Development of an eHealth Tool for Capturing and Analyzing the Immune-related Adverse Events (irAEs) in Cancer Treatment

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ABSTRACT

INTRODUCTION: Immunotherapy has revolutionized the treatment of many different types of cancer, but it is associated with a myriad of immune-related adverse events (irAEs). Patient-reported outcome (PRO) measures have been identified as valuable tools for continuously collecting patient-centered data and are frequently used in oncology trials. However, few studies still research an ePRO follow-up approach on patients treated with Immunotherapy, potentially reflecting a lack of support services for this population.

METHODS: The team co-developed a digital platform (V-Care) using ePROs to create a new follow-up pathway for cancer patients receiving immunotherapy. To operationalize the first 3 phases of the CeHRes roadmap, we employed multiple methods that were integrated throughout the development process, rather than being performed in a linear fashion. The teams employed an agile approach in a dynamic and iterative manner, engaging key stakeholders throughout the process.

RESULTS: The development of the application was categorized into 2 phases: "user interface" (UI) and "user experience" (UX) designs. In the first phase, the pages of the application were segmented into general categories, and feedback from all stakeholders was received and used to modify the application. In phase 2, mock-up pages were developed and sent to the Figma website. Moreover, the Android Package Kit (APK) of the application was installed and tested multiple times on a mobile phone to proactively detect and fix any errors. After resolving some technical issues and adjusting errors on the Android version to improve the user experience, the iOS version of the application was developed.

DISCUSSION: By incorporating the latest technological developments, V-Care has enabled cancer patients to have access to more comprehensive and personalized care, allowing them to better manage their condition and be better informed about their health decisions. These advances have also enabled healthcare professionals to be better equipped with the knowledge and tools to provide more effective and efficient care. In addition, the advances in V-Care technology have allowed patients to connect with their healthcare providers more easily, providing a platform to facilitate communication and collaboration. Although usability testing is necessary to evaluate the efficacy and user experience of the app, it can be a significant investment of time and resources.

CONCLUSION: The V-Care platform can be used to investigate the reported symptoms experienced by cancer patients receiving Immune checkpoint inhibitors (ICIs) and to compare them with the results from clinical trials. Furthermore, the project will utilize ePRO tools to collect symptoms from patients and provide insight into whether the reported symptoms are linked to the treatment.

CLINICAL RELEVANCE: V-Care provides a secure, easy-to-use interface for patient-clinician communication and data exchange. Its clinical system stores and manages patient data in a secure environment, while its clinical decision support system helps clinicians make decisions that are more informed, efficient, and cost-effective. This system has the potential to improve patient safety and quality of care, while also helping to reduce healthcare costs.

KEYWORDS: eHealth innovation, supportive care, computable algorithms, clinical decision support system, health technology, mHealth, Immune-related adverse events

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Introduction

Immunotherapy is rapidly advancing and can now be considered a powerful new tool in the treatment of cancer.[1] However, it is associated with a myriad of Immune-related adverse events (irAEs). These irAEs can affect numerous body organs and are potentially life-threatening if not promptly recognized

and treated.[2] Therefore, early recognition and effective management of these irAEs are critical to reducing treatment sequelae.[3] Patients are often required to monitor and manage a range of potentially diverse and complicated irAEs without readily available clinical support[4] and report poor quality of self-management support in ambulatory cancer care.[5] This sub-optimal irAEs management has resulted in high rates of cancer symptom severity and avoidable emergency department visits and hospitalization.[6] Such rates are costly to the health system[7] and concerning as poor symptom control is associated with higher morbidity, treatment non-adherence, and worse survival.[8,9]

mHealth technologies are emerging as a solution to this problem.[10] Our previous work focused on the Advanced Symptom Management System-Canadian version (ASyMS-Can), a remote symptom monitoring system that provided real-time remote monitoring of systemic chemotherapy toxicities using Common Terminology Criteria for Adverse Events (CTCAE).[3] The system was initially developed in the UK[11] and has since been evaluated in diverse patient populations.[11-18] We enhanced the automated self-care advice provided by ASyMS-Can by tailoring the advice sent to patients based on back-end computations, according to their reported symptoms, ultimately facilitating improved patient self-management. Additionally, we adapted the system's risk-scoring and decision-support algorithms to align with Canadian evidence-based protocols for symptom triage. Building on this foundation, we have developed V-Care, an eHealth platform comprising an electronic patient-reported outcome (ePRO) for a new follow-up pathway for cancer patients receiving immune checkpoint inhibitors (ICIs).

Although immunotherapy is associated with unique irAEs that are more unpredictable than chemotherapy adverse events (AEs),[19-22] early detection and relevant treatment initiation can manage most of these side effects.[23-25] However, there are currently limited ePROs available for the proactive management of irAEs.

This study describes the development of the V-Care platform supporting cancer patients in accessing self-care advice to manage their symptoms better, interacting with healthcare professionals, and enhancing patient participation in care.

Methods

Development of the V-Care is reported according to the British Medical Research Council (MRC) guideline for the development of complex interventions that describes the whole process from development to implementation. In the process of developing and evaluating a complex intervention, the MRC guidance includes 4 phases: development, feasibility and piloting, and evaluation and implementation.[26] During the development phase, the primary objective was to identify existing evidence to inform the intervention design.[27]

Additionally, the Center for eHealth Research and Disease Management (CeHRes) roadmap for the development of eHealth technologies was utilized, which comprises distinct development phases ranging from contextual inquiry to operationalization.[28] The CeHRes model focuses on the development, implementation, and evaluation of eHealth applications through 5 phases with an emphasis on involving all relevant stakeholders (Figure 1).[28,29]

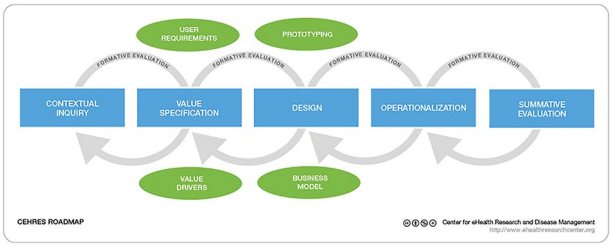

Figure 1. CeHRes Roadmap for the development of eHealth technologies.

The purpose of this paper is to outline the evolution of the V-Care platform, with an emphasis on its initial 3 stages according to the CeHRes roadmap. This paper will not delve into implementation or evaluation (Figure 2). We used multiple methods to operationalize the first 3 phases of the CeHRes roadmap. These phases were not performed sequentially but were interwoven throughout the developmental process.

As shown in Figures 1 and 2, the teams utilized an agile approach in an iterative and dynamic manner while collaborating with all key relevant stakeholders.[30] This approach is particularly has been used foster significant contributions of end users (patients and clinicians) throughout development and in developing similar applications.[31]

Contextual Inquiry

The process of development began by identifying existing evidence and assembling a multidisciplinary team to enable informed decision-making and action. Stakeholders were consulted throughout the process to provide input on the objectives and strategies necessary to address the identified need. The team worked collaboratively to create plans based on the evidence collected and engaged stakeholders in the decision-making process to discuss and define the objectives and strategies necessary for implementation. By working together, the team was able to create plans that addressed the identified need in an informed and effective manner.

Identifying existing evidence

A comprehensive systematic review of the relevant literature, reported elsewhere,[3] was conducted to elucidate the essential design elements and features of ePROs, as well as their related outcome measures. Additionally, a systematic review and meta-analysis is being conducted to identify the potential and limitations of e-health interventions for supporting cancer patients in managing their cancer-related symptoms, which will help inform the development of this ePRO system.[32] Moreover, we conducted semi-structured interviews with 13

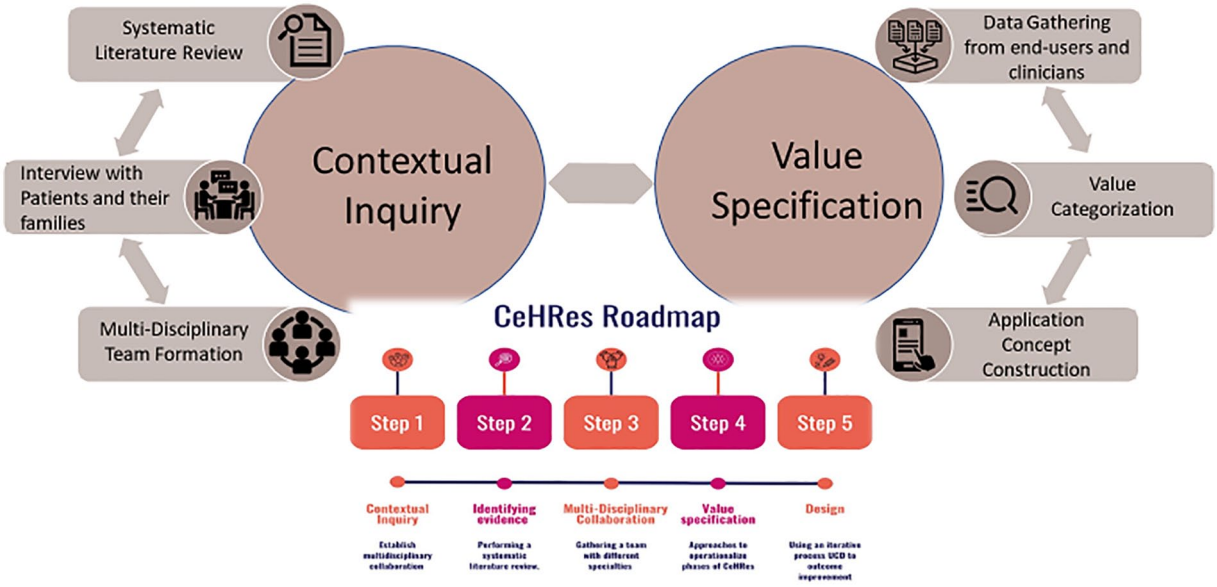

Figure 2. The development process of the contextual inquiry and value specification phases in the V-care platform.

cancer patients who participated in our previous ePRO study[33] in order to gain insight into the acceptability of ePROs, their feasibility within patient care processes and their integration into patients' daily routines. The interview guide, which included a flexible list of open-ended questions, was designed to enable participants to express their experiences, opinions, and emotions in their own words. This approach also allowed for follow-up questions and the exploration of new topics that might emerge during the interview. We explored their experiences in self-management, activation, treatment optimization, m-Health and care coordination partnership. Two members of the research team evaluated and discussed the codes to ensure they possessed face validity. Initially, codes were assigned to meaningful units and then organized into themes. Subsequently, the team identified connections between the established codes. By engaging cancer patients as end users, we gained invaluable insights into their needs and preferences relating to the features, content, and functionality of our platform. Our previous research enabled us to create a product that was tailored to patients' expectations and optimized for a user-friendly experience, making it easier for cancer patients to interact with our new platform. We also made sure to design an interface that was highly intuitive and accessible, ensuring that users will have an optimal experience when using our platform.

Multidisciplinary collaboration

A multi-disciplinary team played a pivotal role in the successful design and development of the V-Care platform. This diverse team, comprised of researchers, oncology clinicians, digital health experts, computer scientists, and patient advocates, exemplified the power of collaboration in overcoming challenges and creating a robust, user-centric system.

In the initial phase of the project, the team focused on aligning their goals and understanding the unique perspectives each member brought to the table. This process was crucial in addressing the diverging priorities, timelines, languages, and expectations that can often exist between different disciplines.[34] Through open communication and mutual respect, the team was able to find common ground and work efficiently toward shared objectives.

In the multidisciplinary collaboration to develop V-Care, clinicians also played a vital role by providing their expertise and perspective on the tool's development. As key stakeholders, they were consulted throughout the process to offer input on the objectives and strategies necessary to address the identified needs. Their practical experience and understanding of patient care allowed the team to develop a more comprehensive and effective solution tailored to the realities of clinical practice.

The team worked collaboratively, leveraging the evidence collected from interviews and literature reviews to create plans that integrated the insights from various stakeholders. This approach ensured that the resulting tool would effectively serve the needs of both patients and healthcare providers. By actively engaging clinicians and patients in the decision-making process, the team was able to discuss and define the objectives and strategies necessary for the successful implementation of V-Care. Clinicians' input was particularly valuable in identifying the most relevant symptoms to track, refining the user interface to optimize ease of use, and providing guidance on communication features to facilitate better patient-provider interactions.

One of the common challenges in using eHealth platforms is data privacy and security concerns.[35,36] Therefore, to ensure a smooth transition to real-world implementation, the team also put considerable effort into establishing practical strategies for privacy and data security. This included adhering to

industry standards, developing tailored solutions to protect sensitive information, and maintaining transparency with all stakeholders.

As the project progressed, the team continued to monitor and evaluate their compatibility and alignment, making adjustments as needed to maintain a productive and harmonious working environment. By actively involving all team members in decision-making processes and recognizing the unique contributions of each discipline, they fostered a sense of ownership and commitment that proved vital to the success of the V-Care platform.

Value specification

Several approaches were employed to operationalize the first 2 phases of the CeHRes Roadmap. Firstly, data was gathered from end users (cancer patients, nurses, and leading clinicians from clinical sites) and clinical administrators from our previous studies.[3,33] Next, the relevant values were carefully categorized based on their importance from both users' perspectives (ie, patients and healthcare providers) and the organizational perspective of this new platform.[28] Values were subsequently formulated, and a concept for the app was built and visualized with a low-fidelity prototype. The development process of the contextual inquiry and value specification phases is shown in Figure 2. Moreover, implementation notes were provided, containing essential information and requirements necessary for project completion. These notes were designed to keep all stakeholders apprised of the necessary details. Through strategic communication and collaborative meetings, the team worked together to ensure the successful completion of the prototypes of the technology interface that adhered to user values and technical specifications established in previous phases. Intensive design efforts were implemented in 2020 to 2022 to create an ePRO that was user-friendly with a simple and straightforward structure to reduce user burden.

Design

User-Centered Design (UCD) is an iterative process that incorporates user perspectives throughout the design cycle to increase user satisfaction and facilitate positive health behaviors and outcomes.[37,38] This approach ensures the development of digital platforms with higher levels of acceptability, understanding, and engagement for the intended user population.[39-41] Based on information gathered during earlier phases, a comprehensive project outline was formulated. This outline included a detailed list of tasks needed to complete the project, along with estimated times needed to complete each component. Through strategic communication and collaborative meetings, the team worked together to ensure the successful completion of the prototypes of the technology interface that adhered to user values and technical specifications established in previous phases. Intensive design efforts were implemented in 2021 to 2022 to create an ePRO that was user-friendly with a simple and straightforward structure to reduce user burden.

Results

Context and values

During the first 2 phases of the CeHRes Roadmap, our focus was on addressing key issues related to contextual inquiry and value specification. A systematic literature review conducted by the research team[42] and interviews with 13 cancer patients and clinicians from our previous ePRO study[33] served as the primary sources of evidence concerning essential design elements, components, and features of eHealth tools. The literature review informed our understanding of state-of-the-art eHealth systems, while the interview data provided valuable insights into the needs and preferences of both patients and clinicians when using digital symptom monitoring tools, promoting earlier intervention and improved outcomes.

The interviews identified several design and functionality challenges with the previous ePRO device that needed to be addressed for optimal efficiency. Enhancements to the user experience in the newly developed ePRO included an intuitive and informative introduction screen, an effective color scheme, advanced options, and seamless communication with clinicians. These improvements proved beneficial for both patients and clinicians, as they ultimately led to increased patient satisfaction and better outcomes.

Although it remains unclear which components of current applications are the most beneficial or commonly used by patients, key considerations include the ability for patients to self-report and capture ePROs for cancer treatment-related symptoms in real-time, patient-articulated experiences with these systems, e-communication between patients and providers, and the use of valid ePRO measures instead of purpose-designed questionnaires.

A multidisciplinary project team led the development of the ePRO system, comprising a mobile application with a symptom questionnaire that enables patients to complete it on their digital devices. The selection of the most relevant symptoms was based on the PRO-CTCAE library,[43-46] the DCTAQ,[47] international guidelines, and the most common irAEs observed during clinical trials.[48-50]

System Architecture

The V-Care system is a user-friendly, visually appealing, and easy-to-navigate healthcare platform. The architecture consists of several interconnected components, including patient terminals, clinician terminals, clinical servers, and researcher terminals (Figure 3).

1. Patient Terminals: These user-friendly interfaces enable patients to access their history of reported irAEs, search for information regarding their cancer and treatments,

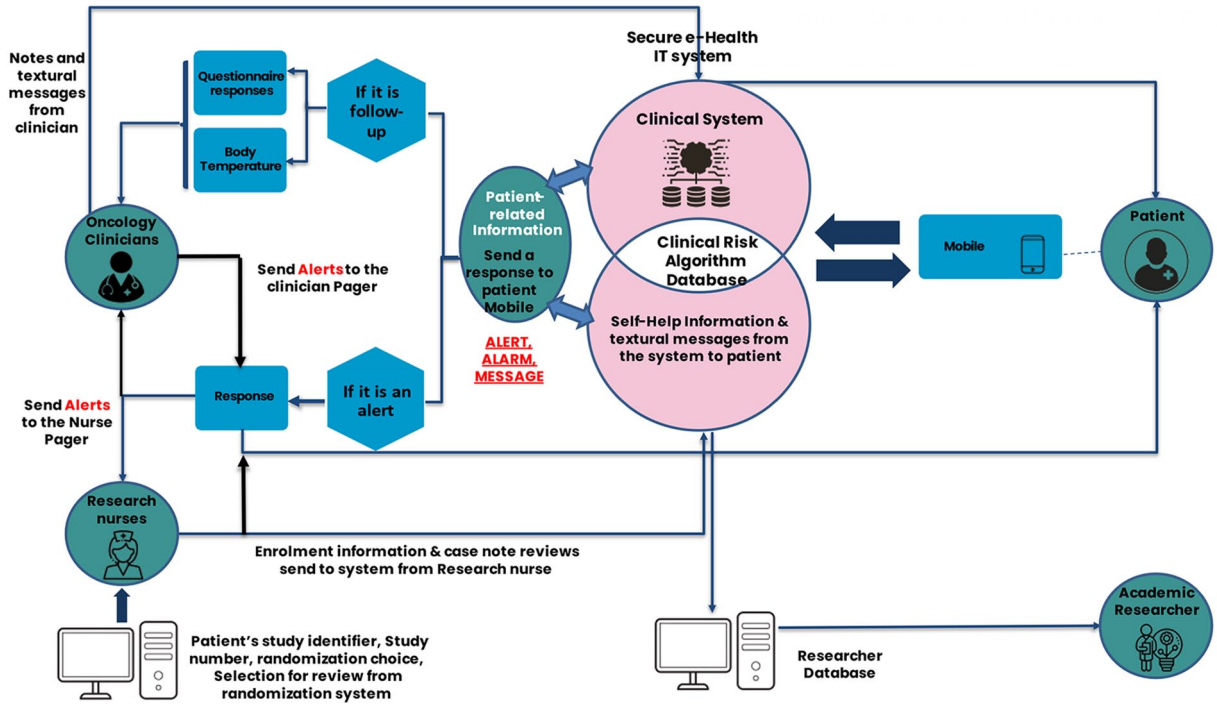

Figure 3. Architecture and workflow of V-care.

and learn how to manage irAEs. Patient terminals prioritize user interface and user experience, ensuring easy navigation and visual appeal.

2. Clinician Terminals: Clinicians utilize these terminals to securely access patient data, monitor e-PROs, communicate with patients, and enhance patient care.
3. Clinical Server: The clinical server is a centralized data management platform responsible for storing patient information, generating alerts, and supporting clinical decision-making. This system maintains patient privacy and security while enabling efficient data exchange between patient and clinician terminals. The server also collects e-PROs and generates alerts or patterns requiring clinical intervention. By automating this process, the e-PROs clinical server helps healthcare providers address potential severe clinical issues as needed.
4. Researcher Terminals: These interfaces allow authorized researchers to access and analyze anonymized patient data for research purposes.

In this paper, we provide an overview of the evolution of patient terminals, from their early inception to the present day.

Development of Patient Terminal

The development of the application was segmented into 2 distinct phases, focusing both on user interface (UI) and user experience (UX) designs. After collecting feedback from all relevant stakeholders, the first phase focused on structuring the application's pages into general categories, such as home, library, messages and my profile, with associated subpages. Based on the feedback, the application was modified accordingly to ensure the optimal user experience. During the second phase of development, UI elements, including menus, buttons, text, and graphics, were evaluated and optimized to enhance the overall user experience while creating a more intuitive and enjoyable experience. Then, the mock-up pages were sent to the Figma website, and the Android Package Kit (APK) of the application was installed and extensively tested on a mobile phone in order to identify and resolve any errors proactively. After successfully addressing technical issues and correcting mistakes on the Android version to ensure an optimal user experience, the iOS version of the application was developed. This version was rigorously tested on multiple devices using Xcode and debugging tools to identify and rectify any remaining errors. The patient interface of the mobile version of the V-Care app is illustrated in Figure 4.

Discussion

The overall advantages of symptom monitoring for quality of care and health-related quality of life (HRQOL) in research settings are well-documented. These benefits typically translate into improved survival rates, enhanced quality of life decreased anxiety levels, better physical health status, increased adherence to therapy, fewer visits to the emergency room, and reduced hospital admissions. Furthermore, symptom monitoring can bolster patients' self-belief and confidence in their ability to manage their condition.[10,51-55]

The V-Care platform aims to bridge the gap in existing ePRO systems by focusing on the unique challenges faced by cancer patients receiving immunotherapy. The platform's goal is to improve patient outcomes, reduce healthcare system

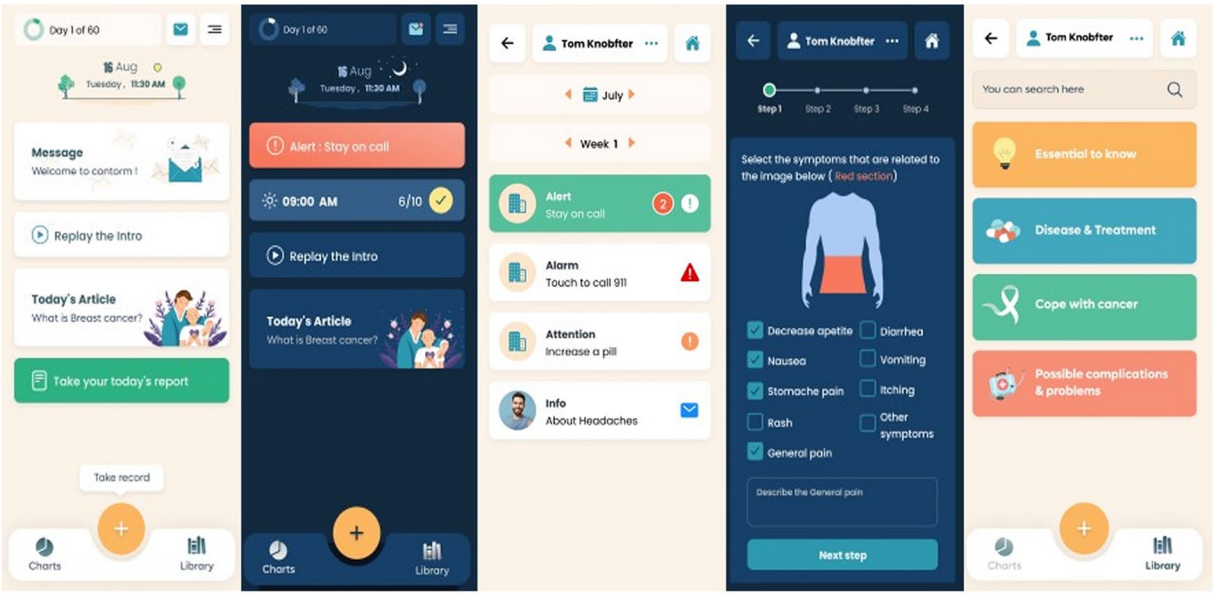

Figure 4. The patient interface of the mobile version of the V-care app.

costs, and promote a more collaborative and personalized approach to cancer care. By providing patients with access to tailored self-care advice and facilitating prompt medical interventions when needed, V-Care has the potential to revolutionize the management of irAEs and improve the quality of life for cancer patients undergoing ICIs treatments. By continuously refining and expanding the ePRO system based on patient feedback and emerging research, V-Care can contribute to the growing body of evidence supporting the use of mHealth technologies in cancer care.

As the field of cancer treatment continues to evolve, it is crucial to develop innovative and patient-centered solutions that can address the unique challenges faced by cancer patients. By harnessing the power of technology and leveraging our previous work with ASyMS-Can, V-Care represents a significant step forward in the proactive management of irAEs and the overall improvement of cancer care. This paper presents an overview of the evolution of V-Care, from its early inception to the present day. We outline the critical advances in V-Care technology and functionality that have been made, highlighting how these developments have enabled cancer patients to receive improved care and an enhanced quality of life. Through the implementation of V-Care, opportunities for early identification and management of irAEs have increased, leading to fewer complications and improved outcomes. This project focuses on identifying and managing irAEs earlier in the treatment process to reduce the incidence of treatment sequelae and improve the health outcomes of cancer patients receiving immunotherapy. This project is the first of its kind in the Canadian ePROs system, and we anticipate that it will serve as the impetus for further research and development of patient-centric technologies.

As with any technological advancement, V-Care has certain limitations. The app is currently only useful in the subset of the population that uses smartphones and has access to an internet connection, which must be always maintained during the treatment period for timely notifications and prompts. Moreover, the app has undergone field testing on a smaller group of patients to check for any major functional flaws. To address these issues, more robust user testing will be conducted a usability testing to evaluate the efficacy and user experience of the app, and strategies will be implemented to reduce any educational obstacles. As a result, the app can be further optimized and tailored to the specific needs of users. Further research and evaluation will be necessary to determine the full impact of V-Care on patient outcomes and healthcare system efficiency, but the potential benefits of this platform are clear and promising.

As a second part of this study, we are now developing computable algorithms to establish threshold alerting scores for the early detection of irAEs through the V-Care platform. This will prevent unnecessary alarms to clinicians, streamline workflows, and ensure patients receive the highest quality care possible. The algorithms will take into account factors such as patient history, the severity of symptoms, and available treatments to accurately predict the potential onset of irAEs. This data-driven approach will enable healthcare providers to make informed decisions on how best to manage a patient's condition and optimize outcomes.

Clinical Resources

https://www.emro.who.int/health-topics/ehealth/
https://ehealthontario.on.ca/en

Author Contributions

Saeed Moradian: conceptualization, methodology, data collection, analysis, and writing of the original draft.

Shive Ghasemi: methodology, data collection, revision of the manuscript.
Babak Boutorab: methodology, contribution to the results section, revision of the manuscript.
Zakieh Sharifian: Literature review, data interpretation, and contribution to the results section.
Fay Dastjerdi: Manuscript editing, language revision, and final approval for publication.
Catriona Buick: Manuscript editing, language revision, and final approval for publication.
Charlotte T. Lee: editing and revision of the manuscript.
Samantha J Mayo: editing and revision of the manuscript.
Plinio P. Morita: revision of the manuscript.
Doris Howel: overall guidance throughout the research process, and revision of the manuscript.

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