in avoiding unnecessary hospital visits. As such, these characteristics are not only well suited to our primary concept of developing a reliable monitoring system, but this tool is particularly well suited for interventions when symptoms occur between clinical visits. Analysis of user feedback supports this assumption, as the patients and their proxies feel safe when using this tool and they even suggest that the interaction be intensified, for example, by adding a video consultation.

It is important to mention the limitations of this study. Our monocentric study design means the sample size is small, which limits the description of the study group and comparison of the characteristics between patient groups (e.g., age, cancer type). The challenge of small sample size is a common aspect of many studies focused on pilot testing of mHealth intervention tools, but nevertheless they are essential for future refinements. We were able to quickly enroll patients, collect comprehensive clinical data, and provide careful and daily supportive care for patients over a relatively long space of time. For the evaluation of ePROtect, we used the recently published MAUQ, which is currently available in English only. Although translated by experts, it has to be considered that neither linguistic validation nor cognitive testing methods were performed.

We provide promising data to show that ePROtect is a reliable, valid, and responsive tool for PROMs in children and adolescents being treated for cancer. Implementation of ePROtect in future clinical studies is eagerly awaited in order to hopefully move into clinical care and improve the life quality of our patients and their families. Future studies let us expect a larger number of participants, and it will be exciting to analyze their data in an effort to better understand symptom trajectory and to establish guidelines on how to treat relevant symptoms. As our study indicates feasibility in clinical practice, more hospitals in Austria and Italy will be included in the near future in order to explore the beneficial value of ePROtect.

ACKNOWLEDGMENT
We are deeply grateful to Petra Shivareddy for graphic and functional design of the web-based application.

CONFLICT OF INTEREST
Bernhard Holzner and Gerhard Rumpold hold IPRs of the CHES software tool. The remaining authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS
Roman Crazzolara, Andreas Meryk, David Riedl, Bernhard Holzner, and Gerhard Rumpold designed the study. Andreas Meryk, Alexandra Haid, Benjamin Hetzer, and Gabriele Kropshofer collected the data. Andreas Meryk, Jens Lehmann, and Roman Crazzolara analyzed the data. Andreas Meryk and Roman Crazzolara wrote the manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Meryk A, Kropshofer G, Hetzer B, et al. Implementation of daily patient-reported outcome measurements to support children with cancer. *Pediatr Blood Cancer*. 2021;68:e29279. [https://doi.org/10.1002/pbc.29279](https://doi.org/10.1002/pbc.29279).