Examining Symptom Burden and the Palliative Care Needs of Patients with Hematologic Malignancies

By

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We acknowledge and respect the lək̓ʷəŋən peoples on whose traditional territory the university stands and the Songhees, Esquimalt and W̱SÁNEĆ peoples whose historical relationships with the land continue to this day.

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Abstract

Despite the proven benefits of integration of palliative care in oncology, it has been well established that patients with hematologic malignancies and those undergoing hematopoietic stem cell transplantation do not routinely receive timely palliative care. Patients with hematologic malignancies are less likely to receive palliative care and more likely to receive aggressive care at end-of- life (such as chemotherapy, admission to hospital, and admission to an intensive care unit) compared to patients with solid tumours. Advances in the understanding and treatment of hematologic malignancies has led to improved survival rates for some patients, but high mortality rates and diminished quality of life for patients who survive persist.

This dissertation includes three studies that are presented in paper-based format. The first paper (Chapter 4) describes the qualitative study that was undertaken to examine the perspective of patients (n=8), family caregivers (n=4), and clinicians (n=16) on integrating palliative care for patients with hematologic malignancies undergoing hematopoietic stem cell transplantation. Findings from this study revealed that patients undergoing hematopoietic stem cell transplant experience an array of physical, psychosocial, and practical concerns, during and after hematopoietic stem cell transplantation. In addition, participants spoke of the unique challenges to integrating palliative care in this population, such as prognostic uncertainty, the curative-intent focus, and misperceptions of palliative care held by clinicians, patients, and family caregivers alike.

The second paper is the protocol for a randomized clinical trial to examine the impact of early palliative care compared to standard care for patients with hematologic malignancies. The study was developed following the completion of the qualitative study, taking into consideration patient, family caregiver, and clinician input on how to best integrate palliative care in this population. Due to the COVID-19 pandemic, there was a delay in opening the trial and there have been subsequent challenges with recruitment. As such, the findings from this study are not presented in this dissertation as the study is ongoing.

The third paper describes a retrospective observational cohort study that examined symptom burden and healthcare utilization in patients with hematologic malignancies (N=7080). This study also involved chart audits of patients who had died within a year of completing symptom questionnaires (n=432) to examine symptom burden and healthcare utilization in this sub-cohort. This study found that patients with hematologic malignancies experience high symptom burden, particularly in the last year of life. In addition, symptom profiles were found to be associated with sociodemographic and clinical variables. In particular, females reported more frequent and severe symptoms compared to males and older adults reported moderate to severe physical symptoms but less frequent and less severe psychological symptoms compared to younger patients. This study also found that symptoms were associated with increased healthcare utilization, particularly emergency department visits. The findings emphasize the need for more supports for patients, particularly for symptom management.

In summary, symptom burden and treatment-related toxicities are known to be high in patients with HMs. Morbidity and mortality associated with HMs and their treatment continue to be high. This research adds to the literature by demonstrating that patients with hematologic malignancies experience high symptom burden, experience high rates of healthcare utilization, and could benefit from integration of palliative care. This research informs implications for clinical practice, education, research, and policy, including better symptom management,

education on the potential benefits of palliative care for patients with hematologic malignancies, the need for research on when and how to best integrate palliative care in this population, and consideration of policy changes to remove restrictive criteria in palliative care and hospice that may be barriers for patients with hematologic malignancies. Preliminary findings from this research have already been shared at local, provincial, national, and international levels. Resources on symptom management and palliative care for patients with hematologic malignancies have been developed with patient support societies across Canada. As such, it is hoped that this research will contribute to improving the patient and family caregiver experience and quality of life after the diagnosis of a hematologic malignancy.

Table of Contents

List of Tables

List of Figures

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Dedication

I dedicate this work to the patients and family caregivers that I have had the privilege of caring for over the years and anyone who has been impacted by cancer.

You were the inspiration for this work and compel me every day to do whatever I can to make your experience even a little bit easier.

Chapter 1: Introduction

Tremendous progress in the understanding of cancer biology, pathophysiology, and genomics has led to an ever-expanding array of treatment options for people with cancer. To illustrate, between January 2000 and October 2022, the Food and Drug Administration approved 573 agents for oncologic indications (Hilas, 2023). While such developments have led to improved survival, attention to quality of life has not always kept pace (Samuel et al., 2022). Treatments for hematologic malignancies (HMs) in particular are known to be intensive, and include modalities such as high dose chemotherapy, total body irradiation, hematopoietic stem cell transplantation (HSCT), and more recently, chimeric antigen receptor (CAR) T-cell therapy (El-Jawahri et al., 2020; Robbins-Welty et al., 2023). Such treatments have the propensity to cause profound symptom burden and treatment-related toxicities (Robbins-Welty et al., 2023). Moreover, some HMs, such as multiple myeloma and some types of lymphoma, are treatable but remain incurable (Howell et al., 2022). Accordingly, patients with HMs face ongoing risks of disease and treatment related morbidity and mortality.

High symptom burden, including physical and psychosocial symptoms, can be challenging for both patients and their family caregivers. Yucel et al. (2021) undertook a literature review (N=71 articles) to examine health-related and economic burden for family caregivers of patients with HMs. The authors found that family caregivers experienced post-traumatic stress disorder, sleep problems, moderate-to-poor health-related quality of life, and negative impacts on family relationships. High symptom burden and impaired quality of life, coupled with risks of relapse and life-threatening treatment related complications, would seem compelling reasons to consider the integration of palliative care (PC) for patients with HMs.

Palliative Care

The roots of PC can be traced back to the work of Canadian surgical oncologist Dr. Balfour Mount, who has been credited with conceiving the term ‘palliative care’ in the mid-1970s (Davis, Bruera & Morganstern, 2013). At the time, the term PC was used to describe the program of hospice care that Mount had established at the Royal Victoria Hospital in Montreal (Hanks, 2008). In the ensuing years, the definition of PC has evolved and despite being aligned with hospice and end-of-life care at its inception, PC is no longer considered solely relevant to the care of the dying (Bauman & Temel, 2014; Davis et al., 2013; Hanks, 2008). Palliative care has been defined by the World Health Organization (WHO) as “an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (WHO, 2020, page 1). The WHO definition of PC further highlights that PC is appropriate early in the disease trajectory and may be delivered alongside life-prolonging therapies, such as radiation or chemotherapy. More recently, the International Association for Hospice and Palliative Care published their consensus-based definition of PC as “the active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life” and stated that PC “aims to improve the quality of life of patients, their families and their caregivers” (Radbruch et al., 2020, p. 755).

In addition to the above definitions of PC, it is important to clarify additional concepts that are relevant to my research. In particular, there are notable differences between specialty PC, primary PC, and a palliative approach to care. Specialist or specialty PC typically involves interdisciplinary, holistic care provided by clinicians with expertise and training in PC (Ernecoff et al., 2020; Hui et al., 2022). In contrast, primary PC can be provided by clinicians who are not specialized in PC and could include tasks such as basic symptom management and preliminary discussions on advance care planning (Ernecoff et al., 2020; Quill & Abernethy, 2013). A palliative approach to care does not require specialty PC services and can be adopted by any clinician by utilizing PC knowledge tailored to the patient's and family's needs (Sawatzky et al., 2016). In the context of HMs, a palliative approach to care may be well suited to meet patients' needs, particularly given the inherent challenges with prognostic uncertainty and variable disease trajectories.

Data from systematic reviews and meta-analyses have confirmed the benefits of PC for patients with solid tumours (Cui et al., 2023; Fulton et al., 2019; Rogers et al., 2020; Vanbutsele et al., 2018). Compared to standard care, PC has been associated with improved quality of life, reduced symptom burden, better illness and prognostic understanding, and improved survival in some contexts (Cui et al., 2023; Rogers et al., 2020). In contrast, lack of PC involvement has been associated with adverse outcomes such as the overuse of life-sustaining therapies, aggressive treatment (including chemotherapy) in the weeks preceding death, intensive care unit admissions, more emergency department visits, hospitalizations, underuse of hospice, and limited access to comprehensive pain and symptom management, psychosocial, and spiritual care support (Bernacki & Block, 2014; Bercow et al., 2021; Hirvonen et al., 2020; Hui et al., 2014).

Despite the known benefits of PC, patients with HMs do not routinely receive PC and if they do, it is typically very late in the disease trajectory (Elliott et al., 2021; Shaulov et al., 2022; Verhoef et al., 2020). To date, there have been only a few randomized clinical trials (RCTs) examining the impact of PC in patients with HMs, although the literature on PC for patients with HMs is growing. Organizations such as the American Society of Clinical Oncology have called for more research on integrating PC for patients with HMs (El-Jawahri et al., 2023; El-Jawahri et al. 2016; Sanders et al., 2024), recognizing the benefits to HM patients and their family members. Within my clinical practice in oncology, including with the Alberta Blood and Marrow Transplant Program and the Palliative Care Consult Service in Alberta, Canada, I have witnessed firsthand the profound disease and treatment-related symptom burden that patients experience and how such symptom burden influences not only their quality of life overall, but also, their end-of-life experience. Disease and treatment-related side effects that are frequently reported by patients with HMs include severe mucositis, fatigue, pain, drowsiness, impaired appetite, insomnia, and neuropathy, to name a few (Allart-Vorelli et al., 2015; Tinsley-Vance et a., 2023). In addition to the multitude of physical concerns after a diagnosis of a HM, patients and their family members may also experience an array of psychosocial and existential concerns (Husted Nielsen et al., 2022; Papathanasiou et al., 2020).

Clinicians have recognized the need for better understanding of the supportive and PC needs of patients with HMs (Helwick, 2016; Wedding, 2021). In their review article on the PC needs of patients with HMs, El-Jawahri et al. (2020) describe the multitude of PC and supportive care needs that patients may experience throughout the disease trajectory, from treatment through survivorship and end-of-life phases. Further, the authors provide an overview of the physical and psychosocial symptoms that may arise in the context of heterogeneous diseases and variable prognoses (El-Jawahri et al., 2020). As has been demonstrated in patients with solid tumours, PC supports and a palliative approach to care might be helpful in alleviating the multidimensional suffering that can occur after the diagnosis of a HM. In addition to reducing symptom burden and improving quality of life, PC may also help patients with HMs and their family members better understand their prognosis and may help with coping (El-Jawahri et al., 2020; Hui et al., 2022).

Professional Context for Undertaking this Research

When I began working with the PC team, I noted that the patients with HMs were infrequently referred to PC and when they were referred, it was often very late in the disease trajectory. What this meant for patients was that they were not able to avail themselves of the services and supports that PC could offer. For example, in Alberta, hospice access is managed by PC. Due to the late referrals to PC, I observed that patients with HMs were often unable to go to hospice given the time it took to arrange hospice transfer.[1] In addition, patients and family caregivers were often shocked and distressed when no more disease-directed options were available and the transition to end-of-life care seemed to occur very rapidly.

Several clinicians on the Palliative Care Consult Service team had been working to better understand the gaps in PC for patients across Alberta and established the Palliative Care – Early and Systematic (PaCES) program, a research collaborative comprised of researchers, healthcare providers, administrators, and patient/family advisors (PaCES, 2024a). When I began my PhD program in September 2018, I had been working with the Palliative Care Consult Service and became involved with the PaCES program, with a focus on patients with HMs (PaCES, 2024b).

My clinical experiences coupled with my involvement with the PaCES program afforded a unique perspective on the real-world issues for patients with HMs. Patients with HMs and those undergoing HSCT often did not receive PC, in spite of the known benefits of integrating

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[1] In Alberta, palliative care can be provided at any point after the diagnosis of a serious illness. Hospice care is 24 hour care that is provided in hospice facilities and is typically provided within the last days to short months of life (Alberta Health Services, 2024). (Alberta Health Services, 2024).

PC into oncologic care. This research, along with my clinical observations, inspired the research contained herein.

I spoke with clinician colleagues in the hematology/HSCT and PC programs in Alberta and met several times with an expert in Boston who has conducted PC research in hematology and with patients undergoing HSCT, Dr Areej El-Jawahri. Several clinician colleagues had recommended that I consider conducting a randomized clinical trial (RCT). In 2010, Temel et al., had published their RCT that showed for patients with advanced lung cancer, early PC led to improved outcomes, including quality of life, mood, and overall survival compared to standard care. Since then, there have been a number of studies, mostly conducted with patients who have solid tumours, on the benefits of integrating PC in cancer care. I will explore this in more detail in Chapter 2. In oncology, where toxicities and outcomes, including survival, are high stakes, RCTs have been held up as the gold standard of evidence (DiMaio et al., 2020; Gyawali et al., 2017). In my own discussions with hematology-oncology clinicians, I had been told that the best way to compel change would be conducting an RCT that could show the potential benefits of PC for patients with HMs. As such, I set my sights on conducting an RCT for my PhD dissertation.

In late 2018, the Tom Baker Cancer Centre announced a new grant competition, the RK Dixon Family Award, established by a large donation from a family who had been impacted by a HM. The grant, administered by Alberta Cancer Foundation, was intended for research on HMs in Alberta. I submitted a letter of intent and was later invited to submit a full application for the grant. The grant review process was rigorous, with a presentation in front of a panel of global experts. The panel included scientists, clinicians, researchers, as well as patient and family advocates. I was also required to do a private presentation for the donor family. Throughout the review process, I learned that it would be important to first understand the local landscape in terms of PC needs and current levels of PC involvement for patients with HMs. In addition, I knew that it would be important to better understand clinicians’ perspectives prior to attempting to introduce practice-changing recommendations. As such, I proposed a multi-phased project that would allow me to better understand the landscape of PC for patients with HMs in Alberta as well as allow for patient, family caregiver, and clinician perspectives to be considered prior to conducting an intervention trial. The overarching purpose of my research was to improve quality of life and reduce symptom burden in patients with HMs by integrating PC supports and a palliative approach to care.

As part of my work with the PACeS program, I had completed two secondary data analyses that have informed my dissertation. The first study involved analyzing data from surveys that had been sent to oncology clinicians across Alberta. The surveys asked questions about integrating PC in oncology. I focused on the hematology-oncology clinicians’ responses which suggested that incorporating PC would require substantial changes in practice (Booker et al., 2020). Further, hematology-oncology clinicians reported that existing PC referral criteria were too strict for patients with HMs. Finally, the survey responses also revealed that clinicians (general oncology clinicians and hematology-oncology clinicians alike) worried that discussing PC could cause distress for patients (Booker et al., 2020).

The second secondary analysis examined quality of end-of-life care in a cohort of decedents of HMs in the Calgary Zone from 2007-2016 (N=1844) (unpublished). Previous work had identified aspects of end-of-life care that are important to patients with HMs (Kuczmarski & Odejide (2021). For example, intensive healthcare utilization at end of life was associated with worse quality of life, while spending time at home with family and loved ones, being able to prepare for death, and having pain well-managed were all associated with better quality of life at end of life (Kuczmarski & Odejide, 2021). Additionally, the authors suggested that early PC could improve quality of life at end of life because of comprehensive symptom management provided by PC.

In the data that I analyzed, I found that most patients had died in hospital. Further, while most patients had some exposure to PC, more than two thirds of those who met with PC did so less than 3 months before death and nearly 20% first met with PC within a week of death. Logistic regression was undertaken to examine predictors of hospital death. Factors associated with increased risk of hospital death included: receipt of chemotherapy in the last 2 weeks of life, ICU admission in the last month of life, and more than one ED visit. After controlling for covariates, any exposure to PC was associated with lower odds of hospital death. These findings are important as it is possible that the absence of PC may have contributed to poor quality end-of-life care. These findings are aligned with those reported by Elliott et al. (2021), who conducted a systematic review of studies on specialty PC interventions for patients with HMs (N=16 studies). The authors reported that PC led to improved symptom management, decreased likelihood of hospital death, and decreased healthcare utilization.

These secondary analyses, done prior to my dissertation research, provided a foundation for my current work. These analyses, and others (Elliott et al., 2021; Shaulov et al., 2022) have highlighted the high symptom burden, manifesting both physically and psychosocially, that patients with HMs experience, the poor-quality end of life care experienced by patients with HMs, and the lack of PC that patients with HMs receive. With this in mind, I began my dissertation work. Working with my supervisory committee, I wrote a grant to better understand patient, family caregiver, and clinician perspectives on the integration of PC for patients with HMs and to assess the impact of an outpatient PC intervention on patients' quality of life, symptom burden, and prognostic understanding. The grant contained proposals for both an interpretive descriptive study and a a randomized clinical trial.

While the interpretive descriptive study was completed (see Chapter 4) and the research for the RCT was funded (see Chapter 5: RCT Study Protocol), due to challenges imposed by the COVID-19 pandemic, my research was delayed and completing the RCT in a timely manner became challenging. Like many PhD students, I had to pivot to complete my dissertation.

Given the inability to complete the RCT for my dissertation, I conducted an additional study to round out the research for my dissertation. Fortuitously, I had access to a large data set of clinical data and symptom scores that had been collected from patients with HMs across Alberta. I conducted a retrospective cohort study to examine symptom burden and examine healthcare utilization in patients with HMs (N=7080). This study was well-aligned with the broader goals of my research, to improve the quality of life of patients with HMs, as it provided relevant information on the types of symptoms that patients with HMs experience and how such symptoms were associated with various clinical and demographic characteristics. Further, knowing more about the types of symptoms and severity of symptoms that patients with HMs experience, helped to identify potential areas where a PC approach could be helpful.

The dataset also included information on healthcare (HC) utilization, such as emergency department (ED) visits and hospital admissions (HAs). Previous work on PC for patients with HMs has explored HC utilization (Cheung et al, 2020; Hui et al, 2014; Soares et al., 2019), particularly in the last months of life, as HC utilization has been associated with quality of end-of-life care (Earle et al, 2003; Kuczmarski, & Odejide, 2021). In addition, the opportunity to conduct chart audits on the patients who had died within a year of completing patient reported outcome measures (PROMs) (n=432) that measured symptoms and overall well-being allowed for better understanding of the reasons why patients visited EDs and were admitted to hospital. I was also able to explore associations between PROs, demographic variables (such as sex, age, and rurality) and various clinical outcomes. More details on this study are discussed in Chapter 6.

Overview of Dissertation

In addition to providing background to my dissertation (Chapter 1), a review of the literature highlighting the state of the knowledge on PC for patients with HMs and the limited available data on symptom burden was undertaken and presented in Chapter 2. In Chapter 3, I describe my methodological approach, providing a brief explanation of the original planned mixed methods research and a summary of the methods utilized for the two primary studies undertaken for my dissertation. Challenges and opportunities related to the COVID-19 pandemic are also discussed.

In Chapter 4, I present the findings from the qualitative study that examined patient, family caregiver, and clinician perspectives on integrating PC for patients with HMs. These findings were published in *Oncology Nursing Forum* in May 2023. Chapter 5 includes the protocol for the RCT described earlier, for which recruitment is ongoing. Findings are forthcoming and not presented as part of this dissertation. Chapter 6 reports findings from the retrospective cohort study on symptoms and healthcare utilization in patients with HMs. Chapter 7 summarizes and discusses findings from this body of research and includes recommendations for practice, education, research, and policy. Examples of knowledge translation activities that have been undertaken and that are forthcoming are discussed. Finally, in Chapter 7, a summary and conclusion of the work described in this dissertation is presented.

Conclusion

Even though advances in treatment have led to improved rates and duration of progression free survival, treatment of HMs is not always curative. Further, patients with HMs experience high symptom burden throughout the illness trajectory and such symptom burden has been found to adversely impact patients' quality of life. Patients with HMs are also at high risk of experiencing poor quality end-of-life care. Accordingly, there is an urgent need to better understand the PC needs of patients with HMs and their family caregivers and identify potential opportunities to integrate palliative care supports and a palliative approach to care in hematology/HSCT. Doing so has the potential to proactively address suffering and improve quality of life for patients with HMs and their family members.

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Chapter 2: Literature Review

Introduction

Given that the aim of my research was to gain a better understanding as to how quality of life could be improved for patients with hematologic malignancies (HMs) and their family caregivers, I have focused this literature review on factors that have been associated with quality of life throughout the HM illness trajectory, including at end-of-life. Much of the literature on quality of life in patients with cancer has focused on the impact of symptoms, including physical and psychological, on quality of life (Allart-Vorelli et al., 2015; Cleeland, 2007; Deshields et al., 2013). For patients with HMs, symptoms can arise due to the underlying disease and can also be a consequence of treatment (Hochman et al., 2018; Manitta et al., 2011). Accordingly, patients with HMs experience symptoms throughout the illness trajectory, including during the end-of-life phase, with associated adverse impacts on quality of life. Additionally, high symptom burden can lead to increased emergency department (ED) visits and hospital admissions (HAs) and may contribute to delays in or abandonment of treatment, the latter of which could impact overall survival (Gapstur, 2007).

In 2016, the American Society of Clinical Oncology published guidelines on the integration of palliative care (PC) into standard oncology care (Ferrell et al., 2016); updated guidelines were published in 2024 (Sanders et al., 2024). The guidelines specify that patients with advanced cancer as well as patients with high symptom burden and/or unmet physical or psychosocial needs should be offered PC services (Ferrell et al., 2016; Sanders et al., 2024). Previous research has shown that integrated PC can reduce symptom burden and improve quality of life. This literature review will include an overview of the research on PC in oncology, with a focus on PC for patients with HMs.

Of the limited literature on palliative care (PC) in patients with HMs, there has been a focus on end-of-life care and in particular, healthcare utilization such as ED visits, HAs and chemotherapy in the final weeks before death (Hui et al., 2014). Some authors have called for early PC for patients with HMs to improve the quality of care and quality of life of patients during the end-of-life phase. As such, I reviewed the literature on care at the end of life for patients with HMs and their family caregivers and have synthesized knowledge about a) the quality of life and symptom burden of patients with HMs throughout the illness trajectory, b) healthcare utilization, particularly at end of life, and c) the potential benefits of integrated PC throughout the disease and treatment trajectories, not solely at end of life.

Quality of Life in Patients with Hematologic Malignancies

Hematologic malignancies comprise a heterogenous group of cancers involving the hematopoietic system and account for approximately 10% of all cancer diagnoses in Canada (Canadian Cancer Society, 2019; Tsatsou et al., 2020). While there are more than a hundred different types of HMs, most can be classified into one of three categories: leukemia, lymphoma, or multiple myeloma (Zhang et al., 2023). Disease trajectories are quite variable with some HMs behaving indolently, such as some types of lymphoma, while other HMs can be very aggressive, such as acute leukemias (Pasquarella et al., 2022). Accordingly, the clinical course and disease and treatment-related symptoms and side effects are highly variable (Boyes et al., 2015; Tzelepis et al., 2018).

Treatment for HMs often involves intense therapies such as high dose chemotherapy, radiotherapy (including total body irradiation), and cellular therapies such as hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor (CAR) T-cell therapy (Alnaeem et al., 2022; Ramsenthaler et al., 2019; Robbins-Welty et al., 2023). Furthermore, patients with HMs often receive prolonged courses of treatment, with some receiving continuous treatment from time of diagnosis through to end of life (El-Jawahri et al., 2020; Ramsenthaler et al., 2019).

In view of the diverse disease trajectories and associated treatments, the impact of HMs on quality of life is complex. In their systematic review, Allart-Vorelli et al. (2015) found that HMs negatively impact several dimensions of quality of life. Of 21 studies on hematologic cancer and quality of life that were included in the review, 12 reported that HMs negatively impacted overall quality of life, 8 studies reported impaired physical quality of life, 11 studies reported on the adverse psychological impact of HMs, 9 studies reported on the social aspect of quality of life impacted by HMs, and 8 studies reported on altered functional and role aspects of quality of life (Allart-Vorelli et al., 2015).

Goswami et al. (2019) reviewed 24 studies with one objective being the creation of a comprehensive list of quality of life issues that were reported to be important to patients with HMs. The authors identified fifty different disease- and treatment-related symptoms and side effects, with 21 issues reported as being important by patients with different HMs (Goswami et al., 2019). The most frequently reported physical symptoms across all studies were tiredness/fatigue, feeling ill, nausea, and weakness while the most frequently reported issues were impact of the disease on daily life, living with uncertainty, and the financial impact of the disease (Goswami et al., 2019). While the authors emphasized that there were different issues for patients with different types of HMs, the domains most affected were common amongst all types of HMs, including physical well-being, social well-being, emotional well-being, and functional well-being.

Esser et al. (2018) conducted a survey study to assess quality of life in survivors of HMs. The authors stratified the sample (N=922) by cancer type, time since diagnosis, and if the participant had been treated with hematopoietic stem cell transplantation (HSCT). Compared to population controls, all subsamples scored lower in functioning and higher in symptom burden (p<.001) with effect sizes considered to be clinically meaningful (Cohen's d≥.5). The largest impairments were seen in social functioning and fatigue. Differences in symptom burden and quality of life were not statistically significant among type of HM, time since diagnosis, or whether the participant had been treated with HSCT (Esser et al., 2018).

More recently, Senf et al. (2020) conducted a cross-sectional questionnaire study that included patients with undergoing treatment for HMs (N=109) to examine distress levels and quality of life. The authors found that participants reported high levels of distress and low quality of life, with role and social functioning being particularly impacted. In terms of physical symptoms, fatigue, appetite loss, and insomnia were the most frequently reported symptoms. Symptom burden was found to be associated with impaired quality of life and distress (Senf et al., 2020).

In summary, existing evidence suggests that patients with HMs experience disease- and treatment-related effects that may impact various aspects/domains of quality of life. Most research to date has focused on the physical and psychological symptoms associated with HMs and their treatment; the following section explores symptom burden in patients with HMs in more depth.

Symptom Burden

Symptom burden has been described as the combined severity and the patient's perceived impact of symptoms (Cleeland, 2007). Gapstur (2007) conducted a concept analysis of symptom burden and described various attributes of symptom burden, including that symptom burden is dynamic, fluctuating throughout the disease trajectory, with periods of remission and periods of exacerbation, and is influenced by an array of factors that themselves can also fluctuate such as stage or progression of disease, treatment, activity level, and patient awareness (Gapstur, 2007). In addition, symptom burden is multidimensional, comprised of symptom prevalence, frequency, and intensity. Further, symptom burden is a subjective awareness of disease, in contrast to signs, which are observable and objective indicators of disease (Gapstur, 2007).

Gill et al. (2012) conducted a qualitative study to examine perceptions of symptom burden in patients with cancer (N=58). The authors found that numerical ratings of symptoms did not always correlate with patients' perceptions of burden. Some participants reported high symptom burden even when Edmonton Symptom Assessment System (ESAS) scores were low or moderate, suggesting that symptom burden is more than simply the sum of numerical scores (Gill et al., 2012). Capturing symptom burden, therefore, remains challenging and many of the tools utilized in research and practice may lack elements that fully capture the patient's experience and distress associated with symptoms. For example, patients may not perceive symptoms as bothersome if they believe that the symptoms reflect something positive, such as the treatment working. In contrast, if a symptom is thought to represent progression of disease, the symptom might be associated with more distress. The impact of symptoms on functional status has also been found to be relevant to patients' perception of distress (Simao et al., 2024; Verkissen et al., 2019). Symptom burden remains a complex concept that may not always be accurately measured. Nevertheless, the consequences of symptom burden are less uncertain. High symptom burden has been associated with impairments in quality of life and functional status. Additionally, high symptom burden can lead to increased ED visits and HAs and may contribute to delays in or abandonment of treatment (Gapstur, 2007). The following section describes the literature on symptom burden in patients with HMs.

Symptom Burden in Hematologic Malignancies

Patients with HMs may experience symptoms associated with the underlying malignancy, disease-directed treatments, or both (Alnaeem et al., 2022; El-Jawahri et al., 2020). Given the variability in the pathophysiology of different HMs as well as differing treatment approaches, it is unsurprising that symptoms and side effects are also variable. Some authors have reported worse physical symptom scores for patients with acute leukemias and multiple myeloma when compared to other types of HMs (Ebert et al., 2023; Hui et al., 2014). Cytopenias often occur because of the disease and/or the treatment and can lead to distressing issues such as bleeding, infections, fatigue (Hui et al., 2014). Patients with multiple myeloma may experience significant pain due to bony myelomatous involvement (Kamal et al., 2021).

In the context of indolent HMs, such as indolent lymphomas or chronic leukemias, patients may not experience acute physical symptom burden in the same way that those with aggressive HMs, such as acute leukemias, experience (El-Jawahri et al, 2020). However, having a chronic HM, particularly one that may evolve or progress to become more aggressive, can impose significant psychosocial burden. Howell et al. (2022) interviewed patients (N=35) with chronic lymphocytic leukemia (N=35), follicular lymphoma, marginal zone lymphoma, or multiple myeloma. The authors found that while some participants felt relieved that the HM was not an immediate threat to survival, others struggled to cope with uncertainty, with one participant stating that not knowing how long the disease would be manageable felt like “Russian roulette (where) someone has got a gun against my head” (Howell et al., 2022, p. 11).

Several studies reported that patients with HMs often experience multiple symptoms. For example, Manitta et al. (2011) found that patients with HMs (N=180) reported a mean number of 8.8 symptoms (+/- 5.9 symptoms). Similarly, Zimmermann et al. (2013) found that patients with newly diagnosed or recently relapsed acute leukemia who had been referred to PC reported a median of 9 physical and 2 psychological symptoms. Other symptoms that were prominent across many studies include: impaired well-being, pain, impaired appetite, drowsiness, tingling hands/feet, insomnia, breathlessness, anxiety, and delirium (Chan et al., 2021; Ebraheem et al., 2021; Ferraz et al., 2022; Goswami et al., 2020; Mian et al., 2022; Shaulov et al. 2022; Sommer et al., 2021). Irrespective of the focus of the study or type of HM, fatigue was reported by many authors as being the most prevalent symptom concern, with between 52%-87.5% of patients reporting fatigue in various studies (Boyes et al., 2015; Goswami et al., 2020; Manitta et al., 2011; Ramsenthaler et al., 2019; Tsatsou et al., 2020; Villalona et al., 2023). Fatigue was reported as both frequent and severe and was a concern for newly diagnosed patients, those who had completed treatment, and those in the end-of-life phase (Mayo et al., 2022; Villalona et al., 2023; Zimmermann et al., 2013).

The coexistence of multiple symptoms occurring concurrently has been found to be associated with impairments in patients' functional status and quality of life (Miaskowski et al., 2017). Previous research has revealed that symptoms might arise as clusters, with possible common underlying etiologic or pathogenic mechanisms (Hammer et al., 2022; Harris et al., 2022; Wallstrom et al., 2022). Symptom clusters have been associated with patient outcomes, including survival (Simao et al., 2024). Better understanding of symptom clusters might help direct interventions that could help relieve more than one symptom at a time (Miaskowski et al., 2017). Most studies on symptom clusters have included patients with solid tumours. There have been a few studies that have examined symptom clusters in patients with a particular type of HMs, such as MM (Brazauskas et al., 2024; Chen et al., 2022; Zeng et al., 2023) or leukemia

(Chen et al., 2021) but there is a lack of studies that have looked at symptom clusters in a group of diverse HMs.

Understanding the types and severity of symptoms experienced by patients with HMs is relevant as symptom burden has been found to impact quality of life (Kamal et al., 2021; Moreno-Alonso et al., 2018), has been associated with healthcare utilization, such as emergency department (ED) visits and hospital admissions (HAs), and may even predict survival. For example, Mian et al. (2022) found that among patients with multiple myeloma (N=2876), higher total Edmonton Symptom Assessment Scale scores were associated with greater odds of ED visits/hospitalizations (Odds Ratio (OR): 1.34, 95% CI: 1.29-1.38). Regarding survival, Villalona et al. (2023) examined symptoms in patients with newly diagnosed acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and myelodysplastic syndrome (MDS) (N=56) and found that patients who reported fatigue scores ≥4 had an increased hazard of death compared to those who reported mild or no fatigue (Hazard Ratio (HR) 2.45, 95% CI: 1.07-5.61).

Symptom Burden at End of Life

As the previous sections described, quality of life may be adversely impacted following the diagnosis of and treatment for HMs. Quality of life may also be negatively impacted in the survivorship phase, with the possibility of late and long-term treatment-related side effects and toxicities as well as issues such financial burden, fear of cancer recurrence, post-traumatic stress symptoms, and neurocognitive dysfunction (El-Jawahri et al. 2020). In addition, quality of life has also been found to be impacted during the end-of-life phase with physical and psychosocial symptom burden, frequent hospitalizations, ED visits, intensive care unit (ICU) admissions, chemotherapy in the last weeks of life, as well as lack of advance care planning, low hospice referrals, and short length of stay in hospice (El-Jawahri et al., 2020).

Health service quality indicators of end-of-life care have previously been described by others (Barbera et al., 2015; Earle et al., 2003). Indicators where higher use is considered lower quality end-of-life care include ED use in the last 2 weeks and 30 days of life, new hospital admissions in last 30 days of life, ICU admission in last 30 days of life, use of chemotherapy in the last 2 weeks of life, and death in an acute care hospital (Earle et al., 2003). Indicators where higher use is considered higher quality care include physician house calls in last 2 weeks and nursing/personal support worker home visits in 6 months before death (Barbera et al., 2015; Khan et al., 2021). From the patient and caregiver perspective, factors that have been identified as being important at end of life include being independent as long as possible, having sufficient pain and symptom control, being able to spend time with family and loved ones, and dying at home or outside of the hospital (Khan et al., 2021). The following section describes healthcare utilization for patients with HMs at end of life.

Healthcare Utilization for Patients with Hematologic Malignancies at End of Life

In addition to high symptom burden throughout the illness trajectory, patients with HMs often undergo chemotherapy, and have frequent ED visits and HAs, including ICU admissions in the last weeks of life (Burstein et al., 2023; Button et al., 2016). For example, Hui et al. (2014) reported that in the last 30 days of life, compared to patients with solid tumours, those with HMs were more likely to have prolonged (>14 days) hospitalizations (38% vs 7%, $p<0.001$), have more ICU admissions (39% vs 8%, $p<0.001$), have fewer PC consults (22% vs 48%, $p=0.003$), and were more likely to die in an acute care facility (33% vs 4%, $p<0.001$). More recently, Shaw et al. (2023) conducted a retrospective cohort study to examine healthcare utilization, supportive care, and interventions at end of life in patients with HMs (N=229) at an Australian tertiary cancer centre. The authors found that in the final 30 days of life, 65% had ED visits, 22% had

ICU admissions, 48% received cytotoxic treatment, and 22% underwent an invasive procedure. More than half of the patients died in hospital (Shaw et al., 2023). Of note, these studies have not evaluated the reasons why patients with HMs experience ED visits and HAs at end of life. It is possible that ED visits and HAs are required to facilitate disease-directed treatment or to manage disease and treatment-related complications, such as bleeding or sepsis, or to assist with symptom management concerns. Further research is needed to examine the reasons why these patients have high rates of healthcare utilization at end of life.

Death in hospital has been described as a negative quality indicator for end-of-life care (Earle et al., 2003; Hoare et al., 2022; Khan et al., 2021) and previous research has found that most patients with cancer prefer to die at home or outside of the hospital (Gomes et al., 2012; Nilsson et al. 2023; Sheridan et al., 2021; Valentino et al., 2023). Fereidouni et al. (2021) undertook a systematic review and meta-analysis to determine the preferred place of death and factors associated with preferred place of death for adult patients with cancer. The review included 27 studies and 14,920 participants and found that 55% of patients preferred home death (Fereidouni et al., 2021).

More recently, Pinto et al. (2024) conducted an umbrella review to examine patient and family preferences for end-of-life care. The authors reported on 15 reviews that included 229 non-overlapping studies and found that home was reported to be the most preferred place for end-of-life care and death for patients and family members (Pinto et al., 2024). The authors also found that a minority of patients prefer facilities, such as hospitals or hospices, for end-of-life care and death. Further, preferred place of death was reported to be associated with variables such rurality, with rural patients preferring hospital or facility death, and patients with worse symptoms also preferring hospital or facility death. Importantly, the authors also reported that patient and family member preferences for location of end-of-life care and death can change over time, particularly when patients' symptoms and the extent of family burden increased (Pinto et al., 2024).

In the context of HMs, it is notable that several authors have reported that some end-of-life indicators may not be suitable for assessing quality of end-of-life care for patients with HMs (Egan et al., 2020; Odejide et al. 2016). For example, oral chemotherapy may be effective at relieving disease-related symptoms without significant side effects for patients with some HMs and thus, receiving chemotherapy in the last weeks of life may be quite appropriate (Roeland & Leblanc, 2016; Weisse et al., 2024). Similarly, while many patients prefer to die at home, research examining preferences of patients with HMs has found that not all patients prefer home death. Howell et al. (2017) conducted a population-based cohort study of patients with HMs who died (N=142) between May 1, 2005 and April 30, 2008. The authors found that while most patients preferred to die at home (n=65, 45.8%), there were also patients who preferred to die in hospital (n=40, 28.2%). Patients may prefer hospital death if there is concern about difficulty to manage symptoms or concerns about situations such as catastrophic bleeding or sepsis (Howell et al., 2017; McCaughan et al., 2019). Other authors have reported that some patients with HMs prefer to die in hospital given the close relationships that they have formed with hospital staff and the familiar environment (McCaughan et al., 2019).

As with quality of life during treatment, quality of life in the end-of-life phase is complex for patients with HMs, with a multitude of patient/family caregiver and disease and treatment-related factors shaping the experience. Understanding the clinical characteristics of HMs, associated symptom burden, and current end-of-life care experiences may aid in the identification of patients who may benefit from PC. The next section of this Literature Review discusses the integration of PC in oncology, with a focus on HMs.

Palliative Care in Oncology

Definitions of Palliative Care

To date, much of the research on PC in oncology has focused on specialty PC. Specialty PC has been defined as interventions involving clinicians who have specific education, training, and experience in PC (Gouldthorpe et al, 2023). In contrast primary PC involves interventions that are provided by non-specialty PC trained clinicians (Gouldthorpe et al., 2023). An additional concept that is often discussed in PC studies is that of a palliative approach to care (Ahmed et al., 2020; Qureshi et al., 2021; Wright et al., 2023). In the document describing the Framework on Palliative Care in Canada, a palliative approach to care has been defined as “a philosophy and set of principles that apply to all people living with and dying from a life-limiting illness” (Health Canada, 2018, p.55). Further, a palliative approach incorporates aspects of PC into other types of care, irrespective of setting or context (Health Canada, 2018).

The demand for PC is anticipated to continue to increase and yet the specialty PC workforce is limited (Ferrell et al., 2020; Gouldthorpe et al., 2023). To ensure equity of and access to PC, there is a need to integrate primary PC skills and competencies within oncology workforce (Ferrell et al., 2020). While it has been recognized that the provision of specialty PC for all is neither feasible nor necessary (Hammond & Baxter, 2019; Sawatzky et al., 2016), a palliative approach to care would allow for provision of care to address the patient’s and family’s comprehensive range of needs, including physical, psychosocial, and spiritual, at all stages of illness and in all settings where patients live and receive care (Hammond & Baxter, 2019).

The Canadian Partnership Against Cancer (CPAC) and Health Canada published a framework on interdisciplinary PC competencies for health care providers, including nurses (CPAC & Health Canada, 2021). The Framework describes 12 domains of practice, with one domain being “principles of a palliative approach to care” (CPAC & Health Canada, p. 8). The framework outlines competencies for both generalist and specialist health care providers. In 2015, the Canadian Nurses Association, the Canadian Hospice Palliative Care Association, and the Canadian Hospice Palliative Care Nurses Group issued a joint position statement asserting that all nurses have a fundamental role in providing a palliative approach to care (Coombs et al., 2015).

In the context of HMs, the best way to integrate PC has yet to be determined (Robbins-Welty et al., 2023; Wedding, 2021). As will be described below, research on specialty PC for patients with HMs is still emerging (Allende-Perez et al., 2023; Elliott et al., 2021; Shaulov et al., 2022) and research on primary PC for patients with HMs is lacking (Ernecoff et al., 2020; Kayastha et al., 2023). The following sections will review the research on PC in oncology and hematologic oncology.

Research on Palliative Care in Oncology

Recent systematic reviews and meta-analyses have reported on the benefits of PC in oncology. For example, Cui et al. (2023) conducted a meta-analysis of the effects of early PC on health-related outcomes among patients with advanced cancer. The authors included 19 studies in their review and found that early PC positively impacted quality of life (Standard Mean Difference (SMD)=0.14, 95% CI: 0.62-0.223) and improved symptom burden (SMD=0.14, 95% CI: .01-.26). However, early PC did not have a significant effect on either survival or anxiety (Cui et al., 2023).

Hoerger et al. (2019) conducted a meta-analysis of randomized clinical trials (RCTs) of outpatient specialty PC on survival and quality of life in adults with advanced cancer. Nine studies were included in the analysis and of the studies considered high-quality with survival data, the authors found that patients who had been randomized to outpatient specialty PC had a 14% absolute increase in 1 year survival compared to controls (56% vs 42%, p<.001). In addition, in the five high-quality studies with quality of life data, the authors found that outpatient specialty PC improved quality of life compared to controls (g=.18, p<.001). Here, '*g*' refers to Hedges' *g* and is a measure of standardized mean difference (SMD) (Taylor & Alanzi, 2023). Of note, while specialty PC was associated with improved quality of life in the Hoerger study, the effect size (SMD=.18) was small (Brydges, 2019).

Rogers et al., (2020) conducted a critical evaluation of 4 meta-analyses of RCTs that examined PC in oncology. The authors found that all 4 meta-analyses reported improved quality of life for patients randomized to receive PC. Two of the meta-analyses that had focused on outpatient settings reported a survival benefit while the other two meta-analyses that included both inpatient and outpatient settings did not find any survival benefit (Rogers et al, 2020). A potential reason for the disparity in survival benefit is that patients who receive PC as inpatients may be more unwell than those who receive PC as outpatients (Yeh et a., 2022).

While improvements in quality of life have been reported in several systematic reviews and meta-analyses, survival benefit has been equivocal (Fulton et al., 2019; Guatama et al., 2023; Kavalieratos et al., 2016; Shih et al., 2022). Further, it is important to note that effect sizes have been variable amongst studies, with most reporting small to moderate effect sizes at best. Potential reasons for disparate results in PC intervention trials include heterogeneity of diagnoses, differences in the PC interventions, timing of the PC intervention and follow-up period, to name a few. For example, earlier RCTs examining early PC in oncology largely focused on patients with solid tumours (Kayastha et al., 2023; Pasquarella et al., 2022). To date, there have been few RCTs that have included patients with HMs (El-Jawahri et al., 2023; Rodin et al., 2020). These will be discussed in more detail below.

The precise mechanisms by which PC improves patient outcomes, including quality of life and survival, remain to be elucidated (Kavalieratros et al., 2019; Kayastha et al., 2023). It is possible that comprehensive symptom management permits patients to tolerate and adhere to treatment schedules (Hui et al., 2022). In addition, involvement of PC has been associated with a reduction in aggressive measures, such as chemotherapy, in the weeks preceding death, perhaps avoiding iatrogenic causes of death (Elliott et al., 2021). Further research is needed to better understand how PC confers benefit to patients with cancer and what the optimal PC ‘dose’ and duration should be (Rogers et al., 2020).

While some researchers have suggested that PC be provided within 8 weeks of an advanced cancer diagnosis, Hui and Bruera (2022) advocate for ‘timely’ PC that is based on patients’ needs rather than being tied to diagnosis or prognosis. In the context of HMs, timely PC may be a better fit than early PC. Hematologic malignancies can have unpredictable trajectories with the potential for rapid deterioration (Elliott et al., 2021; Robbins-Welty et al., 2023). At the same time, HMs can remain responsive to disease-directed treatment with cure being possible even in advanced stages or relapsed disease (Button et al., 2016). Given the inherent prognostic uncertainty coupled with the potential rapidity of decline, timely PC may align well with the needs of patients with HMs.

Research on Palliative Care in Hematologic Oncology

While there have been a number RCTs examining the impact of PC in patients with solid tumours, there have only been 3 RCTs examining PC in patients with HMs. El-Jawahri et al. (2016) conducted an RCT to examine the impact of inpatient PC on quality of life, as measured by the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) questionnaire, for patients undergoing HSCT (N=160). The FACT-BMT is comprised of the Functional Assessment of Cancer – General (FACT-G) and the BMT Subscale (McQuellon et al., 1997). FACT-BMT scores can range from 0 to 200, with higher scores representing better quality of life (El-Jawahri et al., 2016; McQuellon et al., 1997). El-Jawahri et al. (2016) found that patients in the PC intervention group reported a smaller decrease in quality of life from baseline to week 2 post-HSCT (mean baseline score, 110.26; score at 2 weeks: 95.46; mean change, −14.72) compared with patients in the control group (mean baseline score, 106.83; week 2 score, 85.42; mean change, −21.54; difference between groups, −6.82; 95% CI, −13.48 to −0.16; *p* = .045).. The authors considered a 5-point change on the FACT-BMT to be clinically significant and therefore, they considered that the mean change in scores between the intervention and control groups of 6.82 points was within the range of what would be considered clinically meaningful. This is consistent with what other authors have suggested in terms of clinically meaningful changes. For example, Yost & Eaton (2005) suggested that a change between 3 and 7 points on the FACT-G represents a minimally important difference while McQuellon et al. (1997) suggested that a change of 2-3 points on the BMT Subscale is considered clinically meaningful.

El-Jawahri et al. (2021) went on to conduct an RCT on integrated PC for patients with acute myelogenous leukemia undergoing intensive chemotherapy (N=160). The PC intervention was delivered in the inpatient setting. The primary outcome of the study was quality of life at week 2. Quality of life had been measured by the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) scale. The FACT-Leu contains 44 items with scores ranging from 0-176 where higher scores indicate better quality of life (Cella et al., 2012). El-Jawahri et al. (2021) found that compared to standard care, patients who received the PC intervention reported better quality of life (adjusted[1] mean score, 107.59 vs 116.45, *p*=.04). In addition, the authors found that among the patients who died (n=87), those who received PC were more likely to report discussing their end-of-life care preferences (75%, n=21/28 vs 40%, n=12/30, *p*=.01) and less likely to receive chemotherapy near end of life (34.9%, n=15/43 vs 65.9%, n=27/41, *p*=.01).

Finally, El-Jawahri et al. (2023) conducted a multi-site RCT of inpatient PC for patients undergoing HSCT. The study included 360 patients who underwent allogeneic HSCT between October 2018-July 2022. Like their other studies, the primary endpoint of this study was also quality of life at 2 weeks post-HSCT. The authors used the FACT-BMT to assess quality of life. Compared to patients in the standard care group, patients who received the inpatient PC intervention reported better quality of life (95.5 vs 89.3, *p*<.001) at 2 weeks post-HSCT. As above, the range of possible scores on the FACT-BMT is 0-200, where higher scores represent better quality of life. While the results of these studies are encouraging, it is notable that all three studies involved inpatient PC interventions. An advantage of outpatient PC is that it is often provided earlier in the disease trajectory, which may confer particular benefit to patients by proactively preventing distress and suffering and may also help with illness and prognostic understanding, treatment expectations, and medical decision making (Hui et al., 2023).

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[1] Adjusted for baseline scores

In summary, while research is still emerging, available evidence suggests that specialty PC can positively impact outcomes, including patients' quality of life (El-Jawahri et al., 2016; El-Jawahri et al., 2023). Despite the known benefits and lack of evidence of adverse outcomes associated with integrating specialty PC for patients with cancer, routine integration of PC in cancer care, and especially in the care of patients with HMs, is not occurring (Ferraz et al., 2022; Hui et al., 2022; Robbins-Welty et al., 2023; Wedding, 2021). The following section will describe the barriers to integrating PC for patients with HMs.

Barriers to Integrating PC for Patients with HMs

Several barriers have been described in the literature as potential reasons why PC is not being routinely integrated into the care of patients with HMs, including disease-and treatment-related factors, patient-related factors, provider-related factors, and institution/system-related factors, described in more detail below.

Disease and Treatment-related Factors

Hematologic malignancies comprise a heterogeneous group of diseases, with over 100 clinical subtypes (Roman et al., 2022) and significant variation in disease trajectories, treatment approaches, and potential for cure (El-Jawahri et al., 2020; Ferraz et al., 2022; Kayastha et al., 2023). Treatment for HMs can range from watchful waiting/surveillance to high-dose chemotherapy and hematopoietic stem cell transplantation (Wedding, 2021). As one example, patients with multiple myeloma, an HM that is still considered incurable, often receive disease-directed treatment such as chemotherapy and/or immunotherapy indefinitely, from time of diagnosis through to end of life (Rafae et al., 2024; Rajkumar, 2022). In contrast, patients with chronic lymphocytic leukemia do not always require disease-directed treatment at time of diagnosis and may not ever require treatment (Nasnas et al., 2023). Accordingly, the PC needs of patients with HMs vary, contingent upon the underlying disease and associated treatment(s) (El-Jawahri et al., 2020; Robbins-Welty et al., 2023; Wedding, 2021).

An additional challenge with HMs is that the underlying disease may remain sensitive to treatment and cure may be possible, even in the setting of advanced disease (Kayastha et al., 2023). At the same time, treatments for HMs are often associated with risks of serious treatment-related complications, such as profound cytopenias, sepsis, graft-versus-host disease, and cytokine release syndrome, to name a few (El-Jawahri et al. 2020; Wedding, 2021). Further, relapse of disease or life-threatening complications can arise rapidly, sometimes short weeks or even only days before death (Elliott et al., 2021). Unfortunately, predicting which patients will develop serious complications related to the underlying disease or treatment remains difficult. Such difficultly with prognostication and lack of clear signposts heralding the transition from curative-focused care have been cited as important barriers for clinicians referring patients to specialty PC (El-Jawahri et al., 2020; Ferraz et al., 2022; Kayastha et al., 2023; Robbins-Welty et al., 2023).

Rather than considering disease and treatment-related factors as barriers, some authors suggest that these factors are compelling reasons to integrate PC earlier (El-Jawahri et al., 2020; Pasquarella et al., 2022; Shaulov et al., 2022). What remains to be clarified is which patients, in which circumstances will require specialty PC versus a palliative approach to care or primary PC (El-Jawahri et al., 2020; Ferraz et al., 2022).

Patient, Family Caregiver, and Clinician Factors

One of the most cited challenges with integrating PC in oncology is lack of awareness of what PC is. Misperceptions regarding PC are harboured by patients, family caregivers, and clinicians alike (Bandieri et al., 2021; Formagini et al., 2022). Research that has examined the general public’s awareness and knowledge of PC has found that many people lack knowledge of what PC is (Grant et al., 2020; Patel et al., 2020; Zimmermann et al., 2021) and often equate PC with end-of-life or hospice care (Grant et al., 2020). Such misperceptions have the potential to contribute to and create additional challenges and barriers. For example, if PC is perceived of as end-of-life or hospice care, it may become difficult to understand how PC might fit into the care of someone undergoing curative-intent treatment (El-Jawahri et al., 2020). Further, if clinicians consider PC as equivalent to hospice care, referral to PC may be delayed until all cancer-directed treatments have been exhausted, which can perpetuate the stereotype that PC is only reserved for end-of-life care or that PC means giving up (Lundeby et al., 2022; McDarby & Carpenter, 2020).

Zimmermann et al. (2016) interviewed patients with advanced cancer (n=48) and family caregivers (n=23) to examine perceptions of PC and found that initial perceptions of PC included death, hopelessness, dependency, and end-of-life comfort care. The interviews were part of a larger study, a cluster randomized clinical trial, that compared early PC to standard care. Participants who had been in the intervention (PC) arm felt that PC improved their quality of living but still acknowledged that PC carried stigma (Zimmermann et al., 2016).

Collins et al. (2017) conducted a cross-sectional, prospective, exploratory qualitative study and interviewed patients with advanced cancer (n=30) and their family caregivers (n=25) on initial perceptions of PC when PC was first raised with patients and their families in Australia. The authors reported on three major themes that arose including that PC was felt be associated with diminished care, diminished possibility, and diminished choice. Overall, participants felt that PC was considered a ‘lesser’ treatment option and was perceived negatively by patients and family caregivers (Collins et al., 2017). For patients and caregivers, confusion around the meaning of PC can lead to avoidance of discussion of PC and limit referrals to PC, potentially contributing to suboptimal care.

In their systematic review on cognitive barriers and facilitators of PC utilization in oncology from the perspective of clinicians, patients, and family member, Bennardi et al. (2020) found that awareness of PC as well as attitudes and beliefs towards PC were potential barriers to PC use in oncology. Most of the studies included in the review (N=52) had included clinicians (n=37, 71%) while several studies included clinicians, patients, and family caregivers (n=15, 29%).

Prod'homme et al. (2018) examined hematologists' perceptions on end-of-life discussions with patients at the time of recurrent disease. The authors found that hematologists perceived end-of-life discussions to be associated with diminishing patients' hope and that PC was the same as terminal care (Prod'homme et al., 2018). In addition, hematologists harbored beliefs that PC may erode the hematologist's credibility and subsequently, patients' trust. Hematologists also reported that PC might impact patients' tolerance to treatment. Overall, the cure-focused approach of hematologists was felt to influence patients' wishes regarding end-of-life care (Prod'homme et al., 2018). El-Jawahri et al. (2018) conducted a national survey study of transplant physicians in the United States to examine transplant physicians' perceptions and attitudes about PC. Most respondents reported that when patients heard the term PC, they felt scared and anxious and that the name palliative care was a barrier to referral (El-Jawahri et al., 2018). Transplant physicians also felt that PC clinicians lacked knowledge about transplant.

As with misperceptions of PC, an additional barrier to PC integration is that of unrealistic treatment expectations that can be held by patients/family caregivers and clinicians (Franjul Sanchez et al., 2020; Odejide et al., 2016). To some degree, the challenges with prognostic uncertainty may contribute to unrealistic treatment expectations for patients and family caregivers (Gray et al., 2021). However, if integration of PC for patients with HMs became routine, unrealistic or uncertain treatment expectations would no longer be potential barriers as PC would not be tied solely to progress (Hui et al., 2022).

In previous work that I was involved with, we found that oncology clinicians may be reluctant to refer patients to PC or to integrate PC care early in the trajectory of care due to worries about patients' negative perceptions of PC (Booker et al., 2020). Few studies have explored patient and family caregiver perceptions on integrating PC for patients with HMs. Understanding patient, family caregiver, and clinician perspectives is important when considering implementing a shift to incorporate PC earlier in the illness trajectory.

Additional Clinician-related Barriers

An additional provider-related barrier includes clinicians' reluctance to discuss PC for fear of eroding patients' hope (El-Jawahri et al., 2018; Salins et al., 2020) or because they worry that patients may stop disease-directed treatment prematurely (Dowling et al., 2020; Kruser et al., 2020) and/or may forego potentially curative treatment altogether (Leblanc & El-Jawahri, 2015; Vidal et al., 2018). Dowling et al. (2020) undertook a qualitative evidence synthesis of healthcare professionals' experiences and views of PC for patients with HMs. Their review included 17 qualitative studies that involved a total of 260 clinicians from five continents. There were no Canadian studies included in the review. The authors identified three themes, including clinicians' therapeutic optimism, physicians' decision-making about introducing PC, and clinicians' concerns about challenges encountered by patients with HMs at end of life (Dowling et al., 2020). The authors also found that clinicians are reluctant to refer patients with HMs to PC as they worry about taking away patients' hope (Dowling et al., 2020).

Finally, another clinician-related barrier is the lack of formal PC education and training that clinicians receive (Bennardi et al., 2020; Mathews et al., 2021; Parajuli et al., 2021).

System-related Factors

A number of healthcare system and policy challenges have been reported as potential barriers to integrating PC in oncology. Lack of access to specialty PC providers, particularly in community as well as in rural and remote regions, is a concern (Conlon et al., 2019; Parajuli & Hupcey, 2021). Absence of clear policies, guidelines, and/or protocols pertaining to PC referral has also been reported as a challenge (Ferrell et al., 2022; Parajuli & Hupcey, 2021). Perhaps somewhat unique to the HM context, policies that restrict palliative interventions such as palliative-intent chemotherapy and palliative transfusions, have also been described as potential barriers to PC referral for patients with HMs (El-Jawahri et al., 2020; Pisarcik et al., 2024; Shaulov et al., 2022). In addition, referral criteria that are based on prognosis can also serve as a barrier to PC for patients with HMs given the difficulties with prognostic uncertainty. As one example, the referral criteria for palliative home care in the Calgary Zone require that patients have an anticipated prognosis of less than 12 months (AHS, 2024). For patients with cancer, an additional criterion is that there must be “clinical findings of advanced progressive metastatic malignancy and/or inoperable malignant disease” (AHS, 2024, p. 3). These criteria may not be applicable to patients with HMs and may deter clinicians from referring patients to PC. An additional barrier to implementation of PC in oncology is that clinicians are facing increasing workloads (Garattini et al., 2022; Jones et al., 2024) and must navigate among competing priorities (Dunn et al., 2021).

Summary

While there are barriers to integrating PC for patients with HMs, some authors have advocated for early PC because of such barriers (El-Jawahri et al., 2020). For example, if prognostication is difficult and there is potential for rapid decline, early integration of PC may allow for patients to be introduced to the idea of PC early in the disease trajectory so that it is not as distressing if there is a sudden shift in prognosis. Further, introducing PC in a routine and systematic manner might allow for the dispelling of misperceptions that PC is solely for end-of-life care. Future research should examine the impact that early PC has on mitigating the barriers described above. More research is also needed to provide insight as to when and for whom specialty PC should be provided and for whom primary PC should be provided (Hui et al., 2022).

Conclusions

Review of the literature has revealed that patients with HMs experience high symptom burden throughout the disease trajectory, including at end of life. There have been a few Canadian studies on symptom burden in patients with cancer more broadly or in non-hematologic cancers (Bubis et al., 2018; Gupta et al., 2023; Singh et al., 2021; Watson et al., 2023) but I was unable to find any studies exploring symptom burden in patients with HMs in Canada. Moreover, while the literature suggests that patients with HMs experience poor quality end-of-life care, with frequent ED visits and HAs in the last month of life, the reasons for ED visits and HAs have not been reported in the literature. There is a need for Canadian research on symptom burden and quality of life in patients with HMs. Further, given that research has found that early or timely integration of PC can improve outcomes for patients, it is imperative to understand why integration is not occurring routinely.

The overall aim of this research was to learn more about how quality of life could be improved for patients with HMs throughout the illness trajectory. Based upon the existing literature, integrating a palliative approach to care for patients with HMs may help reduce symptom burden and improve quality of life. Therefore, it is important to understand symptom burden in patients with HMs and learn about patient, family caregiver, and clinician perspectives on integrating PC into the care of patients with HMs, with a view to better understand how PC can help improve quality of life for patients with HMs.

Research Questions

1. What is the prevalence and severity of symptoms in patients with HMs?
    a. What is the prevalence and severity of symptoms in patients with HMs during the last year of life?
    b. Are there any symptom clusters/symptom profiles that patients with HMs experience?
    c. What are the relationships among symptoms/symptom clusters/symptom profiles and demographic, clinical (disease-related), and treatment-related variables?
    d. What are the relationships among symptoms, symptom clusters/symptom profiles, and health systems utilization, including ED visits and hospital admissions, for patients with HMs?
2. What are the perspectives of patients, family caregivers, and clinicians on the integration of PC for patients with HMs?

In order to better understand the PC needs of patients with HMs, both quantitative and qualitative approaches were undertaken. Review of the literature revealed few RCTs examining the impact of PC on various outcomes for patients with HMs and those undergoing HSCT and thus, there remains a need for RCTs to assess the effectiveness of PC in this patient population.

While the RCT is still recruiting and results are not yet available, the RCT itself was a product of previous work, including the qualitative study described in Chapter 4. The qualitative study and the retrospective cohort study provide important information on symptom burden, healthcare utilization, end-of-life care experiences, and perspectives on integrating PC for patients with HMs. This research also sheds light on the potential role of PC in alleviating symptom burden and ultimately improving the quality of life for patients with HMs. Chapter 3 will provide an overview of the research design and methods used for the studies undertaken in this dissertation.

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Chapter 3: Methodology

Outline and Introduction

In this Chapter, I will provide a brief overview of the overall research design and the methods undertaken in each of the three studies that are part of my dissertation. I will also discuss the challenges and opportunities that I encountered with my research due to the COVID-19 pandemic and I will share how my clinical experiences during the pandemic influenced my research.

In late 2018, just a few months after I started my PhD program, the Alberta Cancer Foundation announced a new funding opportunity for research on hematologic malignancies (HMs) in Alberta, the RK Dixon Family Award. I submitted a letter of intent and was invited to submit a full proposal. I met with the donor family as well as presented my proposal to a review panel of global experts. Subsequently, there were several months of edits and revisions, with ongoing feedback and suggestions provided by the expert panel. I was notified in September 2019 that I was a recipient of funding. Based on feedback from the expert panel as well as feedback from local stakeholders, including clinicians, patients, and family caregivers, I knew that it would be important to learn more about the local context and existing palliative care (PC) processes in addition to learning more about the patient and family caregiver experiences and perspectives on integrating PC into the care of patients with HMs. The studies undertaken in this dissertation are described below.

My PhD dissertation research began with a qualitative study that sought to learn more about the perspectives of patients, family caregivers, and clinicians on integrating PC into the care of patients with HMs. The results of this study helped to inform the design of a randomized clinical trial (https://clinicaltrials.gov/study/NCT05190653). Unfortunately, due to delays imposed by the COVID-19 pandemic, in addition to ongoing challenges with recruitment, the results of the RCT could not be included in this dissertation. Nevertheless, the RCT itself is a product of the work that I did in my PhD program, including the qualitative study, as much of the work was undertaken to support and inform the RCT. Given that I could not include the results of the RCT in my dissertation, I pivoted and undertook a retrospective cohort study that was well aligned with my research aims. The methods undertaken in each of the three studies will be discussed in more detail below.

Overview of Studies

Prior to entering the PhD program, I had been involved with both quantitative and qualitative research projects. I have always valued and appreciated different ways of asking questions, seeking answers, and sharing findings and results. To that end, I came into the PhD program with a desire to undertake both qualitative and quantitative research. Recognizing that there are limitations of both quantitative and qualitative research and appreciating that such approaches need not be oppositional but rather complementary, I decided to use multiple methods for my dissertation work.

***Study 1: Integrating palliative care in hematopoietic stem cell transplantation: a qualitative study exploring patient, caregiver, and clinician perspectives (*Booker et al., 2023)**

The purpose of this study was to explore patient, family caregiver, and clinician perspectives on integrating palliative care for patients with HMs and those undergoing hematopoietic stem cell transplantation (HSCT). Interpretive description (ID), a qualitative methodology that is aligned with an interpretivist orientation and acknowledges multiple constructed and contextualized realities, was the methodologic approach used (Thorne, 2016). Interpretive description is particularly relevant for clinical practice research where the intent is to capture participants' perspectives and move beyond description to interpret responses and apply them to ongoing research, as well as to inform clinical practice and patient care (Thompson Burdine et al., 2021). ID intends not to generate theory, but rather to generate knowledge that can be applied to real-world settings (Thorne, 2016). Due to the COVID-19 pandemic, all study procedures were conducted remotely. More details on the study as well as study findings are discussed in Chapter 4.

Study 2: Early Integration of Palliative and Supportive Care for Patients and Family Caregivers Undergoing Hematopoietic Stem Cell Transplantation or Chimeric Antigen Receptor T-Cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

We used the findings from the qualitative study as well as findings from previous work (Booker et al., 2018, 2020, 2023) to help inform the design of the RCT. Ethics approval was obtained in early 2022 but we were unable to start recruitment due to the ongoing impact of the COVID-19 pandemic. In particular, operational approval was delayed as nursing managers of the hematology/HSCT team felt that introducing a new study could impose more burden and workload for the nurses at a time when there were staff shortages, burnout, and heavy workloads. We were able to start recruitment for the RCT in Fall 2022. Recruitment has been quite slow to date, in part because of the inability to recruit in-person.

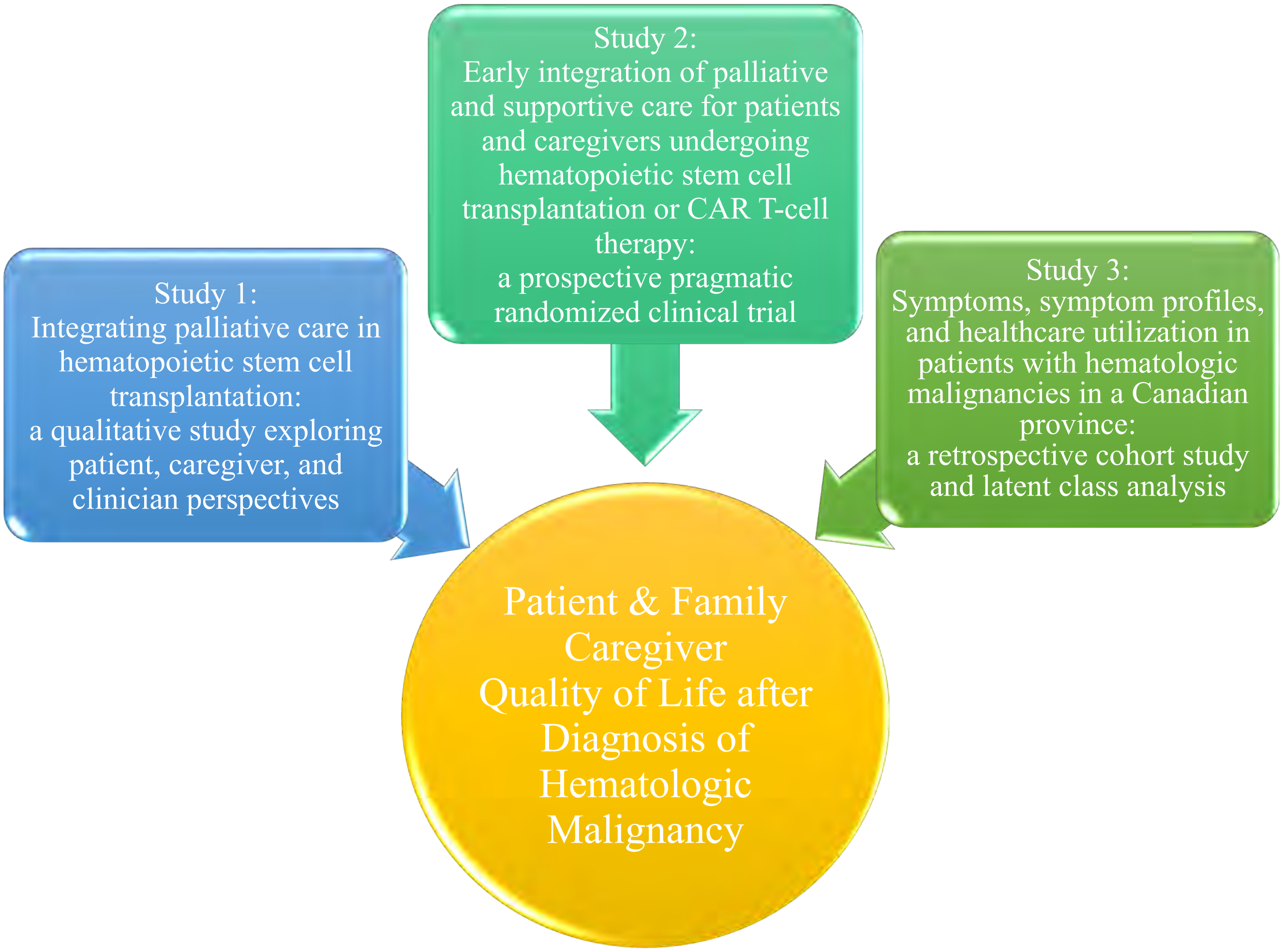
The purpose of this study is to assess the effectiveness of early PC in improving quality of life for patients undergoing HSCT or CAR T-cell therapy for HMs. In addition to the primary outcome of patient quality of life, additional outcomes include symptom burden of patients, family caregiver quality of life, and patient and family caregiver prognostic and illness understanding. Exploratory outcomes include 1-year overall survival, 1-year non-relapse mortality, health services utilization in the last 30 days of life, including emergency department visits, intensive care unit admissions, and chemotherapy. These outcomes had been chosen as they are congruent with patient, family caregiver, and clinician perspectives, based upon the qualitative study described above. The RCT is described in more detail in Chapter 5.

Study 3: Symptoms, symptom profiles, and healthcare utilization in patients with hematologic malignancies in a Canadian province: a retrospective cohort study and latent class analysis

Given the slow recruitment of the RCT and the inability to include findings from the RCT in my dissertation, I completed another study to help supplement the work that I had already done and to help address questions related to my broader research questions and goal of wanting to improve the quality of life of patients with HMs. I was fortunate to have access to a large data set that included patient reported outcomes collected from patients with HMs. Data had also been collected on health care utilization. Understanding more about the types and severity of symptoms that patients with HMs experience could help with development of interventions aimed at reducing symptoms and improving quality of life. We were unaware of any Canadian studies on symptom burden in different types of HMs at different phases of the disease trajectory. The purpose of this study was to gain a better understanding of symptom burden in a cohort of patients with HMs in a Canadian province, including during the end-of-life phase. We also explored relationships among clinical variables, healthcare utilization, and symptom burden. More details on this study are described in Chapter 6. All three studies (Figure 2) have contributed to the broader goal of my research: to improve patient and family caregiver quality after a diagnosis of a hematologic malignancy.

Figure 1

Overview of Studies



Reflexivity

The motivation to undertake this research was based on my own experiences as a clinician in both hematology/oncology and palliative care. I continued to work as a nurse practitioner while conducting my research. Throughout my career to date, I have found that my clinical experiences have been informed by research that I have been involved with and the research that I have been involved with has been informed by my clinical experiences.

Reflexivity is often discussed in the context of qualitative research, but I feel that reflexivity should be practiced irrespective of the type of research being conducted and is helpful even as a practicing clinician. Jamieson et al. (2023) discuss the merits of reflexivity when conducting quantitative research, from time of formulating research questions through data collection and interpretation of findings.

In the earlier phases of my PhD work, I had been required to engage in reflexive writing regularly, as a requirement for several courses. When writing proposals for my studies and when sharing findings, my supervisors and PhD committee helped me reflect on my own assumptions and biases. During the data collection phase of the qualitative study, I kept field notes. I also acknowledged that my positionality as a hematology/oncology clinician may have influenced participants' responses and certainly influenced my interpretation of the findings. I had the opportunity to listen to the interviews as they had all been audio recorded. I was able to hear my reactions to participants' comments. Reflexivity was particularly helpful in the context of doing PhD work during a global pandemic. I will share some of that experience in the next section of this Chapter.

Challenges Encountered due to COVID-19 Pandemic

I had received ethics approval for the qualitative study from the Health Research Ethics Board of Alberta Cancer Committee and the University of Victoria in January 2020. I was awaiting operational approval from the Tom Baker Cancer Centre, the setting where I was planning to recruit participants from, when the World Health Organization (WHO) declared COVID-19 to be a global pandemic (WHO, 2023). I was told by the research department at the Tom Baker Cancer Centre that all non-clinical trial research approvals would be halted indefinitely. I was finally granted operational approval to proceed with my study at the end of May 2020.

By mid/late-2020 and early 2021, international research on COVID-19 revealed that patients with cancer had increased risks of serious illness and increased risks of mortality after SARS-CoV-2 infection (Al-Quteimat & Amer, 2020; Liang et al., 2020; Sharafeldin et al., 2021). For patients with HMs, such risks were even more pronounced (Anand et al., 2024; Langerbeins & Hallek, 2022). Vijenthira et al. (2020) conducted a systematic review that included 34 studies and 3240 adult patients with HMs. The authors found that the risk of death from COVID-19 infection for patients with HMs was 34% (95% CI: 28-39%) (Vijenthira et al., 2020). In contrast, the case fatality rate of COVID-19 infection in the general Canadian population was less than 2% (Government of Canada, 2024).

Given the increased risks associated with COVID-19 infection for patients with cancer, I decided to change all study procedures to virtual in order to reduce the risk of exposure for patients and their family caregivers. This meant submitting an ethics modification request and revising consent forms and recruitment posters. I found virtual recruitment to be more difficult compared to the in-person recruitment experiences that I had pre-pandemic. At the same time, while virtual recruitment had its challenges, the ability to conduct interviews virtually was associated with some positive aspects. For example, participants were not required to travel to the cancer centre or another meeting place for the interviews but rather, interviews could occur at a time/place convenient for the participant. For some of the nurse participants, this meant that it was possible to conduct interviews when they finished their evening shifts, around 12am. Data collection took place between May 2020 and December 2021. Following completion of the qualitative study, I began working on the protocol for the RCT.

In late summer 2021, Alberta began seeing increased numbers of serious COVID-19 infections and the intensive care units (ICUs) were overflowing. I reached out to a Nurse Practitioner colleague who worked in the ICU at one of the large acute care hospitals in Calgary and asked if there was anything I could do to help. Not having any critical care nursing experience or specialty training, I was not sure if I would be of any help. I was surprised when I received an immediate response saying that they would appreciate any and all help and within days, I met with the Nurse Manager and was being re-fit tested for an N95 mask. I can still recall undergoing the phone interview, ordering scrubs, and preparing myself to work in critical care.

Foothills Hospital ICU typically has a capacity of 28 beds. During the 4th wave of COVID-19, in the Fall/Winter of 2021, there were more than 50 patients in the ICU, with the majority having been admitted because of COVID-19 infection. I can still recall walking through the unit, late at night/early in the morning, and seeing all of the patients, lying on their stomachs, connected to ventilators. It was a lot to take in and it was one of the most difficult experiences that I have had in my nursing career. For one, it was not the same type of nursing that I was used to; the kind where I can easily connect with patients and their loved ones. I still talked to my patients in the ICU but most of them did not (could not) respond. Their motionless bodies, rendered so by the sedatives and paralytics required when someone is intubated and ventilated, were so very still. Notably absent were the families that usually keep vigil at someone's bedside. Visitor restrictions were a particularly cruel aspect of the pandemic. I worked in the ICU through the 4th (Delta) wave and into the 5th (Omicron) wave of the pandemic. In early 2022, the number of patients being admitted to the ICU with COVID-19 was decreasing and I turned my focus back to my research and the RCT.

Again, I experienced delays related to ethics and operational approvals. A challenge at the time had been that the outpatient bone marrow transplant clinic, where I would be recruiting patients from, was very short-staffed. The unit manager was concerned that having the clinic nurses pass along information about the RCT would add to the nurses' already overburdened workload. As I waited to receive approval to recruit from the outpatient clinic, I was able to record a two-minute video about the RCT that was shown to all participants who attended patient information sessions held by the psychologists in the Alberta Blood and Marrow Transplant Program. To date, I have only recruited 11 patients and 6 family caregivers; recruitment for the RCT is ongoing. As explained earlier in this Chapter, because I was not able to include the results of the RCT in this dissertation, I needed to pivot and undertake a different study. Thankfully, I had access to a large data set that was well aligned with my research objectives.

My experiences during the pandemic, particularly as related to delays and decreased research productivity, have been experienced by others and reported in the literature (Abshire et al., 2021; Giordano et al., 2021, Maheu et al., 2021). In addition to delays, nurse researchers have had to adapt and modify their research projects to comply with guidelines and restrictions and to minimize risks of exposure to SARS-CoV-2 (Abshire et al., 2021; Hood et al., 2023). In particular, authors have discussed the need to shift study procedures from in-person to virtual (Akard et al., 2022; Giordano et al., 2021; Maheu et al., 2021). Access to data and participants has also been cited as a barrier to research productivity during the pandemic (Akard et al., 2022; Donohue et al., 2021; Phyalto et al., 2023). Dissemination of study findings was also negatively impacted during the pandemic as many meetings and conferences were cancelled (Abshire et al., 2021; Donohue et al., 2021; Lokhtina et al., 2022). In health care, redeployment of staff to critical care areas directly influenced the ability to continue with or start research projects

(Faulkner-Gurstein et al. 2022; Hood et al., 2023). In some jurisdictions, there were periods where schools were closed and parents were required to home school their children (Maheu et al., 2021;). Here in Alberta, we experienced school closures throughout the pandemic, with the longest closures occurring in Spring 2020. As a single parent, I found it incredibly difficult to juggle providing childcare and home schooling with my clinical work and PhD research.

The impact of the COVID-19 pandemic on doctoral students of various disciplines has also been explored. Phyalto et al. (2023) surveyed PhD candidates (N=768) in Finland in the Spring of 2021. The authors found that in addition to the impact of the pandemic on research productivity, participants also reported challenges with poor work-life balance and mental health problems (Phyalto et al., 2023). Donohue et al. (2020) reported similar findings in their study of international doctoral students (N=235) who completed an online questionnaire about their experiences during the pandemic. The authors found that participants reported impacts of the pandemic in the following areas: research design, access to resources, increased workload, worse mental health, and negative impact on finances. Several authors have described that in addition to impacts on research productivity and progress, the pandemic also negatively impacted doctoral students' well-being (Donohue et al., 2020; Lokhtina et al., 2022; Ro et al., 2020).

When I entered the PhD program in 2018, I had every intention of completing the program within 4-5 years. I did not anticipate a global pandemic, nor did I expect to go through a divorce. Reflecting back, I am not regretful that it has taken me so long to finish the program, even though some of the delays were due to me offering to help out with the vaccination program (2021), in the ICU (2021-2022), and at Alberta Children's Hospital (December 2022-January 2023). These experiences enriched my nursing knowledge and contributed so much to my personal and professional growth.

While the time I spent in the ICU was not directly related to my research, there were some interesting parallels between critical care and hematology/oncology. The focus of care in the ICU is often on cure or fixing the underlying problem that brought someone into the ICU. Palliative care is not routinely integrated into the care of patients in the ICU, even though patients frequently experience high symptom burden and many are at high risk of dying. Symptoms are contingent upon the patient's underlying condition, but common acute symptoms include pain, dyspnea, anxiety, thirst/xerostomia, and delirium (Aslakson et al., 2014; Ito et al., 2022). In addition, patients can also experience an array of post-ICU symptoms, including anxiety, depression, chronic pain, post-traumatic stress disorder, challenges with return to work, functional impairment, cognitive impairments, insomnia, and fatigue (Aslakson et al., 2014; Ito et al., 2022). Following an ICU admission, some patients and family members will go on to experience what has been designated "post-intensive care syndrome", a constellation of physical and/or psychological distress following an ICU stay (Ito et al., 2022; Mercadante et al., 2018).

On one particularly difficult night shift, I cared for an elderly gentleman with COVID-19 pneumonia and acute respiratory distress syndrome. He had not been intubated given his advanced age (99 years) and was struggling with dyspnea and increased work of breathing. He was quite distressed by his respiratory symptoms and I asked the on-call resident if we could give him some low-dose hydromorphone to help ease the dyspnea. To my surprise, the resident refused as he was worried that opioids could exacerbate the patient's respiratory symptoms. In the shifts that followed, several nurses discussed their experiences with me and in particular, many felt that more could be done to help ease patients' physical and psychosocial distress in the ICU.

Another similarity between ICU and hematology/oncology is the need for patient and family centered care. Unfortunately, due the potential risks of transmission of SARS-CoV-2, many hospitals implemented visitor restrictions during the pandemic. This was an aspect of my experience in ICU that I had not been prepared for. I will never forget the day that one of my patients was finally extubated. I used an iPad to Facetime his family so that they could see him. It was both heartwarming and heartbreaking. His family was so relieved that he was able to come off the ventilator but after having been on the ventilator for so long and likely still experiencing effects of the numerous medications he had been on, he had a difficult time talking and seemed confused, barely whispering a few words before closing his eyes and ending the call. It was distressing for his young children. I know that the visitor restrictions were intended to protect patients, family members, and staff but in future pandemics, I hope the approach will be more patient and family centered, especially in the context of serious illness and at end-of-life.

In 2022, I was asked to do a presentation on palliative care in the ICU for an e-textbook on critical care nursing (www.continulus.com/library/the-role-of-palliative-care-in-the-icu/?collection=critical+care+nursing&chapter=end+of+life+care). In preparing for the presentation, I reviewed the literature on PC in the ICU. Many of the benefits associated with integrating PC in oncology have also been documented when PC is integrated in critical care. As one example, Metaxa et al. (2021) conducted a systematic review of randomized clinical trials (n=9) and observational studies (n=49) on PC interventions in the ICU. The authors found that compared to standard care, PC interventions were associated with reduced length of stay in the ICU and hospital, decreased anxiety, depression, and PTSD in patients, decreased depression in families, decreased use of dialysis, cardiopulmonary resuscitation, and mechanical ventilation, decreased clinician burnout, decreased stress in nurses, and decreased ICU mortality. In addition, PC interventions were associated with improved communication between patients and clinicians, more frequent family meetings, more discussions on advance care planning and signed goals of care orders, increased frequency of comfort measures, increased use of opioids and benzodiazepines before death, and increased clinician satisfaction with end-of-life care (Metaxa et al., 2021).

My PhD journey has taken longer than anticipated, with a few curves and detours along the way, but it has also been a lot more fulfilling than I expected. I confronted challenges due to the pandemic as well as in my personal life, but I also encountered numerous opportunities. I tried to take advantage of my student status and embrace the opportunities whenever I could.

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Chapter 4: Integrating Palliative Care in Hematopoietic Stem Cell Transplantation: A Qualitative Study Exploring Patient, Caregiver, and Clinician Perspectives

The literature review identified that more research is needed on patient and family perspectives on integrating palliative care (PC) for patients with hematologic malignancies (HMs). As such, I conducted a qualitative study to address this topic. The findings from the study have since been published in *Oncology Nursing Forum* and the published paper is included in this Chapter. I have confirmed with the copyright owner of the published paper, the Oncology Nursing Society, that I have been granted permission to reproduce and publicly display the article if it is for non-profit teaching and research activities (K. Hall, Oncology Nursing Society, personal communication October 3, 2024). In addition, I acknowledge that *Oncology Nursing Forum* was the source of first publication of the article.

My co-authors for this paper were: Andrew McLennan from the University of Regina, Sara Beattie from the Tom Baker Cancer Centre, Kelli Stajduhar from the University of Victoria, and Richard Sawatzky from Trinity Western University. I wrote the original proposal; Dr Beattie and Dr Stajduhar contributed to conceptualization and study design. I undertook data collection and data analysis. Dr Stajduhar and Mr McLennan also participated in data analysis. All authors contributed to manuscript preparation.

Given the word count limitations required by the journal, the Methods section in the published paper was very succinct. More details on the Methods are therefore included in this Chapter to supplement what had been included in the published paper.

Research Design

This study utilized interpretive description (ID), a methodological approach situated within the field of qualitative inquiry (Thorne, 2016). Interpretive description is “a strategy for excavating, illuminating, articulating, and disseminating the kind of knowledge that disciplines with an applicate mandate tend to need in order to enact their mandate…" (Sandelowski, as cited in Thorne, 2016, p. 11). Inductive and iterative in nature, ID intends not to generate theory nor to merely describe a phenomenon of interest but to also interpret that which is being described, ultimately, seeking to enhance understanding of the phenomenon (Hunt, 2009; Thorne, 2018). As Thorne (2016) articulated, ID develops knowledge pertaining to the "subjective, experiential, tacit, and patterned aspects of human health experience – not so that we can advance theorizing, but so that we have sufficient contextual understanding to guide future decisions through which the available evidence will be applied to the lives of real people" (p. 41). To that end, ID was felt to be ideally suited to address questions related to the PC needs of patients undergoing HSCT and their caregivers, and particularly related to potential future interventions that may be developed to address such needs.

Assumptions and philosophical underpinnings of interpretive description.

Interpretive description recognizes and values subjective and experiential knowledge as a source of understanding in applied practice disciplines. Further, ID acknowledges that there may be multiple, even contradictory, realities when considering human experience and that there may be both commonalities as well as individual expressions of variance when examining phenomena. In addition, ID appreciates that human experience is socially constructed. Finally, ID accepts that there is an "inseparable interaction between the knower and the known, such that the inquirer and the "object" of that inquiry influence one another in the production of the research outcomes" (Thorne, 2016, p. 82). The situatedness of the researcher in ID is important and the clinical experience of a researcher is considered beneficial in developing research questions that are clinically meaningful. Accordingly, my experience as a clinician in hematology and HSCT prior to moving to PC affords the unique perspective of having an awareness of both worlds.

Sample

The target population for this study was patients who had undergone or who would be undergoing HSCT, family caregivers of those who had undergone or who would be undergoing HSCT, and clinicians involved in the care of patients who had undergone or who would be undergoing HSCT. The inclusion of family caregivers was important as studies have revealed that caregivers can experience significant physical and psychological distress throughout the HSCT experience as well (Bishop et al., 2007; Jim et al., 2014). Further, limited research has also revealed that bereavement outcomes for caregivers may be influenced by their experiences with their loved ones during HSCT (Snaman et al., 2018). Clinicians involved in the care of patients undergoing HSCT were included to better understand their perceptions of patients' and caregivers' PC needs as well as to better characterize how PC might be integrated into the care of patients undergoing HSCT.

Inclusion criteria.

Inclusion criteria for patients: adult (≥18 years), planned HSCT or already received HSCT (autologous or allogeneic) for a hematologic malignancy, ability to read and understand English, physically well enough to participate in an interview. Inclusion criteria for family caregivers: adult (≥18 years), caregiver for a patient who would be undergoing HSCT or who had already received HSCT (autologous or allogeneic) for a hematologic malignancy, ability to read and understand English. Inclusion criteria for clinicians: any clinician who worked with patients who would undergo HSCT or who had undergone HSCT for a hematologic malignancy, ability to read and understand English.

Exclusion criteria.

Exclusion criteria for patients: patients who would be undergoing HSCT for a non-malignant condition, inability to read and understand English, inability to provide consent to participate in study. Exclusion criteria for family caregivers: caregiver for someone who would be undergoing HSCT for a non-malignant condition, inability to read and understand English, inability to provide consent to participate in study. Exclusion criteria for clinicians: inability to read and understand English, inability to provide consent to participate in study

Sampling strategy. Purposive and theoretical sampling had been undertaken with the latter occurring once data collection and analysis had begun (Hunt, 2009; Oliver, 2012). Purposive sampling was used as it allowed selection of participants for the purpose of describing an experience that they had had (Streubert & Carpenter, 2011). Theoretical sampling was undertaken to help identify additional participants who may not have been included otherwise but whose participation could help with maximal variation (Thorne, 2016). While the criteria defining a purposive sample are determined a priori, theoretical sampling allowed for sampling to occur based on what had been discovered in the data collection and analysis processes (Bagnasco et al., 2014).

While historically, the concept of data saturation has been used in qualitative studies to help determine sample size, data saturation has been disputed in the literature, with some authors suggesting that the very idea of exploring individual perspectives on any phenomenon precludes the possibility of ever achieving true saturation (Bradshaw et al., 2017). Indeed, this would be in keeping with the assumptions of ID, where the researcher and participants are co-creating constructed truths (Thorne et al., 2004). Given the uniqueness of each participant, true saturation seems an improbable endeavor. Therefore, participant recruitment occurred until it was felt that the research questions had been sufficiently addressed, recognizing that such assessment is inherently subjective. The goal was to ensure that our findings resonated with, and had practical applicability, to patients, caregivers, and clinicians. To that end, asking "What might I not be seeing?" (Thorne, 2016, p. 179) was considered and was contingent upon the applied practice thinker's knowledge and experience to consider what possible findings might be missing.

Participant Recruitment

Approval had been granted from the Research Ethics Boards (University of Victoria and the Health Research Ethics Board of Alberta Cancer Committee, Appendix B). Patients and family caregivers were recruited from the outpatient bone marrow transplant clinic and inpatient bone marrow transplant unit at the Tom Baker Cancer Centre. Posters were placed in clinic waiting rooms and inpatient common areas (Appendix C). Clinicians in the outpatient and inpatient areas provided brief study information to potential participants and individuals who were interested in participating were asked to contact the principal investigator (RB) by email or phone. Patients and family caregivers were invited to pass along study information to other potential participants. Clinicians were recruited via posters placed in staff areas in the outpatient clinic and inpatient unit. Clinicians were invited to pass study information on to other colleagues.

Clinic staff and patient support groups, including the Southern Alberta Myeloma Patient Society and the local chapter of the Leukemia and Lymphoma Society of Canada, were given brief information about the study to pass on to potential participants. Interested individuals were asked to contact the principal investigator (RB) via email or phone.

Data Collection

Once patient and family caregiver participants were determined to be eligible for study participation and had provided consent, a date was established for the interview to occur. Due to the COVID-19 pandemic, all interviews were conducted virtually, via phone or Zoom, contingent upon participants' preferences. Congruent with the underpinnings of ID, efforts were made for the interviews to occur in "as naturalistic a context as possible in a manner that [was] respectful of the comfort and ethical rights of participants" (Thorne, 2016, p. 82). To that end, the virtual nature of the interviews allowed for the interviews to occur at a time and place that the participant selected. Many interviews occurred while the participant was in their own home while a few of the clinician interviews occurred while the clinician was at work.

Demographic data were collected on patients, family caregivers, and clinicians at time of the interview. A semi-structured interview guide (Appendix A) was developed based on previous work conducted by Zimmermann et al. (2016) and the Palliative Care – Early and Systematic (PaCES) Program (2019). The interview guide included open-ended questions and prompts.

Interviews were audio recorded and transcribed verbatim. Once an interview was completed, the audio file was uploaded to sync.com. After verification that the audio file was successfully uploaded to sync.com, the audio file was deleted off the audio recorder. Audio files were shared with transcriptionists via sync.com, a secure cloud that provides file sharing with end-to-end encryption. Typed transcripts were stored on sync.com and a password protected, encrypted USB stick. Field notes were stored on a password protected, encrypted USB stick.

Data Analysis

Data analysis in ID is an inductive and iterative process whereby data collection occurs simultaneously with data analysis (Thorne, 2009; Thorne, 2016). Constant comparison, where transcripts were compared repeatedly to one another, was undertaken. In constant comparison analysis, data are initially broken into small units in a process known as open coding (Onwuegbuzie et al., 2009). Codes are then arranged into categories (axial coding) before the researcher develops one or more themes that describe the content of each category (selective coding) (Onweugbuzie et al., 2009). Data analysis was undertaken by two researchers, RB and AM.

Protecting Participants and Minimizing Risks of Harm

We considered that it would be possible that participants could find it uncomfortable or upsetting to discuss topics such as end-of-life care, end-of-life decision making, death, dying. Information was provided to all participants regarding how they could access psychosocial support. This information was included in the consent forms (Appendix D). Patients and caregivers were provided with information about psychosocial support available through the Department of Psychosocial Resources at the Tom Baker Cancer Centre.

Strengths and Limitations of Design

In addition to limitations described in the manuscript below, the use of interviewing in this study was a potential limitation in that there was an asymmetrical power relation (Brinkmann, 2018). Conducting the interviews at a time and location of the participants' choosing may have helped to mitigate the power relation to some degree. Like other qualitative approaches, ID does not seek to produce findings that are generalizable. Rather, ID honours the particular, which seems a desirable end when it comes to human health and experience, particularly when considering such an individual experience as being diagnosed with and treated for cancer (Rolfe 2006). The pragmatic, practice-based orientation of ID makes it a compelling approach for health care research with potential for the findings to be both accessible to and relevant for practicing clinicians (Hunt, 2009). This approach was well-aligned with the overarching goal of my dissertation research: to better understand the PC needs of patients with HMs and their family caregivers and identify potential ways that palliative care supports and a palliative approach to care could be integrated into the trajectory of care.

The paper, as published in *Oncology Nursing Forum,* is presented below.

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Abstract

PURPOSE: To explore patient, caregiver, and clinician perspectives on palliative care for patients undergoing hematopoietic stem cell transplantation
(HSCT).

PARTICIPANTS & SETTING: 8 patients who had undergone or would undergo HSCT, 4 caregivers, and 16 HSCT clinicians.

METHODOLOGIC APPROACH: This qualitative, interpretive descriptive study used semi structured interviews conducted via telephone or videoconference.

FINDINGS: Responses were categorized into the following two themes: concerns and challenges during and after HSCT, and tensions with integrating palliative care into HSCT.

IMPLICATIONS FOR NURSING: The findings from this study highlight the unique and varied needs of patients and their caregivers during and after HSCT. More research is required to determine how to best integrate palliative care in this setting.

KEYWORDS: quality of life; hematopoietic stem cell transplantation; palliative care; caregivers

There is a growing body of literature demonstrating that integrating early palliative care (PC) for patients with advanced cancer is associated with several favorable outcomes. Some commonly cited outcomes include improved symptom management, better prognostic understanding, improved quality of life for patients and caregivers, and even improved survival in some contexts (Bakitas et al., 2015; Ferrell et al., 2017; Greer et al., 2013; Temel et al., 2010, 2017). In 2016, the American Society of Clinical Oncology published guidelines concerning integrating PC in oncology and advocated integrating PC for patients with advanced cancer and patients facing high symptom burden (Ferrell et al., 2017). However, despite the proven benefits of integrating PC in oncology, coupled with the known propensity for patients with hematologic malignancies (HMs) to experience high symptom burden (Boucher et al., 2018; Hochman et al., 2018; Manitta et al., 2011), it has been well documented that patients with HMs and patients undergoing hematopoietic stem cell transplantation (HSCT) do not routinely receive PC (Button et al., 2014; Johnston et al., 2018; Leblanc & El-Jawahri, 2018; Roeland & Ku, 2015; Selvaggi et al., 2014). To date, only one published clinical trial has compared early PC to standard care for patients undergoing HSCT (El-Jawahri et al., 2018). According to Shaulov et al. (2022), there are several ongoing or forthcoming clinical trials on early PC for patients with HMs, and one clinical trial on early PC for patients undergoing HSCT.

HSCT is a treatment approach, used with curative intent, for patients with HMs (Bazinet & Popradi, 2019) and other conditions, including nonmalignant autoimmune conditions (Duarte et al., 2019). In the context of advanced and high-risk HMs, HSCT offers an opportunity for cure with significant potential for severe complications such as graft-versus-host disease (GVHD), organ toxicities, and infections (Bazinet & Popradi, 2019). These complications can be life-threatening and may adversely affect a patient’s quality of life and their ability to function for many months or even years post-transplantation. Symptom burden, manifesting physically and psychosocially, has been reported to be extremely high in patients with HMs and patients undergoing HSCT (El-Jawahri et al., 2020; Manitta et al., 2011). To date, much of the research on integrating PC in oncology has included patients with solid tumors, with few studies including or focusing on patients undergoing HSCT for HMs (El-Jawahri et al., 2020; Ferrell et al., 2017).

Purpose

The palliative and supportive care needs of patients undergoing HSCT for HMs have been well described (Cheng & Lam, 2021; El-Jawahri et al., 2020), as have the potential barriers to and challenges with integrating PC for patients undergoing HSCT (Lewis, 2020; Ruiz et al., 2018; Sánchez et al., 2020; Suthumphong et al., 2021; Wedding, 2021). However, there are few studies that have examined perspectives on PC in HSCT (El-Jawahri et al., 2021; Gemmell et al., 2022). Because the current authors were planning an interventional trial comparing early PC to standard care for patients undergoing HSCT for HMs, they wanted to ensure that the trial development was informed by patient, caregiver, and clinician input. The purpose of this study was to better understand patient, caregiver, and clinician perspectives on integrating PC into the care of patients undergoing HSCT.

Methodologic Approach

Design

This study was part of a multiphase project on integrating PC for patients undergoing HSCT. Interpretive description (ID), a qualitative methodology that aligns with an interpretivist orientation and acknowledges multiple constructed and contextualized realities, was the methodologic approach used (Thorne, 2016). ID is particularly relevant for clinical practice research where the intent is to capture participants' perspectives and move beyond description to interpret responses and apply them to ongoing research, as well as to inform clinical practice and patient care (Thompson Burdine et al., 2021). As Thorne (2016) articulates, ID develops knowledge pertaining to the subjective and experiential aspects of health experiences. ID intends not to generate theory, but rather to generate knowledge that can be applied to real-world settings.

Participants and Setting

Between May 2020 and December 2021, eligible patients, caregivers, and clinicians were invited to participate in an interview. Patients were eligible to participate if they would be undergoing or had undergone HSCT for HM. Caregivers, defined as the patient's family members or close friends, were eligible to participate if they were the primary caregiver for someone who would be undergoing or who had undergone HSCT for HM. Clinicians were eligible to participate if their role involved caring for patients being treated with HSCT for HMs.

Participants were recruited from the outpatient department of a tertiary cancer center in Western Canada. The transplantation program at the cancer center conducts more than 200 transplantations for adults annually, with care being provided by HSCT physicians, nurses, nurse practitioners, pharmacists, and psychosocial clinicians. Although there is no formal survivorship program at the cancer center, there is a clinic for long-term survivors of allogeneic transplantations. Study posters were placed in the outpatient bone marrow transplantation clinic. Individuals who were interested contacted the first author, R.B., directly to learn more about the study and determine eligibility. Because of the COVID-19 pandemic, all study procedures were conducted remotely via email, videoconference, or telephone to minimize participants' risks of exposure to the SARSCoV-2 virus. Purposive and theoretical sampling were undertaken (Hunt, 2009; Oliver, 2012). Theoretical sampling was used to help identify additional participants who may not have been included otherwise but whose participation might help with maximal variation (Thorne, 2016).

Data Collection

A semi structured interview guide (available upon request) was developed based on Zimmermann et al. (2016) and Ahmed et al. (2022). The interview guide included open-ended questions and prompts. Once participants provided informed consent, the interview was scheduled and then conducted by R.B. via telephone or videoconference, whichever the participant preferred. All interviews were audio recorded and transcribed verbatim. Field notes were kept during interviews to capture contextual information, such as the participant's location during the interview and demeanor (Phillippi & Lauderdale, 2018). Because all interviews were conducted virtually, field notes were minimal, particularly for interviews conducted via telephone because it was not possible to see the participant, their body language, or their facial expressions. The average interview duration was 41 minutes (range = 15–71 minutes; median = 39 minutes).

Data Analysis

Data analysis in ID is an inductive, iterative process whereby data collection occurs simultaneously with data analysis (Thorne, 2016). Interview transcripts were read repeatedly to get a sense of the broader themes and to develop an iteratively derived coding scheme that was then used to code the data. Once an initial coding scheme was developed by authors A.I.G.M. and R.B., data were then grouped into categories, paying attention to patterns within the data. These initial interpretive understandings were then discussed by the research team to develop a deeper ID analysis. After several category iterations were developed, consensus was achieved on the final categories. NVivo, version 20.4.0, was used to organize and manage data.

Findings

Participants

A total of 28 participants, consisting of 8 patients, 4 caregivers, and 16 clinicians, agreed to be interviewed. Demographic data are presented in Tables 1–3. Most interviews began with patients and caregivers speaking about their experiences during and following HSCT, and clinicians gave their observations of patient and caregiver symptoms and experiences during and following HSCT. As the interviews progressed, an exploration of the participants' awareness of and experiences with PC ensued. The discussion of patient and caregiver experiences, coupled with their thoughts on PC, contributed to a preliminary understanding of how PC might be integrated into the care of patients undergoing HSCT.

Table 1

Clinician Demographics (n = 16)

Participant	Age (years)	Gender	Profession	Education	Years in Practice	Years in Heme/HSCT
1	26	Female	Nurse	BN	4	2
2	28	Female	Hematology nurse practitioner	MN	7	7
3	28	Female	Nurse	BN; in graduate school for MN	5	4
4	28	Female	Nurse	BN; in graduate school for MN	6	5
5	30	Female	Nurse	BSN; in graduate	8	6

				school for MN		
6	32	Female	Nurse	BN	8	3
7	35	Female	Nurse	BSN	13	13
8	37	Female	Nurse	BN	14	14
9	38	Female	Psychologist	PhD	5	4
10	42	Female	Hematologist	MD	17	12
11	49	Female	Hematologist	MD	17	17
12	52	Female	Nurse	BSN	31	31
13	52	Male	Hematologist	MD	20	20
14	53	Female	Nurse	BN	25	25
15	53	Male	Physician	MD	29	26
16	57	Male	Medical oncologist	MD	26	26

Notes. BN—bachelor of nursing; heme—hematology; HSCT—hematopoietic stem cell transplantation; MD—doctor of medicine; MN—master of nursing

Table 2

Patient Demographics (n=8)

Participant	Gender	Age at Interview	Age at HSCT	Diagnosis	Type of HSCT	Marital Status[a]	Primary Caregiver	Residence
1	Female	30	29	MLL	Allo, unrelated	Married	Spouse, mother-in law	Urban
2	Female	54	47	MDS, smoldering leukemia	Allo, unrelated	Married	Spouse	Rural
3	Female	67	65	AML	Allo, sibling	Divorced	Partner of 2 years, friends	Urban
4	Female	68	53	AML	Allo, unrelated	Married	Spouse	Urban
5	Male	29	27	AML	Allo, unrelated	Married	Spouse	Rural

6	Male	44	-	AML	Allo, unrelated, pre-HSCT	Married	Spouse	Urban
7	Male	47	-	AML	Allo, unrelated, pre-HSCT	Separated	Parents	Rural
8	Male	52	52	Multiple myeloma	Autologous	Married	Spouse	Urban

Notes. [a]At time of interview
allo—allogeneic; AML—acute myelogenous leukemia; HSCT—hematopoietic stem cell transplantation; MDS—myelodysplastic syndrome; MLL—mixed lineage leukemia

Table 3

Caregiver Demographics (n=4)

Participant	Age at Interview	Age at HSCT[a]	Gender	Relation to Patient	Marital Status	Residence
1	29	28	Female	Spouse	Married	Rural
2	53	47	Male	Spouse	Married	Rural
3	70	70	Female	Spouse	Married	Urban
4	69	69	Male	Family friend	Single	Urban

Notes. At time of patient’s HSCT; HSCT – hematopoietic stem cell transplantation

Perspectives on PC in HSCT Concerns and Challenges with HSCT

Patients, caregivers, and clinicians spoke about the intense physical and psychosocial symptoms that occur during and after HSCT. Several participants suggested that there was an expectation that some degree of suffering was inevitable with HSCT. One clinician said, “There is a certain amount of physical suffering that is just assumed. It’s accepted that there’s going to be a high intensity of symptom burden.”

Clinician participants expressed that symptom burden in HSCT could be better managed, particularly psychosocial and existential symptoms. Many participants shared that patients did not always seem to understand or even be aware of the potential side effects and complications associated with HSCT. One clinician explained,

> It's the unknown going into [HSCT]. They get this laundry list of things that could happen to them, and they could be in [the intensive care unit] or anything like that. And for some people, it's much worse than they could ever expect.

Physical Symptom Concerns

Several participants spoke about the multitude of physical symptoms that can arise post-HSCT. Participants acknowledged that patients experienced intense HSCT side effects such as nausea, vomiting, diarrhea, mucositis, and pain. Participants also shared that physical issues may persist for many months or even years post-HSCT, particularly for patients who develop chronic GVHD. Ongoing fatigue and cognitive dysfunction were acknowledged by participants as being persistent and bothersome longer-term physical issues post-HSCT. Participants acknowledged that physical symptoms and side effects associated with HSCT could be particularly intense. One clinician said, "Doing your daily tasks of living become these insurmountable challenges. I think that's what people don't understand. You know, [chemotherapy] in the past made you feel really lousy and nauseous and tired, but this is like times 10."

Psychosocial and Spiritual Concerns

Psychosocial and existential concerns such as anxiety, depression, the inability to return to work, relationship challenges including sexual health concerns, and worries about disease recurrence or development of complications were frequently reported by participants. Patients and caregivers felt that psychosocial needs were not always well managed, and more support was needed. Clinicians also expressed the need for better psychosocial and spiritual support for patients and caregivers, as well as improved coordination of care.

One patient said, “The mental health side, particularly for young adults, I would say . . . they’re just working on getting established in their lives when they’re going through this…The mental health side is not something you cure in a hospital with [chemotherapy].” One clinician said, “Sure, we might cure a lot of people, but they come out of it with, you know, debilitating effects…Like, ‘Your cancer’s gone, so we’ll discharge you, but as a person, you’re still not intact.’”

Concerns After HSCT

Patients and caregivers reported a lack of availability of support for concerns post-HSCT, particularly following discharge. Many participants shared that they had not expected physical and psychosocial symptoms and side effects to be so persistent. In addition, participants who were from rural regions indicated that they struggled to find support in their hometowns, something that became more problematic once they were no longer being closely followed by the HSCT team. One patient said, “There’s by far, in my opinion, not enough being done in order to provide that long-term aftercare support to patients once they check out of the hospital.”

Treatment Expectations and Prognostic Understanding

Clinicians expressed concern that some patients and caregivers may not fully appreciate the possible risks and complications associated with HSCT. Participants were unsure if this was because of insufficient information being provided or patients and caregivers having difficulty understanding provided information, or if patients were intentionally choosing to disregard such information as an avoidance or disassociation tactic. Many participants, including patients, caregivers, and clinicians, felt that patients had a poor understanding of what to expect with

HSCT and were unprepared. One clinician said, “Even a patient that we had who was a physician, they said, ‘I didn’t understand what I was really going to go through.’” Some participants felt that patients understood some aspects of HSCT but did not understand other aspects of transplantation, particularly when it came to the complications associated with HSCT and the effects on their quality of life. Others acknowledged that some patients and caregivers may have preferred not knowing detailed information about the treatment or prognosis as a way of coping with the situation. One clinician said, “Many of them are told the information about the chances of success, but I think even if it’s a very slim number, they all think that they’re going to be those ones that will make it through.” One caregiver said,

> We had the big scary meeting before saying, you know, “These are the statistics, these are your chances.” . . . But to be honest, we kind of just put that to the side because it just put so much fear in our hearts, and if there’s a chance this could work, we clung to that to get us through.

Tensions With Integrating PC in HSCT

Participants’ responses also clustered into another category pertaining to tensions associated with integrating PC in HSCT. Many participants harbored misperceptions about PC, and nearly all participants, including clinicians, felt that PC was associated with end-of-life care. One clinician stated, “I think that [patients] think PC means end of life. And there’s no hope . . . no doctors are coming to see you, no one cares anymore. The very negative connotation that people associated with the word ‘palliative.’” Also within this category was the notion that HSCT is a curative-intent treatment and, therefore, participants found it difficult to see how PC could be integrated into care, particularly if they thought that PC was meant for end-of-life care.

Clinicians emphasized that the unique features of HMs and HSCT created challenges for integrating PC.

Misperceptions of PC

Many participants shared that their experiences with and knowledge of PC were limited. Several recounted experiences when a loved one had received PC prior to death and, as such, they associated PC with dying. One participant said, "My mom was in palliative care and then she died in hospital…That's immediately what I think of. I hate it." Of note, all patients initially indicated that they would feel distressed or anxious if PC had been introduced during their HSCT, as one explained:

> I think my gut reaction would've been, "Ah, OK. Does this mean it's incurable? Uh, am I dying?" It probably would've raised a little bit of anxiety in me had they not explained exactly what they meant…My gut response would've been "end-oflife care."

Another participant stated,

> The first thing I'd think is, "This is not the exact conversation I wanna have." It'd be . . . that whole idea of dying . . . when it comes to the words "palliative care" . . . to me, it seems like we're giving up hope and you're just prepping me for the ultimate death.

Once the definition of PC was shared with participants and it was explained that PC can help with symptom management and other aspects of care, all participants agreed that early PC implementation could be beneficial.

Tensions Between Curative and Palliative Intents

Some clinicians indicated that they found it difficult to bring up PC, and worried that patients might lose confidence in their treatment or even lose trust in their care team. Other clinicians suggested that there was an incongruency with introducing PC in a curative-intent context, such as HSCT, particularly given the misperceptions that PC is the same as end-of-life care. One clinician said,

> If you agree to do a transplant on somebody but you start to have a discussion to say, "Well, you know, you're pretty old and if you need to go to the [intensive care unit], you're going to die, so we recommend against it," then I'm sure the patient starts to think, "I don't know how hard these guys are going to work to save my life if I get sick."

Clinicians also felt that having PC available for difficult conversations and to allow patients to talk about the possible outcomes would be helpful, as expressed by one clinician: "Maybe we don't discuss the downside of the treatment enough, and so sometimes it helps to know that there's another team that's also going to help look after you if the downside comes true."

Tensions Associated with Unique Aspects of HSCT

Clinicians spoke on the unique nature of HMs and HSCT as potential challenges to the integration of PC. For example, many discussed the challenges with prognostic uncertainty and the rapidity of decline for patients with HMs as barriers to knowing when to refer patients to PC. One clinician explained, "You could be doing very, very well and then not, within weeks. You go from full-on cure to end-of-life care within a month. And it's very difficult to switch that mindset." Another clinician said, "Overnight, they can change from curative intent to palliative intent with a very short life expectancy." Other clinicians spoke of the responsiveness of HMs to chemotherapy, even in the context of advanced disease, again making it challenging to know when to refer patients to PC. Clinicians felt that interventions such as blood transfusions or a course of oral chemotherapy were often considered inappropriate by PC clinicians as they considered these interventions to be life-sustaining or life-prolonging rather than being provided with palliative intent. This was seen as a potential barrier to referring patients to PC and an area of misunderstanding between PC and hematology/HSCT clinicians. One clinician said,

> The recommendation is to not give noncurative [chemotherapy] close to the end of life, and that gets you black marks . . . if you're slinging [chemotherapy] in the last few weeks of life. The trouble is, often for the hematologic cancers, the [chemotherapy] can be fairly gentle and well tolerated and often control the cancer symptoms the best. A little bit of daily etoposide can actually control the pain from the lymphoma mass better than morphine.

Discussion

The purpose of this study was to explore the perspectives of patients, caregivers, and clinicians regarding the integration of PC in HSCT. Findings suggest there is a potential role for PC in the care of patients undergoing HSCT, but the way PC is integrated into this clinical context requires careful consideration. Participants in this study spoke of the intense physical and psychosocial symptoms as well as associated distress that can arise during and after HSCT. Other studies have also reported that patients with HMs and patients undergoing HSCT experience a high symptom burden that is at least comparable to, if not more severe than, that of patients with solid tumors (Manitta et al., 2011; Mitchell, 2018; Simon et al., 2021).

Participants in this study also spoke about the persistence of symptom burden, even years post-HSCT, coupled with a perceived lack of long-term support, particularly for participants who reside away from the city where they received their HSCT. An array of late and long-term complications can occur post-HSCT. The incidence of chronic health conditions in patients who have undergone allogeneic HSCT is 64% at 10 years post-HSCT and 71% at 15 years post-HSCT (Bhatia, 2014). Some cancer centers have established survivorship programs or clinics to help address the needs of survivors after HSCT (Battiwalla et al., 2017). However, there may still be a role for PC support, particularly for patients who do not have access to survivorship services.

Along with symptom burden, participants also expressed a need for information and practical support. Many participants felt that treatment expectations did not match reality and that HSCT was much more difficult than anticipated. Participants were unsure if unrealistic treatment expectations were because of insufficient information provided upfront, difficulty comprehending the nature of the potential risks and complications, or a desire to avoid discussing and thinking about the prognosis and complications. Congruent with the literature, clinicians acknowledged the differing degrees that patients want honest disclosure about their prognosis, as well as the varying degrees to which clinicians feel comfortable discussing the prognosis (Bennardi et al., 2020; Derry et al., 2019; Gray et al., 2021; Wedding, 2021). Misperceptions regarding prognosis may be because of inadequate communication and education, inadequate prognostic disclosure, or a patient's individual capacity to process, accept, and discuss their prognosis (Derry et al., 2019; Gray et al., 2021). Treatment expectations and prognostic understanding are essential because they can influence medical decision-making, including treatment wishes at the end of life (Cartwright et al., 2014; El-Jawahri et al., 2015).

In addition to learning more about the PC needs of patients and caregivers, findings suggested that there are tensions associated with integrating PC in HSCT. Such tensions are related to misperceptions held by patients, caregivers, and clinicians, as well as to the integration of PC in a curative-intent context. In addition, unique challenges associated with HMs and HSCT were also raised by participants. Prognostic uncertainty remains a significant challenge in HSCT. Patients whose underlying malignancy might be cured can experience flares of GVHD or other late or long-term complications that can contribute to morbidity and mortality for years to come after HSCT (Inamoto & Lee, 2017; Majhail, 2017). Given these risks and the challenges of prognostic uncertainty, shifting from a prognosis-based model of PC referral to a needs-based model may be helpful (Leblanc & El-Jawahri, 2018; Suthumphong et al., 2021).

As others have reported, participants, including clinicians, harbored misperceptions about PC (Bennardi et al., 2020; Hui et al., 2018). Many participants indicated that they perceived PC to be the same as end-of-life or hospice care and, as such, found it difficult to envision how PC could be delivered alongside a curative-intent treatment such as HSCT. For patients, it seemed that a lack of exposure to PC contributed to their misperceptions. Once PC was explained, participants agreed that it could benefit patients and caregivers during and after HSCT. Education on PC should be incorporated into patient care early in the disease trajectory. Ideally, PC education and training should be part of healthcare provider programs or curricula, and clinicians should possess core competencies and skills to provide at least primary PC and to adopt a palliative approach to care (Evans et al., 2019; Sawatzky et al., 2017). Harden and Schembri (2016) conducted a quality improvement project where patients were provided a PC consultation prior to and shortly after HSCT to potentially increase their knowledge of PC. The authors found that an early PC consultation increased knowledge of PC and recommended that early PC be implemented for patients undergoing HSCT (Harden & Schembri, 2016).

Limitations

There are several limitations that should be noted. The sample size was small, particularly for caregivers, and as such, the results of this study cannot be generalized. Only one patient had undergone autologous HSCT. Although it is well known that the side effects and complications can be quite different for allogeneic and autologous transplantations, the experiences of this participant were similar to those of other patients. The majority of patients and caregivers were post-HSCT. The needs of patients and caregivers likely vary significantly, depending on where the patient is in the treatment trajectory. Needs may also vary depending on the type of HM with which the patient has been diagnosed.

There was a lack of dissenting perspectives regarding the integration of PC, particularly among clinicians. Based on the literature and the authors' experiences, not all HSCT clinicians support integrating PC. It is important to include perspectives opposed to integrating PC, particularly when considering how to implement PC into practice. Participants in this study, particularly clinicians, may have an interest in PC being integrated in HSCT and, therefore, may not be representative of the broader population. As with all research, interpretation of data is influenced by the researchers' experiences and backgrounds. The situatedness of the researcher in ID is important, and the clinical experience of a researcher is considered beneficial in developing research questions that are clinically meaningful. Accordingly, the experience of R.B. as a clinician in HSCT prior to moving to PC affords the unique perspective of having an awareness of these two fields.

Implications for Nursing

Patients and caregivers experience significant physical, psychosocial, and existential symptoms as well as associated distress during and following HSCT. Nurses are ideally suited to assess and assist in managing such distress, including advocating for specialist PC referrals when required. In addition, nurses can play a pivotal role in helping to educate patients, caregivers, and colleagues on the importance of PC in oncology, and help to correct the misperceptions associated with PC. More research is required to gain a comprehensive understanding of the needs of patients and caregivers undergoing HSCT, as well as to determine how to best integrate PC into this care. The current authors are conducting a randomized clinical trial to compare early PC to standard care for patients and caregivers undergoing HSCT (ClinicalTrials.gov, 2023).

Conclusion

The integration of PC in oncology is associated with several positive outcomes for patients and caregivers, yet integrating PC into the care plan for patients undergoing HSCT has not been widely adopted as part of routine care. This study revealed that patients and caregivers undergoing HSCT have significant physical and psychosocial symptoms, that there are barriers to integrating PC (including misperceptions of PC among clinicians, patients, and caregivers), and that there are unique aspects of HMs and HSCT that require special consideration when integrating PC in HSCT. The optimal model for integrating PC remains to be determined. Incorporating PC earlier in the HSCT trajectory of care may mitigate the difficulties associated with prognostic uncertainty and the rapidity of decline that can occur after HSCT, with the goal of ensuring that the HSCT experience is as good as possible for all involved.

KNOWLEDGE TRANSLATION:

- Patients and caregivers experience an array of physical, psychosocial, spiritual, practical, and informational needs during and following hematopoietic stem cell transplantation (HSCT).
- Unique aspects of HSCT may make it challenging to integrate palliative care for patients undergoing transplantation.
- The findings from this study can inform approaches to integrating palliative care for patients undergoing HSCT.

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Chapter 5: Protocol for Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

The results of the qualitative study described in Chapter 4, coupled with the gaps in research identified in the literature review (Chapter 2) and the findings from my clinical and research experiences in my roles with the Alberta Blood and Marrow Transplant Program and the Palliative Care Consult Service, led to the design of a randomized clinical trial (RCT) to examine the impact of early palliative care (PC) for patients undergoing hematopoietic stem cell transplantation (HSCT). The protocol paper for the RCT is described in this chapter.

Abstract

In recent years, research has shown that early palliative care (PC) is not only associated with improved quality of life but also with improved survival in some contexts. Palliative care can provide an additional layer of support to patients and caregivers and help patients live as well as they can for as long as they can. In spite of the proven benefits of integrating PC for people being treated for cancer, it has been well established that patients with hematologic malignancies (HMs) and those undergoing hematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor T-cell (CAR T-cell) therapy do not routinely receive PC and that end-of-life quality measures are typically worse in patients with HMs compared to those with solid tumours. Hematologic malignancies, HSCT, and CAR T-cell therapy are associated with high symptom burden and the potential for serious complications, many of which may be persistent and distressing to patients and their family caregivers and thus, it is thought that this population may benefit from the integration of PC into the trajectory of care. This prospective pragmatic randomized clinical trial will assess the effectiveness of early integration of PC in the outpatient setting for patients undergoing HSCT or CAR T-cell therapy and their family caregivers. The primary outcome of the study is quality of life of patients undergoing HSCT or CAR T-cell therapy. Secondary outcomes include symptom burden, prognostic understanding, non-relapse mortality, and overall survival for patients and quality of life and prognostic understanding of family caregivers.

Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

Introduction

In recent years, research has shown that early palliative care (PC) is not only associated with improved quality of life but also with improved survival in some patients with cancer (Bakitas et al., 2015; Ferrell et al., 2017; Temel et al., 2010). Palliative care can provide an additional layer of support to patients and caregivers and help patients live as well as they can for as long as they can. Despite the proven benefits of integrating PC for people beingtreated for cancer, it has been well established that patients with hematologic malignancies (HMs) and those undergoing hematopoietic stem cell transplantation (HSCT) do not routinely receive PC (Hui et al., 2014). Hematopoietic stem cell transplantation is associated with high symptom burden and the potential for serious complications, many of which may be persistent and distressing to patients and their family caregivers. More recently, chimeric antigen receptor (CAR T-cell) therapy has been incorporated as a treatment modality for patients with some types of lymphoma, multiple myeloma, and leukemia (Brown et al., 2021; Chakraborty et al., 2019; Hayden et al., 2022).

There is a lack of literature on the use of PC in patients undergoing CAR T-cell therapy although it appears that patients receiving CAR T-cell therapy are not routinely referred to PC and have comparably low rates of referral to PC as other patients with HMs (Johnson et al., 2021; Stenson et al. 2022). Given the propensity for high symptom burden, and the risks of morbidity and mortality associated with HSCT and CAR T-cell therapy, integrating PC into the care of patients undergoing HSCT and CAR T-cell therapy may be beneficial to both patients and family caregivers. This research seeks to explore the integration of PC in HSCT and CAR T-cell therapy with a view to improve the experience of patients who undergo these treatments and their family caregivers.

Background

Hematopoietic stem cell transplantation, a curative intent treatment approach, is used in the management of HMs and other non-malignant conditions. While the potential for cure can range from 50 to 80%, HSCT is associated with significant risks of late complications and associated morbidity and mortality (Mitchell, 2018). Patients undergoing HSCT encounter profound symptom burden and toxicities associated with treatment such as nausea, vomiting, pain, anorexia, weight loss or weight gain, bleeding, infections, and mood disturbances (Bevans et al., 2008). In addition to the potential for acute and chronic treatment- related side effects and toxicities, symptom burden has also been reported to be high in patients with HMs (Hochman et al., 2018; Manitta et al., 2011; Tanzi et al., 2020). Further, end-of-life quality indicators have been found to be worse in patients with HMs compared to patients with solid tumours (Hui et al., 2014). Chimeric antigen receptor T-cell therapy is being used to treat some types of relapsed or refractory leukemia, multiple myeloma, and lymphoma (Brown et al., 2021; Chakraborty et al., 2019). While durable responses have been achieved, patients face significant risks of morbidity and life-threatening toxicities (Stenson et al., 2022).

The impact of HSCT on family caregivers has also been described in the literature. For patients undergoing allogeneic HSCT, a designated full-time caregiver must be identified pre-HSCT. The caregiver, often a family member or spouse of the patient, is responsible for an array of activities such as medication administration, tracking and attending patient appointments, managing the patient's central venous catheter, monitoring the patient for symptoms and side effects, and communicating with the medical team (Langer et al., 2020). Further, because of the immunocompromised status of the patient, the caregiver is also responsible for ensuring the home is kept clean and that meals are prepared according to recommendations meant to lower the risk of the patient developing infectious complications (Langer et al., 2020). It is unsurprising that caregivers have reported feelings of anxiety, worry, fear, difficulty adapting to role changes, and challenges managing their own needs while managing those of the patient (Beattie & Lebel, 2011; Langer et al., 2020).

Caregivers have been found to experience distress comparable or higher to that of patients (Beattie & Lebel, 2011). Caregivers play a critically important role in the care of patients undergoing HSCT. Foster et al. (2013) found that patients who had an inpatient lay care partner (n=88) had better overall survival (p=0.017) and relapse-free survival (p=0.020) compared to patients who did not (n=76). The authors found that four-year survival and median relapse-free survival were 39% and 25 months among those with lay care partners compared to 23% and 7 months for those who did not have lay care partners (Foster et al., 2013).

There have been a few studies that have examined the impact of CAR T-cell therapy on caregivers. Stenson et al. (2023) conducted a qualitative longitudinal study with patients undergoing CAR T-cell therapy and their family caregivers. Some participants had been followed prospectively from pre-infusion to 28 days post-infusion while others in the sample had been in follow-up post-CAR T-cell treatment. The authors found that participants reported a wide range of supportive care needs, and that prognostic uncertainty was associated with significant psychological morbidity. The authors suggest that early PC support may be beneficial for patients and family caregivers undergoing CAR T-cell therapy (Stenson et al., 2023). Like HSCT, caregivers for patients undergoing CAR T-cell therapy may be responsible for monitoring for signs and symptoms of toxicities (Spanjaart et al., 2023). Barata et al. (2021) examined quality of life in caregivers (N=99) of patients receiving CAR T-cell therapy and found that some caregivers experienced pain, anxiety, and burden and that the strongest predictor of outcomes at days 90 and 180 post CAR T-cell therapy were baseline levels of the same outcomes. The authors suggest that early intervention and support for caregivers may be beneficial (Barata et al., 2021).

Palliative Care in Oncology

Palliative care has been defined as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (World Health Organization (WHO), 2020, page 1). The WHO definition of PC further highlights that PC is appropriate early in the disease trajectory and may be delivered alongside life-prolonging therapies, such as radiation or chemotherapy. There is a growing body of literature demonstrating that early PC, in the context of advanced cancer, is associated with several favourable outcomes, including: improved symptom management, better prognostic understanding, improved quality of life for patients and family caregivers, and even improved patient survival in some contexts (Bakitas et al., 2015; Ferrell et al., 2017; Temel et al., 2010). In contrast, lack of PC involvement is associated with several adverse end-of-life outcomes, such as: overuse of life-sustaining therapies, aggressive treatment (including chemotherapy) in the weeks preceding death, intensive care unit admissions, more emergency department visits and hospitalizations and underuse of hospice, comprehensive pain and symptom management, psychosocial and spiritual care support (Bernacki & Block, 2014).

For the purposes of this study, we have defined ‘early palliative care’ as PC that is delivered early in the HSCT trajectory. More specifically, participants in the intervention arm of our study will see a PC clinician prior to undergoing HSCT. Hematologic malignancies represent a diverse array of disease such as indolent lymphomas, aggressive lymphomas, chronic leukemias, and acute leukemias (El-Jawahri et al., 2020). It is reasonable to expect that the PC needs of patients may vary contingent upon the type of HM they have and the type of treatment they receive. For example, patients with more slow-growing, indolent disease may not require the same degree of symptom management early in the course of their disease compared to later in the course of their disease or, compared to patients with more aggressive or acute HMs (El-Jawahri et al., 2020). On the other hand, patients with indolent disease and aggressive disease alike may benefit from early discussions on advance care planning and goals of care, assistance with coordination or care, and improved coping skills. Further, early introduction of PC may help better prepare patients and their caregivers for the future introduction of PC rather than waiting for PC to be introduced at a time of crisis or during an acute deterioration in a patient’s health condition. The unpredictable disease trajectory, including the complexity after HSCT, coupled with the propensity for rapid decline after relapse or because of complications, are additional factors that suggest that these patients and caregivers may benefit from early PC. Finally, given that patients who undergo HSCT are known to experience high symptom burden and face significant risks of morbidity and mortality, we believe that early PC may benefit these patients irrespective of the type of underlying HM.

Key Elements of Palliative Care in Oncology

The precise mechanisms that lead to improved outcomes with integration of PC remain to be elucidated. When considering integrating PC in HSCT, it is important to consider the potential ways that PC might benefit patients and their family caregivers. In their qualitative study examining hematologists' perceptions of barriers to end-of-life discussions in patients with HMs, Prod'homme et al. (2018) found that as long as hematologists had therapeutic options available to treat the blood cancer, they seemed unable to discuss end-of-life care. In addition, they found that hematologists worried that end-of-life discussions might adversely impact their credibility and alter the patient's level of trust or influence the tolerability of treatment by impacting the patient's emotional state. Ultimately, the authors indicated that patient wishes regarding end-of-life care are hampered by the hematologists' focus on cure. Similarly, Habib et al. (2019) surveyed hematologist-oncologists in the US and found that respondents (N=349, 57.3% response rate) reported having prognostic discussions with >95% of their patients but that nearly one in five reported never readdressing prognosis or waiting until death was imminent to readdress prognosis.

The importance of addressing prognostic understanding cannot be overstated as patients with HMs and those undergoing HSCT have been found to harbour misperceptions about the risks and benefits of cancer-directed treatment and tend to overestimate the potential benefit of such treatment (Gray et al., 2020). It remains unclear if such misperceptions occur because of poor or insufficient communication and prognostic disclosure on behalf of HSCT clinicians or because of patient factors such as the patient's capacity to process, accept, and discuss prognosis (Gray et al., 2020). In addition, it is noteworthy that one study found that accurate prognostic understanding was associated with greater depression symptoms in patients undergoing HSCT (El-Jawahri et al., 2015). Gray et al. (2020) describe how patients' coping strategies may moderate the relationship between prognostic understanding and psychological distress. Given that PC can assist patients with prognostic and illness understanding as well as may help improve patients' coping skills, Gray et al. (2020) suggest that integrating PC early in the illness trajectory may improve quality of life and increase adaptive coping strategies and prognostic understanding for patients with HMs.

Intervention Trials of PC in Oncology

Hui et al. (2018) described PC as a "highly complex, multidimensional intervention" (p. 357) that is difficult to standardize. Indeed, some would argue against attempts to standardize PC interventions as the very ability to be flexible and responsive to patients' evolving needs is part of what makes PC effective. Given the complexity of PC, some authors have stated that a PC intervention ought to include at least two members of a multidisciplinary team with core members being PC nurses and physicians and involving other disciplines, such as psychology, social work, spiritual care, pharmacy, dietetics, rehabilitation medicine, as needed (Hui et al., 2018).

A potential shortcoming in previous intervention trials examining the impact of PC has been that the intervention has only involved one discipline rather than involving the expertise of the multidisciplinary team (Davis et al. 2015). Given that PC trials that involved a multidisciplinary team rather than a single discipline alone were more likely to be associated with positive findings, a multidisciplinary approach is favored (Hui et al., 2018). In the context of HSCT, this makes sense given the biopsychosocial and spiritual nature of patients' concerns and symptoms. Thus, the PC intervention in this study will involve a PC nurse practitioner, a PC physician, and a psychologist with PC experience as the core team members.

While PC is known to be complex and variable, a recent Lancet Oncology commissioned paper (Kaasa et al., 2018) outlined what the authors considered to be the essential elements of secondary PC:

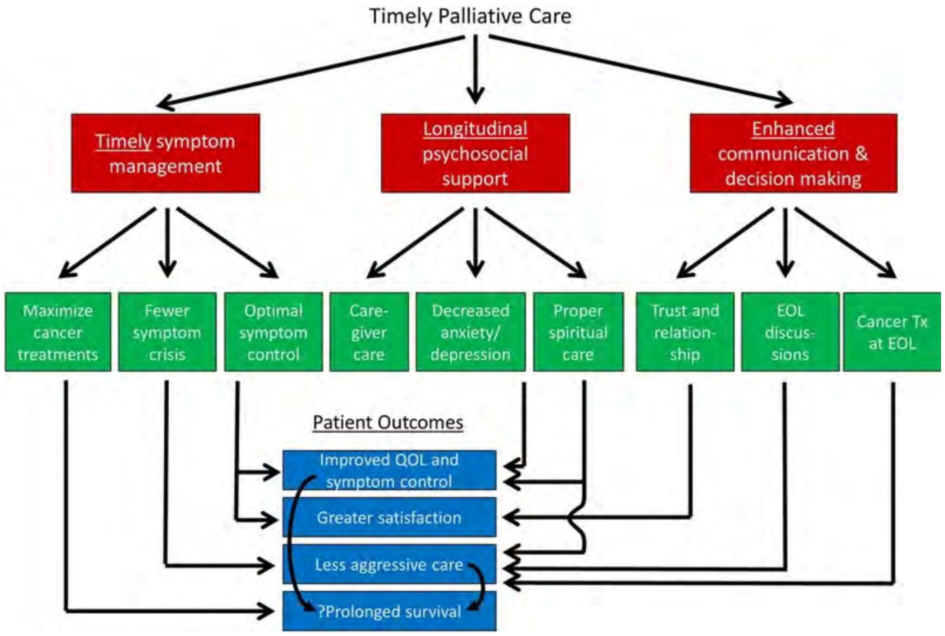
- symptom assessment and management
- psychosocial assessment and management
- spiritual and cultural assessment and management
- communication and shared decision making
- advance care planning
- coordination and continuity of care
- appropriate PC and hospice referral
- family caregiver support
- end-of-life care

Given the complexity of supportive and PC needs, it is unsurprising that PC interventions to address such needs are similarly complex. Complex interventions have been defined as those with "several interacting components that impact the length and complexity of the causal chain from intervention to outcome" (Bleijenbert et al., 2018, p. 87). When utilizing a complex intervention in a study, the intervention should be evidence-based, have a strong conceptual basis or sound theoretical rationale in addition to being aligned with the needs, capacities, and preferences of the patients and health care providers.

A conceptual model on how timely PC can impact outcomes has been described by Hui et al. (2018) and is depicted in Figure 1 below. The model emphasizes the multiple potential ways that PC might impact various outcomes. Reducing symptom burden may minimize symptom crises and patients may tolerate treatment better, leading to the ability to remain on schedule with fewer breaks in anticipated treatment regimens. In addition, improved symptom burden may help to improve quality of life and may reduce healthcare system utilization, such as emergency room visits or hospitalizations. Similarly, longitudinal psychosocial and spiritual care support might help improve emotional and spiritual well-being. Improved communication with the health care team may contribute to improved illness and prognostic understanding, facilitate advance care planning, and lead to fewer hospitalization and aggressive treatment at end of life, the latter of which may have a negative impact on both quality of end-of-life care but also, importantly, on survival (Hui et al., 2018).

Figure 1

Conceptual Framework on How Timely Palliative Care Can Impact Patient Outcomes



Note. From Hui et al. (2018).

El-Jawahri et al., (2020) described the PC needs in patients with HMs during treatment and it would be reasonable for an intervention to aim to address these concerns. Specifically, attention to physical and psychosocial symptoms and distress as well as the provision of information pertaining to illness and prognostic understanding should be undertaken. Further, Hui et al. (2018) state that PC is “most effective as a *preventive* measure when it is introduced *early* in the disease trajectory” (p. 367, emphasis added) and specify that in this context, PC involves patient education, management of symptoms, longitudinal counseling and spiritual care, enhancing illness and prognostic understanding, and advance care planning. Patients undergoing HSCT and CAR T-cell therapy face significant risks of symptom burden and require multidisciplinary care to address their multifaceted, complex PC needs. In spite of these needs, there remains a lack of research on the integration of PC in the care of patients and family caregivers undergoing HSCT and CAR T-cell therapy.

Gaps in Existing Hematological Malignancy Research

Most of the published research on the early integration of PC in oncology describes studies that have involved patients with solid tumours. For example, in their review article on the integration of PC in hemato-oncology, Leblanc & El-Jawahri (2018) reported that among over 1000 patients who were involved in several pivotal randomized trials on PC integration, only one trial allowed patients with HMs and in that study, less than a dozen patients with HMs participated. The authors, like others (Hui et al.,2014; Leblanc, 2014) suggest that more research is needed to determine the unique needs of patients with HMs. Further, it has yet to be established if the same end-of-life care quality indicators (such as hospital admission, use of chemotherapy, or intensive care unit admission in the weeks preceding death) are applicable in hematology and HSCT. For example, in their study examining preferred and actual place of death for patients with blood cancers, Howell et al. (2017) found that 28% of those who expressed a preference for place of death preferred an in-hospital death. The PC needs of this population, therefore, may be quite different from the needs of patients who undergo treatment for solid tumours.

To date, few studies examining the impact of integrated PC among patients undergoing HSCT have been published. El-Jawahri et al. (2016) undertook one such study, which took place in the inpatient setting and randomized 160 patients to either the intervention arm (specialist PC consult and assessment two times per week during admission for HSCT, n=81) or standard care (PC consultation on request, n=79). The authors reported that compared to the standard care arm, patients in the intervention arm reported a smaller decrease in quality of life, as measured by the FACT- BMT, at 2 weeks compared to baseline. Similarly, compared to patients in the standard care arm, patients in the intervention arm reported less depression and anxiety at 2 weeks from baseline (El-Jawahri et al., 2016). To our knowledge, there have been no studies examining the impact of integrated PC on patients undergoing CAR T-cell therapy.

Problem

In spite of the potential for high symptom burden and diminished quality of life, coupled with the risks of morbidity and mortality associated with HSCT and CAR T-cell therapy, there have been few studies examining the impact of the integration of early PC for patients and their family caregivers undergoing HSCT and no studies examining the impact of early PC for patients and their family caregivers undergoing CAR T-cell therapy. Patients undergoing HSCT and CAR T-cell therapy experience high symptom burden (physical, psychological, spiritual), lack illness and prognostic understanding (which can adversely impact medical decision making), and have been found to experience poor end-of-life quality care such as disease-directed therapy in the weeks before death, emergency room visits in the weeks before death, ICU admissions near the end of life, low rates of hospice use, and death in hospital (Earle et al., 2003; Hui et al., 2014).

Family caregivers of patients undergoing HSCT may experience impaired quality of life, physical and psychosocial concerns, and have expressed that their needs have not always been adequately addressed by care teams throughout the HSCT experience (Booker et al., 2023). Palliative care, with its multidisciplinary approach and focus on improving quality of life from a holistic perspective, can help reduce symptom burden and improve quality of life, improve illness and prognostic understanding, and improve end-of-life care for patients undergoing treatment and their family caregivers. We propose a trial to assess the effectiveness of early PC in improving quality of life for patients undergoing HSCT or CAR T-cell therapy for HMs and their family caregivers.

Objectives

The objectives for this study were developed after extensive review of the literature as well as were informed by data derived from a qualitative study that sought the perspectives of patients, family caregivers, and clinicians regarding the integration of PC in HSCT (Booker et al., 2023).

Objective 1: To examine the impact of an outpatient PC intervention on patient-reported quality of life for patients undergoing HSCT or CAR T-cell therapy

Hypothesis: patients randomized to the PC intervention will report greater improvement in quality of life at 1 month and at 3 months post-HSCT or CAR T-cell therapy compared to patients receiving standard care.

Objective 2: To examine the impact of an outpatient PC intervention on patients' symptoms at 2 weeks, 1month, and 3 months post-HSCT or CAR T-cell therapy for patients undergoing HSCT or CAR T-cell therapy

Hypothesis: patients randomized to the PC intervention will report a greater reduction in physical symptoms at 2 weeks, 1 month, and 3 months post-HSCT or CAR T-cell therapy compared to patients receiving standard care

***Objective 3*:** To examine the impact of an outpatient PC intervention on family caregiver quality of life at 1 month and 3 months post-HSCT or CAR T-cell therapy for caregivers of patients undergoing HSCT or CAR T-cell therapy

Hypothesis: family caregivers of patients randomized to the PC intervention will report greater improvement in quality of life compared to family caregivers of patients receiving standard care

In our qualitative study undertaken during Phase 2 of the project, family caregivers commented that the first few months post-HSCT were particularly difficult for them as they monitored the patient's well-being, helped manage and administer medications, and assisted with coordination of the patient's care, including taking the patient to/from frequent medical appointments (Booker et al., 2023). It is possible that 1-month post-HSCT may be too soon to detect any change in quality of life.

Objective 4: To examine the impact of an outpatient PC intervention on patient and family caregiver understanding of prognosis

Hypothesis: patients and family caregivers randomized to the PC intervention will report more accurate prognostic understanding compared to those receiving standard care

Exploratory objective 1: To evaluate whether an outpatient PC intervention is associated with non-relapse mortality and overall survival

Methods

Design

The proposed project is a prospective pragmatic randomized clinical trial to evaluate the effectiveness of an outpatient PC intervention integrated with standard care compared to standard care alone in 152 patients undergoing HSCT or CAR T-cell therapy for HMs. For patients undergoing HSCT, randomization will be stratified by type of transplant, autologous or allogeneic. A pragmatic approach was selected given the desire to assess the effectiveness of integrating early PC in HSCT or CAR T-cell therapy. Previous studies have examined the efficacy of PC in oncology in patients with advanced cancer (Temel et al., 2017; Temel et al., 2010).

This study will build on the work of El-Jawahri et al. (2016) who studied the impact of inpatient PC on patients undergoing HSCT with the main difference being that we will recruit participants in the outpatient setting and the intervention will be delivered in the outpatient setting. Given that we wish to understand if PC will work in the real-world setting, our study goals are more aligned with effectiveness research rather than efficacy research (Meyer et al. 2014). Effectiveness studies emphasize the importance of patient, caregiver, and clinician perspectives. Pragmatic clinical trials can yield more generalizable findings and may be able to overcome some of the limitations of traditional RCTs (Frieden, 2017). Selected outcomes have been chosen as they are congruent with patient, family caregiver, and clinician perspectives, based upon findings from the qualitative study we had conducted (Booker et al., 2023).

The pragmatic nature of this study was confirmed using the PRECIS 2 tool (Loudon et al. 2015), which involves 9 domains that researchers assign scores to with the result revealing if the study is pragmatic vs explanatory. The aim of the study is to assess effectiveness of the PC intervention in a real-world setting, the outpatient blood and marrow stem cell transplant clinic, with participants who would typically undergo HSCT or CAR T-cell therapy (reflected by the minimal inclusion and exclusion criteria). The intervention itself can be delivered in a flexible manner with respect to both the delivery (where the PC intervention will be tailored to the patients' individual needs) as well as to adherence. Regarding the latter, we will endeavor to maintain a schedule with the intervention and assessments but will allow flexibility as required.

The outcomes have been selected with input from patients, family caregivers, and HSCT clinicians and thus, are not only outcomes that matter to these groups but also, should be highly relevant to practice. Intention to treat analysis will be undertaken, utilizing all available data; this approach is congruent with a pragmatic stance (Loudon et al., 2015). There are some aspects of the study that align more with an explanatory approach, most notably, the specialized expertise and resources that will be required to provide the intervention. Overall, the study has been designed to meet the needs of patients, family caregivers, and HSCT clinicians (Zwarenstein et al., 2008).

Like the study conducted by El-Jawahri et al. (2016), this study will include a qualitative component where 5 patients, 5 family caregivers, and 5 clinicians will be interviewed regarding their perspectives on the intervention and if it is meeting their needs. By doing so, the study will seek to learn more about potential facilitators of and barriers to implementing PC in practice. Integrating this qualitative component will help assess both the effectiveness of the intervention and as well, may provide important information on implementation of the intervention and context (Curran et al., 2012; Landes et al., 2020). Doing so may help move the findings into practice more readily (Landes et al., 2020). Adapting a pragmatic stance may help contribute to generalizability and external validity (Frieden, 2017).

Study Sample

We will recruit 152 consecutive adult patients with HMs who present to the Tom Baker Cancer Centre for their pre-HSCT or CAR T-cell therapy assessment. We will ask patients who are interested in study participation to identify a family member or friend who has been designated as their primary caregiver. The local HSCT program requires that all patients going through HSCT or CAR T-cell therapy have a primary caregiver throughout their transplant experience. For this study, it is this primary caregiver who will be considered the family caregiver, recognizing that this individual may be a spouse, parent, child, sibling, or even close family friend. We will invite the family caregiver to participate in the family caregiver portion of the study. Patients without a willing or available family caregiver will still be eligible to participate but only family caregivers whose family member is participating in the study will be eligible to participate. A maximum of 152 family caregivers will be asked to participate in the study.

Inclusion and Exclusion Criteria

Inclusion Criteria - Patients

1. Adult patients (≥18 years) with HMs who are scheduled to undergo HSCT or CAR T-cell therapy
2. Ability to speak, read, and understand English or, be able to complete questionnaires with minimal assistance required from an interpreter

Exclusion Criteria – Patients

1. Patients undergoing HSCT for a non-malignant hematologic condition
2. Inability to provide informed consent

Inclusion Criteria – Family Caregivers

1. Adult caregivers (≥18 years) of patients undergoing HSCT or CAR T-cell therapy for a HM at the Tom Baker Cancer Centre who agree to participate in the study
2. A spouse, relative, or friend, identified by the patient, who either lives with the patient or has in-person contact with the patient at least twice per week. Only one family caregiver per patient will be asked to participate
3. Ability to speak, read, and understand English or willing to complete questionnaires with minimal assistance required from an interpreter

Exclusion Criterion – Family Caregivers

1. Inability to provide informed consent

Trials involving PC have been critiqued for not explaining how treatment fidelity was upheld. In their study examining the impact of a nurse-led care management approach to providing PC for patients with advanced cancer and their family caregivers, Becker et al. (2017) indicated that they would audio record all study visits and randomly select 2% for audit to assess treatment fidelity and quality. To demonstrate how treatment fidelity was maintained, we will audio record all study visits and randomly select 2% of the audio recorded visits for audit. Study team members will also keep field notes of what was discussed during visits with participants in the intervention arm.

Study Procedures

Intervention Arm

Participants randomized to the intervention arm will meet virtually (either by phone or Zoom, contingent upon participant preference) with a PC nurse practitioner or PC physician, both part of the study team. During the first meeting, pre-HSCT/CAR T-cell therapy, content will focus on the provision of information and education, including: what PC is, symptom management, advance care planning, prognostic and illness understanding and treatment expectations, and coping strategies. All subsequent visits will include these topics, tailored to patients' needs. It is anticipated that not all patients will require discussion or intervention for all topics, that some visits may contain more information on one topic, and that topics may change as the patient's needs change throughout the illness and treatment trajectories. Due to the unpredictability of the COVID-19 pandemic and given that patients with HMs are at high risk of adverse outcomes of COVID-19 infection (Grivas et al., 2021; Zhang et al., 2021), participant recruitment and data collection will take place virtually, via phone or Zoom. All meetings will be audio recorded using a handheld audio recorder; the record feature of Zoom will not be utilized given that Zoom stores its data in the United States. Participants in the intervention arm will meet with a member of the study team (PC nurse practitioner or PC physician) one to two times weekly, or more frequently if requested by the patient and/or caregiver, until 3 months post-HSCT/CAR T-cell therapy. This meeting schedule reflects the schedule utilized by El-Jawahri et al. (2016) in their study on inpatient PC for patients undergoing HSCT.

Standard Care Arm

Standard care will involve the usual care that patients undergoing HSCT or CAR T-cell therapy would be expected to receive, including PC consultation as needed or upon request. Palliative care interventions beyond what are provided in the study will be tracked in both the intervention and the standard care arms. For example, it is possible that participants in either arm may receive PC from their family physicians or home care. We will review PC consult notes for patients in the standard care arm as well as for patients in the intervention arm who received PC recommendations, discussions regarding advance care planning, discussions pertaining to coping, and any other intervention that occurred. It is possible that not all PC interventions will be fully documented in patient charts and consult notes. Additionally, it is possible that PC may be provided by a non-PC clinician and this may not always be captured in patients' charts. As an example, a nurse may discuss a patient's goals and wishes and may not characterize this as a discussion about advance care planning. As such, this may not be documented and/or noted as a PC intervention. The possibility of missed or undocumented PC in either arm may influence outcomes and could be a limitation of our study.

An important consideration is that it is possible that patients in the intervention arm may experience improved outcomes because of the extra care they receive rather than the outcomes being influenced by the provision of PC specifically. We recognize this as a potential limitation of our study. The qualitative component of the study will seek participants' input as to what it was about the intervention that they felt was most beneficial to them during the study.

From data obtained in a previous local study, we know that most patients with HMs in the Calgary Zone *do* receive some PC prior to death. However, most of these patients receive PC quite late in the disease trajectory. For example, in our study examining end-of-life patterns of care in decedents of HMs (n=1844) between January 2003 and December 2016, fewer than 30% (n=325) had been seen by PC more than 3 months prior to death. It is therefore anticipated that cross contamination will be unlikely. Nevertheless, as mentioned above, we will track the number of PC referrals in the standard care arm and review PC consult notes to track the PC interventions that occur in the standard care arm.

Outcomes

Primary Outcome

The primary outcome of the study, quality of life, will be assessed using the McGill Quality of Life Questionnaire – Expanded (MQOL-E) summary score of quality of life monthly for a period of three months. The trajectories of quality of life will be evaluated rather than looking at change in scores given that we anticipate significant fluctuation in quality of life scores over time. The Functional Assessment of Cancer Therapy – Bone Marrow Transplant (FACT-BMT) will also be used to measure quality of life (McQuellon et al., 1997). The FACT-BMT is more specific to BMT and may capture issues that are unique to BMT (Shaw et al., 2016; Solle et al., 2020). Many studies to date have used FACT-BMT, including the inpatient PC intervention study by El-Jawahri et al. (2016) and therefore, using the FACT-BMT will allow for our study to be compared with other studies that have used this tool. Of note, there are two items on the FACT-BMT that specifically mention ‘transplant’. We have been in touch with the authors of the FACT-BMT and have permission to edit these two items to read ‘treatment’ instead of ‘transplant’ to accommodate the patients undergoing CAR T-cell therapy.

The MQOL was first reported in the literature in 1995 and was developed to assess quality of life, across any phase of the disease trajectory, for people with a life-threatening illness (Cohen et al., 1995). Since then, the MQOL has been utilized in numerous clinical trials and recently, underwent revision to include additional domains (Cohen et al., 2019). The original version of the MQOL included 16 items that assessed four domains: physical, psychological, existential, and support and included a global quality of life item. A revised version of the MQOL, the MQOL- R, was published in 2017 (Cohen et al., 2017). Notable changes to the MQOL-R included the creation of a new physical subscale that combined physical symptoms, physical well-being, and a new item pertaining to physical functioning. In addition, the Existential subscale was reduced to four items from six, the Support subscale was renamed to Social, and items were added to that focused more on relationships. The wording of several of the items on the MQOL was modified for the MQOL-R. Psychometric properties of the MQOL-R were assessed and found to be acceptable. Confirmatory factor analysis was undertaken, and results supported the changes made to the original MQOL. Further, internal reliability was acceptable (α=0.94).

In 2019, Cohen et al. published an expanded version of the MQOL-R, the MQOL-E. The authors recognized that domains other than those most commonly assessed (physical, psychological, social, spiritual/existential) might influence quality of life. The MQOL-E has 21 items and includes the additional domains of cognition, healthcare, environment, and feeling like a burden. A version of the MQOL-E is available that includes an item pertaining to financial concerns though this item is not to be used in computing the summary score (Cohen et al., 2019). The MQOL-E was tested in people with life-threatening illness, including cancer, from 15 health care sites in seven provinces across Canada. The authors found that the new items did not load >/0.6 on existing M-QOL-R factors and therefore, could reflect new domains (Cohen et al., 2019). Further, the authors found good model fit when the new domains were added separately to the MQOL- R as well as when they were added together to the MQOL-R. The psychometric properties of theMQOL-E are being examined in another study conducted by the authors (Cohen et al., 2019).

All items on the MQOL-E use a numeric response scale that ranges from 0 to 10 with verbal responses used to anchor either end (Axelsson et al., 2020). The MQOL-E was selected to assess quality of life for this study as it provides one of the most comprehensive assessments available while remaining brief. The domains assessed by the MQOL-E align with the symptoms and concerns frequently experienced by patients undergoing HSCT and CAR T-cell therapy. An additional feature of the MQOL-E that is appealing is that respondents are asked to report on their experience over the previous 2 days, whereas other quality of life tools ask respondents to report on their experience over the previous week. This is relevant for patients undergoing HSCT and CAR T-cell therapy as symptoms can fluctuate dramatically over the course of a few days, particularly early post-HSCT/CAR T-cell therapy and thus, the MQOL-E might be able to provide a more accurate representation of the patient's experience at the time of assessment.

The FACT-BMT version 4, is a self-reported questionnaire that measures quality of life and consists of 27 general questions (comprising the FACT-G) and 23 questions pertaining to

HSCT (comprising the BMT subscale). The tool assesses physical well-being, social and family well- being, emotional well-being, functional well-being, and BMT specific concerns. Respondents areasked to consider their experience over the past 7 days. Respondents are asked to rank each item on a scale of 0-4, from ‘not at all’ to ‘very much’. Higher scores on the FACT-BMT reflect better quality of life. In the first published paper on the FACT-BMT, the authors reported that the FACT-BMT (including the FACT-G and BMT subscale) had acceptable reliability with alpha coefficients ranging from 0.85-0.92. The authors tested the tool on 182 patients who had undergone HSCT and reported that the tool had acceptable construct validity (McQuellon et al., 1997). As per the current scoring manual instructions, only 37 items are scored, for a total possible score of 148 (Cohen et al., 2012).

McCaffrey et al. (2016) conducted a systematic review of qualitative studies to identify the aspects of quality of life that are important from patients’ perspectives. The authors found that eight aspects of quality of life were found to be most important, including: physical, personal autonomy, emotional, social, spiritual, cognitive, healthcare, and preparatory (McCaffrey et al., 2016). Quality of life is inherently subjective and variable amongst patients. Thus, utilizing two quality of life patient-reported outcome measures (PROMs) may better capture the full experience rather than only using one PROM alone. Further, the MQOL-E is not disease or treatment specific while the FACT-BMT does assess unique aspects of the HSCT experience. The primary outcome will be quality of life as measured by the MQOL-E. Importantly, given the structure of the questions on the FACT-BMT, it can only be administered after HSCT/CAR T-cell therapy while the MQOL-E can be administered at any point throughout the treatment trajectory.

Secondary Outcomes

Patient Symptom Burden

The Edmonton Symptom Assessment System (ESAS) is a validated scale that assesses symptom burden in patients with cancer (Hui & Bruera, 2017). While several iterations of the ESAS are available, we will use the ESAS-revised (ESAS-r) which includes 10 items scored using a numeric rating scale (Hui & Bruera, 2017). The ESAS assesses physical symptoms (pain, fatigue, nausea, drowsiness, dyspnea, loss of appetite), emotional symptoms (anxiety and depression), and well-being. We will track individual patient scores over time to assess the trajectory of symptom burden.

Patient and Family Caregiver Prognostic Understanding

The Perception of Treatment and Prognosis Questionnaire (PTPQ) is 10 item self-report questionnaire that assesses patients' and caregivers' beliefs about the likelihood of cure, the importance and helpfulness of knowing about prognosis, the perceived primary goal of cancer treatment, preferences for information about treatment, and the satisfaction with quality of information provided regarding prognosis and treatment (El-Jawahri et al., 2015). Items on the questionnaire are scored individually with statements about the degree to which the patient agrees with each item (El-Jawahri et al., 2015). We will have patients and caregivers complete the PTPQ pre-HSCT/CAR T-cell therapy and at 3 months post-HSCT/CAR T-cell therapy.

Caregiver Quality of Life

The Quality of Life in Life-Threatening Illness – Family carer version (QOLLTI-F) will be used to assess caregiver quality of life. The QOLLTI-F is a 17-item questionnaire that includes seven subscales that assess the following domains: environment, patient condition, the caregiver's condition, quality of care, relationships, and financial worries (Axelsson et al.., 2020). In addition, there is a single item that pertains to overall quality of life (Axelsson et al., 2020). The QOLLTI-F has been validated with caregivers of patients with cancer (Alnjadat et al., 2014; Schur et al., 2014). Caregivers in both the intervention and standard care arms will complete the QOLLTI-F pre-HSCT/CAR T-cell therapy, and at 2 weeks, 1-month, and 3-months post-HSCT/CAR T-cell therapy.

Exploratory Outcomes

We will collect the following outcomes from patients' electronic medical records: 1-year overall survival, 1-year non-relapse mortality, and health care services utilization in last 30 days of life: ER visits, ICU admissions, and chemotherapy.

Sample Size Calculation

While the significance of changes in quality of life can be interpreted using statistical hypothesis testing using p-values, statistical significance is not always correlated with clinical significance (Hong et al., 2013). When measuring quality of life, the minimal clinically important difference (MCID) can be used as a point of reference to assess effectiveness of an intervention and may be more meaningful clinically than statistical significance alone (Hong et al., 2013). In studies assessing quality of life, 0.3 and 0.5 standard deviations of baseline patient-reported outcome (PRO) scores are often used as benchmarks for MCID (Hui et al. 2016). Norman et al. (2003) conducted a systematic review to identify studies that computed a minimally important difference (MID) and included enough information to calculate an effect size. The authors found that for 32 of 38 studies, the MID estimates were approximately a half standard deviation. Thus, for our sample size calculation, we will use a half standard deviation.

To detect a significant difference of a half standard deviation, with an alpha level of 0.05 and power set to 80%, 64 cases in each group would be required. However, it is known that attrition is a likelihood and can be as high as 30% or more in PC studies (Hui et al., 2016). El-Jawahri et al. (2016) used an anticipated attrition rate of 15% for their study. Thus, using an attrition rate of 20% should result in a realistic, conservative estimate and would require 76 participants per arm (N=152 total participants). This estimation is congruent with Fayers and Machin (2016) who provide an estimation of a sample size of 130 participants required to detect a moderate effect size (0.5), using a two-sample t-test to compare two unpaired means with a significance level of 5% and power of 80%.

Randomization

Randomization (permuted block randomization, variable block size) will be undertaken with patients being allocated to either standard care or early PC. For patients undergoing transplant, stratification based upon type of transplant (autologous versus allogeneic) is necessary given the differences in treatment-related side effects and potential complications between the two types of transplants. Randomization will be conducted by a member of the study team but not the PI (RB) to keep the PI blinded to randomization allocation of participants. Randomization will be done using computer software.

Blinding

It will not be possible to blind participants or researchers (PC clinicians who will be involved in delivery the intervention) to the intervention but the individual doing the data collection, the research assistant, will be blinded to the randomization allocation. An additional important consideration is the possibility of contamination bias whereby participants in the control arm may receive PC intervention as part of standard care (Magill et al., 2019). However, based upon the current patterns of PC referrals, it is unlikely that participants would meet with PC prior to their transplant, as will occur with the intervention arm. Nevertheless, contamination is a possibility. Charts of those in the control arm will be reviewed to track any PC intervention that participants may have received outside of the study.

Data Collection

Participants will be emailed a secure link for the questionnaires. Data from questionnaires will be collected electronically using Research Electronic Data Capture (REDCap). Email reminders will be sent to participants to remind them to complete the surveys and if necessary, a research assistant will contact patients and family caregivers to provide reminders to complete the surveys. Following randomization, participants (patients and family caregivers) will be asked to complete baseline questionnaires and provide demographic information (such as age, sex, diagnosis, urban/rural residence, religious affiliation, highest level of education, main caregiver (for patients), main source of support (for family caregivers)). The next evaluation will occur during the second week of hospitalization for HSCT/CAR T-cell therapy. For participants undergoing autologous HSCT (and their family caregivers), the second evaluation will occur on day +5 (with a 48-hour window). For participants undergoing allogeneic HSCT (and their family caregivers), the second evaluation will occur on day +8 (with a 72-hour window). These time points were chosen based upon the study conducted by El-Jawahri et al. (2016) who indicated they selected the time points to coincide with the peak of severity in symptoms based upon the type of transplant being performed. All patients and family caregivers will also complete questionnaires at 1- and 3-months post-HSCT/CAR T-cell therapy. The schedule for data collection is shown in Table 1.

During the consenting process, participants will be asked if they would consider completing questionnaires at 6 and 12 months post-HSCT/CAR T-cell therapy. Patient participants will also be asked if they consent to the researchers accessing their medical charts until 5 years post-HSCT/CAR T-cell therapy in order to collect disease and treatment related information.

Table 1

Administration of Patient and Caregiver Reported Outcomes

	Baseline	Week 2	1 month	3 months
Patient measures:				
Demographics	X			
MQOL-E	X	X	X	X
FACT-BMT	-	X	X	X
ESAS	X	X	X	X
ECOG PS	X	X	X	X
PTPQ	X	-	-	X
Family caregivers:				
Demographics	X			
QOLLTI-F	X	X	X	X
PTPQ	X	-	-	X

Note. MQOL-E=McGill Quality of Life Questionnaire-Expanded; FACT-BMT=Functional Assessment of Cancer Therapy-Bone MarrowTransplantation; ESAS=Edmonton Symptom Assessment System; ECOG PS=Eastern Cooperative Oncology Group Performance Status; QOLLTI-F=Quality of Life in Life Threatening Illness – Family Carer Version; PTPQ=Prognosis and Treatment Perception Questionnaire

** if patient & family caregiver consent, they may be asked to complete questionnaires at 6 & 12 months post-HSCT/CAR T-cell therapy*

Data Analysis

Murray et al. (2020) suggest that exclusive ITT analysis may not be aligned with patient-centered outcomes research because “the ITT effect is, in many cases, not a patient-centered effect measure" given that the ITT effect is the effect of the treatment assignment rather than the effect of treatment (p. 10). The authors provide draft guidelines for the analysis of randomized controlled trials in real-world settings and advocate for estimating both the ITT effect as well as the per protocol (PP) effect (Murray et al., 2020). Further, they suggest that sufficient data be collected to determine if participants adhered to their assigned treatment (or control). We will follow these recommendations in our study. For any imbalances between the intervention and control groups, sensitivity analyses while be conducted and we will use g-methods to adjust for confounders that may vary over time. As per the revised CONSORT guidelines for reporting parallel-group randomized trials, we will collect and report the reasons for participants lost to follow-up as well as the reasons why any participants' data were excluded from analysis (Moher et al., 2001).

Analysis Plan - Primary Outcome

To assess the primary outcome of the study, we will compare differences in quality of life between the intervention group and the standard care group. Because we will be assessing quality of life at multiple time points, we will use area under the curve (AUC) to calculate a summary score for each patient (Fayers & Machin, 2016). Assessing multiple domains over time, as we intend to do, increases the possibility of Type I error (Jensen et al. 2012). Because we expect that patient trajectories of quality of life will be non-linear and will fluctuate over time, AUC seems more appropriate than using specific time points as the latter may underestimate or overestimate treatment differences (Bell etal., 2014; Jensen et al., 2012). Summary scores will be averaged across all patients in both the intervention and standard care arms and differences between the groups will be assessed using t-tests. We will present the summary profiles for patients in graphical form for the MQOL-E and FACT-BMT.

Analysis Plan – Secondary Outcomes

Family caregiver quality of life will be analyzed using AUC and comparing the two groups using t-tests. For patient symptom burden, as measured by the ESAS-r, we will track symptom scores over time for each patient. We will not use a summary score for the ESAS-r given the diversity of symptoms assessed by the ESAS-r as well as the option on the ESAS-r that allows patients to add another symptom or concern. The latter would mean that there could be different symptoms being reported amongst participants, thereby making it difficult to compare groups. Patient and family caregiver prognostic understanding will be assessed using t-tests to compare the intervention group and standard care group at two time points, pre-HSCT/CAR T-cell therapy and at 3 months post-HSCT/CAR T-cell therapy.

Exploratory objectives: We will assess overall survival and non-relapse mortality using Kaplan Meier estimates. The differences between study arms will be assessed using Chi-square or Fisher's exact test.

Response Shift

The experience of going through HSCT and CAR T-cell therapy is likely to be very fluctuant with profound changes in symptom burden over time. Such changes may alter patients' perception of their health and quality of life. This may be particularly germane in HSCT and CAR T-cell therapy where the diagnosis of a HM and subsequent treatment could potentially impact how a patient responds to and interprets questions about their health (Sajobi et al., 2018). The experience of going through such an intense, potentially traumatic experience, might significantly impact how a patient assesses their health and quality of life. In an intervention study, response shift (RS) is an important consideration as it is possible that participants in the study might alter their perception of the same question(s) when asked at different times and it may be the shift in perception rather than the intervention that has influenced the change in quality of life scores (Donaldson, 2005).

Possible options to test for RS include the then-test approach or structural equation modelling (SEM). The latter approach allows for retrospective analysis of data to examine for all 3 components of RS while the then-test may potentially be impacted by recall bias (Murata et al., 2020; Oort, 2005). Indeed, in the context of HSCT and CAR T-cell therapy, recall bias may be particularly important. The treatment itself is associated with significant side effects and symptom burden. Further, the medications used to manage such side effects can also contribute to symptom burden and can also impact cognition. Some patients may find it difficult to remember the details of their inpatient stay.

We will undertake a secondary data analysis of the MQOL-E data and use SEM to assess for RS. We will look for measurement invariances of the common factor loadings, intercepts, and residual variances between pre-HSCT/CAR T-cell therapy and at the 1 and 3-month post-HSCT/CAR T-cell therapy time points. We will utilize an approach like that outlined by Murata et al. (2020) where we will first establish a measurement model, assess for the presence of RS and then, for the type of RS (reconceptualization, reprioritization, and/or recalibration). Dr Robin Cohen, developer of the original MQOL and co-developer of the QOLLTI-F, has created a series of questions that can be used retrospectively to assess change for each of the domains in the tools. She has kindly agreed to share these questions and has provided permission for us to use them in our study (R. Cohen, personal communication, March 23, 2021).

Missing Data

Given the longitudinal nature of the study as well as the multiple instruments that will be used in the study, it is probable that there will be missing data. Missing data may include individual items on a questionnaire or entire questionnaires. The potential consequences of missing data include diminished precision (wider confidence intervals) and reduced power due to reduction in data (Bell & Fairclough, 2014). Missing data can lead to bias, with an overestimate of the treatment effect, both within groups over time and between groups (Bell & Fairclough, 2014).

Efforts will be undertaken to minimize missing data during data collection (Bell & Fairclough, 2014; Little et al., 2012). For example, we have endeavored to minimize participant burden by selecting questionnaires that are easy and quick to complete (Bell & Fairclough, 2014). Phone call, text, and/or email reminders will be sent to participants to remind them to complete the questionnaires. The questionnaires will include notices at the top and at the bottom to ask participants to ensure they are answering every question.

Missing data will be described. Multiple imputation will be used with the assistance of statistical software. A minimum of 40 imputed data sets will be created and analyzed. A sensitivity analysis will be conducted and will include a comparison of all available data for primary and secondary outcomes of the groups who withdrew from each arm with the remaining participants (Currow et al, 2012). Given the variability in symptom burden in patients undergoing HSCT, the last observation carried forward method is not felt to be an appropriate approach in dealing with missing data.

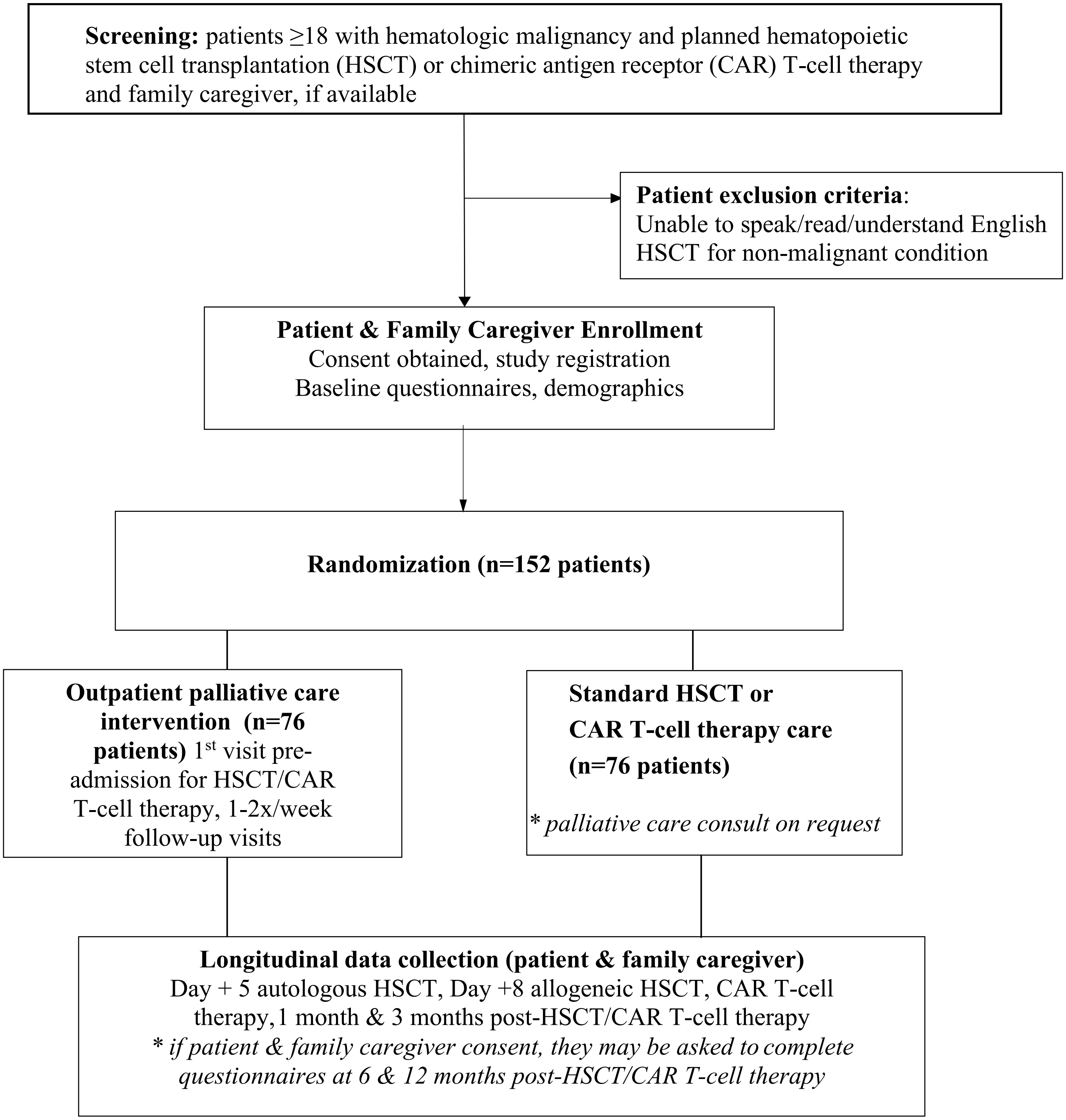
We will document, as much as possible, the reasons why data are missing (Bell & Fairclough, 2014; Currow et al., 2012). Attempts will be made to determine if data are Missing Completely at Random, Missing at Random, or Missing Not at Random (Bell & Fairclough, 2014; Fayers & Machlin, 2016). Collecting ECOG performance status at each assessment will also help provide context if a participant does not complete entire questionnaires and/or withdraws from the study. (Little et al., 2012).

Participant Recruitment

Once approval has been granted from the Research Ethics Boards (University of Victoria and the Health Research Ethics Board of Alberta Cancer Committee), recruitment strategies will be undertaken. Patients and family caregivers will be recruited from the outpatient bone marrow transplant clinic at the Tom Baker Cancer Centre. The Alberta Blood and Marrow Transplant Program in Calgary coordinates all Calgary-zone autologous HSCT and CAR T-cell treatments and all allogeneic HSCTs in Alberta. Clinicians in the HSCT program will provide a study poster to patients who attend the HSCT outpatient clinic before their transplant. Patients will be asked to contact a research team member directly, via phone or email, if interested in learning more about the study. If Infection and Prevention Control permits, we will place study posters in the HSCT clinic areas. We will also contact the local Chapters of the Leukemia and Lymphoma Society of Canada and the Southern Alberta Multiple Myeloma Patient Society to request that the study poster be sent out to their members. Individuals who are interested in the study will be asked to contact a research team member directly, via phone or email, as indicated on the study poster. Figure 2 outlines the study procedures.

Figure 2

Study Schema



A research team member will review the consent form, discuss study procedures, time requirements and frequency of self-report questionnaires, and answer any question that the patient and/or family caregiver may have. Written informed consent will be obtained from the patient and their family caregiver, if a family caregiver is available and interested in participating. After providing written informed consent, participants will complete baseline study questionnaires before being randomized to the PC intervention arm or the standard care arm using a computer generated 1:1 randomization process, stratified by type of HSCT for patients undergoing transplant (allogeneic or autologous).

If HSCT or CAR T-cell therapy is aborted due to illness or infection, the participant will be deemed ineligible for the study and will not be counted toward accrual. Participants who withdraw from the study or who die during the study period will be counted in the accrual numbers.

Ethical Considerations and Minimizing Risks of Harm

This study will be conducted in compliance with the protocol approved by the Health Research Ethics Board of Alberta-Cancer Committee (HREBA-CC) and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the HREBA-CC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the HREBA-CC as soon as possible.

All subjects with capacity will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in the study. The formal consent of a subject, using the HREBA-CC approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form will be signed by the subject and the investigator-designated research professional obtaining the consent.

Risks

It is possible that participants may find it uncomfortable or upsetting to discuss topics that may come up during the PC visits, including but not limited to topics such as end-of-life care, end-of-life decision making, death, and dying. Information will be provided to all participants regarding how they can access psychosocial support. For patients and family caregivers, psychosocial support through the Department of Psychosocial Resources at the Tom Baker Cancer Centre, is offered free of charge to all patients and their family members. Contact information for the Department of Psychosocial Resources will be provided to patient and family caregivers. An additional after-hours phone number for support in the event of distress will be provided to participants.

Benefits

Potential benefits to study participants include encouragement to talk about their health care experiences and concerns. The results of the study may help improve quality of care patients receive in the future. As other intervention studies on PC in oncology have found, participants in the intervention arm may experience improvements in symptom management and less depression and/or anxiety. They may also experience improved prognostic understanding that might help with medical decision making. It is also possible that participants in the standard care arm experience benefits as well by reporting their symptoms and their experiences regularly. Basch et al. (2016) found patients (n=441) who self-reported symptoms weekly had less of a decline in health-related quality of life (1.4 v 7.1-point drop, $p<0.001$) compared to patients in the usual care arm (n=325). The authors also reported that 75% of patients in the intervention arm were alive at 1 year, compared to 69% of those inthe standard care arm (mean of 8.7 v 8.0. months, *p*=0.004). Thus, it is possible that participants in both arms of our study may benefit simply by reporting their symptoms and experiences regularly.

Data Handling and Record Keeping

Participants will be assigned a unique study identification (ID) number. Only this study ID number will be used on research-related documentation and research data collected during the study so that a participant's identity will remain confidential. Information that directly discloses a participant's identity will remain with the Principal Investigator. Participants will not be identified by name or any other identifiable information in any reports of the completed study.

A list of all study participants will be created to link study participant information to the assigned study ID number. The list that links names to the unique identifier that is used on research-related information will not be removed or released without consent unless required by law. Access to this list will be approved only for researchers involved in the study. The list of study participants and consent forms will be kept separate from study data, in a locked filing cabinet in the locked office of the Principal Investigator.

Answers to questionnaires will be entered into REDCap using Alberta Health Services computers. REDCap is a secure, web-based application locally hosted by the University of Calgary's Clinical Research Unit. All electronic data will be uploaded and stored on an encrypted, password protected USB stick. Access to study data will be restricted only to study personnel and the HREBA-CC, who may review identifiable medical/clinical study records for quality assurance purposes. Participant consent forms and the list of study participants will be kept for 5 years from the end of the project to comply with federal regulations and to accommodate data validation queries. More detailed information pertaining to data management can be found in the Data Management Plan (Appendix E).

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Chapter 6: Symptoms, Symptom Profiles, and Healthcare Utilization in Patients with Hematologic Malignancies in a Canadian Province: A Retrospective Cohort Study and Latent Class Analysis

Background

Advances in the treatment for hematologic malignancies (HMs), such as targeted therapies, immunotherapies, and chimeric antigen receptor (CAR) T-cell therapy, have led to improvements in survival yet people with HMs still face significant risks of morbidity and mortality (El-Jawahri et al., 2020; Gebel et al., 2024; Robbins-Welty et al., 2023). Patients with HMs may experience disease and treatment-related symptoms that can adversely impact quality of life (Cleeland, 2007). Symptom burden, a concept that considers symptom prevalence, frequency, and intensity, can fluctuate through the disease and treatment trajectories and has also been associated with diminished quality of life (Gapstur, 2007). Previous research has found that symptom burden is high in patients with HMs, with patients reporting both frequent and severe symptoms throughout the disease trajectory (Hochman et al., 2018; Manitta et al., 2011).

More recently, research has found that symptoms in patients can co-occur as symptom clusters (Harris et al., 2022; Morse et al. 2024; Simao et al., 2024). To date, most research on symptom clusters in patients with HMs has focused on one type of HM such as lymphoma (Lee et al., 2024; Wu et al., 2023), leukemia (Fang et al., 2023; Lin et al., 2019), or multiple myeloma (Brazauskas et al., 2024, Chen et al., 2022; Zeng et al., 2023). Better understanding symptoms in a diverse population of patients with different types of HMs may allow for interventions that can better address symptom management with the goal of improving quality of life for patients with HMs more broadly. Further, considering associations among patient sociodemographic factors, clinical variables, and symptoms in patients with HMs may lead to targeted interventions and strategies to help reduce symptoms.

The treatments available for patients with HMs vary considerably as HMs comprise a diverse and heterogeneous group of diseases (Kantabanlang et al., 2023; Kuczmarski et al., 2024). Treatment for HMs includes modalities such as chemotherapy, radiotherapy, surgery, targeted therapy, immunotherapy, and cellular therapies such as hematopoietic stem cell transplantation (HSCT) and CAR T-cell therapy (Gebel et al., 2024; Sochacka-Cwikla et al., 2021). Both the underlying HM as well as the associated treatments can contribute to an array of physical and psychosocial symptoms (Kuczmarski et al., 2024). Some HMs are considered incurable but may be responsive to treatment, such as multiple myeloma and some types of lymphoma (Howell et al., 2022). Patients with multiple myeloma often experience periods of remission followed by relapse, with treatment often continuing indefinitely with maintenance therapy in between relapses (Rajkumar, 2022). For other HMs, observation may be indicated and as such, patients may not experience physical symptoms or side-effects from treatment but still must contend with the burden and threat that the disease may progress (Kuczmarski et al., 2024). Coping with such uncertainty and the associated emotional distress has been reported by some patients to be even more burdensome than physical symptoms (Howell et al., 2022). On the other hand, some HMs are aggressive at time of diagnosis, such as acute leukemias, and require immediate treatment that can lead to physical and psychological symptom burden (El-Jawahri et al., 2020).

Symptom Burden in Hematologic Malignancies

Patients with HMs face the possibility of multiple co-occurring symptoms that may be disease- and/or treatment-related and that may occur throughout the illness trajectory (El-Jawahri et al., 2020; Tsatsou et al., 2020). Patients may experience cytopenias, due to the disease and/or the treatment, which can lead to distressing symptoms and complications such as fatigue, bleeding, and infections (Chan et al., 2022; Hui et al., 2014). Several studies have found that patients with HMs often experience multiple symptoms. For example, Manitta et al. (2011) found that patients with HMs (N=180) reported a mean number of 8.8 symptoms (range 2.9-14.7). Similarly, Zimmermann et al. (2013) found that patients with newly diagnosed or recently relapsed acute leukemia who had been referred to palliative care (PC) reported a median of 9 physical and 2 psychological symptoms. Other symptoms that were prominent across many studies include: impaired well-being, pain, lack of appetite, drowsiness, tingling hands/feet, insomnia, breathlessness, anxiety, and delirium (Chan et al., 2022; Ebraheem et al., 2021; Ferraz et al., 2022; Goswami et al., 2020; Mian et al., 2022; Shaulov et al. 2022; Sommer et al., 2021). Irrespective of the focus of the study or type of HM, fatigue was reported by many authors as being the most prevalent symptom concern, with between 52%-87.5% of patients reporting fatigue in various studies (Boyes et al., 2015; Goswami et al., 2020; Manitta et al., 2011; Ramsenthaler et al., 2019; Tsatsou et al., 2020; Villalona et al., 2023). Fatigue has been reported to be a concern throughout the disease trajectory, including for newly diagnosed patients, those who have completed treatment, and those in the end-of-life (EOL) phase (Mayo et al., 2022; Villalona et al., 2023; Zimmermann et al., 2013).

Understanding the types and severity of symptoms experienced by patients with HMs is relevant as symptom burden has been found to adversely impact quality of life (Kamal et al., 2021; Moreno-Alonso et al., 2018), has been associated with increased healthcare utilization, such as emergency department (ED) visits and hospital admissions (HAs), and may even predict survival. For example, Mian et al. (2022) found that among patients with multiple myeloma

(N=2876), higher total Edmonton Symptom Assessment Scale scores were associated with greater odds of ED visits/hospitalizations. Regarding survival, Villalona et al. (2023) examined symptoms in patients with newly diagnosed acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL) and myelodysplastic syndrome (MDS) (N=56) and found that patients who reported fatigue scores ≥4 had an increased hazard of death compared to those who reported mild or no fatigue (Hazard Ratio (HR) 2.45, 95% CI: 1.07-5.61).

Symptom Clusters

The notion that symptoms occur concurrently or, in clusters, first appeared in the literature in 2001 (Dodd et al., 2001; Harris et al., 2022). Since then, the definition of symptom clusters has evolved with the current definition emphasizing that symptom clusters consist of at least two or more concurrent symptoms that may have a shared underlying etiology and may have shared outcomes (Harris et al., 2022; Lee et al., 2024; Miaskowski et al., 2017). Symptoms in a cluster may share a common underlying biological etiology or pathogenic mechanism, such as being driven by inflammatory cytokines, hormones, neurotransmitters, or other immunomodulators (Lynch Kelly et al., 2016; Simao et al, 2024). The co-occurrence of multiple symptoms has been associated with impairments in patients' functional status and quality of life (Dong et al., 2014; Miaskowski et al., 2017; Simao et al., 2024). In addition, some symptom clusters have been associated with reduced survival (Simao et al., 2024). A better understanding of symptom clusters might help direct interventions that could help relieve more than one symptom at a time (Miaskowski et al., 2017).

There are two main conceptual approaches to symptom cluster research that have been described in the literature. One such approach to symptom cluster research involves what is known as the variable-centered approach, where symptoms that cluster together are thought to do so based on a common underlying mechanism (Harris et al., 2022). In contrast, the patient-centered approach categorizes subgroups of patients with distinct symptom profiles which represent the types and severity of symptoms endorsed by patients (Harris et al., 2022; Miaskowsi et al., 2017). In this approach, latent variable modelling is undertaken to look for subgroups (classes) of patients within a sample who have similar symptom experiences. Harris and colleagues published an important paper on conceptual and methodological issues pertaining to symptom cluster research in 2022. The authors specified that if symptom clusters are being studied, a symptom cluster must be pre-specified. However, latent variable modelling can still be done to identify subgroups of patients who have distinct symptom profiles such as the patient's experience of symptom frequency and severity (Harris et al., 2022).

Most studies to date on symptom clusters and symptom profiles have included patients with solid tumors. Of the studies that have included patients with HMs, there have been a number of different symptom clusters described, including a cluster of anxiety, drowsiness, fatigue, and dyspnea (Lee et al., 2024). Other studies have focused on particular contexts, such as patients who had been receiving chemotherapy (Wu et al., 2023) and patients with post-chemotherapy febrile neutropenia (Chan et al., 2020). Chan et al. (2020) found three distinct symptom clusters: a sickness behavior cluster that included fatigue, disturbed sleep, feelings of being distressed, feeling drowsy, lack of appetite, dry mouth, pain, and feeling sad; a chemotherapy neurotoxicity cluster than included problems remembering things, shortness of breath, and numbness or tingling; and an emesis cluster that included nausea and vomiting. While the study did include patients with different types of HMs, the context of febrile neutropenia after chemotherapy is quite specific and may not be applicable to all patients with HMs.

Other studies have looked at symptom clusters in patients with one type of HM such as multiple myeloma (Brazauskas et al., 2024; Chen et al., 2022; Zeng et al., 2023) and lymphoma (Lee et al., 2024; Wu et al., 2023). These studies found a variety of different symptom clusters, including clusters with predominantly physical symptoms while other clusters included more emotional and psychological symptoms (Brazauskas et al., 2024; Chen et al., 2022; Wu et al., 2023). There is a lack of research on patients with different types of HMs and including a diverse population of patients with HMs could be helpful as there may be shared underlying mechanisms of both disease and treatment related symptoms in patients with HMs.

Sociodemographic Factors Associated with Symptoms and Healthcare Utilization

Previous research has explored the association between sociodemographic factors and symptoms in patients with cancer. Several authors have reported that demographic factors such as younger age, being female, not having a partner, not being employed, and lower income are associated with worse quality of life in patients with cancer (Andreu et al., 2022; Jordhoy et al., 2001; Thomas et al., 2014). Studies on patients with HMs have reported similar findings, with being female (Boyes et al., 2014; Oerlemans et al., 2011; Shreders et al., 2018), of younger age (Boyes et al., 2014), having a lower education level (Pulgar et al., 2015), not having a partner (Pulgar et al., 2015), and not being employed (Boyes et al., 2014) as being associated with worse symptoms and worse quality of life. Of note, other studies on patients with HMs have found that older age (Oerlemans et al., 2011; Pulgar et al., 2015) and being married (Shreders et al., 2018) were associated with worse quality of life. These differences in terms of age and marital/partner status may be due to a variety of factors, including different HMs and/or treatments, different contexts (such as chemotherapy/disease-directed treatment versus palliative-intent treatment settings), or other patient or clinical factors.

An additional demographic factor that has been associated with symptoms in patients with cancer is rurality. Tulk et al. (2024) found that young adults with cancer who resided rurally (n=99) reported more distress and worse physical health-related quality of life compared to survivors from urban areas (n=280). Healthcare utilization has also been found to be higher among patients who reside rurally, with more ED visits and hospital admissions compared to patients from urban regions (Cerni et al., 2020). Rurality has also been found to impact survival after a cancer diagnosis (Bhatia et al.,2022; Loughery & Woodgate, 2015). Better understanding the impact of rurality on symptoms in patients with HMs and healthcare utilization in patients with HMs could lead to the development of targeted interventions and supports for these patients.

Problem

Existing literature has revealed that patients with HMs experience an array of physical and psychosocial symptoms throughout the illness and treatment trajectories. While there have been several studies that have focused on specific types of HMs, few have examined HMs as a heterogeneous group of diseases. Previous research has found that patients with HMs experience multiple symptoms (Hochman et al., 2018; Manitta et al., 2011) and that symptoms might arise as clusters, with possible common underlying etiologic or pathogenic mechanisms **(**Harris et al., 2022; Lee et al., 2024; Miaskowski et al., 2017). Examining symptoms in a heterogeneous group of diseases, such as HMs, may allow for identification of symptom profiles, which could help identify potential opportunities for tailored treatments/interventions to help reduce symptoms and improve quality of life. As discussed in Chapter 2, research on early palliative care (PC) for patients with HMs has found that PC is associated with reduced symptom burden and improved quality of life (El-Jawahri et al., 2020). There is a need to better understand symptoms, including symptom profiles, in patients with HMs so that interventions can be tailored to help reduce symptoms and improve quality of life.

Research Questions

1. What is the prevalence and severity of symptoms in patients with HMs?
    a. What is the prevalence and severity of symptoms in patients with HMs during the last year of life?
2. Are there any symptom profiles that patients with HMs experience?
3. What are the relationships among symptoms/symptom profiles and demographic, clinical (disease-related), and treatment-related variables?
4. What are the relationships among symptoms, symptom profiles, and healthcare utilization, including ED visits and hospital admissions, for patients with HMs?

Methods

Study Design

In Cancer Care Alberta, patients' symptoms are measured using patient reported outcome measures (PROMs); such data are typically collected at routine clinic and treatment visits. For this study, a secondary analysis of data previously collected for an observational retrospective cohort study was undertaken. The larger cohort (N=38,442) included patients with cancer who were at least 18 years of age or older and who had filled out at least one PROM questionnaire between October 1, 2019, and April 1, 2020 (n=29,242) and those who did not complete any PROMs (n=9200) (Watson et al., 2023). Of the larger cohort, 7080 patients had a diagnosis of an HM with 6136 having completed at least one PROM during the study period (n=944 did not complete any PROMs during the study period).

Data on demographic characteristics, patient-reported outcomes, and acute care data were collected from the Alberta Cancer Registry, electronic medical records, the Discharge Abstract Database, and the National Ambulatory Care Reporting System. Data were analyzed and organized by cohort where Cohort A (n=944) consisted of patients who did not complete PROMs, Cohort B (n=6136) consisted of patients who completed PROMs, and Cohort C consisted of patients who died within a year of completing PROMs (n=432). Cohorts B and C were not mutually exclusive.

Data Sources

The Putting Patients First (PPF) questionnaire was launched in 2012 at all 17 cancer care facilities in Alberta and is the PROM that is used to assess patients' symptoms at clinic and treatment appointments. The PPF questionnaire includes the Edmonton Symptom Assessment System – revised (ESAS-r) and the Canadian Problem Checklist (CPC) (Ashbury et al., 1998; Bultz et al., 2011). ESAS-r scores were used to address questions pertaining to symptom prevalence and severity. For patients who had completed the PPF multiple times during the study period, the last ESAS-r scores collected during the study period were used.

To answer the research questions pertaining to mortality and treatment-related complications, chart audits were conducted for all patients who had died within one year of PROM completion. The dataset used was part of a larger study that received ethics approval from the Health Research Ethics Board of Alberta—Cancer Committee (certificate number HREBA.CC-20-0022). Data collection via chart audits was approved via an ethics medication request submitted for the above ethics certificate.

Instruments

Patient-reported outcomes have been incorporated into routine clinical cancer care in Alberta since 2012, with patients completing the PPF at clinic consults, treatment visits, and follow-up visits (Cuthbert et al., 2019).

Edmonton Symptom Assessment System – Revised (ESAS-r).

The ESAS is a PROM that was developed in 1991 to assess symptoms in patients with advanced cancer (Bruera et al., 1991). A revised version of the ESAS, the ESAS-r, was developed to address concerns with the original version that had been raised by patients (Hui & Bruera, 2017; Watanabe et al., 2012). For example, the time frame of 'now' was included to have patients report the severity of symptoms at the time of ESAS-r completion (Nekolaichuk et al., 2019). In addition, brief definitions were added for tiredness, drowsiness, depression, anxiety, and well-being and 'appetite' was changed to 'lack of appetite' (Nekolaichuk et al., 2019). Symptoms that were thought to be related were listed next to each other (tiredness and drowsiness, nausea and appetite, and depression and anxiety) and well-being was moved to the end of the questionnaire (Nekolaichuk et al., 2019).

The ESAS-r includes 9 symptoms (pain, tiredness, breathlessness, drowsiness, well-being, nausea, anxiety, appetite, and depression) with the option for patients to add an additional 10th symptom (Watanabe et al., 2012; Watson et al., 2023). Severity of symptoms is rated on a scale of 0 to 10, with 10 indicating the highest severity (Hui & Bruera, 2017; Watson et al., 2023). Importantly, the ESAS-r intends to capture the presence and severity of symptoms but does not assess associated distress, symptom frequency, or interference of symptoms with daily activities.

Psychometric properties of the ESAS have been reported in several studies as well as in review articles (Aktas et al., 2015; Diplock et al., 2019; Hui & Bruera, 2017; Nekolaichuk et al., 2008; Richardson & Jones, 2009). Review of the literature revealed no studies that had formally assessed reliability exclusively in patients with HMs although there have been studies that reported reliability in patients with different types of cancer, including HMs. Internal consistency has been reported for individual symptom scores as well as overall symptom scores with Cronbach's alpha being >0.70 (Noel et al., 2021). Noel et al. (2021) indicated that studies have found that test-retest reliability has been reported to be good, with moderate agreement of scores within 24 hours. As one example, Chang et al. (2000) reported good internal consistency (Cronbach alpha 0.79) and good test-retest reliability (Spearman r=0.86 on Day 2) in their study examining symptoms and quality of life in patients with cancer (N=240). Of note, Noel et al. (2021) cautioned that in settings where symptoms may fluctuate, test-retest reliability may not be appropriate. This may be relevant in settings such as end-of-life and post-hematopoietic stem cell transplant, where symptoms are dynamic and can change rapidly (Azhar & Hui, 2022; Kroemeke et al., 2018).

In terms of validity, content validity (the extent to which the instrument captures the issue that the tool is supposed to address) and construct validity (the degree to which evidence from other variables supports use of the measure) have previously been reported (Hui & Bruera, 2017; Stromgren et al., 2002; Watanabe et al., 2011). Evidence of content validity has been reported by several authors, including review articles that have examined multiple validation studies (Chang et al., 2000; Hannon et al., 2015; Nekolaichuk et al., 2008; Richardson & Jones, 2009; Watanabe et al., 2012). The ESAS-r has been evaluated in both inpatient and outpatient settings and with patients with different cancer diagnoses (Nekolaichuk et al., 2019; Richardson & Jones, 2009).

As one example, Hannon et al. (2015) undertook a study to validate the numerical rating scale, in outpatients with advanced cancer (N=202) at a Canadian cancer centre. Participants completed the ESAS, ESAS-r, the Memorial Symptom Assessment Scale (MSAS), and a patient-rated version of the Eastern Cooperative Oncology Group performance status measure. The authors found that both ESAS and ESAS-r scores were positively correlated with MSAS scores (Spearman's rho 0.62 and 0.64).

In summary, the ESAS-r has been widely used in both research and clinical contexts. While there have not been any validation studies that have included only patients with HMs, patients with HMs have been included in studies that have also included patients with solid tumours (Ripamonti et al., 2014). A potential limitation of using the ESAS-r in patients with HMs is that the ESAS-r may not capture symptoms that are most salient to patients with HMs, thereby impacting face validity (Aktas et al., 2015). For example, patients with HMs often report neuropathy, dry mouth, and sleep problems (El-Jawahri et al., 2024; Manitta et al., 2011) and these symptoms are not included on the ESAS-r. As with any PROM, it is important to consider context when using a PROM such as the ESAS-r. Richardson and Jones emphasize that to ascertain the meaning for any ESAS score requires dialogue with the patient and the "tool has to be embedded within a strong clinical context such that ESAS values can be dialogically validated and translated into actions" (Richardson & Jones, 2009, p. 59). While the ESAS-r has some limitations, it has been widely used in cancer care and has routinely been used in Cancer Care Alberta since 2012 (Watson et al., 2024).

Sociodemographic and Disease-Specific Variables

Sociodemographic data had previously been collected by Watson et al. (2023), including age, sex, diagnosis, Charlson comorbidity index (CCI), mean and median income, and rurality.

The CCI was developed to classify comorbidities with the intent of being able to estimate the risk of death due to comorbid disease(s) (Charlson et al., 1987). The original CCI included 19 conditions with weights assigned to each condition. The total CCI score is calculated by summing the weights, with high scores reflecting a greater risk of mortality as well as more severe comorbid conditions (Charlson et al., 2022). The CCI has been used to predict mortality in a variety of different medical conditions, including cancer and more specifically, HMs such as acute myeloid leukemia (Dhakal et al., 2020), multiple myeloma (Jung et al., 2016), lymphoma (Mihaljevic et al., 2016; Mozas et al., 2021), and HMs more broadly (Chou et al., 2015). For the current cohort study, CCI scores had been calculated according to diagnoses coded in the Discharge Abstract Database in the 12 months prior to patients' first PPF completion in the study period. Cancer Care Alberta uses a modified version of the CCI that excludes cancer given that all patients have a diagnosis of cancer (Quan et al., 2005).

Age was collapsed into ≤60 and >60, congruent with the World Health Organization who defines aging populations as those over 60 years (World Health Organization, 2022). Marital status had not previously been collected and was extracted during the chart audits of patients who died within one year of completing the PPF.

Acute Care Utilization Outcomes

Emergency department (ED) visits and hospital admissions (HAs) were extracted from the National Ambulatory Care Reporting System and the Discharge Abstract Database respectively; ED visits and HAs within 7 days of completed PROM were included. The 7-day interval for ED visits and HAs was used as Watson et al. (2023) had found literature that a similar study (Barbera et al., 2013) used the same interval. As per Barbera et al. (2013), the 7-day window could allow for the patient's provider to potentially respond to the symptom scores while still potentially contributing to the ED visit or hospital admission. For patients who had died within 1 year of completing PROMs, ED visits and HAs were also extracted during chart audits, described in more detail below.

Disease and Treatment-Related Variables

Disease and treatment related variables were extracted during the chart audits. Where available, data were collected on disease status, such as progressive or relapsed disease. Data were also collected data on treatment regimens, including medications used in the regimens, dates of treatment, and complications associated with HSCT or CAR T-cell therapy. Supportive care medication use was collected from patient charts during the chart audits.

Chart Audits

Chart audits were completed for patients who died during the study period and had completed at least one PPF with the year prior to death (n=432). Chart audits were undertaken to answer research questions pertaining to relationships among clinical and demographic data, symptom scores, healthcare utilization, and mortality. Variables abstracted from chart audits included demographic and clinical variables that had not been captured or available via Registry Data. Such variables included marital status, reasons for ED visits and hospital admissions, disease status (relapsed or progressive disease), cancer-directed treatments received, if the patient had undergone HSCT and if so, the type of HSCT (allogeneic or autologous), complications, medical comorbidities, and if supportive care medications were used and if so, the type(s) of supportive care medications used.

Chart Audit Procedures

At the time of ethics approval, Cancer Care Alberta had been utilizing an electronic health record system called ARIA (Varian Medical Services, 2024). ARIA is an EHR that captures data throughout a patient’s care trajectory, including information about the diagnosis, treatment, comorbidities, and medications used (Varian Medical Services, 2024).

Ensuring Rigour and Reliability of Data Abstraction

Chart audits were completed by Reanne Booker, the principal investigator of this study. Given that Ms Booker was not blinded to study objectives, there was potential for bias when data were collected (Kaji et al., 2014). However, the data collected via chart audits were considered objective with no interpretation required (Siems et al., 2020). Additional strategies to help mitigate bias included the use of an electronic standardized data abstraction instrument (Vassar & Holzmann, 2013). For many variables, the instrument allowed for only certain responses to be selected when entering data (Vassar & Holzmann, 2013). For these variables, a drop-down menu with pre-specified options was used. For other variables, such as comorbid conditions, supportive care medications, and treatment-related complications, free text was entered manually.

Consideration was given to where in the EHR data were housed (Siems et al., 2020). For example, the EHR has a section for demographic data. Information on diagnosis, stage, and treatment history is typically be found in consult notes. Reasons for ED visits and hospital admissions are usually included in admission notes and discharge summaries (Siems et al., 2020). Current and previous medication use is usually documented in the EHR. Alzu’bi et al. (2021) and Pan et al. (2005) recommend that data abstractors have experience with data collection from an EHR as well as clinical and research experience relevant to the study. Ms Booker has extensive clinical and research experience in hematology and HSCT and had previous experience with the EHR. Such experience allowed Ms Booker to readily identify treatment-related complications such as graft versus host disease, cytokine release syndrome, and immune effector cell associated neurotoxicity. Because Ms Booker conducted all chart audits and data abstraction, inter-rater reliability was not evaluated.

As has been recommended in the literature on chart audit methodology, a pilot chart audit was undertaken with 10 charts to test the data abstraction instrument, ensure that requisite data are consistently available, and to allow for refinement of the instrument, if required (Spratling & Powers, 2017). The data abstraction instrument was developed in Excel. As much as possible, drop-down options were created to minimize data entry errors and to reduce the need for any interpretation of variables (Vassar & Holzmann, 2013).

Ethical Considerations

Chart audits require attention to ethical considerations such as protection of privacy and safeguarding of health information (Sarkar & Seshadri, 2014). Chart audits were conducted using an Alberta Health Services computer with Alberta Health Services security and privacy features. Participants were assigned a study identification number, and no identifiable information was abstracted (Spratling & Powers, 2017). Ethical approval was obtained via the Health Research Ethics Board of Alberta – Cancer Committee to conduct chart audits and abstract the variables described above (approval number HREBA.CC-20-0022).

Data Analysis

Demographic, disease and clinical/treatment characteristics, and healthcare utilization data were summarized with frequencies, means, standard deviations, medians, and ranges for Cohorts A, B, and C. Chi-square analyses were undertaken to examine differences in categorical variables. A value of $p<0.05$ was used as a cutoff to indicate statistical significance. Statistical analyses were performed using SPSS statistical software (Version 25, IBM corp.) and MPlus (Version 8.10, Muthen & Muthen, 2023).

Symptom prevalence and severity

For symptom prevalence, the number and types of symptoms that each participant reported were assessed. For symptom severity, as has been described by other authors (Hui & Bruera, 2017; Oldenmenger et al., 2013; Sutradhar et al., 2019), ESAS-r scores were collapsed into the following categories: none (score of 0), mild (score of 1-3), moderate (score of 4-6), and severe (score of 7-10). Descriptive statistics for ESAS-r scores were calculated.

Symptom Profiles

Given our interest in examining the association(s) between clinical and sociodemographic variables and symptoms, we elected to use a patient-centred approach to look for symptom profiles by using latent class analysis (LCA) to look for subgroups (latent classes) of patients who had similar symptom profiles based on the prevalence and severity of each symptom. Each symptom was represented as an ordinal variable with values 0 (= none), 1 (=mild), 2 (=moderate), and 3 (= severe). To identify the latent classes, we started with a one-class model and then added additional classes, one at a time, until the best fitting model was identified. Model fit was assessed based on guidelines described in the literature and interpretability (Naldi & Cazzaniga, 2020; Weller et al., 2020). Bayesian information criterion (BIC) was used to compare the relative fit of models with k and k-1 classes where lower values for the BIC indicate better fit (Lee et al., 2024; Weller et al., 2020). We also used the bootstrapped likelihood ratio test and the Vuong-Lo-Mendell-Rubin adjusted likelihood ratio test (Lee et al., 2024) to determine the statistical significance of the difference between k and k-1 class models. Entropy, a diagnostic statistic that is used to examine how accurately the model defines the classes, was also examined (Lee et al., 2024; Weller et al., 2020). An entropy value of greater than 0.80 is typically recommended (Sinha et al., 2021).

To look for associations among categorical sociodemographic and clinical variables and latent class membership, bivariate regression analyses were undertaken using the ‘DCAT’ procedure (Asparouhov & Muthen, 2014; Nylund-Gibson et al., 2019). DCAT is a syntax statement that is used in MPlus to analyze distal categorical outcomes following the procedures described by Lanza et al. (2013). This approach factors in the possibility of participants’ partial membership or, imperfect entropy, in latent classes (Sinha et al., 2021; Weller et al., 2020). Latent class analysis provides probabilities of class membership but does not ascertain absolute membership in each class as it is possible for individuals to have partial membership in multiple classes (Sinha et al., 2021). Latent class proportions for each sociodemographic and clinical variable were estimated and the Wald Chi-square test was used to look for differences in proportions among the classes. MPlus version 8.10 (Muthen & Muthen, 2023) was used for latent class analysis. We did not perform multivariate analyses as we did not intend to make claims about predicting latent class membership.

Results

Demographics

Demographic information is shown in Table 1. The cohort (N=7080) was comprised of 6136 patients who completed PROMs and 944 patients who did not complete PROMs. There were more males (n=4055, 57.3%) compared to females (n=3025, 42.7%). Mean age was 64.12 years (range 18-100, standard deviation 15.16). Most patients were from urban settings (n=5533, 78.1%) with only 21.7% (n=1534) residing in rural regions. Most patients had CCI scores of 0 (n=5932, 83.8%); just over 7% of patients (n=525) had CCI scores of 2 or higher.

While we had not intended to compare those who completed PROMs and those who did not, there were notable differences observed during the data analysis that were relevant to the research questions and we report these findings here for generalizability purposes. Notably, age, CCI, and rurality were associated with PROM completion. In addition, healthcare utilization differed among patients who completed PROMs and those who did not. These differences are described below and displayed in Table 1.

Patients who did not complete PROMs were more likely to be >60 years old (66.0% of patients >60y completed PROMs compared to 34.0% of patients </=60y who completed PROMs, *p*=.045). Of those who did not complete PROMs, 21.5% had a CCI score of >/=2 while 12.3% had a CCI of 0; of those who did complete PROMs, 78.5% had a CCI score of >/=2 while 87.7% had a CCI score of 0 (*p*<.001). In terms of rurality, rural patients were less likely to have completed PROMs (21.2% had completed PROMs compared with 25.2% who did not complete PROMs) (*p*=.006). In contrast, patients residing in urban areas were more likely to have completed PROMs (78.8%) compared to not having completed PROMs (74.8%) (*p*=.006).

Regarding healthcare utilization, patients who did not complete PROMs were more likely to have had any ED visits (46.9%) compared to those who did complete PROMs (40.8%), *p*<.001. Similarly, patients who did not complete PROMs were more likely to have had any HAs (28.0%) compared to those who did complete PROMs (23.5%). Patients who did not complete PROMs were more likely to have died (12.2%) compared to those who did complete PROMs (7.3%), *p*<.001.

Table 1

Demographic Data, Cohorts A and B

Variable		Cohort A: No PROMS N=944 (%)	Cohort B: PROMs N=6136 (%)	X^2(df), *p*
Age	≤60	352 (37.3)	2084 (34)	4.007 (1), .045

	>60	592 (62.7)	4052 (66.0)	
Sex	Male	513 (54.3)	3542 (57.7)	3.823 (1),
	Female	431 (45.7)	2594 (42.3)	.051
Type of HM	Leukemia	261 (27.6)	1605 (26.2)	62.711 (5),
	HL	56 (5.9)	373 (6.1)	<.001
	NHL	357 (37.8)	2260 (36.8)	
	MM	84 (8.9)	1022 (16.7)	
	IP diseases	48 (5.1)	340 (5.5)	
	Other	138 (14.6)	535 (8.7)	
CCI[a]	0	732 (77.5)	5200 (84.7)	39.071 (2),
	1	99 (10.5)	524 (8.5)	<.001
	≥2	113 (12.0)	412 (6.7)	
Rurality	Rural	237 (25.2)	1297 (21.2)	7.624 (2),
	Urban	705 (74.8)	4828 (78.8)	.006
ED Visits	No	499 (52.9)	3632 (59.2)	12.609 (1),
	Yes	445 (47.1)	2504 (40.8)	<.001
Number of ED Visits[a]	None	499 (52.9)	3632 (59.2)	22.996 (3),
	1-3	342 (36.2)	2044 (33.3)	<.001
	4-6	59 (6.3)	302 (4.9)	
	7+	44 (4.7)	158 (2.6)	
Hospital Admissions	No	680 (72.0)	4691 (76.5)	8.715 (1),
	Yes	264 (28.0)	1445 (23.5)	.003
Number of HAs[a]	None	680 (72.0)	4691 (76.5)	16.375 (3),
	1-3	228 (24.2)	1283 (20.9)	<.001
	4-6	27 (2.9)	144 (2.3)	
	7+	9 (1.0)	18 (.3)	
Deceased	No	829 (87.8)	5691 (92.7)	27.298 (1),
	Yes	115 (12.2)	445 (7.3)	<.001

Note. Due to missing data, the frequencies do not add up to the total sample size for some of the variables. The percentages are out of the number of participants who did not have missing data for the corresponding variable. *p* = *p*-value based a chi-square test. HM = hematologic malignancy, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, MM = multiple myeloma, CCI =

Charlson Comorbidity Index, ED = emergency department, HA = hospital admission. [a] Count variables were discretized to facilitate interpretation.

Demographic data for Cohort C are shown in Table 2. Most patients in Cohort C were older than 60 years of age (86.8%) and most patients were male (63.2%).

Table 2

Demographic Data, Cohort C

Variable		N	%
Age	≤60	57	13.2
	>60	375	86.8
Sex	Male	273	63.2
	Female	159	36.8
Type of HM	Acute Leukemia	61	14.1
	Chronic Leukemia	39	9.0
	Lymphoma	177	41.0
	Multiple Myeloma	107	24.8
	Myelodysplastic Syndrome	34	7.9
	Other	14	3.2
CCI	0	269	62.3
	1	90	20.8
	≥2	73	16.9
Rurality	Urban	332	76.9
	Rural	100	23.1
Marital Status	Not Married	148	34.3
	Married	284	65.7
ED Visits	No	45	10.4
	Yes	387	89.6
Number of ED Visits[a]	None	45	10.4
	1-3	256	59.3
	4-6	87	20.1
	7+	44	10.2

Reasons for ED Visits	Symptom Management	207	47.9
	Disease/treatment	33	7.6
	Complications	111	25.7
	Other	35	8.1
	n/a	46	10.6
Hospital Admissions	No	43	10.0
	Yes	389	90.0
Number of HAs[a]	None	43	10.0
	1-3	326	75.5
	4-6	56	13.0
	7+	7	1.6
Reasons for HAs	Symptom Management	50	11.6
	Disease/treatment	9	2.1
	Complications	292	67.6
	Other	38	8.8
	n/a	43	10.0
Transplant	No	358	82.9
	Yes	74	17.1
Lines of Treatment[a]	None	54	12.5
	1-3	247	57.2
	4-6	95	22.0
	7+	36	8.3
Supportive Care Medications	No	171	39.6
	Yes	261	60.4
	Opioid pain medication[b]	187	43.3
	Non-opioid pain medication	97	22.5
	Anxiolytic	29	6.7
	Antidepressant	103	23.8
Progressive Disease[c]	No	253	58.6
	Yes	179	41.4
Place of Death	Hospital	278	64.4
	Home	82	19.0
	Hospice	51	11.8
	Other	12	2.8
	Unknown	9	2.1

Note. Due to missing data, the frequencies do not add up to the total sample size for some of the variables. The percentages are out of the number of participants who did not have missing data for the corresponding variable. HM = hematologic malignancy, CCI = Charlson Comorbidity Index, ED = emergency department, HA = hospital admission, n/a = not available. [a]Count variables were discretized to facilitate interpretation. [b]Some patients had multiple types of supportive care medications; [c]Documented progressive, relapsed, recurrent, or refractory.

Prevalence and Severity of Symptoms

Symptom prevalence and severity for Cohorts B and C are shown in Figure 1. The most frequently reported symptoms in Cohort B were tiredness, (impaired) well-being, and drowsiness; these were also the symptoms that were rated the most severe. Tiredness, (impaired) well-being, and drowsiness were also the most reported symptoms in Cohort C. As with Cohort B, tiredness was the symptom that was rated severe most often. Patients in Cohort C rated breathlessness, drowsiness, (impaired) well-being, lack of appetite, and pain as severe. In terms of numbers of symptoms, the mean number of symptoms for patients in Cohorts B and C was 4.3 and 5.8 respectively. Most patients in Cohort B reported having more than 3 symptoms (58.5%) and more than 20% of patients reported 3 or more moderate/severe symptoms (Figure 2). Most patients in Cohort C also reported having more than 3 symptom (81.3%), and nearly half of patients in Cohort C reported having 7+ symptoms (Table 4). More than half (57.7%) of patients in Cohort C reported having 3 or more moderate/severe symptoms; 12.9% reported having 7 or more moderate/severe symptoms (Figure 2).

Figure 1

Symptom Prevalence and Severity – Cohorts B and C

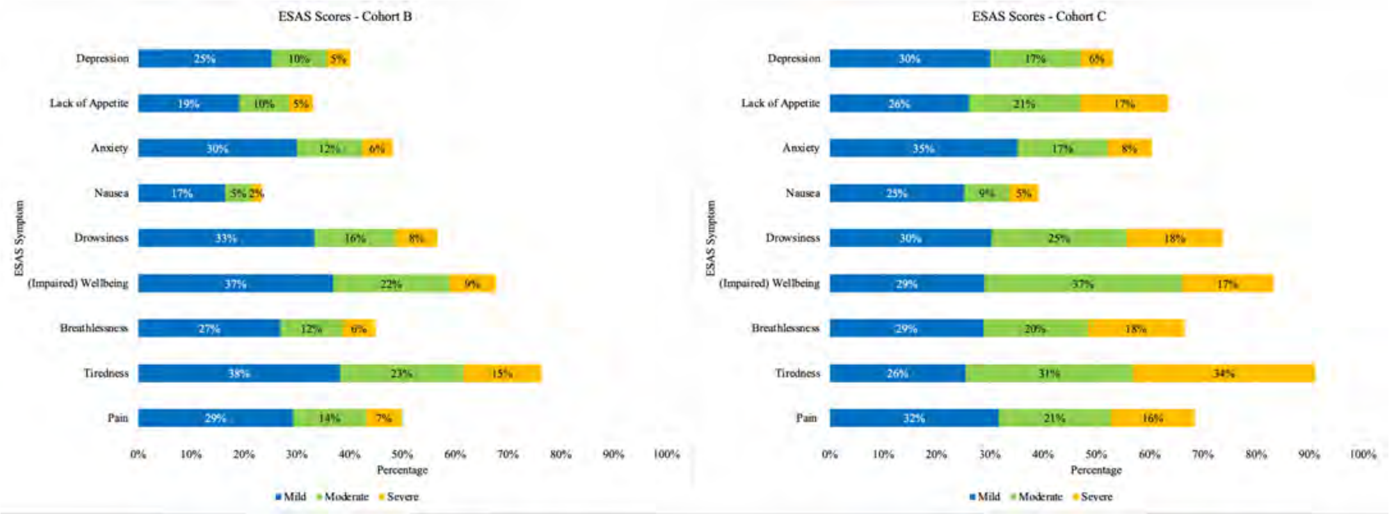
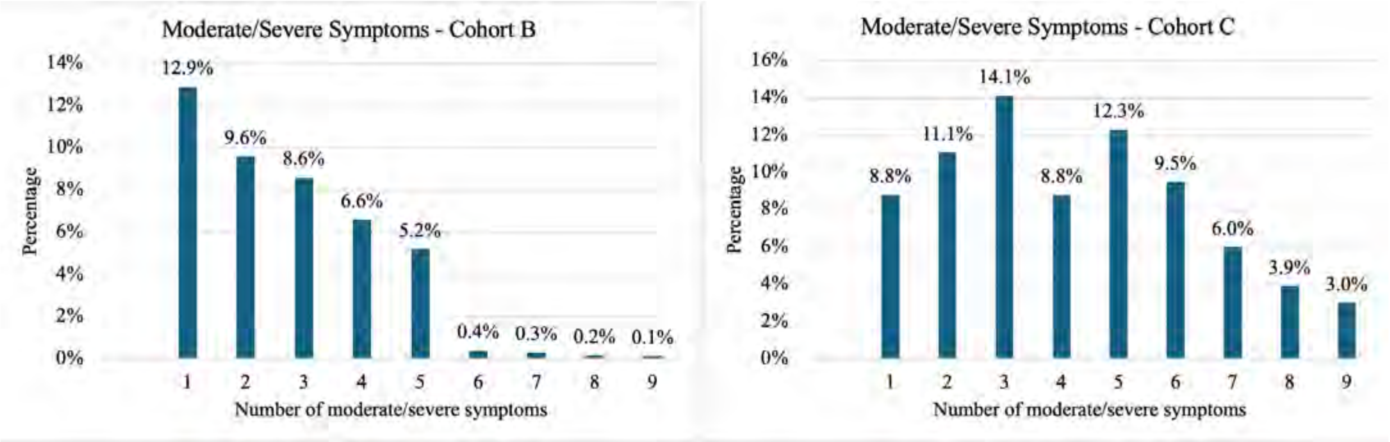


Figure 1. Symptom Prevalence and Severity – Cohorts B and C.

Note. For each bar, the stacks represent symptom severity as ‘mild’, ‘moderate’, and ‘high’, and the total length of each bar represents the overall prevalence (i.e., whether the symptom occurred or not). To improve visualization of symptom prevalence, the category ‘none’ is not shown.

Figure 2

Number of Moderate and Severe Symptoms – Cohorts B and C



Symptom Profiles

The latent class analysis identified 6 classes in Cohort B and 3 classes in Cohort C. Information about the fit of the latent class models is show in Tables 3 and 4. For Cohort B, even though the information criteria continued to decline when more classes were identified, the VLMR likelihood ratio test suggested a 6-class model as being more defensible. The symptom profiles for the 6 classes are shown in Figure 3. The probability of belonging to Class 6 was highest (28.0%) while the probability of being in Class 4 was lowest (6.5%).

Table 3

Latent Classes, Cohort B

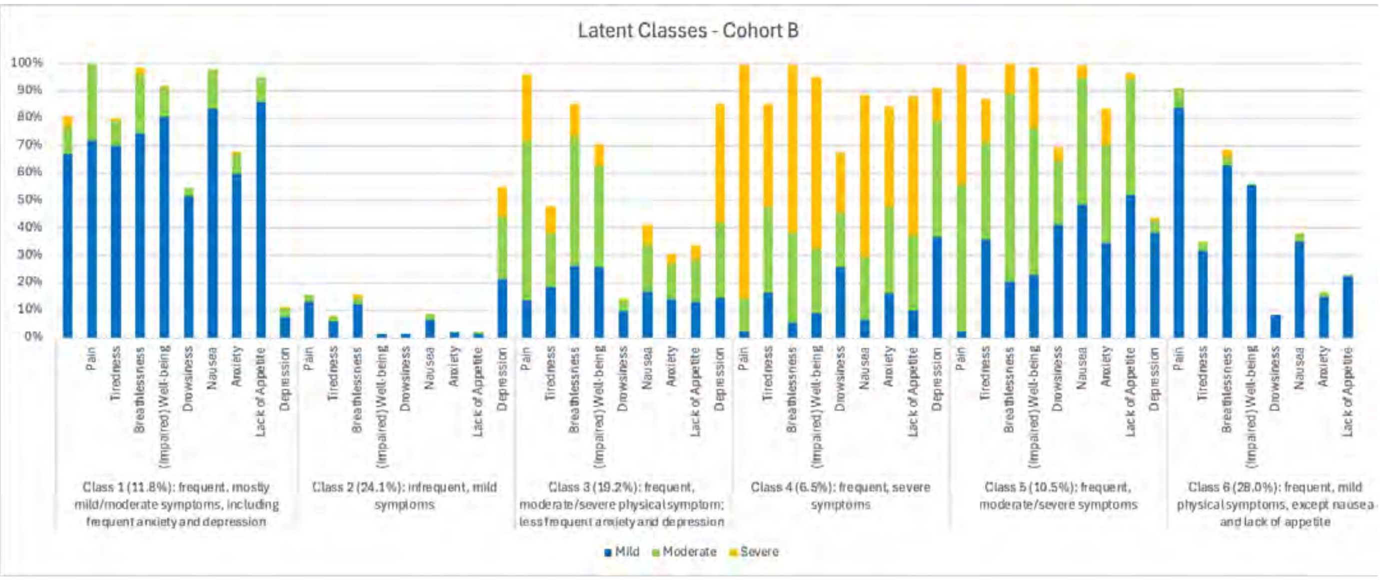
k	BIC	Entropy	VLMR	BLRT	P: class 1	P: class 2	P: class 3	P: class 4	P: class 5	P: class 6	P: class 7
1	118983.509	n/a	n/a	n/a	1						
2	104160.718	.857	*p*<.001	*p*<.001	.438	.562					
3	99493.395	.828	*p*<.001	*p*<.001	.257	.399	.344				
4	97730.511	.838	*p*<.001	*p*<.001	.136	.252	.383	.230			
5	96279.902	.830	*p*<.001	*p*<.001	.137	.247	.290	.127	.199		
6	95792.966	.826	*p*<.001	*p*<.001	.118	.241	.192	.065	.105	.280	
7	95402.231	.824	*p*=.703	*p*<.001	.079	.114	.247	.075	.122	.211	.153

Note. BIC: Bayesian Information Criterion; VLMR: Vuong-Lo-Mendell-Rubin Likelihood Ratio Test *p*-value comparing k and k-1 class models; BLRT: Bootstrapped likelihood ratio test *p*-value comparing k and k-1 class models; P: Probability of latent class membership predicted by the model (for some models, the probabilities do not add exactly to 1 due to rounding).

The symptom profile for Class 1 included frequently reported symptoms (all ESAS-r symptoms) that were predominantly mild. Tiredness, (impaired) well-being and anxiety were the most frequently reported symptoms while nausea was the least commonly reported symptom. The symptom profile for Class 2 included infrequently reported and mild symptoms. Class 3 included frequently reported and moderately severe physical symptoms, including pain, tiredness, (impaired) well-being, and drowsiness being frequently reported with less anxiety and depression compared to Class 1. Again, nausea was the least commonly reported symptom for Class 3. Class 4 represented patients who reported frequent and severe symptoms, including nausea. Tiredness and (impaired) well-being were the most reported; anxiety and depression were also commonly reported and were reported as being moderate/severe. Patients in Class 5 reported all symptoms frequently and were reported as moderate/severe. Pain, tiredness, (impaired) well-being, drowsiness, anxiety, and depression were the most commonly reported with prevalence rates greater than 90%. The symptom profile for Class 6 included frequent, mild physical symptoms with nausea and lack of appetite being less commonly reported. For all classes, tiredness was one of the most commonly reported symptoms and, often reported as moderate or severe. Nausea was the least reported symptom. Symptom profiles for each class are shown in Figure 3.

Figure 3

Latent Classes, Cohort B



For Cohort C, latent class analysis found that a 3-class model was the most defensible. When a 4-class model was tested, the *p* value for the VLMR was large, even though the BIC was a bit lower than the 3-class model. The probability of belonging to Class 3 was highest (38.3%), followed closely by Class 2 (37.4%) with the probability of belonging to Class 1 was the least (24.4%).

Table 4

Latent Classes, Cohort C

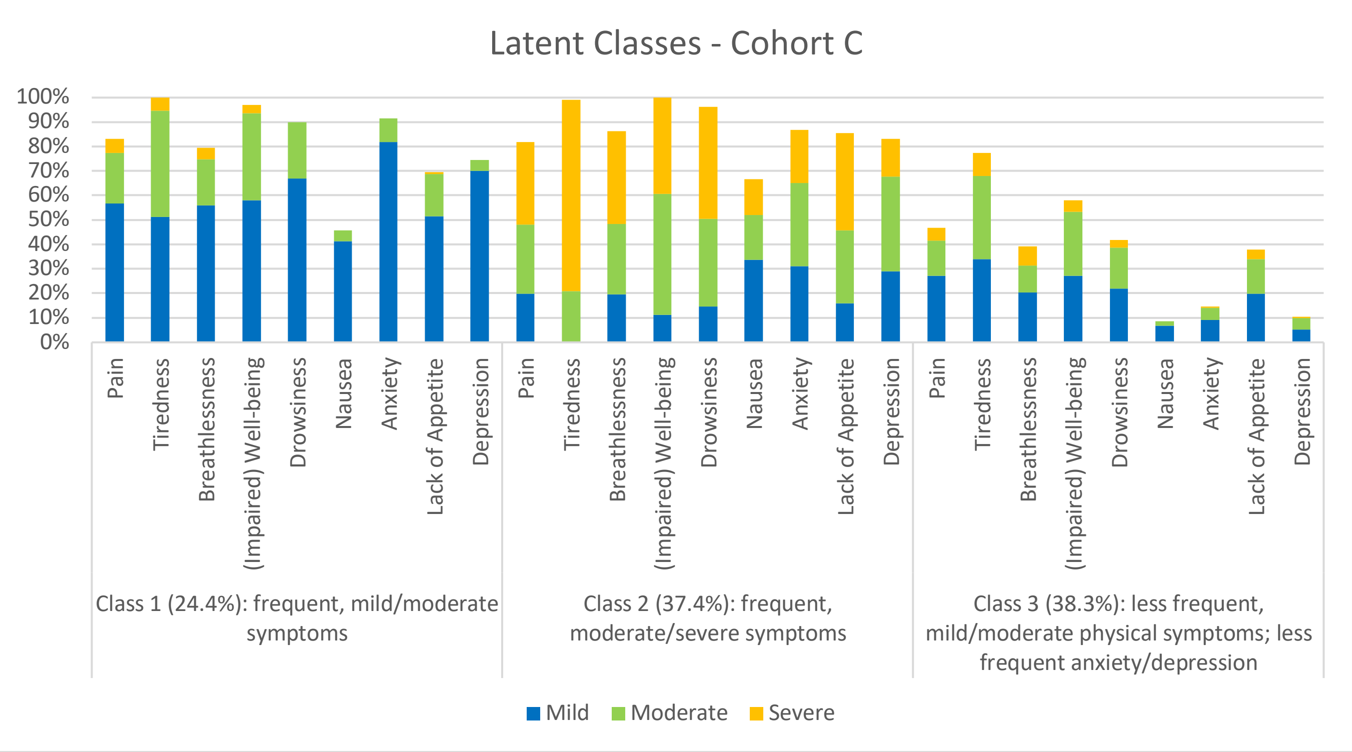
k	BIC	Entropy	VLMR	BLRT	P: class 1	P: class 2	P: class 3	P: class 4
1	9798.993	n/a	n/a	n/a	1			
2	9014.756	.870	*p*<.001	*p*<.001	.442	.558		
3	8842.289	.858	*p*=.0058	*p*<.001	.244	.374	.383	
4	8835.933	.864	*p*=0.7651	*p*<.001	.317	.242	.210	.230

Note. BIC: Bayesian Information Criterion; VLMR: Vuong-Lo-Mendell-Rubin Likelihood Ratio Test *p*-value comparing k and k-1 class models; BLRT *p*-value: Bootstrapped likelihood ratio test *p* value comparing k and k-1 class models; P: Probability of latent class membership predicted by the model (for some models, the probabilities do not add exactly to 1 due to rounding).

The symptom profile for Class 1 included frequent, mild/moderate symptoms, except for nausea, which was less frequent and less severe. Tiredness and (impaired) well-being were the most reported symptoms while anxiety and depression were also frequently reported. Nausea was the least commonly reported symptom. Class 2 represented patients who reported frequent and moderate to severe symptoms. The prevalence of all symptoms, except nausea, was greater than 80%. Patients in Class 3 reported predominantly mild to moderate physical symptoms with lack of appetite and nausea less commonly reported. Symptom profiles for each class are shown in Figure 4.

Figure 4

Latent Classes, Cohort C



Correlates of Class Membership

There were several demographic and clinical differences between the subgroups for Cohort B (Table 5). Sex distribution varied from 33.6% (Class 2) to 60.3% (Class 4). Patients in Class 2 were more likely to be younger (≤60 years). Charlson Comorbidity Index score was associated with class membership with patients in Class 4 (frequent, severe symptoms) being more likely to have higher CCI scores and patients in Class 2 (infrequent, mild symptoms) being more likely to have low CCI scores. Class membership was associated with type of HM, with Class 2 having the highest percentage of patients with HL (38.4%), while Class 4 had the highest percentage of patients with ‘other’ HMs.

In addition, healthcare utilization differed among classes with differences in any ED visits, number of ED visits, any HAs, and number of HAs. Classes 4 and 5 had the highest likelihood of having any ED visits (56.1% and 57.0% respectively) and highest percentage of 7+ ED visits (5.6%). Class 2 had the lowest percentage of any ED visits (28.3%) and lowest percentage of 7+ ED visits (1.9%). Similarly, Class 4 had the highest percentage of any HA (39.4%) and 7+ HAs (0.9%). Class 2 had the lowest percentage of any HA (12.5%) and 7+ HAs (0.2%).

Table 5

Correlates of Class Membership, Cohort B

Variable	Class 1 n=720 11.8% %	Class 2 n=1470 24.1% %	Class 3 n=1174 19.2% %	Class 4 n=397 6.5% %	Class 5 n=639 10.5% %	Class 6 n=1707 28.0% %	x^2 *p*
Sex							
Male	62.5	66.4	51.5	39.7	54.8	58.0	101.655
Female	37.5	33.6	48.5	60.3	45.2	42.0	*p*<.001
Age							
≤60	35.4	38.6	28.9	30.3	32.2	34.6	25.11
>60	64.6	61.4	71.1	69.7	67.8	65.4	*p*<.001
Type of HM							
Leukemia	4.1	8.7	5.2	4.4	3.9	6.4	90.322
HL	35.1	38.4	36.4	35.5	35.3	37.4	*p*<.001
NHL	22.9	27.9	27.6	24.6	24.4	26.0	
MM	24.0	11.6	14.8	16.5	19.9	18.0	
IP	5.6	5.5	6.4	6.8	6.6	4.4	
Other	8.3	7.8	9.6	12.2	10.0	7.7	
CCI							
0-1	94.0	95.9	92.2	86.4	87.2	95.5	64.718
2+	6.0	4.1	7.8	13.6	12.8	4.5	*p*<.001

Rurality							
Urban	81.4	78.5	78.0	78.3	80.0	78.2	3.557
Rural	18.6	21.5	22.0	21.7	20.0	21.8	*p*=.615
ED Visits							
No	55.8	71.7	51.5	43.9	43.0	65.3	235.283
Yes	44.2	28.3	48.5	56.1	57.0	34.7	*p*<.001
Number of ED Visits							
None	55.8	71.7	51.4	44.0	43.0	65.3	252.704
1-3	37.1	24.5	38.8	41.2	43.6	29.5	*p*<.001
4-6	5.2	2.4	6.4	9.2	8.4	3.6	
7+	1.9	1.4	3.3	5.6	5.0	1.6	
Hospital Admissions							
No	72.5	87.5	73.6	60.6	61.9	80.1	223.421
Yes	27.5	12.5	26.4	39.4	38.1	19.9	*p*<.001
Number of HAs							
None	72.5	87.5	73.7	60.5	62.0	80.0	230.429
1-3	25.1	11.5	23.1	31.9	33.1	18.3	*p*<.001
4-6	2.2	0.8	2.8	6.8	4.7	1.5	
7+	0.3	0.2	0.4	0.9	0.3	0.2	
Deceased							
No	93.2	93.7	91.6	94.1	91.6	92.6	5.006
Yes	6.8	6.3	8.4	5.9	8.4	7.4	*p*=.415

Notes. HM = hematologic malignancy, HL = Hodgkin lymphoma, NHL = non-Hodgkin lymphoma, MM = multiple myeloma, IP = immunoproliferative disorder, CCI = Charlson Comorbidity Index, ED = emergency department, HA = hospital admission

For Cohort C, there were no differences in demographic variables across the three latent classes (Table 5). There were differences among classes only for supportive care medication use. Class 2 (frequent, severe symptoms) had the highest probability of supportive care medication use (62.7%) while Class 3 (less frequent, less severe symptoms compared to Class 2) had the lowest probability of support care medication use (38.3%).

Table 6

Correlates of Class Membership, Cohort C

Variable	Class 1 n=105 24.4% %	Class 2 n=161 37.4% %	Class 3 N=165 38.3% %	x^2 *p*
Sex				
Male	69.0	58.3	63.7	2.102
Female	31.0	41.7	36.3	*p*=.350
Age				
≤60	8.8	15.9	13.5	1.347
>60	91.2	84.1	86.5	*p*=.510
Type of HM				
Acute Leukemia	16.1	10.9	16.4	11.946
Chronic Leukemia	6.8	11.6	7.8	*p*=.289
Lymphoma	36.5	37.5	47.2	
Multiple Myeloma	32.8	25.3	19.6	
Myelodysplastic Syndrome	7.0	11.0	4.7	
Other	.70	3.0	4.3	
Rurality				
Urban	76.1	75.6	78.2	.278
Rural	23.9	24.4	21.8	*p*=.870
Marital Status				
Not Married	26.1	36.6	36.8	2.025
Married	73.9	63.4	63.2	*p*=.363
ED Visits				
No	12.0	10.5	8.3	.780
Yes	88.0	89.5	91.7	*p*=.677

Number of ED Visits				
None	13.0	10.4	8.3	5.993
1-3	55.9	61.0	60.4	*p*=.424
4-6	19.4	16.0	24.3	
7+	11.7	12.6	7.0	
HAs				
No	7.8	10.6	10.8	.469
Yes	92.2	89.4	89.2	*p*=.791
Number of HAs				
None	7.8	10.6	10.8	1.324
1-3	80.4	72.8	74.6	*p*=.970
4-6	9.8	15.0	13.1	
7+	1.9	1.6	1.4	
Supportive Care Medications				
No	55.6	37.3	61.7	17.744
Yes	44.4	62.7	38.3	*p*<.001
Progressive Disease				
No	62.5	60.8	54.5	1.403
Yes	37.5	39.2	45.5	*p*=.496

Notes. HM = hematologic malignancy, ED = emergency department, HAs = hospital admissions

Discussion

This cohort study examined symptom prevalence, severity, and symptom profiles associated with sociodemographic and clinical variables in patients with HMs. Notable findings include that patients in this study reported multiple symptoms co-occurring at the time of PROM completion, with more than half of patients reporting 4 or more symptoms. In addition, patients frequently experienced moderate/severe symptoms. The most reported symptoms in Cohort B were tiredness, (impaired) well-being, and drowsiness while nausea was the least commonly reported. The most reported symptoms in Cohort C were the same and reported more frequently. Nausea was also the least reported symptom in Cohort C. These findings are similar to those reported by others. In their study on symptom burden in patients with HMs (N=180), Manitta et al. (2011) found that patients reported an overall mean of 8.8 (+/-5.9) symptoms. Fatigue was found to be most prevalent (69%) and vomiting least prevalent (9%). Zimmermann et al. (2013) also found that patients reported multiple symptoms in their study of with newly diagnosed or recently relapsed acute leukemia who had been referred to palliative care (PC). The authors found that patients reported a median of 9 physical and 2 psychological symptoms. As discussed in Chapter 2, previous research has found that patients with HMs experience an array of different physical and psychosocial symptoms such as impaired well-being, pain, lack of appetite, drowsiness, tingling hands/feet, insomnia, breathlessness, anxiety, and delirium (Chan et al., 2022; Ebraheem et al., 2021; Ferraz et al., 2022; Goswami et al., 2020; Mian et al., 2022; Shaulov et al. 2022; Sommer et al., 2021).

Across many studies, tiredness (also referred to as fatigue) is consistently the most frequently reported and often, most severe symptom experienced by patients with HMs, with prevalence rates between 60-90% (Bower et al., 2024; Goswami et al., 2020; Manitta et al., 2011; Ramsenthaler et al., 2019; Tsatsou et al., 2020; Villalona et al., 2023; Yennurajalingam et al., 2023). The etiology of cancer-related fatigue is complex and often multifactorial (Bower et al., 2024; Fabi et al., 2020). Both the underlying disease process as well as the treatment for HMs can contribute to fatigue (Alnaeem et al., 2022; El-Jawahri et al., 2020). In addition, physical and psychological comorbidities, other symptoms, physical inactivity, and medications can also influence cancer-related fatigue (Bower et al., 2024). Cancer-related fatigue has been reported by patients who are newly diagnosed, those undergoing disease-directed treatment, and those in the end of life phase (Mayo et al., 2022; Villalona et al., 2023; Zimmermann et al., 2013) and has been found to have a greater impact on function and quality of life than pain or depression (Thong et al., 2020).

Despite the prevalence of cancer-related fatigue and its propensity to cause distress and impair function and quality of life, management of cancer-related fatigue remains challenging (Stone et al., 2023; Thong et al., 2020). Bower et al. (2024) examined 113 randomized clinical trials on interventions for cancer-related fatigue, including studies on exercise, cognitive behaviour therapy, mindfulness-based therapy, Tai chi, qigong, yoga, acupressure, moxibustion, and various pharmacotherapeutics and dietary supplements. While the authors reported that the quality of evidence was low to moderate, they recommended education, exercise, and psychosocial interventions (such as cognitive behaviour therapy or mindfulness-based programs) to help reduce the severity of cancer-related fatigue (Bower et al., 2024). The European Society of Medical Oncology made similar recommendations in their clinical practice guidelines for the diagnosis and management of cancer-related fatigue. Unfortunately, evidence suggests that cancer-related fatigue guidelines are not routinely being implemented and patient-provider communication regarding cancer-related fatigue is poor (Berger & Mooney, 2016; Jones et al., 2021; Milzer et al., 2024; Pearson et al., 2017; Schmidt et al., 2021).

Unsurprisingly, patients who died within a year of completing PROMs (Cohort C) reported frequent and severe symptoms. This finding is consistent with others who have found high symptom burden during the end of life phase for patients with HMs. Leblanc et al. (2015) conducted a retrospective cohort study to examine symptom scores in patients with HMs (N=4638). The authors found that patients reported high scores for fatigue (mean 5.2, SD 2.7) and loss of appetite (mean score 2.3, SD 2.9) and that both symptoms worsened as death approached (Leblanc et al., 2015). Button et al. (2016) undertook a literature review to examine signs and symptoms associated with end of life in patients with HMs. The review included 12 studies, and the authors founds that the most frequently reported signs/symptoms associated with end of life included pain, hematopoietic dysfunction, dyspnea, and reduced oral intake (Button et al., 2016).

We did not find that any individual ESAS-r scores were associated with mortality, contrary to what Villalona et al., 2023 found in their study on patients with newly diagnosed patients with AML, ALL, and MDS (N=56). The authors found that fatigue severity was associated with a 41% increased hazard of death (HR 1.41, 95% CI: 1.03-1.93). Others have also reported prognostic significance of particular PRO scores in cancer care (Basch et al., 2018; Basch et al., 2017).

While we did not find individual PRO scores or latent classes to be associated with mortality, it is notable that patients who completed PROMs were less likely to have died compared to patients who did complete PROMs. This finding is aligned with previous research. For example, Barbera et al. (2020) conducted a retrospective matched cohort study of adults diagnosed with cancer (N=128,893 matched pairs). The authors found that the probability of survival was higher for patients exposed to ESAS questionnaires compared to those who were not (81.9% versus 76.4% survival at 1 year, 68.3% versus 66.1% at 3 years, and 61.9% versus 61.4% at 5 years, $p<.0001$). There are many potential reasons why PROM completion may be associated with improved survival. It is possible that patients who did not complete PROMs were too unwell to do so and as such, may have already been more likely to die due to advanced disease, relapse, and/or treatment-related complications (Barbera et al., 2020; Mierzynska et al., 2019). In addition, PROM completion may lead to improved symptom management which may result in patients staying on treatment as scheduled and/or longer than patients with no PROM completion (Basch et al., 2017; Caminiti et al., 2022; Lizan et al., 2021). In our study, we found that patients who resided rurally/remotely were less likely to complete PROMs. It is possible that patients who reside rurally/remotely may have disparate access to diagnosis, treatment, and/or supportive care (Bhatia et al., 2022; Chan et al., 2019).

In this study, latent class analysis identified distinct symptom profiles for both Cohorts B and C. Both Cohorts had classes with frequent and severe symptoms (Classes 4 and 5 for Cohort B and Class 2 for Cohort B) and both Cohorts had classes with less frequent and mild symptoms (Class 2 for Cohort B and Class 3 for Cohort C). For Cohort B, classes differed based on frequency and severity of symptoms. Patients in classes 1, 4, and 6 reported more anxiety and depression compared to Classes 2, 3, and 5. Physical symptoms, aside from nausea, were reported frequently for all Classes except for Class 2 for Cohort B. For Cohort C, anxiety and depression were more prevalent in Classes 1 and 2 and least commonly reported in Class 3. Physical symptoms were commonly reported among Class 1 and 2 (>70% prevalence) except for nausea.

There were statistically significant associations among demographic variables and probability of class membership for Cohort B. Healthcare utilization was associated with class membership for patients in Cohort B. We found that female patients in Cohort B were more likely to be in the class of prevalent and severe symptoms (Class 4). Previous research has found that females with HMs are more likely to report symptoms compared to males. In their integrative review of sex differences in quality of life and symptoms in patients with HMs that included 11 studies, Tinsley-Vance et al. (2023) found that female patients were more likely to report moderate to severe symptoms of nausea, anxiety, drowsiness, poor well-being, and tiredness compared to male patients. Ebraheem et al. (2021) also found that female sex was associated with higher odds of reporting many symptoms, including impaired well-being (OR 1.27, 95% CI 1.04-1.54), pain (OR 1.30, 95% CI 1.05-1.54), loss of appetite (OR 1.52, 95% CI

1.25-1.82), anxiety (OR 1.59, 95% CI 1.30-1.92), nausea (OR 1.56, 95% CI 1.27-1.92). There were no differences in class membership based on sex for patients in Cohort C. It is possible that factors other than sex, such as advanced/progressive disease, were more influential than sex for these patients.

Patients older than 60 were more likely to be in Class 3 (frequent, moderate/severe physical symptoms; less anxiety and depression) in Cohort B. Research has been conflicting in terms of age and symptoms, with some studies reporting increased symptoms in patients who are older, thought to possibly be due to the contribution of comorbidities on symptom burden (Flannery et al., 2021; Gaudernack et al., 2021; Morse et al., 2024). In contrast, other studies have reported that younger patients experience more symptoms, particularly more psychological symptoms such as anxiety and depression (Cataldo et al., 2013; Goerling et al., 2024; Wu & Harden, 2015). Such variability and discordance in findings could reflect the different populations being studied, including different types of cancer, different treatment contexts (cancer-directed treatment, observation/follow-up, survivorship, end-of-life care, age cutoffs used). Nevertheless, our finding that older adults were in a class with lower rates of anxiety and depression is consistent with previous work.

Type of HM was associated with class membership for Cohort B with patients diagnosed with ‘other’ HMs being more likely to be in Class 4 (frequent, severe symptoms). It is difficult to know why patients with ‘other’ HMs might have worse symptoms but review of demographic data revealed that patients with ‘other’ HMs were older and more likely to be female compared to the broader cohort.

Analysis of class membership probability also revealed that for patients in Cohort B, Class 4 (severe symptoms) was associated with higher percentages of both ED visits and HAs while Class 2 (infrequent and mild symptoms) was associated with lower probabilities of ED visits and HAs. These findings are congruent with what has been reported previously. For example, Nipp et al. (2017) examined the relationship between physical and psychological symptoms and healthcare utilization in patients with advanced cancer (N=1036). The authors found that high symptom burden was associated with prolonged hospital admissions and readmissions. Similarly, Mian et al. (2022) found that among patients with multiple myeloma (N=2876), higher total Edmonton Symptom Assessment System scores were associated with greater odds of ED visits/hospitalizations (Odds Ratio (OR): 1.34, 95% CI: 1.29-1.38).

The only statistically significant association among class membership and variables for patients in Cohort C was supportive care medication use. Class 2 (prevalent and moderate/severe symptoms) had the highest percentage of supportive care medication use while Class 3 (prevalent and mild/moderate symptoms) had the lowest percentage of supportive care medication use.

As with other studies on symptom burden in patients with HMs, we also found that patients with HMs experienced high symptom burden in the last year of life (Hui et al., 2014; Seow et al., 2011). Health care utilization also increased in the last year of life with 90% of patients having had both ED visits and HAs. This is consistent with previous research (Hui et al., 2014; Shaw et al., 2023). Unsurprisingly, Classes 4 and 5 (frequent severe and frequent moderate/severe symptoms) were associated with increased likelihood of HC utilization. The chart audits had also found that most ED visits had been for symptom management. These findings suggest that more supports for symptom management could possibly reduce ED visits. Our findings align with a study by Phung et al. (2024) who conducted a descriptive, retrospective study to review after-hours calls to the hematology/oncology clinic. Of 500 calls representing

398 unique patients, the authors found that most calls were to report symptoms (n=325, 65%); 120 (24%) of the calls had been from patients with HMs. Oncology nurses are ideally suited to help assess and manage cancer and treatment-related symptoms (Gobel et al., 2023; Young et al., 2020). In Ontario, an after-hours telephone triage support line was established to help address patient concerns and reduce ED utilization (Martelli et al., 2023). The program was started in 2018 and as of a report published in 2023, the service has resulted in more than 5000 ED visits being avoided (Martelli et al., 2023). Better outpatient symptom management and earlier integration of palliative care could potentially help avert ED visits and HAs in patients with HMs.

In summary, the findings of this cohort study show that patients with HMs experience high prevalence and severity of symptoms, particularly in the last year of life. Symptoms were also found to co-occur frequently, and classes of co-occurring symptoms were associated with demographic and clinical factors as well as with healthcare utilization.

Limitations

There are some important limitations in our study. Given that not all patients completed PROMs at more than one time point, we elected to use only one time point for PROM scores. Tracking patient symptom scores over time would have allowed for a more complete picture of the symptom experience. Patients with HMs may experience rapid deterioration and as such, we may have missed important symptom scores or, conversely, may have captured symptom scores at a time when patients were quite unwell. There were several potentially relevant variables that had not been available for our study, including educational level, employment status, preferred language, and stage of disease. While steps were taken to minimize the potential risk of bias, particularly during the data abstraction for chart audits, it is possible that researcher bias influenced data abstraction to some degree. An additional limitation is that the ESAS-r may not capture all the symptoms and concerns that are important for patients with HMs. As one example, many patients with HMs experience peripheral neuropathy but this concern is not included on the ESAS-r. Additional potential concerns that may be relevant for patients with HMs include night sweats, insomnia/sleep problems, and constipation. The ESAS-r does allow for patients to add one additional symptom/concern manually. However, additional symptom concerns had not been included in the data set used in this study. It is also important to note that the ESAS-r has not been validated in patients with HMs in the outpatient setting.

The large sample size and ability to examine symptom experience and healthcare utilization in a diverse population are strengths of the study. In addition, the data collection occurred throughout the province, across multiple sites. The limited time frame for data collection is a limitation. In addition, the heterogeneity of HMs and associated variable trajectories and diverse treatments are also limitations. For example, for Cohorts A and B, type of leukemia had not been differentiated. The anticipated symptom experience and treatment approaches are inherently different for patients with acute versus chronic leukemias. An additional potential issue that must be considered is that some of the data collection occurred during the COVID-19 pandemic. The first case of COVID-19 in Alberta was announced in early March 2020 with restrictions on gatherings and school closures coming into effect on March 12, 2020 (Karstens-Smith, 2020). Cancer Care Alberta implemented virtual care for many patients, including virtual clinic visits, as early as March 2020 (Watson et al., 2021). This shift to virtual care, in addition to the additional stressors of the pandemic, may have influenced patients' symptom experiences and PRO results.

Conclusion

This retrospective observational study contributes to the literature on symptom burden in patients with HMs and confirms that patients with HMs experience significant symptom burden, particularly in the last year of life. In addition, this study found that symptoms and symptom profiles are associated with demographic factors as well as with healthcare utilization, particularly ED visits. This study also yields important information regarding patient groups who may benefit from more targeted symptom management interventions, such as female patients and older adults. There is a growing body of evidence demonstrating that patients with HMs may benefit from integration of palliative care, particularly as related to reduced symptom burden and improved quality of life. Future research should continue to examine how best to integrate palliative care into the care of patients with HMs.

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Chapter 7 – Discussion and Conclusions

The overall intent of this research was to learn more about improving the quality of life of patients with hematologic malignancies (HMs) and to better understand patients’ palliative care (PC) needs. The findings from the studies described in Chapters 4 and 6 make evident the need for interventions aimed at improving the quality of life for patients with HMs and their family caregivers. The qualitative study (Chapter 4) explored patient, family caregiver, and clinician perspectives on the integration of PC into the trajectory of care for patients with HMs. Patients and family caregivers spoke of various challenges and unmet needs prior to, during, and following hematopoietic stem cell transplantation (HSCT). Participants also discussed the intense physical symptoms and psychosocial concerns that arose throughout the treatment trajectory, which persisted for years beyond the completion of treatment for some patients. The cohort study (Chapter 6) found that patients with HMs experienced frequent and often, severe symptoms and that symptoms were associated with healthcare utilization, such as emergency department (ED) visits.

In this Chapter, I will discuss the implications of the key findings from the qualitative and cohort studies for clinical practice, education, research, and policy.

Clinical Practice

The qualitative study and cohort study both found that patients with HMs experience high symptom burden, including physical and psychological symptoms, and that symptoms may persist well beyond completion of treatment. The qualitative study found that patients and family caregivers desired more informational and practical supports throughout the illness trajectory. Clinicians in the qualitative study shared that patients and family caregivers could benefit from better prognostic and illness understanding, clarification of treatment expectations, and more support for psychosocial concerns.

As described in Chapter 2, previous research has found that early PC for patients with solid tumors can help alleviate symptom burden, improve quality of life, and reduce healthcare utilization (Fulton et al., 2019; Gautama et al., 2023; Hoerger et al., 2019; Kassianos et al., 2018; Sanders et al., 2024). Yet despite the research on the positive outcomes of PC coupled with the known propensity for symptom burden for patients with HMs, PC referrals occur infrequently and late in the illness trajectory for patients with HMs (Seecof et al., 2024).

An important finding that came out of the qualitative study is that there are unique challenges and potential barriers to integrating PC for patients with HMs. The potential for rapidity of decline, the possibility for HMs to remain responsive to treatment even in the setting of advanced or relapsed disease, and prognostic uncertainty, have been cited as potential barriers to integrating PC (El-Jawahri et al., 2024; Elliott et al., 2021). In addition, the focus of treatment for patients with HMs is often on cure and treatments such as HSCT and chimeric antigen receptor (CAR) T-cell therapy are often associated with high risk of morbidity, late/long-term toxicities and complications, and even mortality (El-Jawahri et al., 2024).

These challenges, combined with the high likelihood of patients with HMs experiencing high symptom burden, are compelling reasons to integrate PC early and as part of routine care. The American Society of Clinical Oncology published updated guidelines on PC for patients with cancer that call for patients with advanced cancer and HMs to be referred to specialized interdisciplinary PC teams early in the disease trajectory, alongside cancer-directed treatment (Sanders et al., 2024). Specialty PC can help with comprehensive symptom management, assist with practical considerations, aid in medical decision making, and help clarify prognostic understanding and treatment expectations. Even in the absence of formal PC programs, hemato-oncology clinicians should possess basic PC competencies and skills to be able to provide primary PC and adopt a palliative approach to care. Nurses are ideally suited to promote and practice a palliative approach to care (Rosa et al., 2022).

As more and more treatment options become available for patients with HMs, there is an imperative for clinicians to ensure that patients understand the risks and benefits of such treatments. In the United States, the Alliance of Dedicated Cancer Centers published a call to action to "that all patients with cancer and their families should receive care that aligns with their values and unique priorities" (McNiff et al., 2021, p. 534). To ensure goal concordant care, the authors recommend skills training for hematologists/oncologists and advanced practice professionals, creating structured goals of care documentation in electronic health records, establishing expectations regarding goals of care communication, particularly for patients with advanced cancer as well as for patients with relapsed HMs and patients receiving HSCT or CAR T-cell therapy.

In Canada, global oncologists, academics, and patient advocates convened a meeting to develop the 'Common Sense Oncology (CSO)' approach which endeavors to ensure that oncology trials and treatments consider outcomes that matter to patients (Booth et a., 2023). The CSO approach has three core pillars: evidence generation, evidence interpretation, and evidence communication. One of the guiding principles of the CSO approach is that timely integration of PC is required for comprehensive, patient centered cancer care (Booth et al., 2023). As Booth et al. (2023) explain, when faced with an incurable illness, sometimes clinicians and patients may feel driven to do 'something' rather than 'nothing', even if that something might have nominal benefit and could cause side-effects. Clear communication around treatment expectations can help patients navigate treatment decision-making.

Participants in the qualitative study also acknowledged the need for more supports for patients and family caregivers in rural regions. A potential strategy to address challenges for patients who reside in rural and remote regions is virtual care/telehealth. Virtual cancer care allows for the remote delivery of health care, typically through telephone or video visits (Booker & Haase, 2022). During the COVID-19 pandemic, the use of virtual cancer care become more frequent (Watson et al., 2021) and many centres, including cancer centres in Alberta, continue to use virtual care. Virtual care may help to mitigate issues related to access, allowing patients in rural/remote regions to access care, including specialty PC (Booker & Haase, 2022; Sanders et al., 2024).

The cohort study (Chapter 6) revealed that symptom profiles were associated with sociodemographic factors, with female sex being associated with frequent and severe symptoms. Older age was associated with frequent and moderate/severe symptoms but less frequent anxiety/depression. Attention to symptom assessment and management in these patients could lead to improved quality of life. In addition, symptom prevalence and severity were associated with ED visits, highlighting a potential opportunity for more supports for symptom management, particularly in the outpatient setting. Chart audits in the cohort study also revealed that the primary reason that patients sought care in the ED was due to symptom concerns. This finding is congruent with what others have reported. For example, Grewal et al. (2020) conducted a retrospective study to examine ED visits (n=218,459 visits) among patients receiving chemotherapy (n=87,555) in Ontario between 2013 and 2017. The authors reported that the top three reasons for ED visits had been for fever/infection, gastrointestinal issues (nausea, vomiting, diarrhea), and pain (Grewal et al., 2020). Lash et al. (2022) estimate that approximately 4% of all ED visits in the US are cancer-related and that roughly two thirds of these patients go on to be admitted to hospital. In addition, they report that symptom management is a common reason that patients seek care in the ED throughout the cancer trajectory, from time of diagnosis through to survivorship and end-of-life care (Lash et al., 2022).

Palliative care has been associated with reduction in symptom burden for patients with cancer and has been found to be associated with reduced healthcare utilization. As one example, Robertson et al. (2023) conducted a retrospective review of patients with advanced cancer treated at a tertiary cancer centre in Canada between April 2013 and March 2014 to examine the impact of PC consultation on various end-of-life care outcomes. The authors found that compared to patients who had no PC consultation (n=303), patients who received PC consultation (n=1111) were less likely to have any ED visits (43.1% versus 59.1%, $p<.001$) and less likely to have ≥ 2 ED visits (12.0% versus 20.1%, $p<.001$).

In summary, the qualitative and cohort studies revealed that patients with HMs experience high symptom burden and have an array of unmet needs. Existing literature has found that PC can help reduce symptom burden, improve quality of life, address practical and informational needs, improve prognostic understanding and treatment expectations, and reduce healthcare utilization such as ED visits (Fulton et al., 2019; Hoerger et al., 2019; Hui & Bruera, 2020; Shih et al., 2022). Based upon the findings of our research and the growing body of evidence from clinical trials, PC should routinely be integrated into the care of patients with HMs (El-Jawahri et al., 2024; Sanders et al., 2024). Successful integration of PC for patients with HMs will require education and policy changes and further research. These topics will be discussed below.

Education

As above, the qualitative and cohort studies revealed that patients with HMs experience an array of physical and psychological symptoms. The cohort study found that of the 432 patients who died within a year of completing patient reported outcome measures, symptoms were both prevalent and severe. Interestingly, while pain, anxiety, and depression were reported by 66.5%, 58.5%, and 51.7% of patients respectively, only 43.3% of patients had documentation of opioid pain medication use, 6.7% had documentation of anxiolytic use, and 23.8% had documentation of antidepressant use. Other authors have reported that patients often underreport, and clinicians often underestimate symptoms (Arenare et al., 2024; Basch, 2014; Hannon et al., 2024; Martin et al., 2022; Pakhomov et al., 2008). As we found in the qualitative study, some patients and clinicians expect that some degree of suffering is unavoidable during treatment for HMs. This has been reported by others (Martin et al., 2022) along with other reasons such as patients not wanting their treatment to be interrupted or discontinued or feeling as if their symptoms were not severe enough to warrant mention to their healthcare providers (Di Maio et al., 2016). Patient education on cancer and treatment-related symptoms as well as systematic assessment of symptoms may help to improve symptom detection and management (Basch et al., 2022; Emery et al., 2022; Lewandowska et al., 2020). The routine use of patient reported outcome measures may also help clinicians recognize and better manage symptoms that are bothersome to patients (Hannon et al., 2024; Watson et al., 2024).

In addition to patient and clinician education on symptoms, education on the potential role of PC may also be helpful. As we found in our qualitative study, patients, family caregivers, and clinicians harboured misperceptions about PC. Such misperceptions, including that PC is the same as end-of-life or hospice care, have been reported by others and extend beyond the healthcare setting to the general public (Chosich et al., 2020; Hugar et al., 2023; Patel & Lyons, 2020; Zimmermann et al., 2024). Batzler et al. (2024) conducted a systematic review that included 60 articles published between 2008 and 2023 on the general public's and young adults' knowledge and perceptions of PC. The authors found that the general public continues to associate PC with death and dying (Batzler et al., 2024). Oncology clinicians have also been found to misunderstand PC and equate PC with end-of-life care (Alcalde & Zimmermann, 2022; El-Jawahri et al., 2024). Educating patients, family caregivers, and clinicians on what PC is and how it can help, is essential.

In our qualitative study, most clinicians indicated that they had not received any formal PC training. Gagnon et al. (2020) examined PC training provided in Canadian medical schools (N=17) and found that between 2008 and 2018, most PC rotations were optional (n=13) with only two schools requiring mandatory PC rotations and two schools not offering PC rotations at all. Wilson et al. (2011) surveyed 35 university nursing schools in 2010 and found that of the respondents (N=29), 28 schools provided education on death and dying, with 8 schools also offering additional electives on palliative or end-of-life care. In 2018, Health Canada published the Framework on Palliative Care in Canada that called for increased PC training and education for healthcare providers and other clinicians (Health Canada, 2018). Since then, several educational initiatives have been developed in Canada, including Project ECHO, a project that is led by Pallium Canada, to help build local capacity to provide PC (Canadian Institute for Health Information, 2023). Another initiative is the Canadian Interdisciplinary Palliative Care Competency Framework, developed by Health Canada and the Canadian Partnership Against

Cancer, and outlines specific PC competencies for various disciplines, including nursing (Canadian Partnership Against Cancer & Health Canada, 2021).

I have been involved in various PC educational initiatives throughout the past few years. I provided webinars for patients and family caregivers on PC for Myeloma Canada (www.youtube.com/watch?v=XSxDHMEksyE) and the Leukemia and Lymphoma Society of Canada (www.youtube.com/watch?v=_B0PvqoBcjU). I also helped Myeloma Canada develop a handout on PC (https://myeloma.ca/wp-content/uploads/2023/12/Palliative-Care-InfoSheet_8_5-x-11_EN-rev-1.pdf). I have been involved in educational initiatives for health care providers as well, including presenting on PC at Hematology Rounds at the Tom Baker Cancer Centre, to inpatient hematology/hematopoietic stem cell transplant nurses at the Foothills Medical Centre, and annually for the past 4 years to the new medical and radiation oncology residents coming to the Tom Baker Cancer Centre. I presented at the Canadian Association of Nurses in Oncology annual conference in 2023 on PC for patients with HMs. I have been involved with global oncology initiatives and presented (virtually) at the 6ª Reunión Virtual de Enfermería, Argentine Society of Hematology in 2020 on the topic of PC for patients with HMs. In February 2024, I presented an oral session and a half-day workshop on PC for patients with cancer at the Precision Oncology Saudi Summit in Madinah, Saudi Arabia.

In summary, there is a need for more education on PC and how it can fit into the care of patients with HMs. Franjul Sanchez et al. (2020) advocate for bidirectional training and collaboration among PC and hemato-oncology clinicians. Education on PC for patients and family caregivers, as well as for the general public, may help to erode some of the misperceptions and stigma associated with PC (Pal, 2015). Finally, integrating PC content into undergraduate and graduate healthcare provider curricula and training may help providers gain the necessary skills and competencies to provide at primary PC to patients with HMs (El-Jawahri et al., 2020; Webb et al., 2019).

Research

Approximately 9.5% of all cancer deaths are caused by HMs in the United States and yet only 0.4% of published studies on PC are in patients with HMs (Wedding, 2021). Our qualitative and cohort studies contribute to the literature on the symptoms and PC needs experienced by patients with HMs. However, more research is needed to both determine the unique needs of patients with HMs and to assess the effectiveness and role of PC for patients with HM (Shaulov et al., 2022). For example, while death in hospital has been reported as a poor quality end-of-life indicator, some authors have reported that patients with HMs might prefer to die in hospital due to risks such as catastrophic bleeding and infection that can occur for patients with HMs at end of life (Howell et al., 2017; Odejide et al., 2014). Further, as clinicians in our qualitative study discussed, other end-of-life quality indicators used for patients with solid tumours may not be appropriate for patients with HMs. As one clinician in our study reported, chemotherapy in the last 30 days of life is considered a poor quality end-of-life indicator but low-dose oral chemotherapy might be a better option than an opioid in controlling the pain from a lymphoma mass (Booker et al., 2023).

More research should examine how and when to integrate PC for patients with HMs. Given that HMs represent a heterogeneous group of diseases, with varying risks of morbidity and mortality and diverse PC needs, some PC experts advocate for timely PC, based on the patient's needs, rather than being tied to the particular disease or prognosis (El-Jawahri et al., 2020; Hui et al., 2018). Temel et al. (2024) conducted a randomized clinical trial to evaluate a stepped-care model to provide PC to patients with advanced lung cancer (N=507) at key points in the patients' illness trajectories. The authors found the stepped-care model, where PC visits happened only at key points (triggered by decreases in quality of life scores), was non-inferior to early PC, where visits occurred every 4 weeks from time of study enrolment. The stepped PC model resulted in fewer specialty PC visits and was felt to be a more scalable option to deliver PC and improve patients' quality of life (Temel et al., 2024). Increasing the provision of primary PC by oncology clinicians may be an additional strategy to help address the demand for PC amidst a lack of specialty PC providers. Sanders et al. (2024) recommend additional research be undertaken to examine the role of primary PC (compared to specialty PC) for patients with cancer. Further research on specific PC interventions and various outcomes, including survival, is needed as is research on the types of PC interventions that are most helpful for family caregivers (Sanders et al., 2024)

In addition to research on integrating PC for patients with HMs, better understanding of disease and treatment-related side effects and symptoms for patients with HMs is also needed. As we found in the cohort study, symptom profiles may occur in patients with HMs and further research on symptom profiles and symptom clusters may reveal shared pathologic processes that contribute to both the underlying disease as well as to the development of symptoms (Kwekkeboom et al., 2018; Nilsberth et al., 2023). Further research is also needed on pharmacologic and non-pharmacologic interventions for the most prevalent and severe symptoms experienced by patients with HMs. Better understanding of the pathophysiology of chemotherapy-induced nausea and vomiting (CINV) has led to the development of antiemetics such as 5-hydroxytryptamine 3 (5-HT3) receptor antagonists and neurokinin-1 receptor antagonists, which have reduced the incidence of CINV (Gupta et al., 2021; Navari, 2020). In our cohort study, nausea was one of the least reported and least severe symptoms reported.

Unfortunately, fewer options are available to help manage symptoms such as fatigue and drowsiness and more research is needed on interventions that might help alleviate these symptoms (Emery et al., 2022; Fabi et al., 2020).

Policy

Accessible and integrated PC is recognized globally as a human right and yet universal PC remains elusive, even within Canada (Brennan, 2007; Ezer et al., 2018). A Canadian Institutes of Health Information (CIHI) report on access to PC in Canada indicated that less than 15% of people who died in 2016-2017 had received publicly funded palliative home care (CIHI, 2018). An updated report was published in 2023 and found that more people in Canada had received some form of PC compared to the 2018 report (CIHI, 2023). However, the updated report indicated that some people do not receive PC until just before they die and that many people are still dying in hospital.

As we and others have found, there are barriers that may preclude integration of PC as well as hospice access for patients with HMs. For example, some patients with HMs may derive significant symptom relief from palliative transfusions (Shaulov et al., 2022; Wedding, 2021). However, in some jurisdictions, hospice agencies may not permit transfusion support, even if the intent is to relieve symptoms, due to logistics and costs (Knight et al., 2024; Odejide & Steensma, 2020). Further, there may be misperceptions that transfusions are intended to be a life-prolonging or life-sustaining measure rather than a symptom relief measure (Chin-Yee et al., 2018; Yasinski, 2022). Such restrictions have been reported to be a potential barrier to referring patients with HMs to PC (Booker et al., 2020; El-Jawahri et al., 2020). Similarly, the use of palliative-intent chemotherapy or anti-microbials may provide significant symptom relief for patients with advanced HMs but may not always be accepted or permitted if the patient is receiving PC or hospice care (Webb et al., 2019). Policy that permits patients to receive palliative-intent transfusions and palliative-intent chemotherapy may lead to more patients being referred earlier to PC. In addition, there is a need for policy that supports PC integration, even in the context of curative-intent treatment (Shaulov et al., 2022; Wedding, 2021). As an example of policy that could benefit from change, the Calgary Zone recently published guidelines for eligibility for palliative home care. For patients with cancer, the guidelines stipulate that patients must have "clinical findings of advanced progressive metastatic malignancy and/or inoperable malignant disease" as a baseline requirement (Palliative and End-of-Life Care Services – Calgary Zone, 2024). The terms "metastatic malignancy" and "inoperable malignant disease" are not always applicable to patients with HMs. For instance, even in the situation where leukemia cells are widely disseminated in the blood, bone marrow, or even if leukemia cells are found in the central nervous system, such disease is not typically referred to as "metastatic leukemia" (Whiteley et al., 2021). In addition, surgery is not a modality used in the treatment of acute leukemias and thus, the term "inoperable malignant disease" is not appropriate in this context. The use of such terminology in the eligibility criteria for referrals to palliative home care might deter hematology-oncology clinicians from referring their patients with advanced HMs as they might think that such patients are ineligible for palliative home care.

As discussed in the section above on research, an emerging concern is that of a lack of specialty PC providers, particularly in rural and remote regions (Bakitas et al., 2020; Conlon et al., 2019). There is growing recognition that specialty PC providers may not be able to keep up with the demand in oncology. A palliative approach to care incorporates principles of PC but allows for care to be tailored to the patient's and family's needs, is dynamic, can be provide early in the disease trajectory, involves open and sensitive communication, advance care planning, psychosocial and spiritual support, and symptom management (Canadian Nurses Association, 2015). Nearer the end-of-life phase, the focus may shift to goals of care, continued psychosocial support and symptom management, and engagement of specialist PC if required (Bacon, 2012). Like PC, a palliative approach to care values patient autonomy and honours the patient's right to be involved in care, both of which may help confer a sense of control to patients and families. New advances in the treatment of cancer and other chronic illnesses have meant that people are living longer, but not always better; a palliative approach recognizes the need to focus on quality of life and may provide benefit to all people with serious illness (Bacon, 2012). Importantly, as the number of people living with chronic illnesses continues to grow, a palliative approach to care can be adopted by all clinicians, not just specialty PC providers (Henderson et al., 2019; Sawatzky et al., 2017). Specialty PC providers could be called upon to assist in complex cases or when the patient requires more than primary PC. A palliative approach to care aligns with patient centered care and should be considered a core competency of nursing (Canadian Nurses Association, 2015). In the context of HMs, adopting a palliative approach to care would eliminate the need for hard signposts for when to transition from cancer-directed care to PC and care would be adjusted as needed, even in the case of rapid decline in the patient's condition, as can occur in patients with HMs.

Conclusion

Despite the evidence demonstrating that PC can help improve outcomes for patients with solid tumours, few studies have explored the integration of PC for patients with HMs. This is not because patients with HMs do not have needs that could be addressed by PC as we and others have demonstrated. Patients with HMs and their family caregivers have significant PC needs, including physical, psychological, existential, practical, informational, and relational needs and yet are infrequently referred to PC (Amonoo et al., 2021; El-Jawahri et al., 2020; Elliott et al., 2021; Gray et al., 2020). Previous research has found that there can be unique challenges associated with HMs and the associated treatments that may make it difficult to integrate PC into the care of patients with HMs (Elliott et al., 2021; Wedding, 2021). Nevertheless, these challenges need not preclude PC integration but rather, make a compelling case for why PC should be routinely integrated for patients with HMs. Specialty PC has been found to improve symptom management, improve quality of life, assist with illness and prognostic understanding, reduce healthcare utilization, and improve quality of end-of-life care (Gebel et al., 2024). Allowing for more flexible delivery of PC, titrated to patient need rather than being tied to diagnosis or prognosis, and ensuring policy aligns with the unique characteristics of HMs and their treatment, may help better address patient needs and help mitigate challenges such as prognostic uncertainty, rapidity of decline, and the heterogeneity of diseases and treatments in malignant hematology. Continued progress and advances in tumor biology, immuno-oncology, and cancer-directed treatments for patients with HMs will undoubtedly save lives; the integration of PC can help save quality of lives.

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Appendix A

Chapter 4: Integrating Palliative Care in Hematopoietic Stem Cell Transplantation: A Qualitative Study Exploring Patient, Caregiver, and Clinician Perspectives

Interview Questions

Interview Questions: Patients

Adapted, with permission, from Zimmermann et al. (2016) and PaCES Program (2019)

Introduction/preamble

The overall goal of our project is to learn about how we can optimize the quality of life of patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. Part of this research is to learn more about your experiences in being a patient before/during/after the blood stem cell transplantation process and the impact on your quality of life. We have invited you to (be interviewed/participate in this focus group) because of your experience as a patient. We remind you that your participation is free and voluntary. You are welcome to skip answering any of the questions that we ask. We also remind you that we will be recording the (interview/focus group) and that your name will be replaced with a code. Our final report will not include any identifying information, and although we might use quotes, any data we present will be anonymized. We have reviewed the consent forms; I have collected those. To protect confidentiality, please do not use any identifying names of other patients, family members, or staff members when discussing examples. In the event that you do use someone's name, we will remove the name from the transcripts. Before we begin, do you have any questions?

We are curious about the patient and caregiver experience of preparing for, undergoing, and living after blood stem cell/bone marrow transplant. We want to know about your experiences and needs, no matter where you are in the transplant journey (pre or post-transplant). I will begin by asking some questions about your experience.

Symptoms and functional status

I'd like to know more about how your diagnosis and the treatment have impacted you. Can you tell me about your symptoms (physical, emotional, psychological, spiritual)? What have been your most bothersome symptoms?

Illness comprehension, coping;

Can you tell me about your understanding of your cancer?

Do you feel that you (and your caregivers) have a good understanding of your cancer?

How are you coping with this? Have you found that there have been enough supports provided to you and your caregivers to help with coping?

Advance care planning and patient’s preferred method of decision making

Have you discussed ACP with anyone? If so, do you recall who you discussed ACP with?
Do you have a Goals of Care Designation?

Coordination of care

Who do you consider to be the main members of your care team?

Who do you think should be the main coordinator of your care (? Health care team, family/main caregiver, pt, etc.)

Are there aspects of your care that you feel are not being adequately covered/addressed?

Have you had any challenges with coordination of care (getting appointments, referrals, etc.)?

Do you know who to call with various questions/problems that come up?

Questions about palliative care

I’d now like to ask you some questions about what you think of palliative care. When you think of palliative care, what is it that first comes to mind for you?

Where did you first hear about palliative care? For example, reading about it in newspapers, talking to family or friends, etc.

Was palliative care ever discussed between you and the doctor/oncologist? When did this take place? What was your reaction? How did you feel?

Palliative care focuses on support of a patient and their families' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. Therefore, it’s now recommended that palliative care is provided alongside cancer treatments right from the beginning.

From your perspective, how would you feel if your oncologist (cancer doctor) was to bring up palliative care soon after your initial meeting with him/her?

Knowing that early palliative care leads to better quality of life and sometimes even longer life, how should this information be communicated to patients with cancer? And how should requesting a visit from the palliative care team be brought up with patients and their families?

From your perspective, ideally how should the palliative nurses and doctors work with your oncologist (cancer doctor)?

Is there anything else that you would like to add? Is there any important issue in your life that we haven't talked about that you would like to share with me?

How have you felt about taking part in this interview? Is there anything you would like to ask me about the interview?

Interview Questions: Family Caregivers

Adapted, with permission, from Zimmermann et al. (2016) and PaCES Program (2019)

Introduction/preamble

The overall goal of our project is to learn about how we can optimize the quality of life of patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. Part of this research is to learn more about your experiences in being a family caregiver before/during/after the blood stem cell transplantation process and the impact on your quality of life. We have invited you to (be interviewed/participate in this focus group) because of your experience as a family caregiver. We remind you that your participation is free and voluntary. You are welcome to skip answering any of the questions that we ask. We also remind you that we will be recording the (interview/focus group) and that your name will be replaced with a code. Our final report will not include any identifying information, and although we might use quotes, any data we present will be anonymized.

We have reviewed the consent forms; I have collected those. To protect confidentiality, please do not use any identifying names of patients, family members, or staff members when discussing examples. In the event that you do use someone's name, we will remove the name from the transcripts. Before we begin, do you have any questions?

We are curious about the patient and caregiver experience of preparing for, undergoing, and living after blood stem cell/bone marrow transplant. We want to know about your experiences and needs, no matter where you are in the transplant journey (pre or post-transplant). I will begin by asking some questions about your experience.

Symptoms and functional status

I'd like to know more about how your diagnosis and the treatment have impacted you. Can you tell me about your family member's symptoms (physical, emotional, psychological, spiritual)? What have been your family member's most bothersome symptoms?

Illness comprehension, coping;

Can you tell me about your understanding of your family member's cancer?

Do you feel that you (and your family member) have a good understanding of your family member's cancer?

How are you coping with this? Have you found that there have been enough supports provided to you and your family member to help with coping?

Advance care planning and patient's preferred method of decision making

Has your family member discussed ACP with anyone? If so, do you recall who your family member discussed ACP with?

Does your family member have a Goals of Care Designation?

Coordination of care

Who do you consider to be the main members of your care team?

Who do you think should be the main coordinator of your family member's care (? Health care team, family/main caregiver, pt, etc.)

Are there aspects of your family member's care that you feel are not being adequately covered/addressed?

Have you had any challenges with coordination of care (getting appointments, referrals, etc.)?

Do you know who to call with various questions/problems that come up?

Questions about palliative care

I'd now like to ask you some questions about what you think of palliative care. When you think of palliative care, what is it that first comes to mind for you?

Where did you first hear about palliative care? For example, reading about it in newspapers, talking to family or friends, etc.

Was palliative care ever discussed between your family member and the doctor/oncologist? When did this take place? What was your reaction? How did you feel?

Palliative care focuses on support of a patient and their families' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. Therefore, it's now recommended that palliative care is provided alongside cancer treatments right from the beginning.
From your perspective, how would you feel if your family member's oncologist (cancer doctor) was to bring up palliative care soon after the initial meeting with him/her?

Knowing that early palliative care leads to better quality of life and sometimes even longer life, how should this information be communicated to patients with cancer?

And how should requesting a visit from the palliative care team be brought up with patients and their families?

From your perspective, ideally how should the palliative nurses and doctors work with the oncologist (cancer doctor)?

Is there anything else that you would like to add? Is there any important issue in your life that we haven't talked about that you would like to share with me?

How have you felt about taking part in this interview? Is there anything you would like to ask me about the interview?

Interview Questions: Clinicians

Adapted, with permission, from Zimmermann et al. (2016) and PaCES Program (2019)

Introduction/preamble

The overall goal of our project is to learn about how we can provide the best support to patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. Part of this research is to learn more about your experiences in being a clinician for patients during/after the blood stem cell transplantation process. We have invited you to (be interviewed/participate in this focus group) because of your experience as a clinician. We remind you that your participation is free and voluntary. You are welcome to skip answering any of the questions that we ask. We also remind you that we will be recording the (interview/focus group) and that your name will be replaced with a code. Our final report will not include any identifying information, and although we might use quotes, any data we present will be anonymized. We have reviewed the consent forms; I have collected those. To protect confidentiality, please do not use any identifying names of patients, their family members, or colleagues when discussing examples. In the event that you do use someone's name, we will remove the name from the transcripts. Before we begin, do you have any questions?

To begin with, I'd like to ask you a few questions about patients' experiences before/during/after blood stem cell transplantation.

Symptoms and functional status

What do you think is the most challenging aspect of transplant for patients? For caregivers? What kinds of symptoms (physical, emotional, psychological, spiritual) do you see most often?

Illness comprehension, coping

Do you think that patients have a good understanding of their illness/prognosis?

Advance care planning and patient's preferred method of decision making

Are discussions on advance care planning happening with patients? If so, when do these conversations typically occur?

Coordination of Care

Who do you think should be the main coordinator of patients' care (? Health care team, family/main caregiver, pt, etc.)

Questions about palliative care

I'd now like to ask you to provide basic information about what you think of palliative care.

When you think of palliative care, what is it that first comes to mind for you?
Do you refer patients to palliative care? If so, when do you typically refer patients to palliative care?
What do you think patients and family caregivers think of palliative care?
What do you think patients' palliative care needs are during and after HSCT? ? Prompts here to elicit responses pertaining to: physical needs [symptoms etc.], psychosocial needs, spiritual needs)
Do you think the name "palliative care" should be changed? Why/why not?

The Palliative Care Early and Systematic Survey of oncology clinicians in Alberta asked about clinicians' thoughts on early integration of palliative care in oncology. Hematology-oncology clinicians reported that integrating early palliative care would require substantial changes to their practice. What do you think of this? Can you comment on what might be required of hematology-oncology clinicians in order to integrate early palliative care into their practice?

The survey also found that hematology-oncology clinicians felt that the referral criteria for palliative care were too restrictive. What do you think? (If prompts needed, ask re: concerns with transfusions, palliative chemo)
What is your understanding of the criteria for palliative care referral? What do you think could be done to modify the criteria to improve the referral process for clinicians (and/or improve access for patients)?

Palliative care focuses on support of a patient and their families' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. Therefore, it's now recommended that palliative care is provided alongside cancer treatments right from the beginning.

After having heard this description, is your impression/perception of palliative care different at all (from earlier response)?

With this description in mind, what do you think of palliative care being integrated alongside treatment for patients undergoing HSCT?

When should palliative care be introduced to patients? How should palliative care be introduced to patients?

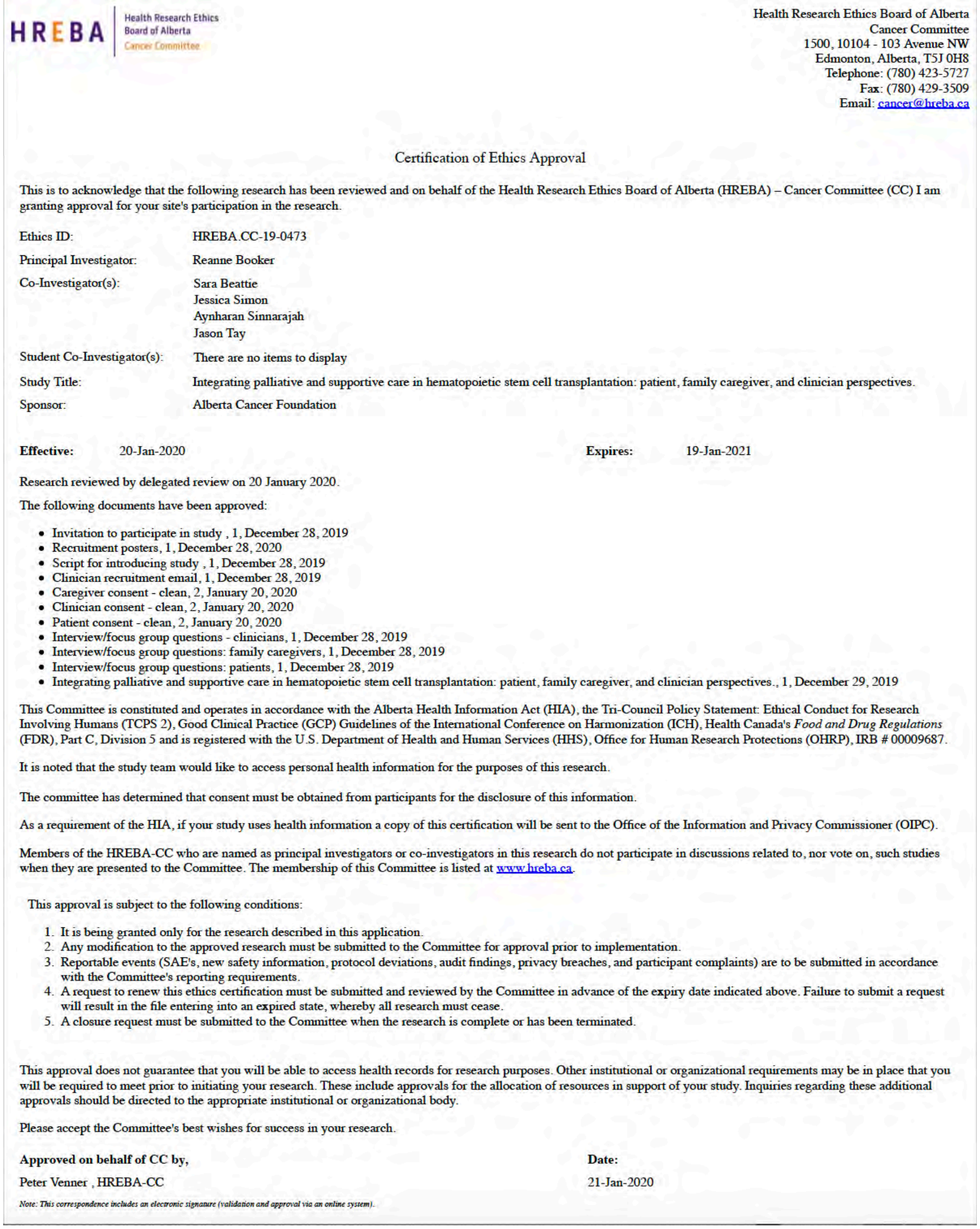
Is there anything else that you would like to add?

How have you felt about taking part in this interview? Is there anything you would like to ask me about the interview?

Appendix B

Chapter 4: Integrating Palliative Care in Hematopoietic Stem Cell Transplantation: A Qualitative Study Exploring Patient, Caregiver, and Clinician Perspectives

Ethics Certificates



HREBA | Health Research Ethics Board of Alberta Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Certification of Ethics Approval

This is to acknowledge that the following research has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC) I am granting approval for your site's participation in the research.

Ethics ID:	HREBA.CC-19-0473
Principal Investigator:	Reanne Booker
Co-Investigator(s):	Sara Beattie Jessica Simon Aynharan Sinnarajah Jason Tay
Student Co-Investigator(s):	There are no items to display
Study Title:	Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.
Sponsor:	Alberta Cancer Foundation

Effective: 20-Jan-2020 **Expires:** 19-Jan-2021

Research reviewed by delegated review on 20 January 2020.

The following documents have been approved:

- Invitation to participate in study , 1, December 28, 2019
- Recruitment posters, 1, December 28, 2020
- Script for introducing study , 1, December 28, 2019
- Clinician recruitment email, 1, December 28, 2019
- Caregiver consent - clean, 2, January 20, 2020
- Clinician consent - clean, 2, January 20, 2020
- Patient consent - clean, 2, January 20, 2020
- Interview/focus group questions - clinicians, 1, December 28, 2019
- Interview/focus group questions: family caregivers, 1, December 28, 2019
- Interview/focus group questions: patients, 1, December 28, 2019
- Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives., 1, December 29, 2019

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 00009687.

It is noted that the study team would like to access personal health information for the purposes of this research.

The committee has determined that consent must be obtained from participants for the disclosure of this information.

As a requirement of the HIA, if your study uses health information a copy of this certification will be sent to the Office of the Information and Privacy Commissioner (OIPC).

Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

This approval is subject to the following conditions:

1. It is being granted only for the research described in this application.
2. Any modification to the approved research must be submitted to the Committee for approval prior to implementation.
3. Reportable events (SAE's, new safety information, protocol deviations, audit findings, privacy breaches, and participant complaints) are to be submitted in accordance with the Committee's reporting requirements.
4. A request to renew this ethics certification must be submitted and reviewed by the Committee in advance of the expiry date indicated above. Failure to submit a request will result in the file entering into an expired state, whereby all research must cease.
5. A closure request must be submitted to the Committee when the research is complete or has been terminated.

This approval does not guarantee that you will be able to access health records for research purposes. Other institutional or organizational requirements may be in place that you will be required to meet prior to initiating your research. These include approvals for the allocation of resources in support of your study. Inquiries regarding these additional approvals should be directed to the appropriate institutional or organizational body.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by, **Date:**

Peter Venner , HREBA-CC 21-Jan-2020

Note: This correspondence includes an electronic signature (validation and approval via an online system).

HREBA | Health Research Ethics Board of Alberta
Cancer Committee

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Email: cancer@hreba.ca

Modification of Ethics Approval

This is to acknowledge that the modification to the research indicated below has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC), I am pleased to advise that approval has been granted.

Ethics ID:	HREBA.CC-19-0473_MOD1
Principal Investigator:	Reanne Booker
Co-Investigator(s):	Jessica Simon Sara Beattie Jason Tay Aynharan Sinnarajah
Student Co-Investigator(s):	Andrew McLennan
Study Title:	Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.
Sponsor:	Alberta Cancer Foundation

Effective: 20-Jan-2020 **Expires:** 19-Jan-2021

Modification reviewed by delegated review on 14 April 2020.

The following documents have been approved:

- Updated Recruitment Posters , 3, March 30, 2020
- Revised clinician consent form , 3, April 9, 2020
- Revised caregiver consent form , 3, April 9, 2020
- Revised patient consent form , 3, April 9, 2020

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 00009687.

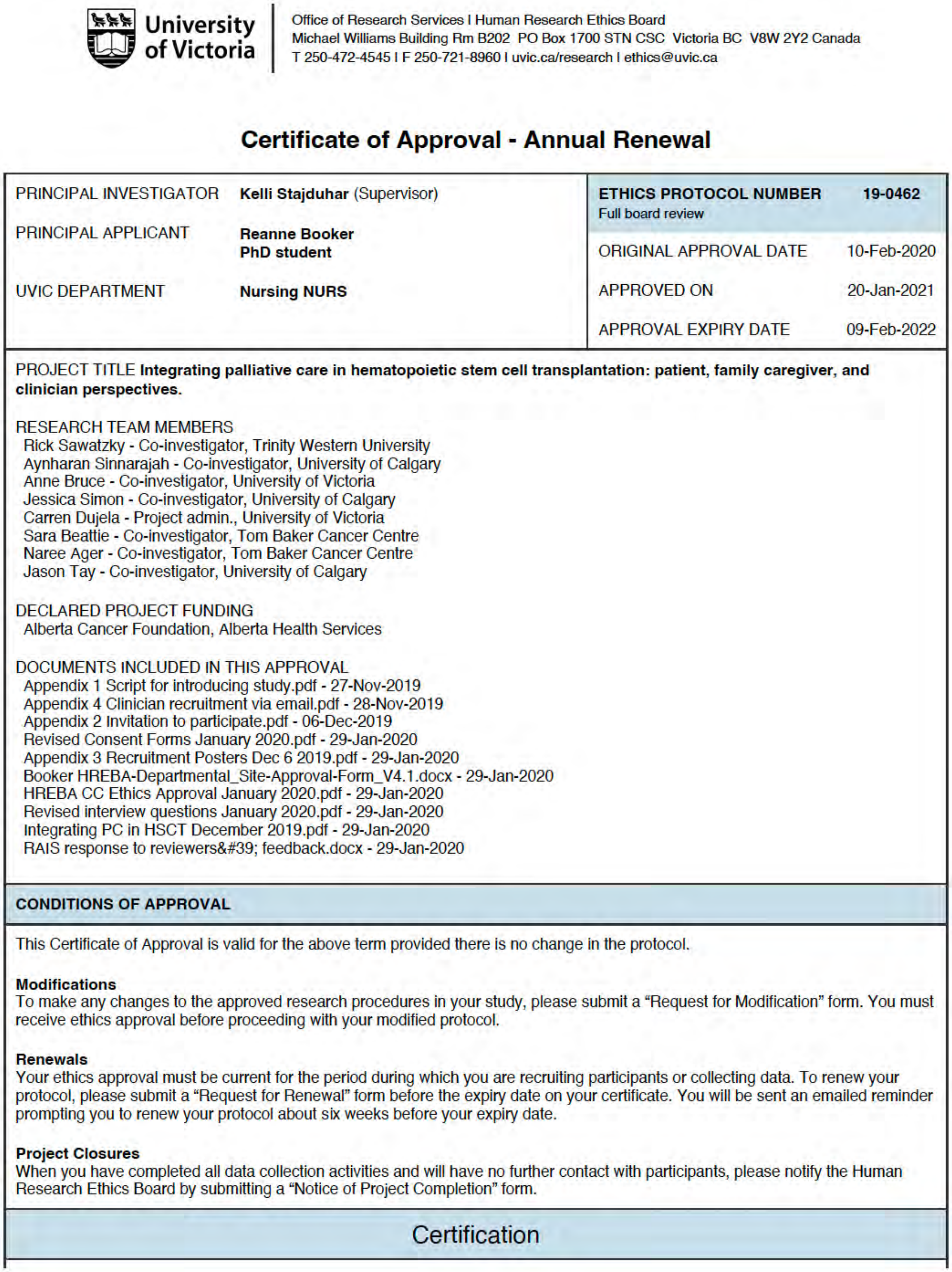
Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

Please note that the approval of this modification does not change the effective or expiry dates of this study as indicated above.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by,	**Date:**
Dale Dewhurst, Chair , HREBA-CC	15-Apr-2020

Note: This correspondence includes an electronic signature (validation and approval via an online system).



University of Victoria
Office of Research Services I Human Research Ethics Board
Michael Williams Building Rm B202 PO Box 1700 STN CSC Victoria BC V8W 2Y2 Canada
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Certificate of Approval - Annual Renewal

PRINCIPAL INVESTIGATOR	**Kelli Stajduhar** (Supervisor)	**ETHICS PROTOCOL NUMBER** Full board review	**19-0462**
PRINCIPAL APPLICANT	**Reanne Booker** **PhD student**	ORIGINAL APPROVAL DATE	10-Feb-2020
UVIC DEPARTMENT	**Nursing NURS**	APPROVED ON	20-Jan-2021
		APPROVAL EXPIRY DATE	09-Feb-2022

PROJECT TITLE **Integrating palliative care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.**

RESEARCH TEAM MEMBERS
Rick Sawatzky - Co-investigator, Trinity Western University
Aynharan Sinnarajah - Co-investigator, University of Calgary
Anne Bruce - Co-investigator, University of Victoria
Jessica Simon - Co-investigator, University of Calgary
Carren Dujela - Project admin., University of Victoria
Sara Beattie - Co-investigator, Tom Baker Cancer Centre
Naree Ager - Co-investigator, Tom Baker Cancer Centre
Jason Tay - Co-investigator, University of Calgary

DECLARED PROJECT FUNDING
Alberta Cancer Foundation, Alberta Health Services

DOCUMENTS INCLUDED IN THIS APPROVAL
Appendix 1 Script for introducing study.pdf - 27-Nov-2019
Appendix 4 Clinician recruitment via email.pdf - 28-Nov-2019
Appendix 2 Invitation to participate.pdf - 06-Dec-2019
Revised Consent Forms January 2020.pdf - 29-Jan-2020
Appendix 3 Recruitment Posters Dec 6 2019.pdf - 29-Jan-2020
Booker HREBA-Departmental_Site-Approval-Form_V4.1.docx - 29-Jan-2020
HREBA CC Ethics Approval January 2020.pdf - 29-Jan-2020
Revised interview questions January 2020.pdf - 29-Jan-2020
Integrating PC in HSCT December 2019.pdf - 29-Jan-2020
RAIS response to reviewers' feedback.docx - 29-Jan-2020

CONDITIONS OF APPROVAL

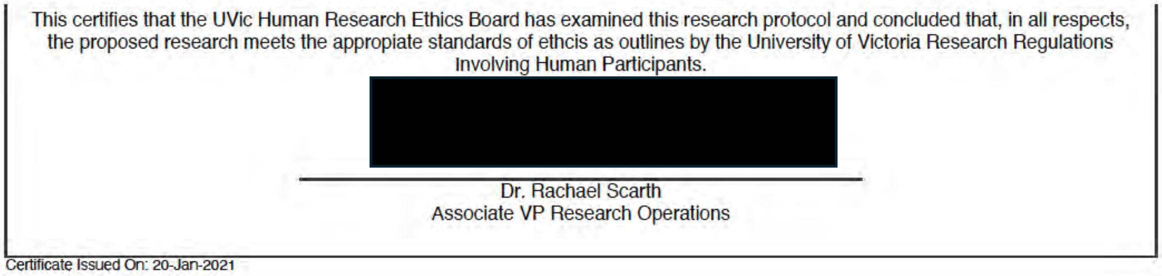
This Certificate of Approval is valid for the above term provided there is no change in the protocol.

Modifications
To make any changes to the approved research procedures in your study, please submit a “Request for Modification” form. You must receive ethics approval before proceeding with your modified protocol.

Renewals
Your ethics approval must be current for the period during which you are recruiting participants or collecting data. To renew your protocol, please submit a “Request for Renewal” form before the expiry date on your certificate. You will be sent an emailed reminder prompting you to renew your protocol about six weeks before your expiry date.

Project Closures
When you have completed all data collection activities and will have no further contact with participants, please notify the Human Research Ethics Board by submitting a “Notice of Project Completion” form.

Certification



This certifies that the UVic Human Research Ethics Board has examined this research protocol and concluded that, in all respects, the proposed research meets the appropiate standards of ethcis as outlines by the University of Victoria Research Regulations Involving Human Participants.

[redacted]

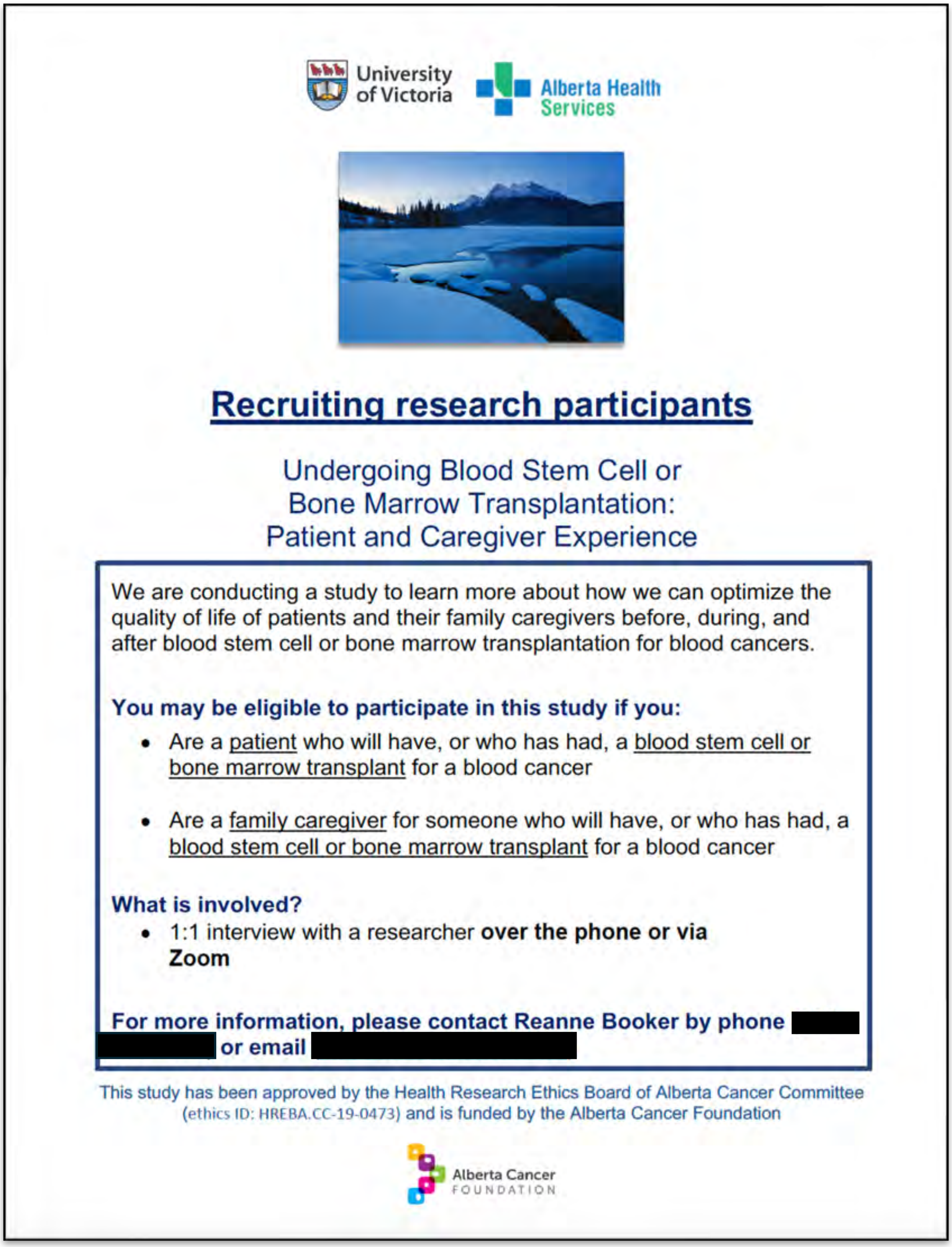
Dr. Rachael Scarth
Associate VP Research Operations

Certificate Issued On: 20-Jan-2021

Appendix C

Chapter 4: Integrating Palliative Care in Hematopoietic Stem Cell Transplantation: A Qualitative Study Exploring Patient, Caregiver, and Clinician Perspectives

Recruitment Posters



University of Victoria

Alberta Health Services

Recruiting research participants

Undergoing Blood Stem Cell or Bone Marrow Transplantation: Patient and Caregiver Experience

We are conducting a study to learn more about how we can optimize the quality of life of patients and their family caregivers before, during, and after blood stem cell or bone marrow transplantation for blood cancers.

You may be eligible to participate in this study if you:

- Are a patient who will have, or who has had, a blood stem cell or bone marrow transplant for a blood cancer
- Are a family caregiver for someone who will have, or who has had, a blood stem cell or bone marrow transplant for a blood cancer

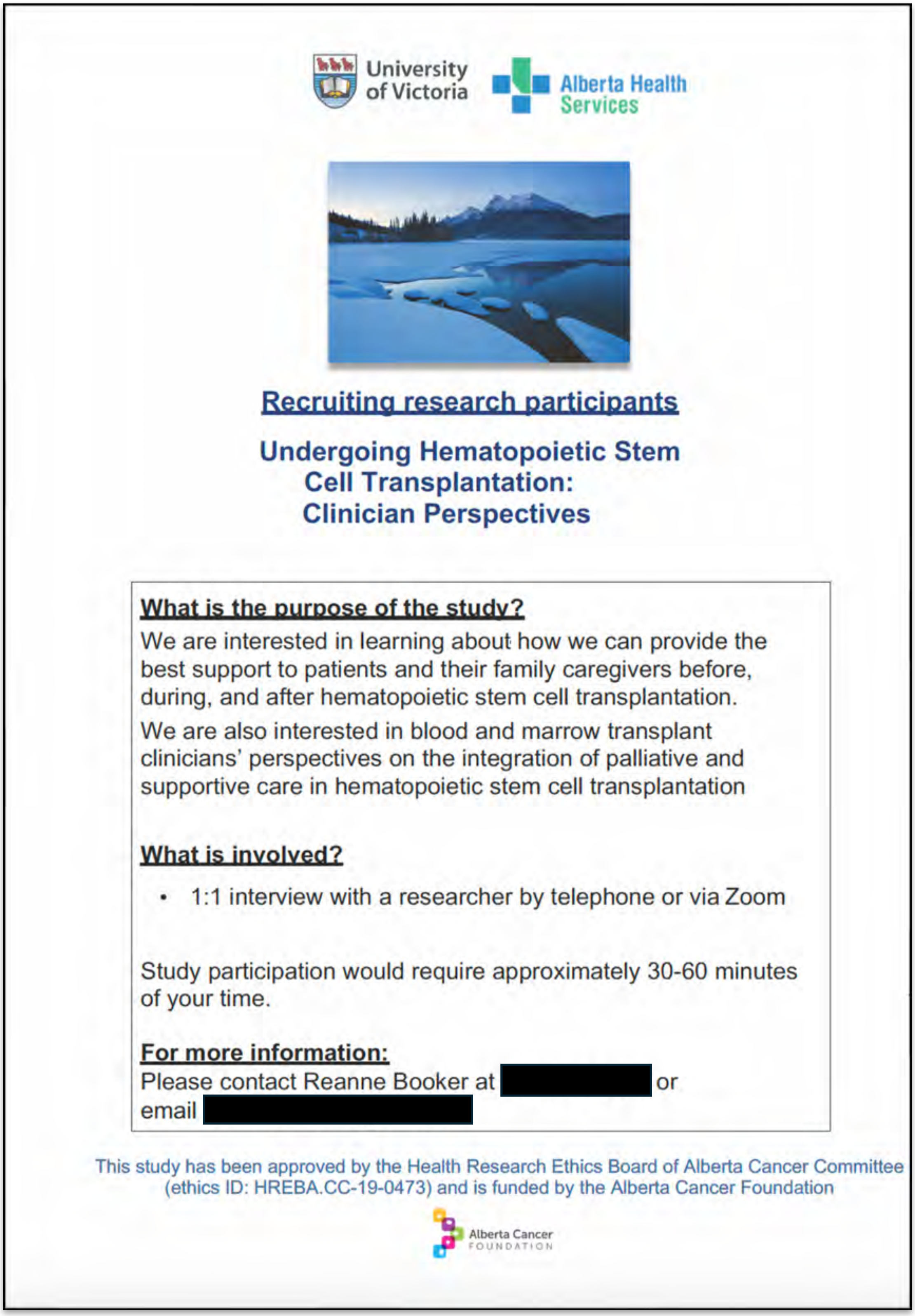
What is involved?

- 1:1 interview with a researcher **over the phone or via Zoom**

For more information, please contact Reanne Booker by phone [redacted] or email [redacted]

This study has been approved by the Health Research Ethics Board of Alberta Cancer Committee (ethics ID: HREBA.CC-19-0473) and is funded by the Alberta Cancer Foundation

Alberta Cancer FOUNDATION



University of Victoria

Alberta Health Services

Recruiting research participants

Undergoing Hematopoietic Stem Cell Transplantation: Clinician Perspectives

What is the purpose of the study?

We are interested in learning about how we can provide the best support to patients and their family caregivers before, during, and after hematopoietic stem cell transplantation.

We are also interested in blood and marrow transplant clinicians' perspectives on the integration of palliative and supportive care in hematopoietic stem cell transplantation

What is involved?

- 1:1 interview with a researcher by telephone or via Zoom

Study participation would require approximately 30-60 minutes of your time.

For more information:

Please contact Reanne Booker at [redacted] or email [redacted]

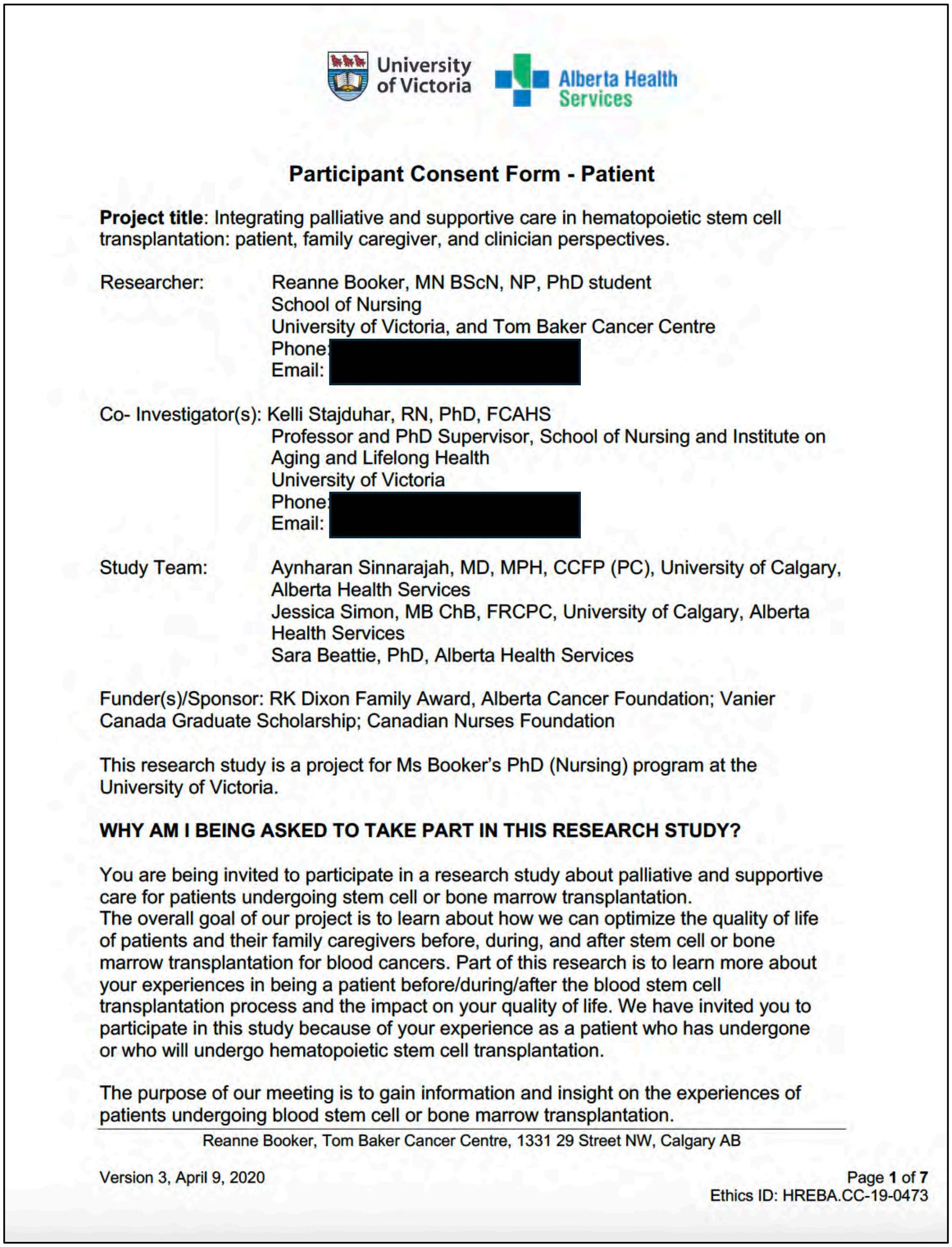
This study has been approved by the Health Research Ethics Board of Alberta Cancer Committee (ethics ID: HREBA.CC-19-0473) and is funded by the Alberta Cancer Foundation

Alberta Cancer FOUNDATION

Appendix D

Chapter 4: Integrating Palliative Care in Hematopoietic Stem Cell Transplantation: A Qualitative Study Exploring Patient, Caregiver, and Clinician Perspectives

Consent Forms



University of Victoria

Alberta Health Services

Participant Consent Form - Patient

Project title: Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.

Researcher:
Reanne Booker, MN BScN, NP, PhD student
School of Nursing
University of Victoria, and Tom Baker Cancer Centre
Phone: [redacted]
Email:

Co- Investigator(s): Kelli Stajduhar, RN, PhD, FCAHS
Professor and PhD Supervisor, School of Nursing and Institute on Aging and Lifelong Health
University of Victoria
Phone: [redacted]
Email:

Study Team:
Aynharan Sinnarajah, MD, MPH, CCFP (PC), University of Calgary, Alberta Health Services
Jessica Simon, MB ChB, FRCPC, University of Calgary, Alberta Health Services
Sara Beattie, PhD, Alberta Health Services

Funder(s)/Sponsor: RK Dixon Family Award, Alberta Cancer Foundation; Vanier Canada Graduate Scholarship; Canadian Nurses Foundation

This research study is a project for Ms Booker's PhD (Nursing) program at the University of Victoria.

WHY AM I BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being invited to participate in a research study about palliative and supportive care for patients undergoing stem cell or bone marrow transplantation.
The overall goal of our project is to learn about how we can optimize the quality of life of patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. Part of this research is to learn more about your experiences in being a patient before/during/after the blood stem cell transplantation process and the impact on your quality of life. We have invited you to participate in this study because of your experience as a patient who has undergone or who will undergo hematopoietic stem cell transplantation.

The purpose of our meeting is to gain information and insight on the experiences of patients undergoing blood stem cell or bone marrow transplantation.

Reanne Booker, Tom Baker Cancer Centre, 1331 29 Street NW, Calgary AB

Version 3, April 9, 2020

Page **1** of **7**
Ethics ID: HREBA.CC-19-0473

This consent form provides information about the study to assist you with making an informed decision. The researcher will discuss this study with you and will answer any questions you may have. You are encouraged to ask questions. When all of your questions have been answered to your satisfaction, you can decide if you want to be in the study or not. Interviews will be conducted to gain patients' perspectives.

Taking part in this study is voluntary. You may choose whether or not you take part. If you choose to participate, you may leave the study at any time without giving reason or without penalty. Deciding not to take part or deciding to leave the study early will not result in any penalty or affect current or future care.

If you decide to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Palliative care focuses on support of a patient and their family's' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. We know from research that has been done with patients who have other types of cancer, that when palliative care is introduced early, patients and their caregivers may experience better quality of life, and patients may experience fewer symptoms and side effects of treatment.

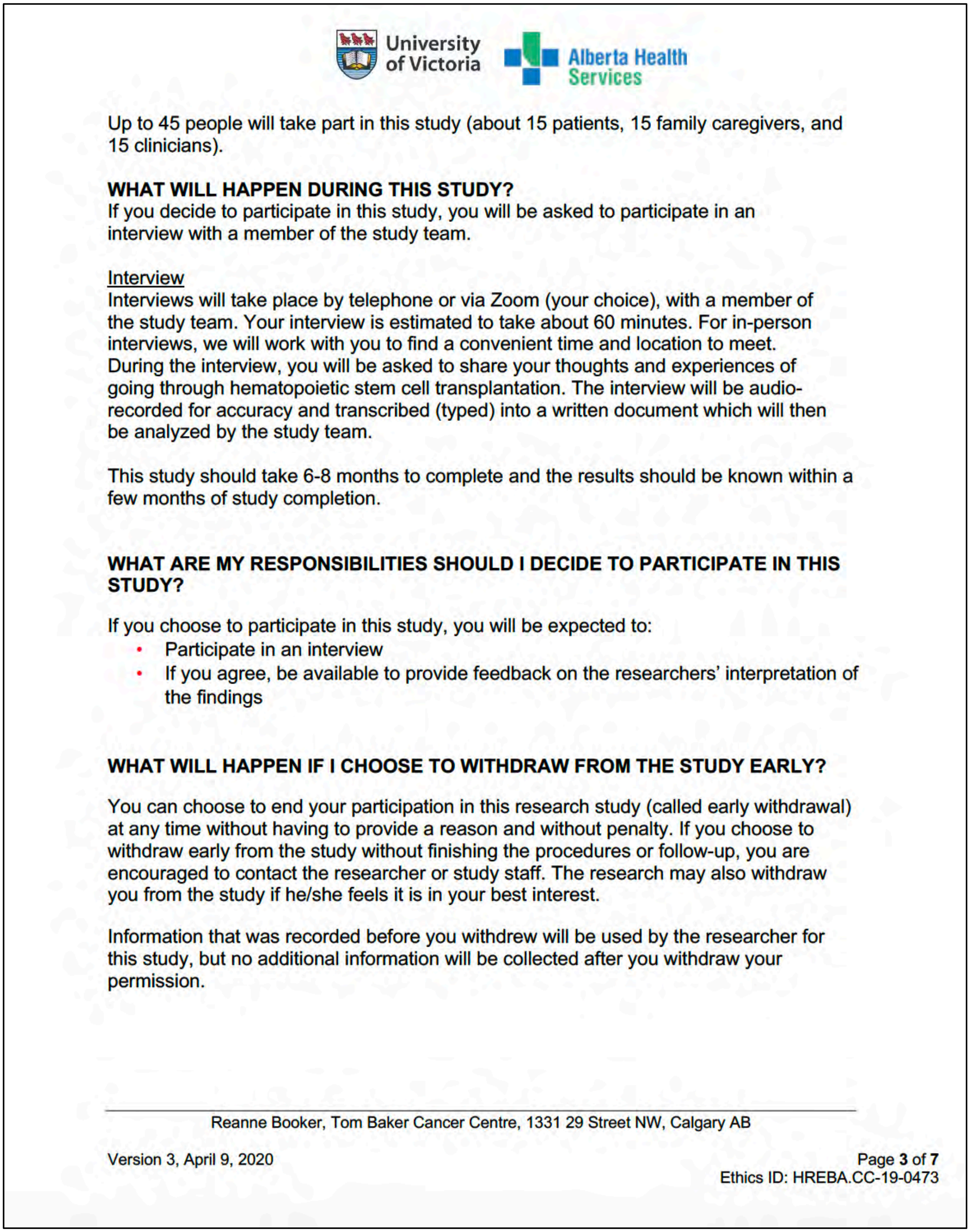
There have not been many studies on how palliative care might help patients and their family caregivers before, during, and after hematopoietic stem cell transplantation. The study aims to gain input from patients who will undergo or who have undergone hematopoietic stem cell transplantation and their family caregivers about how we can best integrate palliative care.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study. The Human Research Ethics Board, University of Victoria, has also reviewed and granted ethics approval for this study (UVic Ethics ID: 19-0462).

WHAT ARE MY OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study in order to receive continued medical care. Your participation is entirely voluntary and if you choose not to participate, you will continue to receive the best care available.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?



Up to 45 people will take part in this study (about 15 patients, 15 family caregivers, and 15 clinicians).

WHAT WILL HAPPEN DURING THIS STUDY?
If you decide to participate in this study, you will be asked to participate in an interview with a member of the study team.

Interview
Interviews will take place by telephone or via Zoom (your choice), with a member of the study team. Your interview is estimated to take about 60 minutes. For in-person interviews, we will work with you to find a convenient time and location to meet. During the interview, you will be asked to share your thoughts and experiences of going through hematopoietic stem cell transplantation. The interview will be audio-recorded for accuracy and transcribed (typed) into a written document which will then be analyzed by the study team.

This study should take 6-8 months to complete and the results should be known within a few months of study completion.

WHAT ARE MY RESPONSIBILITIES SHOULD I DECIDE TO PARTICIPATE IN THIS STUDY?

If you choose to participate in this study, you will be expected to:

- Participate in an interview
- If you agree, be available to provide feedback on the researchers' interpretation of the findings

WHAT WILL HAPPEN IF I CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to end your participation in this research study (called early withdrawal) at any time without having to provide a reason and without penalty. If you choose to withdraw early from the study without finishing the procedures or follow-up, you are encouraged to contact the researcher or study staff. The research may also withdraw you from the study if he/she feels it is in your best interest.

Information that was recorded before you withdrew will be used by the researcher for this study, but no additional information will be collected after you withdraw your permission.

WHAT ARE THE RISKS/DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

You may be exposed to the following risks and inconveniences:

- You may feel uncomfortable emotion or feel upset talking about your experiences.
- Inconvenience due to time commitment

To reduce these risks, the following steps will be taken:

- You do not have to answer any question you do not wish to answer. There are no right or wrong answers, we are seeking your opinion and insights. If at any time you find the discussion or telling of your experiences upsetting, you are welcome to leave the interview temporarily to compose yourself or withdraw from it all together without consequence. We can also offer you further support through a list of available resources.
- The interview will be scheduled at a time and location to reduce inconveniences as much as possible.

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING IN THIS STUDY?

There may or may not be direct benefits to you from taking part in this study. We hope that the information learned from this study can be used to improve the palliative and supportive care of people who undergo blood stem cell or bone marrow transplantation and the care provided to their family caregivers. The findings from this study will be used by the Alberta Blood and Marrow Transplant Program and nationally to improve the care provided to other Canadians undergoing blood stem cell or bone marrow transplantation.

HOW WILL MY PERSONAL INFORMATION BE KEPT PRIVATE?

If you decide to participate, the researcher and study staff will only collect information they need for this study. They will do everything that they can to make sure that this data is kept private/confidential. No data relating to this study that includes your name will be released outside of the study site nor will it be published by the researcher.

Sometimes, by law, the researcher may have to release information including names and therefore absolute confidentiality cannot be guaranteed. However, every effort will be made to make sure that your information is kept confidential.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Zoom is a videoconferencing tool that allows for participants to see and hear each other during the call. Because Zoom is a web-based tool, there can be increased risks in terms of security and specifically, risks to privacy and confidentiality.

If you choose Zoom for the interview, the researchers will take extra steps to ensure that your privacy and confidentiality are protected. For example, you will be given a unique password that you will need to enter before being able to join the Zoom meeting. In addition, the researcher can lock the meeting once the meeting has started so that no other participants can join. The interview will be recorded using the researcher's audio recorder and will not be recorded using Zoom so your data will not be stored on external servers.

By signing this consent form, you are allowing the study team to collect, use and disclose information about you from your personal medical records.

After the study is done, we will still need to securely store your data that was collected as part of the study. We will keep your data and study records stored for 7 years after the end of the study.

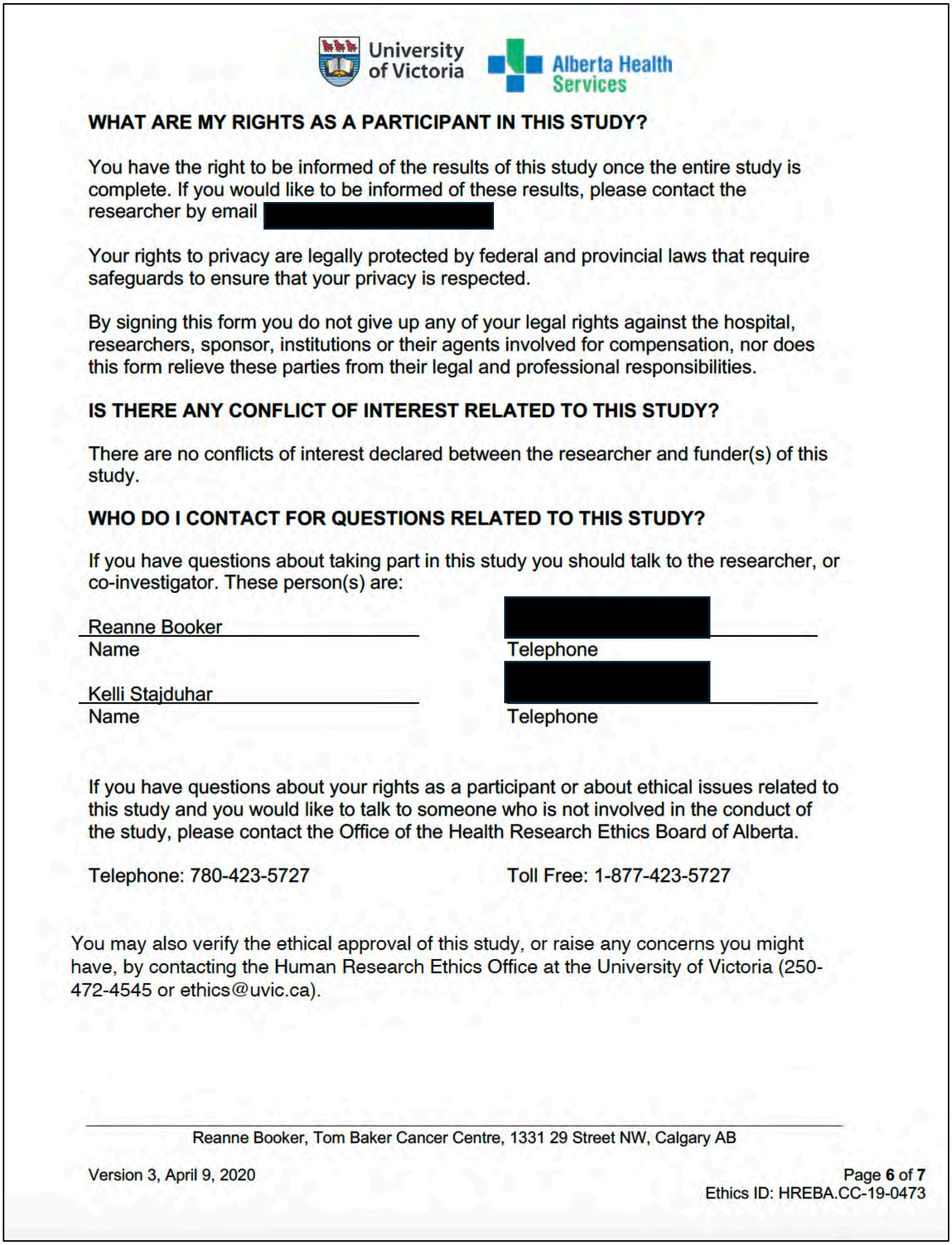
Audio recordings from the interviews will be uploaded to a secure cloud and listened to only by members of the research team. The recordings will be kept until they have been transcribed (turned into written records), and then they will be destroyed.

WILL THERE BE COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participating in the study will not involve any additional costs.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.



University of Victoria Alberta Health Services

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the researcher by email [redacted]

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the hospital, researchers, sponsor, institutions or their agents involved for compensation, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE ANY CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the researcher and funder(s) of this study.

WHO DO I CONTACT FOR QUESTIONS RELATED TO THIS STUDY?

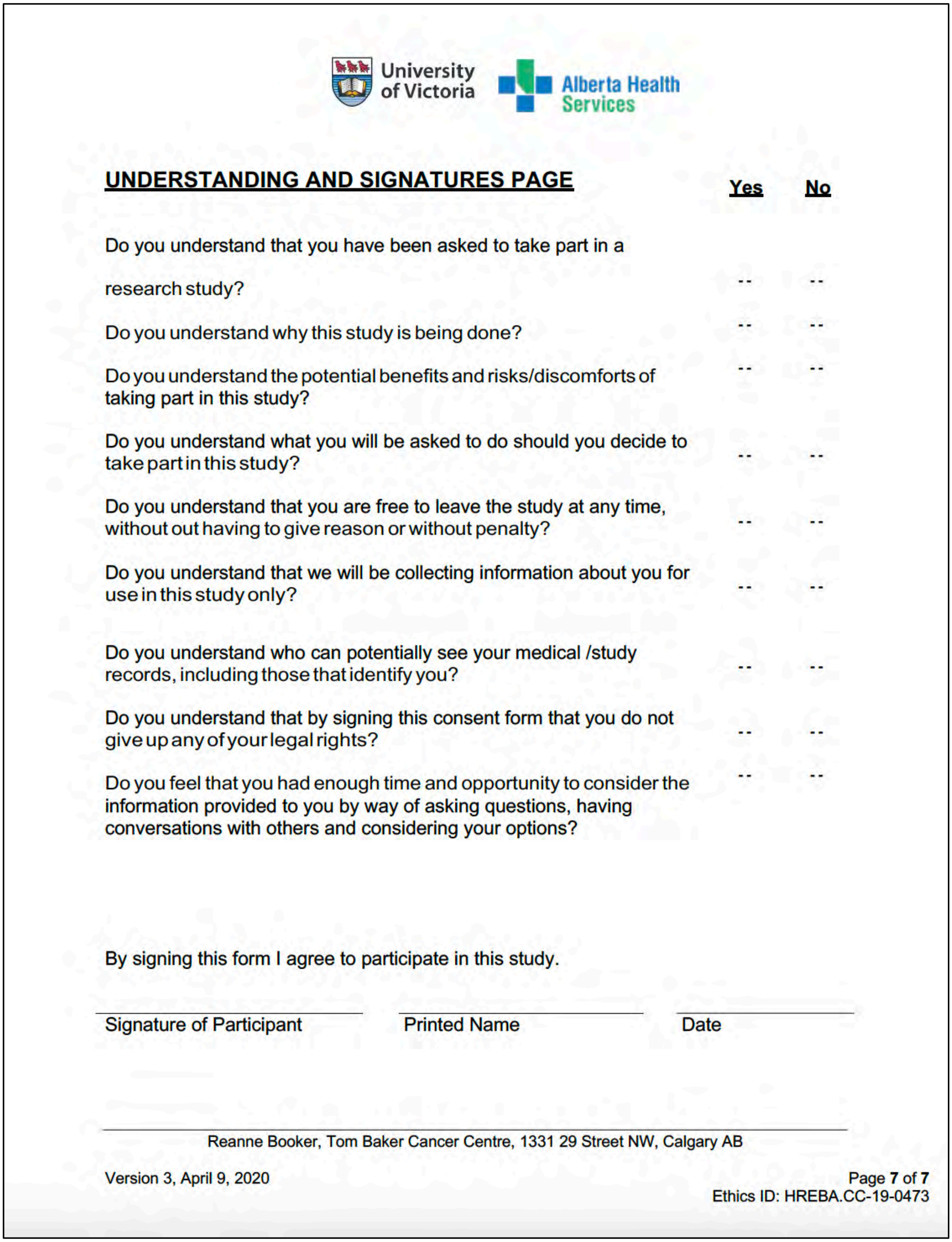
If you have questions about taking part in this study you should talk to the researcher, or co-investigator. These person(s) are:

Reanne Booker	[redacted]
Name	Telephone
Kelli Stajduhar	[redacted]
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta.

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

You may also verify the ethical approval of this study, or raise any concerns you might have, by contacting the Human Research Ethics Office at the University of Victoria (250-472-4545 or ethics@uvic.ca).



University of Victoria
Alberta Health Services

UNDERSTANDING AND SIGNATURES PAGE

	Yes	No
Do you understand that you have been asked to take part in a research study?	--	--
Do you understand why this study is being done?	--	--
Do you understand the potential benefits and risks/discomforts of taking part in this study?	--	--
Do you understand what you will be asked to do should you decide to take part in this study?	--	--
Do you understand that you are free to leave the study at any time, without out having to give reason or without penalty?	--	--
Do you understand that we will be collecting information about you for use in this study only?	--	--
Do you understand who can potentially see your medical /study records, including those that identify you?	--	--
Do you understand that by signing this consent form that you do not give up any of your legal rights?	--	--
Do you feel that you had enough time and opportunity to consider the information provided to you by way of asking questions, having conversations with others and considering your options?	--	--

By signing this form I agree to participate in this study.

Signature of Participant ______ Printed Name ______ Date ______

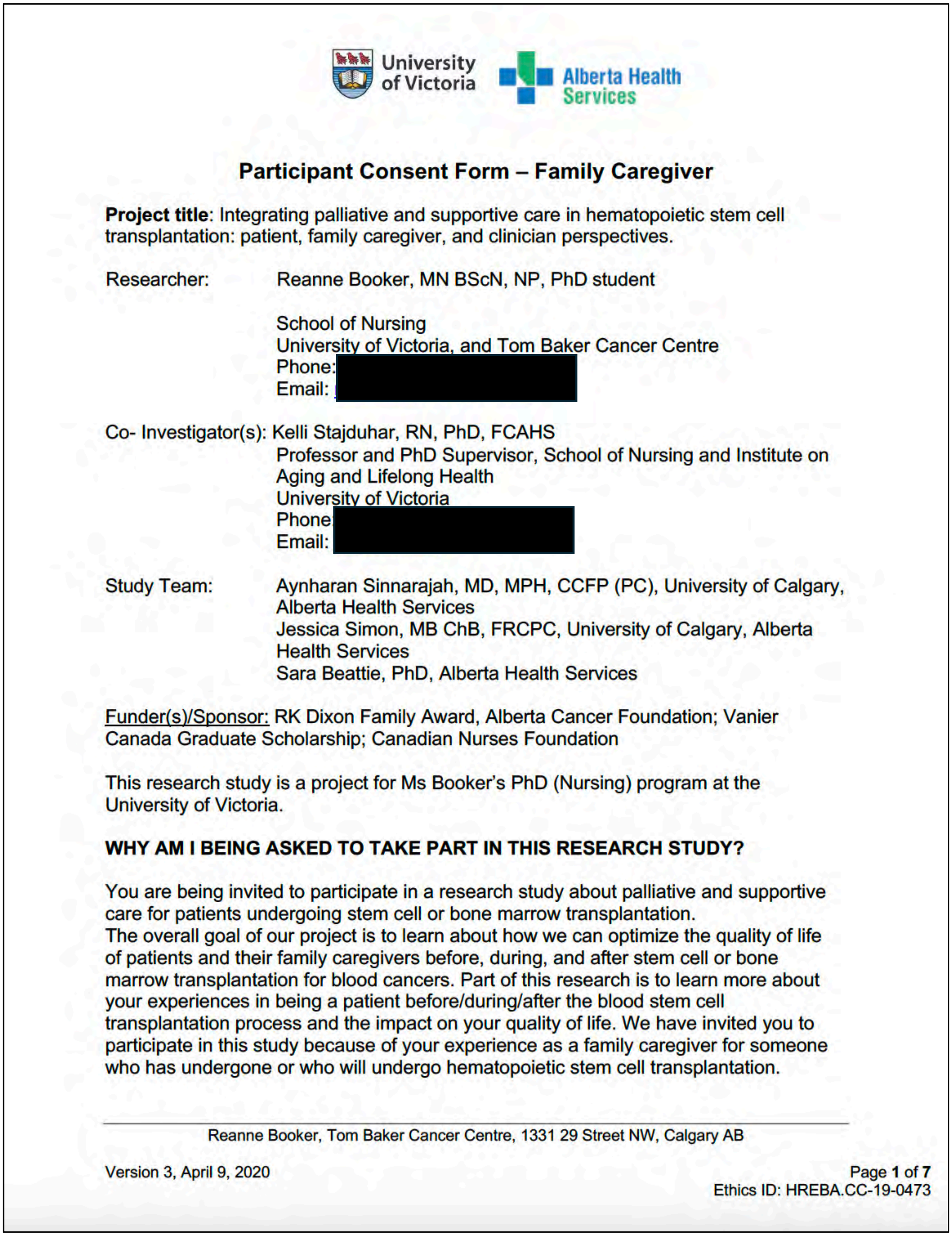
STUDY TEAM ACKNOWLEDGEMENT

I believe the person signing this form understands what is involved in this research study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	Printed Name	Date

Contact information for the Department of Psychosocial Resources at Tom Baker Cancer Centre: Phone: [redacted]

You will be given a copy of this signed and dated consent form prior to participating in this optional research.



Participant Consent Form – Family Caregiver

Project title: Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.

Researcher: Reanne Booker, MN BScN, NP, PhD student

School of Nursing
University of Victoria, and Tom Baker Cancer Centre
Phone: [redacted]
Email:

Co- Investigator(s): Kelli Stajduhar, RN, PhD, FCAHS
Professor and PhD Supervisor, School of Nursing and Institute on Aging and Lifelong Health
University of Victoria
Phone: [redacted]
Email:

Study Team: Aynharan Sinnarajah, MD, MPH, CCFP (PC), University of Calgary, Alberta Health Services
Jessica Simon, MB ChB, FRCPC, University of Calgary, Alberta Health Services
Sara Beattie, PhD, Alberta Health Services

Funder(s)/Sponsor: RK Dixon Family Award, Alberta Cancer Foundation; Vanier Canada Graduate Scholarship; Canadian Nurses Foundation

This research study is a project for Ms Booker's PhD (Nursing) program at the University of Victoria.

WHY AM I BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being invited to participate in a research study about palliative and supportive care for patients undergoing stem cell or bone marrow transplantation.
The overall goal of our project is to learn about how we can optimize the quality of life of patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. Part of this research is to learn more about your experiences in being a patient before/during/after the blood stem cell transplantation process and the impact on your quality of life. We have invited you to participate in this study because of your experience as a family caregiver for someone who has undergone or who will undergo hematopoietic stem cell transplantation.

The purpose of our meeting is to gain information and insight on the experiences of family caregivers for people undergoing blood stem cell or bone marrow transplantation.

This consent form provides information about the study to assist you with making an informed decision. The researcher will discuss this study with you and will answer any questions you may have. You are encouraged to ask questions. When all of your questions have been answered to your satisfaction, you can decide if you want to be in the study or not. Interviews will be conducted to gain family caregivers' perspectives.

Taking part in this study is voluntary. You may choose whether or not you take part. If you choose to participate, you may leave the study at any time without giving reason or without penalty. Deciding not to take part or deciding to leave the study early will not result in any penalty or affect current or future care.

If you decide to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Palliative care focuses on support of a patient and their family's' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. We know from research that has been done with patients who have other types of cancer, that when palliative care is introduced early, patients and their caregivers may experience better quality of life, and patients may experience fewer symptoms and side effects of treatment.

There have not been many studies on how palliative care might help patients and their family caregivers before, during, and after hematopoietic stem cell transplantation. The study aims to gain input from patients who will undergo or who have undergone hematopoietic stem cell transplantation and their family caregivers about how we can best integrate palliative care.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study. The Human Research Ethics Board, University of Victoria, has also reviewed and granted ethics approval for this study (UVic Ethics ID: 19-0462).

WHAT ARE MY OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study in order for you or your family member to receive continued medical care. Your participation is entirely voluntary and if you choose not to participate, your family member will continue to receive the best care available.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 45 people will take part in this study (about 15 patients, 15 family caregivers, and 15 clinicians).

WHAT WILL HAPPEN DURING THIS STUDY?

If you decide to participate in this study, you will be asked to participate in a private interview with a member of the study team.

Interview

Interviews will take place by telephone or via Zoom (your choice), with a member of the study team. Your interview is estimated to take about 60 minutes. We will work with you to find a convenient time and location to meet. During the interview, you will be asked to share your thoughts and experiences of being a family caregiver throughout the hematopoietic stem cell transplantation process. The interview will be audio-recorded for accuracy and transcribed (typed) into a written document which will then be analyzed by the study team.

This study should take 6-8 months to complete and the results should be known within a few months of study completion.

WHAT ARE MY RESPONSIBILITIES SHOULD I DECIDE TO PARTICIPATE IN THIS STUDY?

If you choose to participate in this study, you will be expected to:

- Participate in an interview
- If you agree, be available to provide feedback on the researchers' interpretation of the findings

WHAT WILL HAPPEN IF I CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to end your participation in this research study (called early withdrawal) at any time without having to provide a reason and without penalty. If you choose to withdraw early from the study without finishing the procedures or follow-up, you are encouraged to contact the researcher or study staff. The research may also withdraw you from the study if he/she feels it is in your best interest.

Information that was recorded before you withdrew will be used by the researcher for this study, but no additional information will be collected after you withdraw your permission.

WHAT ARE THE RISKS/DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

You may be exposed to the following risks and inconveniences:

- You may feel uncomfortable emotion or feel upset talking about your experiences.
- Inconvenience due to time commitment

To reduce these risks, the following steps will be taken:

- You do not have to answer any question you do not wish to answer. There are no right or wrong answers, we are seeking your opinion and insights. If at any time you find the discussion or telling of your experiences upsetting, you are welcome to leave the interview temporarily to compose yourself or withdraw from it all together without consequence. We can also offer you further support through a list of available resources.
- The interview will be scheduled at a time and location to reduce inconveniences as much as possible.

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING IN THIS STUDY?

There may or may not be direct benefits to you from taking part in this study. We hope that the information learned from this study can be used to improve the palliative and supportive care of people who undergo blood stem cell or bone marrow transplantation and the care provided to their family caregivers. The findings from this study will be used by the Alberta Blood and Marrow Transplant Program and nationally to improve the care provided to other Canadians undergoing blood stem cell or bone marrow transplantation.

HOW WILL MY PERSONAL INFORMATION BE KEPT PRIVATE?

If you decide to participate, the researcher and study staff will only collect information they need for this study. They will do everything that they can to make sure that this data is kept private/confidential. No data relating to this study that includes your name will be released outside of the study site nor will it be published by the researcher.

Sometimes, by law, the researcher may have to release information including names and therefore absolute confidentiality cannot be guaranteed. However, every effort will be made to make sure that your information is kept confidential.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Zoom is a videoconferencing tool that allows for participants to see and hear each other during the call. Because Zoom is a web-based tool, there can be increased risks in terms of security and specifically, risks to privacy and confidentiality.

If you choose Zoom for the interview, the researchers will take extra steps to ensure that your privacy and confidentiality are protected. For example, you will be given a unique password that you will need to enter before being able to join the Zoom meeting. In addition, the researcher can lock the meeting once the meeting has started so that no other participants can join. The interview will be recorded using the researcher's audio recorder and will not be recorded using Zoom so your data will not be stored on external servers.

After the study is done, we will still need to securely store your data that was collected as part of the study. We will keep your data and study records stored for 7 years after the end of the study.

Audio recordings from the interviews will be uploaded to a secure cloud and listened to only by members of the research team. The recordings will be kept until they have been transcribed (turned into written records), and then they will be destroyed.

WILL THERE BE COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participating in the study will not involve any additional costs.

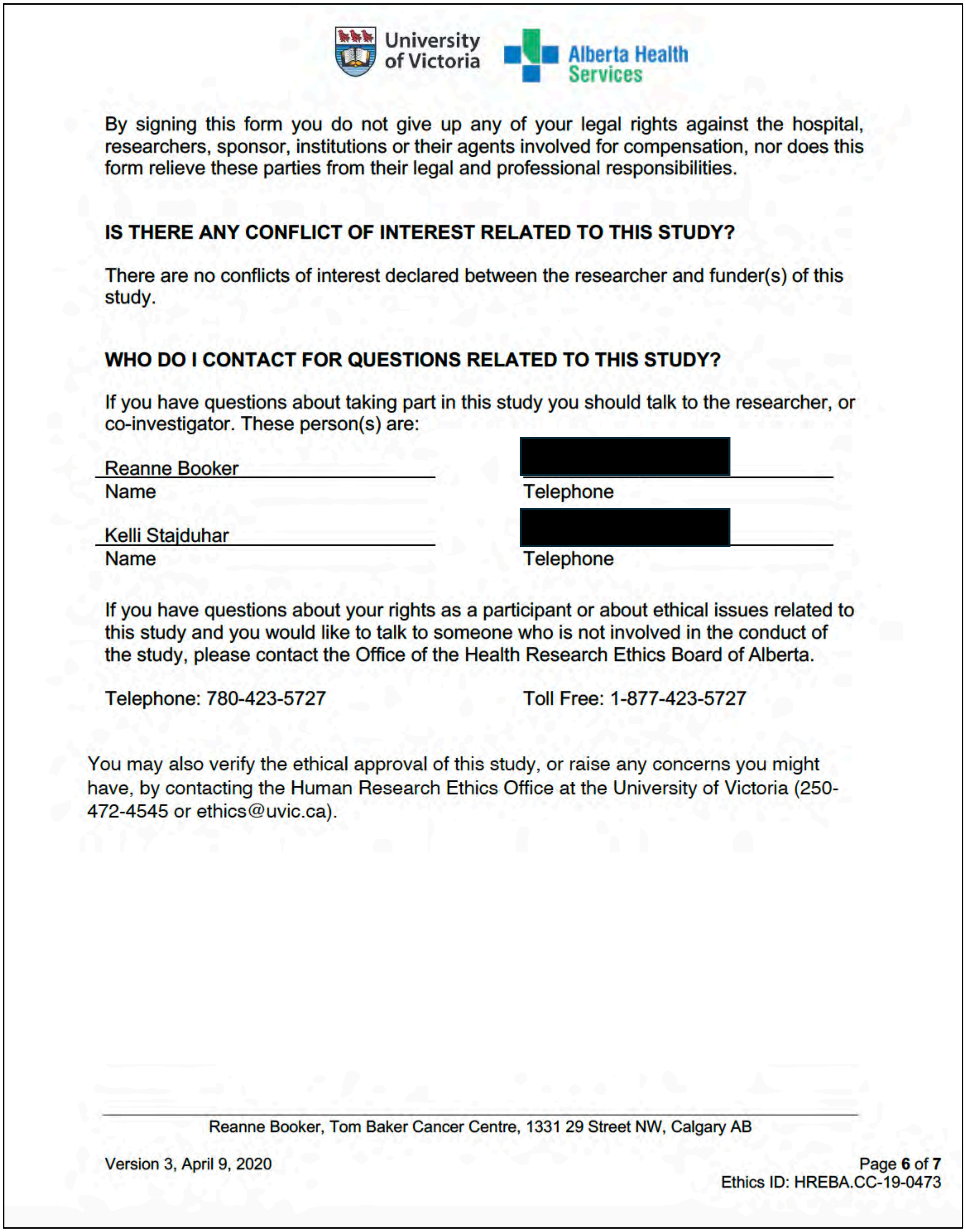
WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the researcher by email [redacted]

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.



By signing this form you do not give up any of your legal rights against the hospital, researchers, sponsor, institutions or their agents involved for compensation, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE ANY CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the researcher and funder(s) of this study.

WHO DO I CONTACT FOR QUESTIONS RELATED TO THIS STUDY?

If you have questions about taking part in this study you should talk to the researcher, or co-investigator. These person(s) are:

Reanne Booker	[redacted]
Name	Telephone
Kelli Stajduhar	[redacted]
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta.

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

You may also verify the ethical approval of this study, or raise any concerns you might have, by contacting the Human Research Ethics Office at the University of Victoria (250-472-4545 or ethics@uvic.ca).

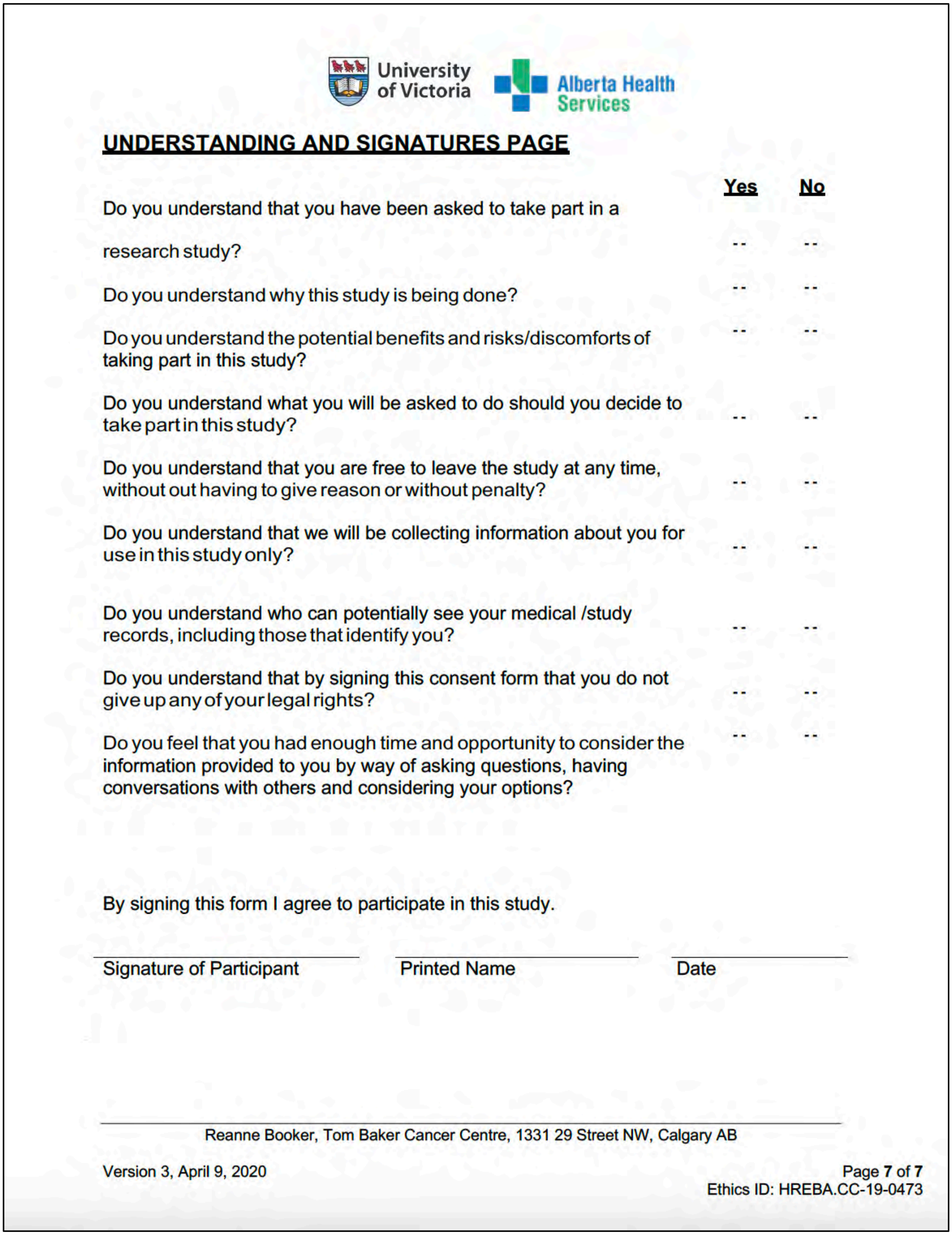
STUDY TEAM ACKNOWLEDGEMENT

I believe the person signing this form understands what is involved in this research study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	Printed Name	Date

Contact information for the Department of Psychosocial and Rehabilitation Oncology at Tom Baker Cancer Centre: Phone: [redacted]

You will be given a copy of this signed and dated consent form prior to participating in this optional research.



University of Victoria

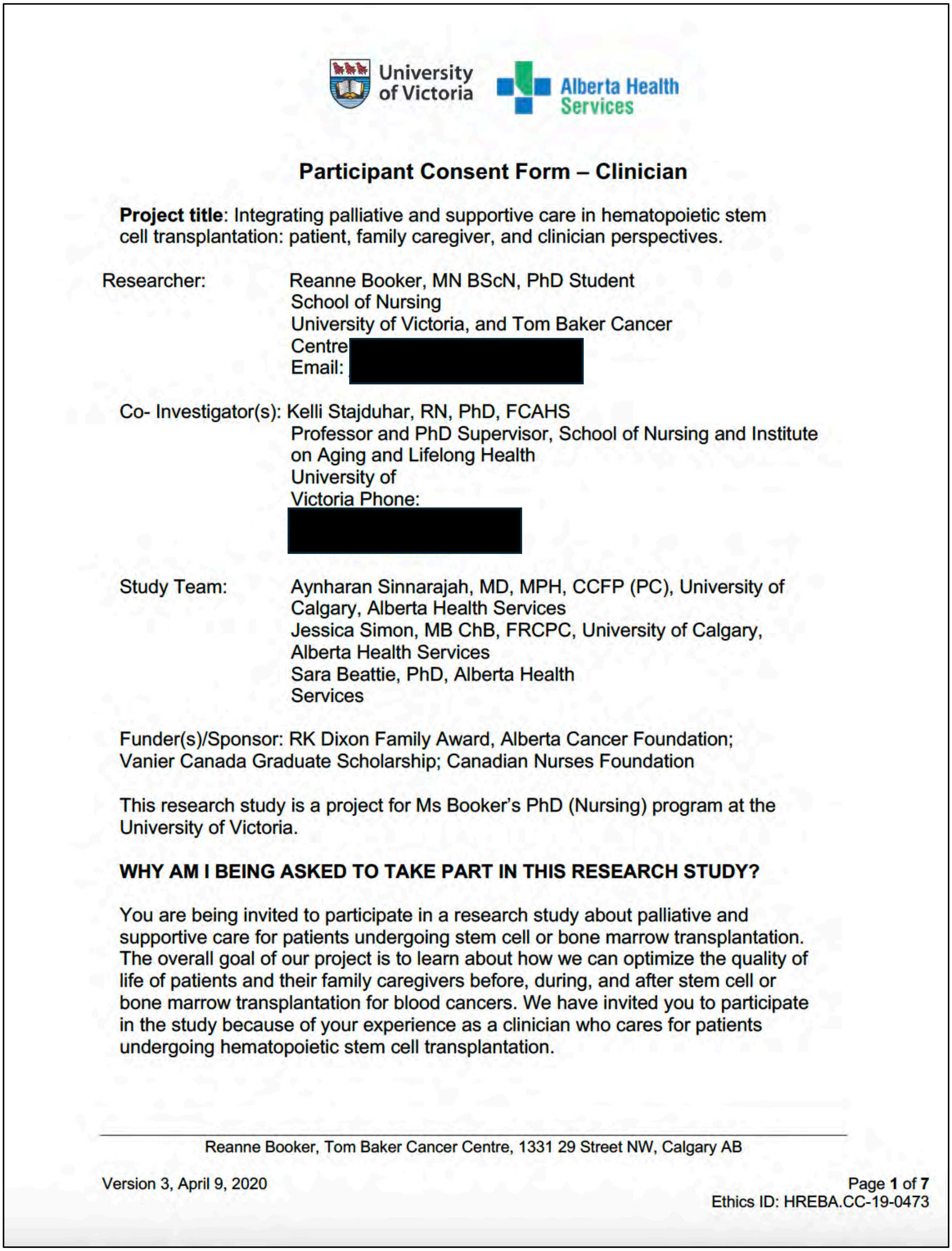
Alberta Health Services

UNDERSTANDING AND SIGNATURES PAGE

	Yes	No
Do you understand that you have been asked to take part in a research study?	--	--
Do you understand why this study is being done?	--	--
Do you understand the potential benefits and risks/discomforts of taking part in this study?	--	--
Do you understand what you will be asked to do should you decide to take part in this study?	--	--
Do you understand that you are free to leave the study at any time, without out having to give reason or without penalty?	--	--
Do you understand that we will be collecting information about you for use in this study only?	--	--
Do you understand who can potentially see your medical /study records, including those that identify you?	--	--
Do you understand that by signing this consent form that you do not give up any of your legal rights?	--	--
Do you feel that you had enough time and opportunity to consider the information provided to you by way of asking questions, having conversations with others and considering your options?	--	--

By signing this form I agree to participate in this study.

Signature of Participant	Printed Name	Date



University of Victoria
Alberta Health Services

Participant Consent Form – Clinician

Project title: Integrating palliative and supportive care in hematopoietic stem cell transplantation: patient, family caregiver, and clinician perspectives.

Researcher: Reanne Booker, MN BScN, PhD Student
School of Nursing
University of Victoria, and Tom Baker Cancer Centre [redacted]
Email: [redacted]

Co- Investigator(s): Kelli Stajduhar, RN, PhD, FCAHS
Professor and PhD Supervisor, School of Nursing and Institute on Aging and Lifelong Health
University of Victoria Phone: [redacted]

Study Team: Aynharan Sinnarajah, MD, MPH, CCFP (PC), University of Calgary, Alberta Health Services
Jessica Simon, MB ChB, FRCPC, University of Calgary, Alberta Health Services
Sara Beattie, PhD, Alberta Health Services

Funder(s)/Sponsor: RK Dixon Family Award, Alberta Cancer Foundation; Vanier Canada Graduate Scholarship; Canadian Nurses Foundation

This research study is a project for Ms Booker's PhD (Nursing) program at the University of Victoria.

WHY AM I BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being invited to participate in a research study about palliative and supportive care for patients undergoing stem cell or bone marrow transplantation. The overall goal of our project is to learn about how we can optimize the quality of life of patients and their family caregivers before, during, and after stem cell or bone marrow transplantation for blood cancers. We have invited you to participate in the study because of your experience as a clinician who cares for patients undergoing hematopoietic stem cell transplantation.

The purpose of our meeting is to better understand what blood stem cell and bone marrow transplant clinicians think about integrating palliative and supportive care alongside stem cell or bone marrow transplant.

This consent form provides information about the study to assist you with making an informed decision. The researcher will discuss this study with you and will answer any questions you may have. You are encouraged to ask questions. When all of your questions have been answered to your satisfaction, you can decide if you want to be in the study or not. Interviews will be conducted to gain clinicians' perspectives on the integration of palliative and supportive care in hematopoietic stem cell transplantation.

Taking part in this study is voluntary. You may choose whether or not you take part. If you choose to participate, you may leave the study at any time without giving reason or without penalty. Deciding not to take part or deciding to leave the study early will not result in any penalty or affect current or future employment.

If you decide to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Palliative care focuses on support of a patient and their family's' physical, emotional and psychosocial needs (including help with decision making), while continuing with advanced cancer-focused treatments (e.g. chemotherapy, radiation). Palliative care provides an additional layer of support. We know from research that has been done with patients who have other types of cancer, that when palliative care is introduced early, patients and their caregivers may experience better quality of life, and patients may experience fewer symptoms and side effects of treatment.

There have not been many studies on how palliative care might help patients and their family caregivers before, during, and after hematopoietic stem cell transplantation. The study aims to gain input from patients who will undergo or who have undergone hematopoietic stem cell transplantation and their family caregivers about how we can best integrate palliative care into the care of people undergoing hematopoietic stem cell transplantation.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 45 people will take part in this study (about 15 patients, 15 family caregivers, and 15 clinicians).

WHAT WILL HAPPEN DURING THIS STUDY?

If you decide to participate in this study, you will be asked to participate in a private interview with a member of the study team.

Interview

Interviews will take place by telephone or via Zoom (your choice), with a member of the study team. Your interview is estimated to take about 60 minutes. For in-person interviews, we will work with you to find a convenient time and location to meet. During the interview, you will be asked to share your thoughts and experiences of being a clinician for patients undergoing hematopoietic stem cell transplantation process. You will also be asked to share your thoughts and perspective on the integration of palliative and supportive care in hematopoietic stem cell transplantation. The interview will be audio-recorded for accuracy and transcribed into a written document which will then be analyzed by the study team.

This study should take 6-8 months to complete and the results should be known within a few months of study completion.

WHAT ARE MY RESPONSIBILITIES SHOULD I DECIDE TO PARTICIPATE IN THIS STUDY?

If you choose to participate in this study, you will be expected to:

- Participate in an interview
- If you agree, be available to provide feedback on the researchers' interpretation of the findings

WHAT WILL HAPPEN IF I CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can choose to end your participation in this research study (called early withdrawal) at any time without having to provide a reason and without penalty. If you choose to withdraw early from the study without finishing the procedures or follow-up, you are encouraged to contact the researcher or study staff. The research may also withdraw you from the study if he/she feels it is in your best interest.

Information that was recorded before you withdrew will be used by the researcher for this study, but no additional information will be collected after you withdraw your permission.

WHAT ARE THE RISKS/DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

You may be exposed to the following risks and inconveniences:

- You may feel uncomfortable emotion or feel upset talking about your experiences.
- Inconvenience due to time commitment

To reduce these risks, the following steps will be taken:

- You do not have to answer any question you do not wish to answer. There are no right or wrong answers, we are seeking your opinion and insights. If at any time you find the discussion or telling of your experiences upsetting, you are welcome to leave the interview temporarily to compose yourself or withdraw from it all together without consequence. We can also offer you further support through a list of available resources.
- The interview will be scheduled at a time and location to reduce inconveniences as much as possible.

WHAT ARE THE POTENTIAL BENEFITS OF PARTICIPATING IN THIS STUDY?

There may or may not be direct benefits to you from taking part in this study. We hope that the information learned from this study can be used to improve the palliative and supportive care of people who undergo blood stem cell or bone marrow transplantation and the care provided to their family caregivers. The findings from this study will be used by the Alberta Blood and Marrow Transplant Program and nationally to improve the care provided to other Canadians undergoing blood stem cell or bone marrow transplantation.

HOW WILL MY PERSONAL INFORMATION BE KEPT PRIVATE?

If you decide to participate, the researcher and study staff will only collect information they need for this study. They will do everything that they can to make sure that this data is kept private/confidential. No data relating to this study that includes your name will be released outside of the study site nor will it be published by the researcher.
Sometimes, by law, the researcher may have to release information including names and therefore absolute confidentiality cannot be guaranteed. However, every effort will be made to make sure that your information is kept confidential.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Zoom is a videoconferencing tool that allows for participants to see and hear each other during the call. Because Zoom is a web-based tool, there can be increased risks in terms of security and specifically, risks to privacy and confidentiality.

If you choose Zoom for the interview, the researchers will take extra steps to ensure that your privacy and confidentiality are protected. For example, you will be given a unique password that you will need to enter before being able to join the Zoom meeting. In addition, the researcher can lock the meeting once the meeting has started so that no other participants can join. The interview will be recorded using the researcher's audio recorder and will not be recorded using Zoom so your data will not be stored on external servers.

By signing this consent form, you are allowing the study team to collect, use and disclose information about you from your personal medical records.

After the study is done, we will still need to securely store your data that was collected as part of the study. We will keep your data and study records stored for *7* years after the end of the study.

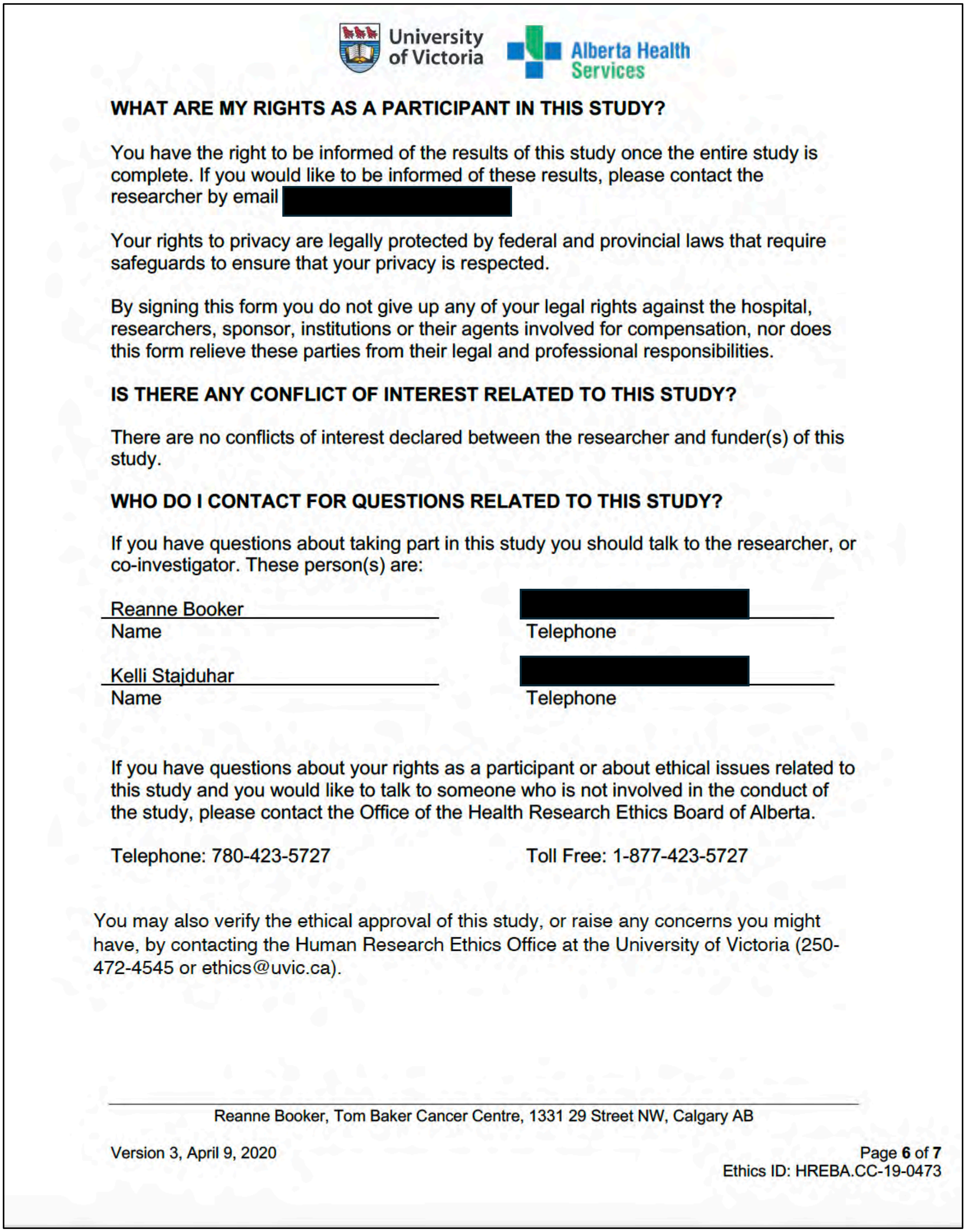
Audio recordings from the interviews will be uploaded to a secure cloud and listened to only by members of the research team. The recordings will be kept until they have been transcribed (turned into written records), and then they will be destroyed.

WILL THERE BE COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participating in the study will not involve any additional costs.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.



University of Victoria Alberta Health Services

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the researcher by email [redacted]

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the hospital, researchers, sponsor, institutions or their agents involved for compensation, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE ANY CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest declared between the researcher and funder(s) of this study.

WHO DO I CONTACT FOR QUESTIONS RELATED TO THIS STUDY?

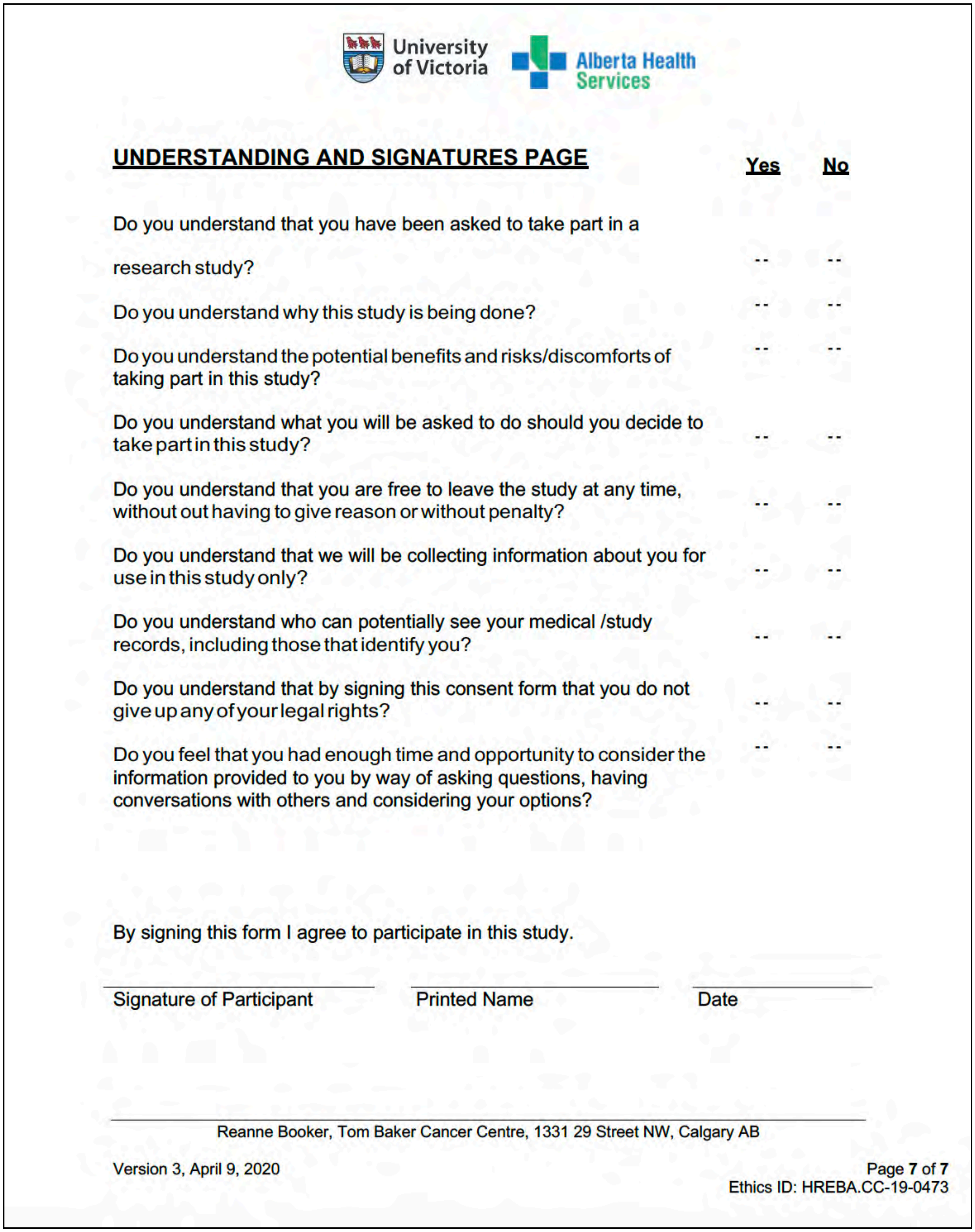
If you have questions about taking part in this study you should talk to the researcher, or co-investigator. These person(s) are:

Reanne Booker	[redacted]
Name	Telephone
Kelli Stajduhar	[redacted]
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta.

Telephone: 780-423-5727	Toll Free: 1-877-423-5727

You may also verify the ethical approval of this study, or raise any concerns you might have, by contacting the Human Research Ethics Office at the University of Victoria (250-472-4545 or ethics@uvic.ca).

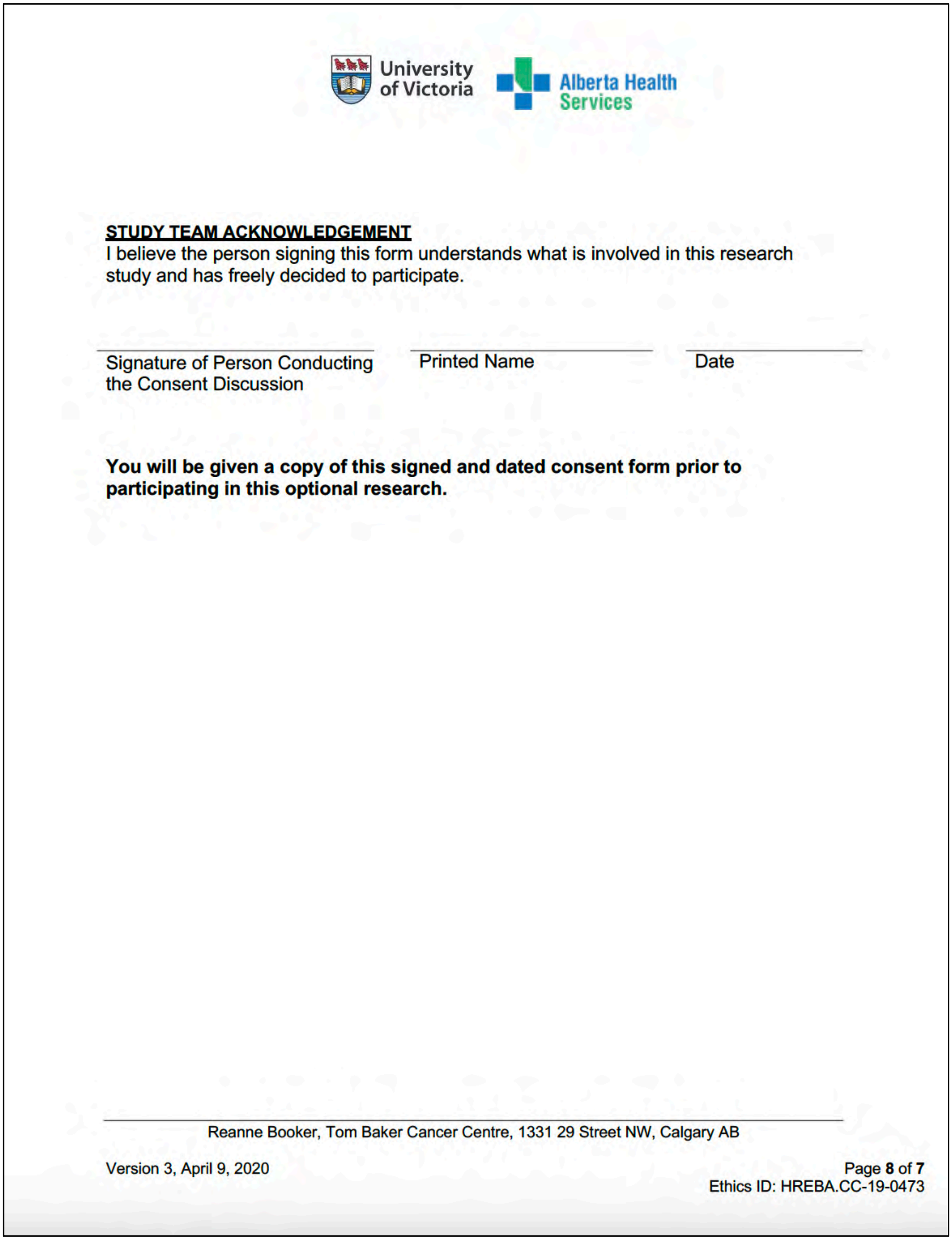


University of Victoria | Alberta Health Services

UNDERSTANDING AND SIGNATURES PAGE	**Yes**	**No**
Do you understand that you have been asked to take part in a research study?	--	--
Do you understand why this study is being done?	--	--
Do you understand the potential benefits and risks/discomforts of taking part in this study?	--	--
Do you understand what you will be asked to do should you decide to take part in this study?	--	--
Do you understand that you are free to leave the study at any time, without out having to give reason or without penalty?	--	--
Do you understand that we will be collecting information about you for use in this study only?	--	--
Do you understand who can potentially see your medical /study records, including those that identify you?	--	--
Do you understand that by signing this consent form that you do not give up any of your legal rights?	--	--
Do you feel that you had enough time and opportunity to consider the information provided to you by way of asking questions, having conversations with others and considering your options?	--	--

By signing this form I agree to participate in this study.

Signature of Participant	Printed Name	Date



STUDY TEAM ACKNOWLEDGEMENT
I believe the person signing this form understands what is involved in this research study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	Printed Name	Date

You will be given a copy of this signed and dated consent form prior to participating in this optional research.

Appendix E

Chapter 5: Protocol for Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

Data Management Plan

What types of data will you collect, create, link to, acquire and/or record?

We will collect 3 types of data:

1. Audio files of intervention group meetings (1 population)
2. Questionnaire data (4 populations: patients in the standard care arm, family caregivers in the standard care arm, patients in the intervention arm, family caregivers in the intervention arm)
3. De-identified health data (2 populations: patients in the standard care arm; patients in the intervention arm)

What file formats will your data be collected in? Will these formats allow for data re-use, sharing, and long-term access to data?

Data will be collected via RedCap and exported to Microsoft Excel and SPSS. Audio from intervention group meetings will be saved as mp3 files. Research team members will be able to access data files in these formats. Long-term access to the data will be facilitated by saving the aggregate data and findings as xml, jpg, txt, and/or PDF files as appropriate.

What conventions and procedures will you use to structure, name, and version-control your files to help you and others better understand how your data are organized?

Depending on the data being saved, two conventions will be used for file naming:

1. DATE_FileName
2. FileName_YYYYMMDD_version

If necessary, the document owner will be indicated by initials at the end of the file name.

Documentation and Metadata

What documentation will be needed for the data to be read and interpreted correctly in the future?

Each data source will have a separate metadata file. Metadata files will be documented through the use of a codebook. The codebook will include research methodology (data collection methods and protocols); sample descriptions; classification or coding systems used to organize the data; definitions of variables; final versions of output tables used for formal reports and/or publications; a list of individuals who worked on the project and/or task assignment.

How will you make sure that documentation is created or captured consistently throughout your project?

The primary investigator (PI) and research assistant (RA) are the primary creators of documentation. All work will flow through these two positions. Task assignment to specific positions will assist with the accuracy, consistency, and completeness of the documentation. Members of the research team will be consulted with on a regular basis to communicate any changes in data collection and/or processes that require documentation.

Storage and Backup

What are the anticipated storage requirements for your project, in terms of storage space (in megabytes, gigabytes, terabytes, etc.) and length of time you will be storing it?
We anticipate that we will require approximately 40 GB of storage on the University of Victoria network for working data files and project files. Project files will be stored for five years and then destroyed. At the end of the project, the processed data and metatdata files will be held in UVic's DataVerse repository.

How and where will your data be stored and backed up during your research project?
Data will be stored on the University of Victoria Network following protocols defined by the University of Victoria.

Preservation

Where will you deposit your data for long-term preservation and access at the end of your research project?
Processed data will be deposited with the University of Victoria's DataVerse Network repository.

Indicate how you will ensure your data is preservation ready. Consider preservation-friendly file formats, ensuring file integrity, anonymization and deidentification, inclusion of supporting documents.
De-identified processed data will be saved in a data format that is most suitable for long-term preservation, such as text, xml, and PDF files.

Sharing and Reuse

What data will you be sharing and in what form? (e.g. raw, processed, analyzed, final).

We will be analyzing 3 data types. Sharing and form are described below.

1. Audio files from intervention group meetings will be shared with research team members in 3 formats: processed data (cleaned and de-identified), analyzed data (analysis of processed data), and final data, as appropriate.
2. Questionnaire data from RedCap will be exported to SPSS and/or Excel. Questionnaire data will be shared with research team members in 3 formats: processed data (cleaned and de-identified), analyzed data (analysis of processed data), and final data, as appropriate.
3. Health records data will be shared with research team members in 3 formats: processed data (cleaned and de-identified), analyzed data (analysis of processed data), and final data, as appropriate.

Disease status (relapse, no evidence of relapse), survival data

Label	Data element name	Description	Codes	Notes
DS1	Disease status	The disease status of the patient collected at specific points in time.	1 relapse, 0 no evidence of relapse	Frequency of data
SD1	Survival data	AHS health records that indicate health outcome	1 deceased, 0 living	Internal AHS record, not linked to Vital Statistics

Have you considered what type of end-user license to include with your data?

n/a

What steps will be taken to help the research community know that your data exist?
Research results will be communicated in report form (written, electronic, presentation) and through publication of papers. Whenever possible, a repository that will assign a persistent identifier, such as DOI, will be selected. As appropriate, publications and reports will be available upon request.

Responsibilities and Resources

Identify who will be responsible for managing this project's data during and after the project and the major data management tasks for which they will be responsible.

During the project, data will be managed by the PI and RA. The PI and RA will work together to move data from raw form into processed form in order for it to be shared with other research team members. Only the PI will have access to health records.

How will responsibilities for managing data activities be handled if substantive changes happen in the personnel overseeing the project's data, including a change of Principal Investigator?

This project is being conducted as Ms Booker's PhD dissertation research. We do not anticipate a change of Principal Investigator.

What resources will you require to implement your data management plan? What do you estimate the overall cost for data management to be?

The cost of the implementation of the data management plan will be absorbed by project management funds.

Ethics and Legal Compliance

All identifying information will be removed from data files. Questionnaire data will not include any identifying information and be associated with participants' unique study identification number.

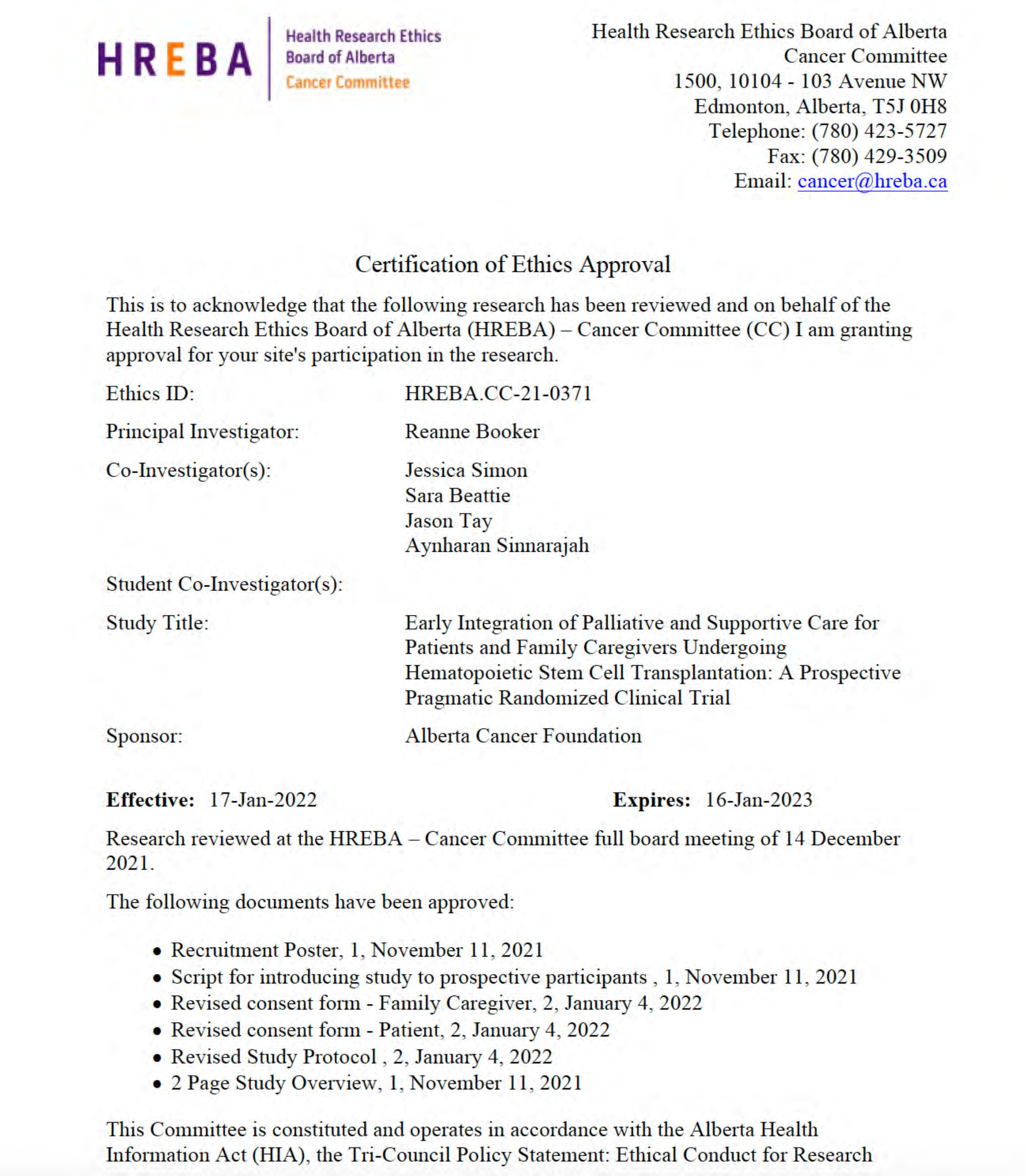
If applicable, what strategies will you undertake to address secondary uses of data?
Not applicable. There will not be any secondary uses of data.

How will you manage legal, ethical, and intellectual property issues?
All research activities are governed by the Health Research Ethics Board of Alberta Cancer Committee and secondarily, the University of Victoria.

Appendix F

Chapter 5: Protocol for Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

Ethics Certificates



HREBA
Health Research Ethics
Board of Alberta
Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Certification of Ethics Approval

This is to acknowledge that the following research has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC) I am granting approval for your site's participation in the research.

Ethics ID:	HREBA.CC-21-0371
Principal Investigator:	Reanne Booker
Co-Investigator(s):	Jessica Simon Sara Beattie Jason Tay Aynharan Sinnarajah
Student Co-Investigator(s):	
Study Title:	Early Integration of Palliative and Supportive Care for Patients and Family Caregivers Undergoing Hematopoietic Stem Cell Transplantation: A Prospective Pragmatic Randomized Clinical Trial
Sponsor:	Alberta Cancer Foundation

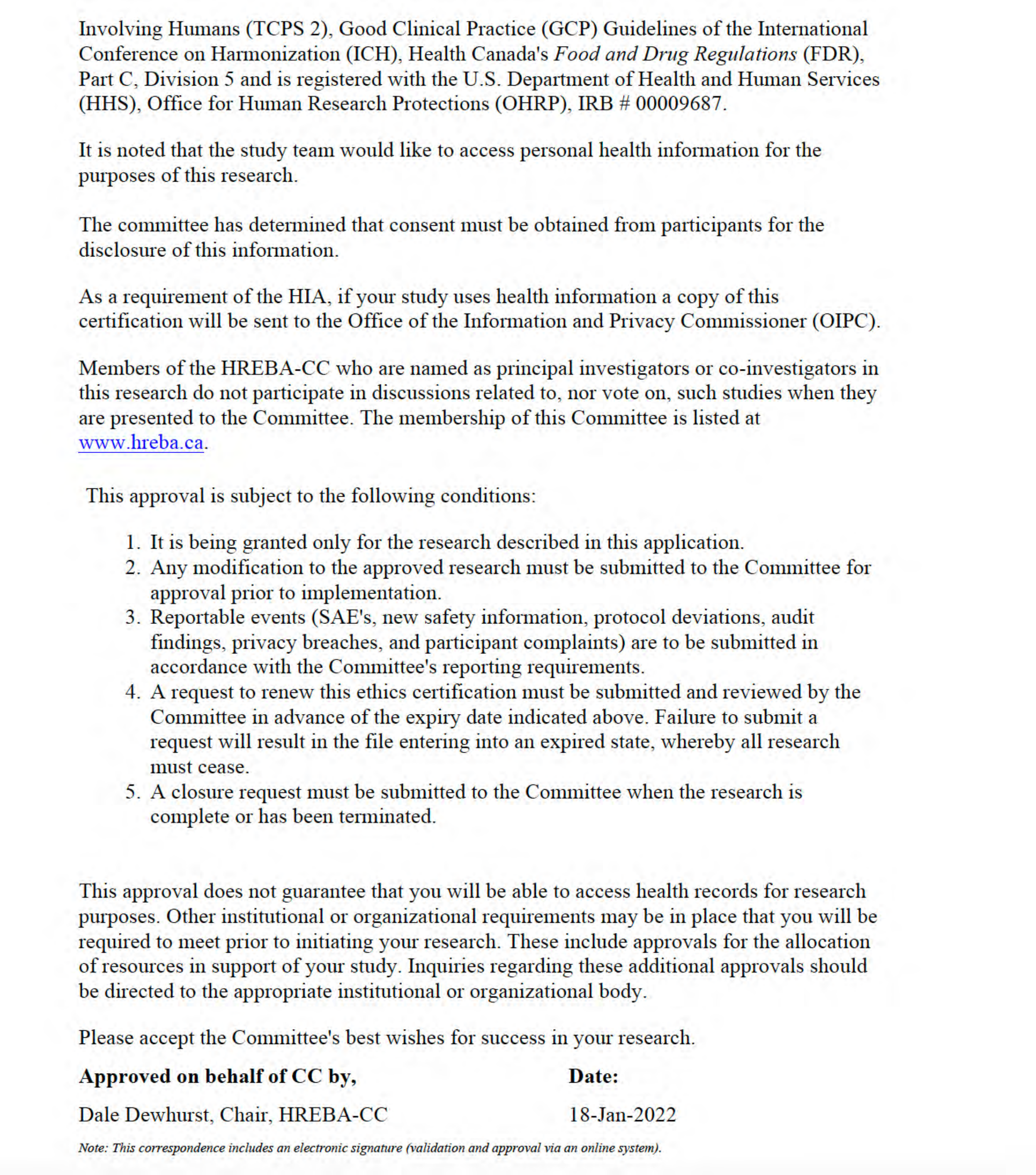
Effective: 17-Jan-2022 **Expires:** 16-Jan-2023

Research reviewed at the HREBA – Cancer Committee full board meeting of 14 December 2021.

The following documents have been approved:

- Recruitment Poster, 1, November 11, 2021
- Script for introducing study to prospective participants , 1, November 11, 2021
- Revised consent form - Family Caregiver, 2, January 4, 2022
- Revised consent form - Patient, 2, January 4, 2022
- Revised Study Protocol , 2, January 4, 2022
- 2 Page Study Overview, 1, November 11, 2021

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research



Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 00009687.

It is noted that the study team would like to access personal health information for the purposes of this research.

The committee has determined that consent must be obtained from participants for the disclosure of this information.

As a requirement of the HIA, if your study uses health information a copy of this certification will be sent to the Office of the Information and Privacy Commissioner (OIPC).

Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

This approval is subject to the following conditions:

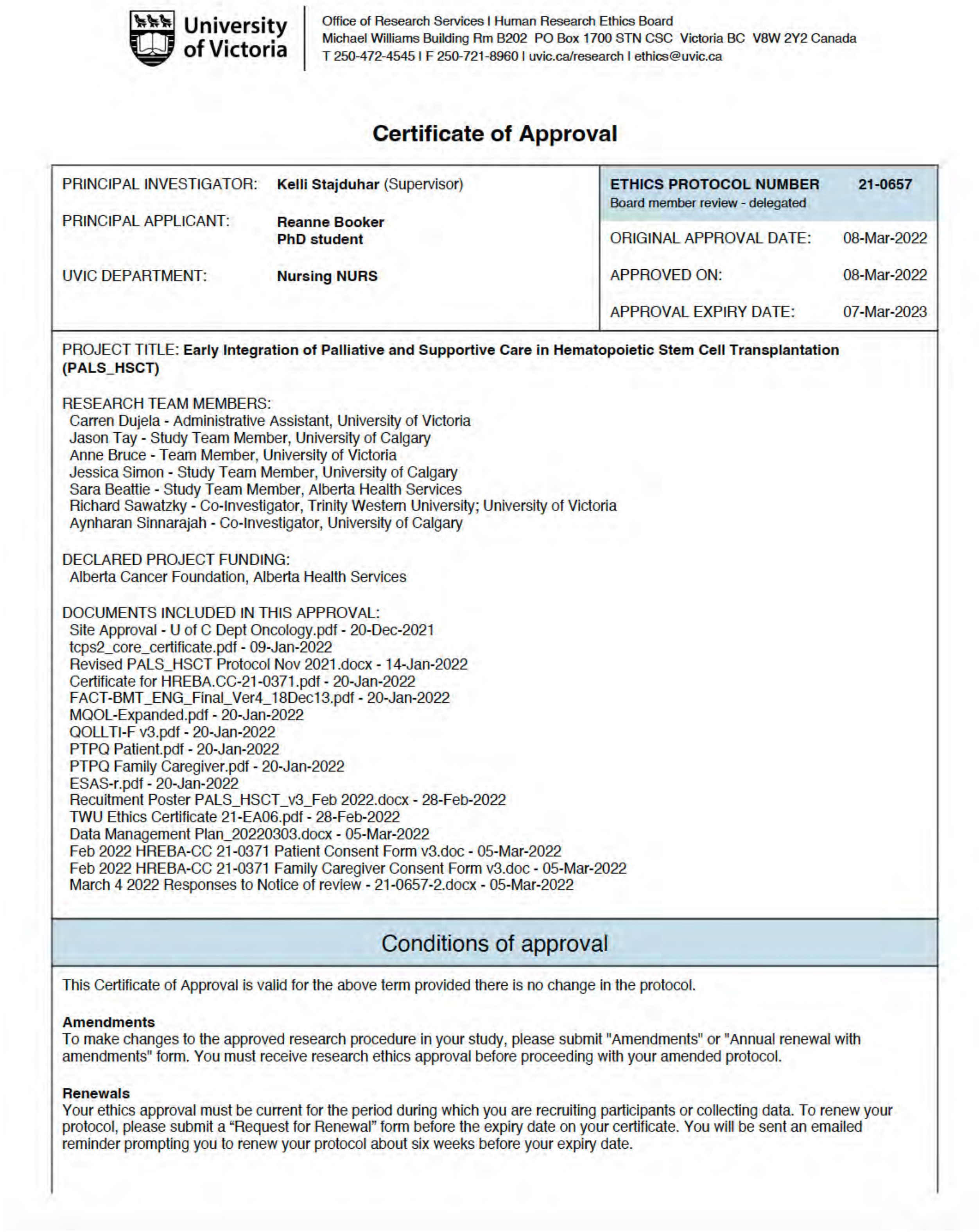
1. It is being granted only for the research described in this application.
2. Any modification to the approved research must be submitted to the Committee for approval prior to implementation.
3. Reportable events (SAE's, new safety information, protocol deviations, audit findings, privacy breaches, and participant complaints) are to be submitted in accordance with the Committee's reporting requirements.
4. A request to renew this ethics certification must be submitted and reviewed by the Committee in advance of the expiry date indicated above. Failure to submit a request will result in the file entering into an expired state, whereby all research must cease.
5. A closure request must be submitted to the Committee when the research is complete or has been terminated.

This approval does not guarantee that you will be able to access health records for research purposes. Other institutional or organizational requirements may be in place that you will be required to meet prior to initiating your research. These include approvals for the allocation of resources in support of your study. Inquiries regarding these additional approvals should be directed to the appropriate institutional or organizational body.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by,	**Date:**
Dale Dewhurst, Chair, HREBA-CC	18-Jan-2022

Note: This correspondence includes an electronic signature (validation and approval via an online system).



University of Victoria
Office of Research Services I Human Research Ethics Board
Michael Williams Building Rm B202 PO Box 1700 STN CSC Victoria BC V8W 2Y2 Canada
T 250-472-4545 I F 250-721-8960 I uvic.ca/research I ethics@uvic.ca

Certificate of Approval

PRINCIPAL INVESTIGATOR:	**Kelli Stajduhar** (Supervisor)	**ETHICS PROTOCOL NUMBER** Board member review - delegated	**21-0657**
PRINCIPAL APPLICANT:	**Reanne Booker** **PhD student**	ORIGINAL APPROVAL DATE:	08-Mar-2022
UVIC DEPARTMENT:	**Nursing NURS**	APPROVED ON:	08-Mar-2022
		APPROVAL EXPIRY DATE:	07-Mar-2023

PROJECT TITLE: **Early Integration of Palliative and Supportive Care in Hematopoietic Stem Cell Transplantation (PALS_HSCT)**

RESEARCH TEAM MEMBERS:
Carren Dujela - Administrative Assistant, University of Victoria
Jason Tay - Study Team Member, University of Calgary
Anne Bruce - Team Member, University of Victoria
Jessica Simon - Study Team Member, University of Calgary
Sara Beattie - Study Team Member, Alberta Health Services
Richard Sawatzky - Co-Investigator, Trinity Western University; University of Victoria
Aynharan Sinnarajah - Co-Investigator, University of Calgary

DECLARED PROJECT FUNDING:
Alberta Cancer Foundation, Alberta Health Services

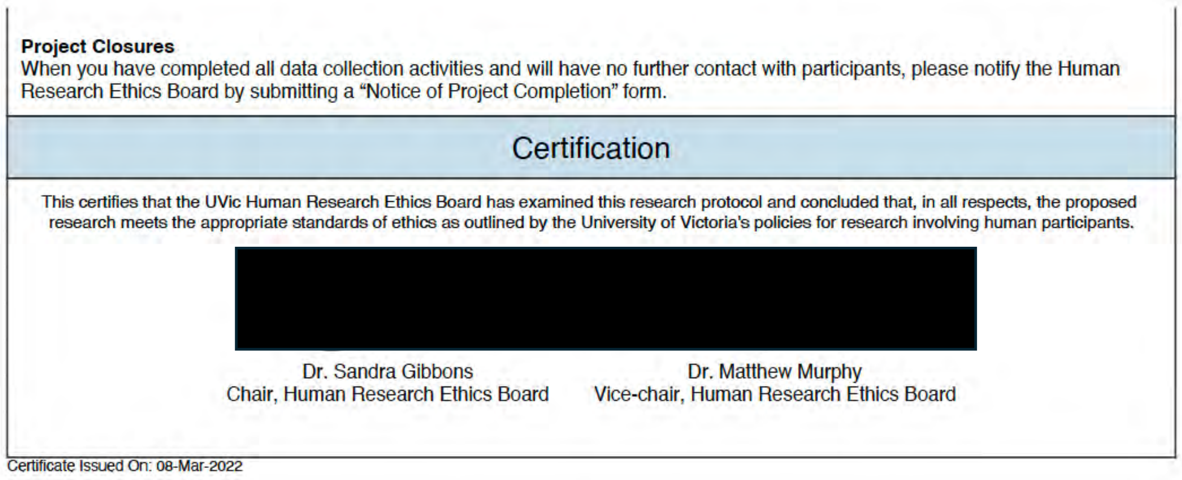
DOCUMENTS INCLUDED IN THIS APPROVAL:
Site Approval - U of C Dept Oncology.pdf - 20-Dec-2021
tcps2_core_certificate.pdf - 09-Jan-2022
Revised PALS_HSCT Protocol Nov 2021.docx - 14-Jan-2022
Certificate for HREBA.CC-21-0371.pdf - 20-Jan-2022
FACT-BMT_ENG_Final_Ver4_18Dec13.pdf - 20-Jan-2022
MQOL-Expanded.pdf - 20-Jan-2022
QOLLTI-F v3.pdf - 20-Jan-2022
PTPQ Patient.pdf - 20-Jan-2022
PTPQ Family Caregiver.pdf - 20-Jan-2022
ESAS-r.pdf - 20-Jan-2022
Recuitment Poster PALS_HSCT_v3_Feb 2022.docx - 28-Feb-2022
TWU Ethics Certificate 21-EA06.pdf - 28-Feb-2022
Data Management Plan_20220303.docx - 05-Mar-2022
Feb 2022 HREBA-CC 21-0371 Patient Consent Form v3.doc - 05-Mar-2022
Feb 2022 HREBA-CC 21-0371 Family Caregiver Consent Form v3.doc - 05-Mar-2022
March 4 2022 Responses to Notice of review - 21-0657-2.docx - 05-Mar-2022

Conditions of approval

This Certificate of Approval is valid for the above term provided there is no change in the protocol.

Amendments
To make changes to the approved research procedure in your study, please submit "Amendments" or "Annual renewal with amendments" form. You must receive research ethics approval before proceeding with your amended protocol.

Renewals
Your ethics approval must be current for the period during which you are recruiting participants or collecting data. To renew your protocol, please submit a “Request for Renewal” form before the expiry date on your certificate. You will be sent an emailed reminder prompting you to renew your protocol about six weeks before your expiry date.



Project Closures
When you have completed all data collection activities and will have no further contact with participants, please notify the Human Research Ethics Board by submitting a "Notice of Project Completion" form.

Certification

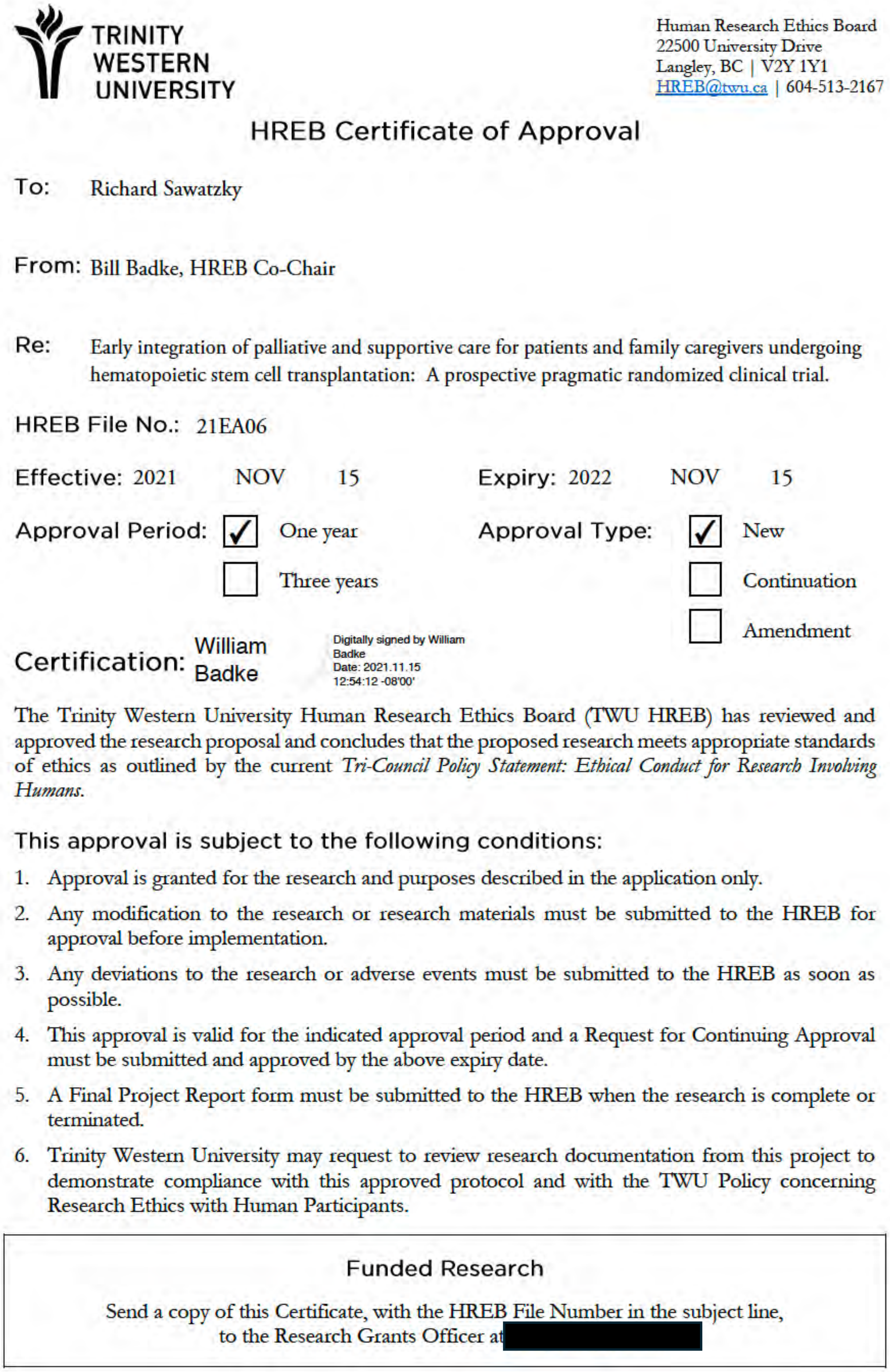
This certifies that the UVic Human Research Ethics Board has examined this research protocol and concluded that, in all respects, the proposed research meets the appropriate standards of ethics as outlined by the University of Victoria's policies for research involving human participants.

[redacted]

Dr. Sandra Gibbons
Chair, Human Research Ethics Board

Dr. Matthew Murphy
Vice-chair, Human Research Ethics Board

Certificate Issued On: 08-Mar-2022



TRINITY
WESTERN
UNIVERSITY

Human Research Ethics Board
22500 University Drive
Langley, BC | V2Y 1Y1
HREB@twu.ca | 604-513-2167

HREB Certificate of Approval

To: Richard Sawatzky

From: Bill Badke, HREB Co-Chair

Re: Early integration of palliative and supportive care for patients and family caregivers undergoing hematopoietic stem cell transplantation: A prospective pragmatic randomized clinical trial.

HREB File No.: 21EA06

Effective: 2021 NOV 15 **Expiry:** 2022 NOV 15

Approval Period: ☑ One year ☐ Three years

Approval Type: ☑ New ☐ Continuation ☐ Amendment

Certification: William Badke Digitally signed by William Badke Date: 2021.11.15 12:54:12 -08'00'

The Trinity Western University Human Research Ethics Board (TWU HREB) has reviewed and approved the research proposal and concludes that the proposed research meets appropriate standards of ethics as outlined by the current *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.*

This approval is subject to the following conditions:

1. Approval is granted for the research and purposes described in the application only.
2. Any modification to the research or research materials must be submitted to the HREB for approval before implementation.
3. Any deviations to the research or adverse events must be submitted to the HREB as soon as possible.
4. This approval is valid for the indicated approval period and a Request for Continuing Approval must be submitted and approved by the above expiry date.
5. A Final Project Report form must be submitted to the HREB when the research is complete or terminated.
6. Trinity Western University may request to review research documentation from this project to demonstrate compliance with this approved protocol and with the TWU Policy concerning Research Ethics with Human Participants.

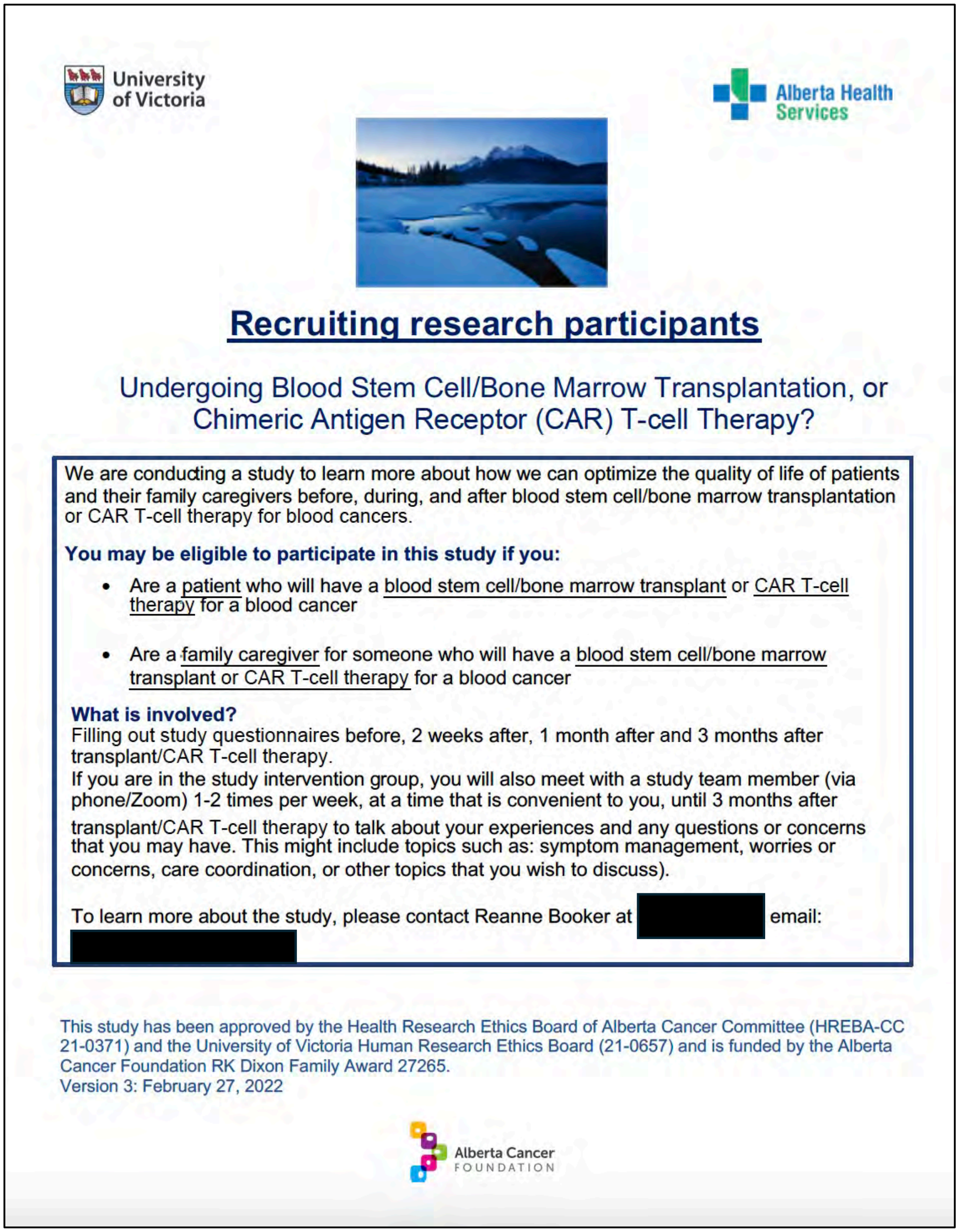
Funded Research

Send a copy of this Certificate, with the HREB File Number in the subject line, to the Research Grants Officer at [redacted]

Appendix G

Chapter 5: Protocol for Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

Recruitment Poster



University of Victoria

Alberta Health Services

Recruiting research participants

Undergoing Blood Stem Cell/Bone Marrow Transplantation, or Chimeric Antigen Receptor (CAR) T-cell Therapy?

We are conducting a study to learn more about how we can optimize the quality of life of patients and their family caregivers before, during, and after blood stem cell/bone marrow transplantation or CAR T-cell therapy for blood cancers.

You may be eligible to participate in this study if you:

- Are a patient who will have a blood stem cell/bone marrow transplant or CAR T-cell therapy for a blood cancer
- Are a family caregiver for someone who will have a blood stem cell/bone marrow transplant or CAR T-cell therapy for a blood cancer

What is involved?

Filling out study questionnaires before, 2 weeks after, 1 month after and 3 months after transplant/CAR T-cell therapy.

If you are in the study intervention group, you will also meet with a study team member (via phone/Zoom) 1-2 times per week, at a time that is convenient to you, until 3 months after transplant/CAR T-cell therapy to talk about your experiences and any questions or concerns that you may have. This might include topics such as: symptom management, worries or concerns, care coordination, or other topics that you wish to discuss).

To learn more about the study, please contact Reanne Booker at [redacted] email: [redacted]

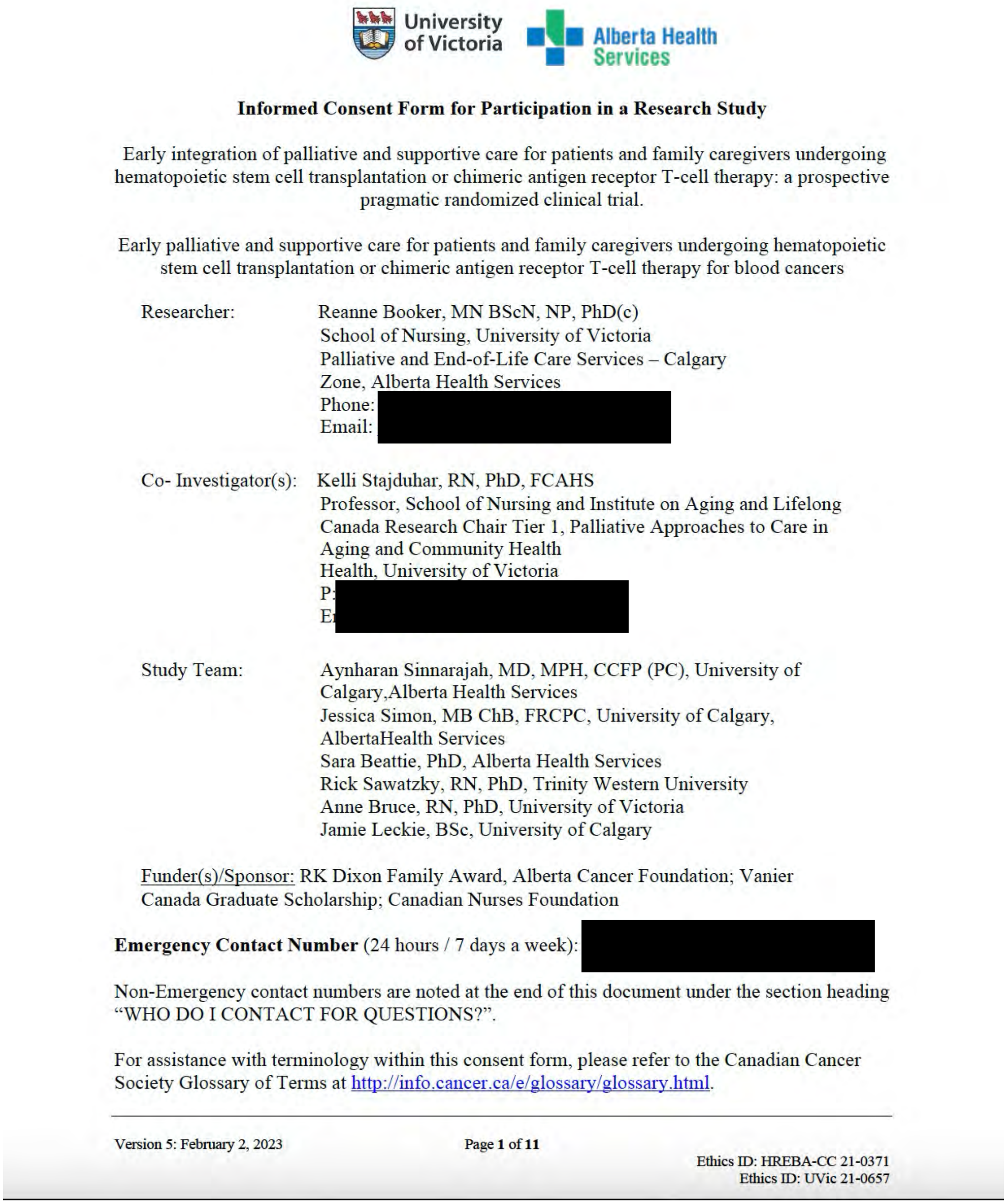
This study has been approved by the Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC 21-0371) and the University of Victoria Human Research Ethics Board (21-0657) and is funded by the Alberta Cancer Foundation RK Dixon Family Award 27265.
Version 3: February 27, 2022

Alberta Cancer FOUNDATION

Appendix H

Chapter 5: Protocol for Early Integration of Palliative and Supportive Care for Patients and Caregivers Undergoing Hematopoietic Stem Cell Transplantation or CAR T-cell Therapy: A Prospective Pragmatic Randomized Clinical Trial

Consent Forms



University of Victoria
Alberta Health Services

Informed Consent Form for Participation in a Research Study

Early integration of palliative and supportive care for patients and family caregivers undergoing hematopoietic stem cell transplantation or chimeric antigen receptor T-cell therapy: a prospective pragmatic randomized clinical trial.

Early palliative and supportive care for patients and family caregivers undergoing hematopoietic stem cell transplantation or chimeric antigen receptor T-cell therapy for blood cancers

Researcher:	Reanne Booker, MN BScN, NP, PhD(c) School of Nursing, University of Victoria Palliative and End-of-Life Care Services – Calgary Zone, Alberta Health Services Phone: [redacted] Email:
Co- Investigator(s):	Kelli Stajduhar, RN, PhD, FCAHS Professor, School of Nursing and Institute on Aging and Lifelong Canada Research Chair Tier 1, Palliative Approaches to Care in Aging and Community Health Health, University of Victoria P[redacted] E
Study Team:	Aynharan Sinnarajah, MD, MPH, CCFP (PC), University of Calgary,Alberta Health Services Jessica Simon, MB ChB, FRCPC, University of Calgary, AlbertaHealth Services Sara Beattie, PhD, Alberta Health Services Rick Sawatzky, RN, PhD, Trinity Western University Anne Bruce, RN, PhD, University of Victoria Jamie Leckie, BSc, University of Calgary

Funder(s)/Sponsor: RK Dixon Family Award, Alberta Cancer Foundation; Vanier Canada Graduate Scholarship; Canadian Nurses Foundation

Emergency Contact Number (24 hours / 7 days a week): [redacted]

Non-Emergency contact numbers are noted at the end of this document under the section heading "WHO DO I CONTACT FOR QUESTIONS?".

For assistance with terminology within this consent form, please refer to the Canadian Cancer Society Glossary of Terms at http://info.cancer.ca/e/glossary/glossary.html.

Version 5: February 2, 2023 Page **1** of **11**

Ethics ID: HREBA-CC 21-0371
Ethics ID: UVic 21-0657

You are being invited to participate in a research study because you have a blood cancer and will be undergoing hematopoietic stem cell transplantation or chimeric antigen receptor (CAR) T-cell therapy . This consent form provides detailed information about the study to assist you with making an informed decision. Please read this document carefully and ask any questions you may have. All questions should be answered to your satisfaction before you decide whether to participate.

The study staff will tell you about timelines for making your decision. You may find it helpful to discuss the study with family and friends so that you can make the best possible decision within the given timelines.

Taking part in this study is voluntary. You may choose not to take part or, if you choose to participate, you may leave the study at any time without giving a reason. Deciding not to take part or deciding to leave the study will not result in any penalty or any loss of medical or health-related benefits to which you are entitled.

One of the study researchers will discuss this study with you and will answer any questions you may have. If you do consent to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Palliative and supportive care focus on support of a patient and their family's physical, emotional and psychosocial needs, including help with decision making, while continuing with cancer-focused treatments such as chemotherapy, radiation. Palliative and supportive care provide an additional layer of support. We know from research that has been done with patients who have other types of cancer that when palliative care is introduced early, patients and their caregivers may experience better quality of life and patients may experience fewer symptoms and side effects of treatment.

There have not been many studies on how palliative and supportive care might help patients and their family caregivers before, during, and after hematopoietic stem cell transplantation or CAR T-cell therapy. This study aims to compare early palliative and supportive care to regular care for patients and their family caregivers who undergo hematopoietic stem cell transplantation or CAR T-cell therapy.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study (HREBA-CC 21-0371). The Human Research Ethics Board, University of Victoria, has also reviewed and granted ethics approval for this study (UVic Ethics ID: 21-0657).

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if integrating palliative and supportive care early in the treatment course of someone going through hematopoietic stem cell transplantation or CAR T-cell therapy is better than accessing palliative and supportive care later in the course of treatment. To do this, some of the participants in this study will get palliative and supportive care early, even before their transplant or CAR T-cell therapy starts, and some will receive standard care, where palliative and supportive care may still be provided but may be provided later in the course of treatment.

WHAT ARE OTHER OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study in order for you to receive continued medical care. Your participation is entirely voluntary and if you choose not to participate, you will still continue to receive the best care available.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 152 patients and 152 family caregivers will take part in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate then you will be "randomized" into one of the groups described below. Randomization means that you are put into a group by chance (like flipping a coin). There is no way to predict which group you will be assigned to. You will have a 50/50 chance of being placed in either group. Neither you nor the study team can choose what group you will be in.

STUDY INTERVENTION – Early palliative and supportive care

If you decide to participate in this study, you will meet with a member of the research team (via email/phone/Zoom) to complete some questionnaires before being randomized into either group. If you are randomized to the study intervention group, you will meet with a palliative and supportive care clinician 1-2 times per week, via phone or Zoom, at a time that is convenient to you, until 3 months after your transplant or CAR T-cell therapy. The meetings will include discussion about your experiences and may include topics such as your symptoms and side effects, any concerns or worries that you may have, care coordination, and your goals and wishes for treatment. Palliative and supportive care are intended to provide an additional layer of support to you and your family caregiver.

If you agree, we may contact you again at 6-12 months after your transplant or CAR T-cell therapy and ask you to complete questionnaires at those times. With your consent, we will also check your medical chart to keep track of your treatment and the medications and interventions used to help manage your symptoms and side effects. If you agree, we will check your medical chart up to 5 years after your transplant or CAR T-cell therapy to collect information about your cancer and treatment.

Group 2 (Non-experimental intervention): standard care

If you decide to participate in this study, you will meet with a member of the research team (via email/phone/Zoom) to complete some questionnaires before being randomized into either group.

If you are randomized into the non-experimental group you will be asked to complete questionnaires at 2 weeks, 1 month, and 3 months after transplant or CAR T-cell therapy.

If you are randomized into the non-experimental group, you can still receive palliative and supportive care.

If you agree, we may contact you again at 6-12 months after your transplant or CAR T-cell therapy and ask you to complete questionnaires at those times. With your consent, we will also check your medical chart to keep track of your treatment, and the medications and interventions used to help manage your symptoms and side effects. If you agree, we will check your medical chart up to 5 years after your transplant or CAR T-cell therapy to collect information about your cancer and treatment.

STUDY PROCEDURES

Questionnaires

You will be provided with some questionnaires; the type of questionnaires and the timing of when we will ask you to complete them are explained below. Each questionnaire will take about 5-10 minutes to complete.

The information you provide is for research purposes only and will remain strictly confidential. Some of the questions are personal; you may choose not to answer them.

Even though you may have provided information on a questionnaire, these responses will not be reviewed by individuals not involved in this study, e.g., your health care practitioner/team. If you would like them to know this information, please bring it to their attention.

The questionnaires include:

The McGill Quality of Life Questionnaire – Expanded (MQOL-E). This questionnaire asks questions about your quality of life. We will ask you to complete this questionnaire before you are randomized and then 2 weeks, 1 month, and 3 months after your transplant or CAR T-cell therapy.

The Functional Assessment of Cancer Therapy Bone Marrow Transplant (FACT-BMT) is another questionnaire that asks more specific questions about quality of life for someone going through hematopoietic stem cell transplantation. We will ask you to complete this questionnaire at 2 weeks, 1 month, and 3 months after your transplant or CAR T-cell therapy.

The Edmonton Symptom Assessment System (ESAS) asks you to rate 10 symptoms on a scale of 0 to 10. The ESAS assesses physical symptoms (pain, fatigue, nausea, drowsiness, dyspnea, loss of appetite), emotional symptoms (anxiety and depression), and well-being. We will ask you to complete this scale before you are randomized and then at 2 weeks, 1 month, and 3 months after your transplant or CAR T-cell therapy.

The Perception of Treatment and Prognosis Questionnaire (PTPQ) is a questionnaire that asks questions about treatment expectations, the importance and helpfulness of knowing about prognosis, the preferences for information about treatment, and the satisfaction with quality of information provided regarding prognosis and treatment. We will ask you to complete this questionnaire before you are randomized and then again at 3 months after your transplant or CAR T-cell therapy.

We may review your medical chart during the study and up to 5 years after the study to collect information about your cancer and treatment.

WHAT ARE THE POTENTIAL RISKS FROM PARTICIPATING IN THIS STUDY?

It is expected that participation in this study will be associated with minimal risk and not any greater than what would be expected in your regular care. It is possible that you may be exposed to the following risks and inconveniences:

- You may feel uncomfortable emotion or feel upset talking about your experiences.
- Inconvenience due to time commitment

To reduce these risks, the following steps will be taken:

- You do not have to answer any question(s) you do not wish to answer. There are no right or wrong answers, we are seeking your opinion and insights. If at any time you find the discussion or sharing of your experiences upsetting, you are welcome to stop completing the questionnaires.

- Support is available through the Department of Psychosocial Resources at the Tom Baker Cancer Centre. It is offered free of charge to all patients and their family members. Please call [redacted] if you need to speak with someone.

- The meetings with research team members will occur at times that are convenient to you and your family member and will occur via phone or Zoom.

A Data and Safety Monitoring Board (DSMB), an independent group of experts, will be reviewing the data throughout the conduct of the study to ensure continuing participant safety as well as scientific validity and quality of the research.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Participation in this study may or may not be of personal benefit to you.

We hope that the information learned from this study can be used to improve the quality of life and experiences of people who undergo blood stem cell or bone marrow transplantation or CAR T-cell therapy and the care provided to their family caregivers. The findings from this study will be used by the Alberta Blood and Marrow Transplant Program and nationally to improve the care provided to other Canadians undergoing blood stem cell, bone marrow transplantation or CAR T-cell therapy. Some people may find it helpful to talk about their experiences and concerns. Other researchers have found that patients with cancer who regularly report their symptoms and experiences have better quality of life and reduced symptoms and side effects associated with treatment.

However, based on the results of this study, it is hoped that in the long-term, patient care can be improved.

WHAT ARE MY RESPONSIBILITIES AS A STUDY PARTICIPANT?

If you choose to participate in this study, you will be expected to:

- Complete the questionnaires described above

HOW LONG WILL I BE PARTICIPATING IN THIS STUDY?

You will be participating in the study until 3 months after your transplant or CAR T-cell therapy. If you agree, the researchers may contact you at 6 and 12 months after your transplant or CAR T-cell therapy to ask you to complete the same questionnaires.

WILL THERE BE ANY LONG-TERM FOLLOW-UP INVOLVED WITH THIS STUDY?

We would like to contact you at 6 months and 12 months after your transplant or CAR T-cell therapy to complete questionnaires. Do you agree to someone from the research team contacting you at 6 months and 12 months after your transplant or or CAR T-cell therapy.?

☐ Yes ☐ No Participant's Initials: _________

No matter which group you are randomized to, we would like to keep track of your health for 5 years to look at the long-term effects of your participation in the study. We would review your medical chart at 1 year and 5 years after your transplant or CAR T-cell therapy. You would not be required to do anything.

You give permission to the study team to attempt to obtain study-related information about your health status at 1 and 5 years after your transplant or CAR T-cell therapy:

☐ Yes ☐ No Participant's Initials: _________

CAN I CHOOSE TO LEAVE THIS STUDY EARLY?

You can choose to end your participation in this research (called early withdrawal) at any time without having to provide a reason. If you choose to withdraw early from the study without finishing the intervention, procedure or follow-up, you are encouraged to contact the study team.

You may be asked questions about your experience with the study.

Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no additional information will be collected after you withdraw your permission. If you do not want the information collected by the researchers before you withdrew to be used, you can request that the researchers not use your information.

HOW WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study team will only collect the information they need for this study. You will be given a unique study identification number that will be used in place of your name.

Records identifying you, including information collect from your medical files/records, such as your Electronic Medical Records (EMR), Netcare, charts, etc., will be kept confidential to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document.

Authorized representatives of the following organizations may look at your identifiable medical/clinical study records at the site where these records are held for quality assurance purposes and/or to verify that the information collected for the study is correct and follows proper laws and guidelines:

- The Health Research Ethics Board of Alberta – Cancer Committee, which oversees the ethical conduct of this study

Any disclosure of your identifiable health information will be done in accordance with federal and provincial laws including the Alberta Health Information Act (HIA). The organizations listed above are required to have organizational policies and procedures to protect the information they see or receive about you, except where disclosure may be required by law. The principal investigator will ensure that any personal health information collected for this study is kept in a secure and confidential location as also required by law.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during the study will be published in medical or nursing journals and presented to the medical and nursing community at meetings. Research results will be published on the University of Victoria Library's site 'UVic Space'.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your identifiable information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information. Study data will be stored on the University of Victoria's secure server; this network storage is hosted solely in Canada.

WILL MY HEALTHCARE PROVIDER(S) BE INFORMED OF MY PARTICIPATION IN THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like. If you are undecided, the principal investigator can discuss this with you.

WILL THERE BE ANY COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participation in this study will not involve any additional costs to you or your private health care insurance.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the principal investigator.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form you do not give up any of your legal rights against the hospital, investigators, sponsor, involved institutions for compensation or their agents, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE CONFLICT OF INTEREST RELATED TO THIS STUDY?

Alberta Health Services is receiving financial payment from the Alberta Cancer Foundation to cover the cost of conducting this study. The researchers at this centre will not receive any direct benefit for conducting the study.

WHERE CAN I FIND ONLINE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on www.clinicaltrials.gov/ct2/show/NCT05190653. This website will not include information that can identify you. You can search for this website at any time.

WHO DO I CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, you should talk to the principal investigator or co-investigator. These person(s) are:

Reanne Booker	[redacted]
Name	Telephone
Kelli Stajduhar	[redacted]
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta – Cancer Committee at:

Telephone: 780-423-5727 Toll Free: 1-877-423-5727

SIGNATURES

Part 1 - to be completed by the potential participant.

	Yes	**No**
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits of taking part in this study?	☐	☐
Do you understand the risks of taking part in this study and the risks of becoming pregnant or fathering a child during this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand the alternatives to participating in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason and without affecting your future health care?	☐	☐
Do you understand who will see your records, including health information that identifies you?	☐	☐
Do you understand that by signing this consent form you are giving us permission to access your health information and specimens if applicable?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Have you had enough opportunity to ask questions and discuss this study?	☐	☐

By signing this form I agree to participate in this study.

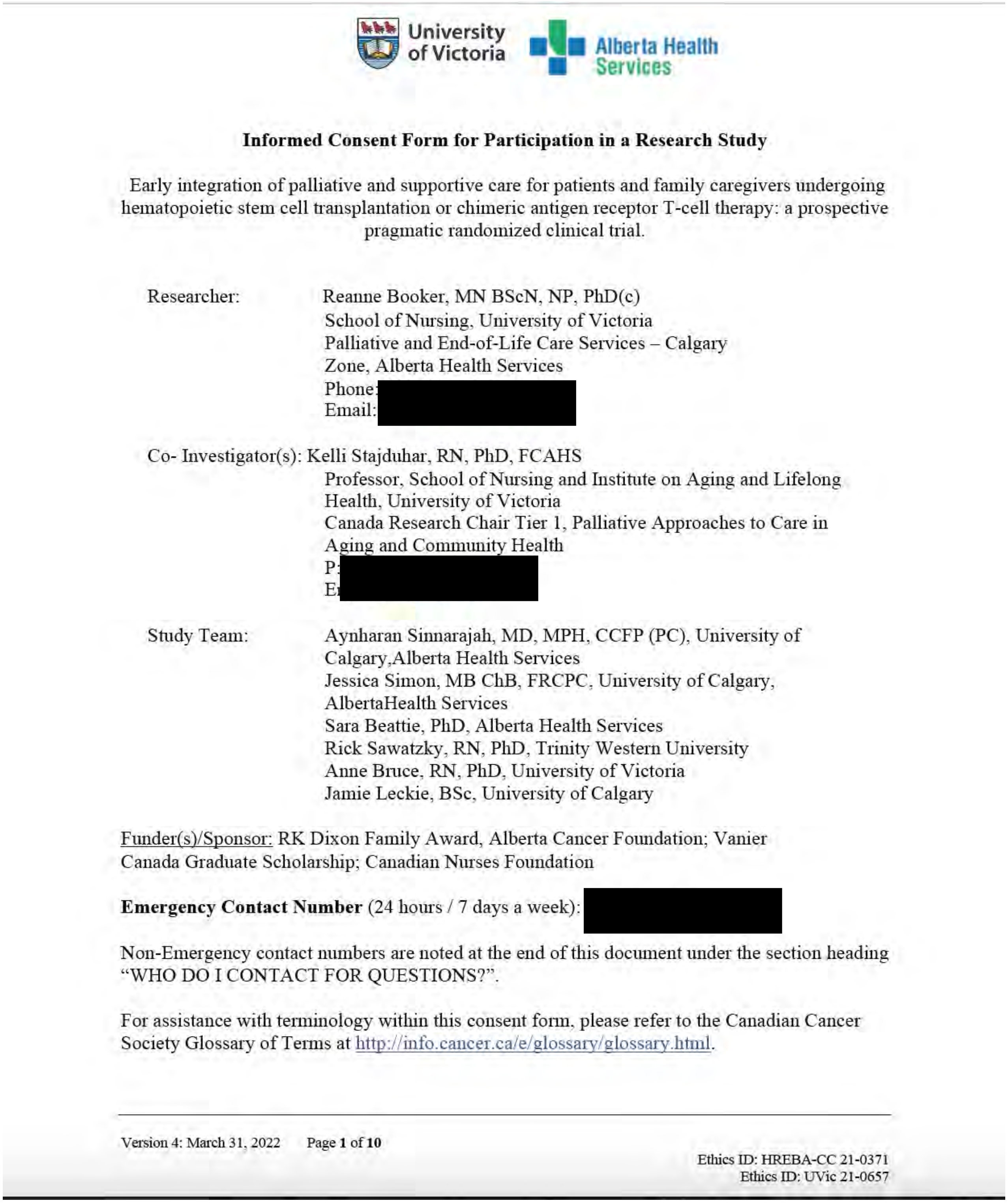
______________________	______________________	______________________
Signature of Participant	PRINTED NAME	Date

<u>Part 2</u> - to be completed by the study team member who conducted the informed consent discussion. Only compete this section if the potential participant has **<u>agreed</u>** to participate.

I believe that the person signing this form understands what is involved in the study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	PRINTED NAME	Date

You will be given a copy of this signed and dated consent form prior to participating in this study.



Informed Consent Form for Participation in a Research Study

Early integration of palliative and supportive care for patients and family caregivers undergoing hematopoietic stem cell transplantation or chimeric antigen receptor T-cell therapy: a prospective pragmatic randomized clinical trial.

Researcher: Reanne Booker, MN BScN, NP, PhD(c)
School of Nursing, University of Victoria
Palliative and End-of-Life Care Services – Calgary Zone, Alberta Health Services
Phone
Email: [redacted]

Co- Investigator(s): Kelli Stajduhar, RN, PhD, FCAHS
Professor, School of Nursing and Institute on Aging and Lifelong Health, University of Victoria
Canada Research Chair Tier 1, Palliative Approaches to Care in Aging and Community Health
P
E [redacted]

Study Team: Aynharan Sinnarajah, MD, MPH, CCFP (PC), University of Calgary,Alberta Health Services
Jessica Simon, MB ChB, FRCPC, University of Calgary, AlbertaHealth Services
Sara Beattie, PhD, Alberta Health Services
Rick Sawatzky, RN, PhD, Trinity Western University
Anne Bruce, RN, PhD, University of Victoria
Jamie Leckie, BSc, University of Calgary

Funder(s)/Sponsor: RK Dixon Family Award, Alberta Cancer Foundation; Vanier Canada Graduate Scholarship; Canadian Nurses Foundation

Emergency Contact Number (24 hours / 7 days a week): [redacted]

Non-Emergency contact numbers are noted at the end of this document under the section heading "WHO DO I CONTACT FOR QUESTIONS?".

For assistance with terminology within this consent form, please refer to the Canadian Cancer Society Glossary of Terms at http://info.cancer.ca/e/glossary/glossary.html.

Ethics ID: HREBA-CC 21-0371
Ethics ID: UVic 21-0657

You are being invited to participate in a research study because you are the family caregiver of someone who has a blood cancer and will be undergoing hematopoietic stem cell transplantation or chimeric antigen receptor (CAR) T-cell therapy. This consent form provides detailed information about the study to assist you with making an informed decision. Please read this document carefully and ask any questions you may have. All questions should be answered to your satisfaction before you decide whether to participate.

The study staff will tell you about timelines for making your decision. You may find it helpful to discuss the study with family and friends so that you can make the best possible decision within the given timelines.

Taking part in this study is voluntary. You may choose not to take part or, if you choose to participate, you may leave the study at any time without giving a reason. Deciding not to take part or deciding to leave the study will not result in any penalty or any loss of medical or health-related benefits to which you are entitled.

One of the study researchers will discuss this study with you and will answer any questions you may have. If you do consent to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

Palliative and supportive care focus on support of a patient and their family's physical, emotional and psychosocial needs, including help with decision making, while continuing with cancer-focused treatments such as chemotherapy, radiation.Palliative and supportive care provide an additional layer of support. We know from research that has been done with patients who have other types of cancer that when palliative care is introduced early, patients and their caregivers may experience better quality of life and patients may experience fewer symptoms and side effects of treatment.

There have not been many studies on how palliative and supportive care might help patients and their family caregivers before, during, and after hematopoietic stem cell transplantation or CAR T-cell therapy. This study aims to compare early palliative and supportive care to regular care for patients and their family caregivers who undergo hematopoietic stem cell transplantation or CAR T-cell therapy.

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study (HREBA-CC 21-0371). The Human Research Ethics Board, University of Victoria, has also reviewed and granted ethics approval for this study (UVic Ethics ID: 21-0657).

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out if integrating palliative and supportive care early in the treatment course of someone going through hematopoietic stem cell transplantation or CAR T-cell therapy is better than accessing palliative and supportive care later in the course of treatment. To do this, some of the participants in this study will get palliative and supportive care early, even before their transplant or CAR T-cell therapy starts, and some will receive standard care, where palliative and supportive care may still be provided but may be provided later in the course of treatment.

WHAT ARE OTHER OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study. Your participation is entirely voluntary and if you choose not to participate, you will still continue to receive the best care available.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 152 patients and 152 family caregivers will take part in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

You will be assigned to a group depending on which group your family member has been assigned to.

Group 1: Study Intervention – Early palliative and supportive care

If you decide to participate in this study, you will meet with a member of the research team (via email/phone/Zoom) to complete some questionnaires. If your family member is randomized to the study intervention group, you will meet with a palliative and supportive care clinician 1-2 times per week, via phone or Zoom, at a time that is convenient to you, until 3 months after the transplant or CAR T-cell therapy. The meetings will include discussion about your experiences and may include topics such as your family member's symptoms and sides effects, any concerns or worries that you or your family member may have, care coordination, and your family member's goals and wishes for treatment. Palliative and supportive care are intended to provide an additional layer of support to you and your family member.

If you agree, we may contact you again at 6-12 months after the patient's transplant or CAR T-cell therapy and ask you to complete questionnaires at those times.

Group 2: Non-experimental intervention: standard care

If you decide to participate in this study, you will meet with a member of the research team (via email/phone/Zoom) to complete some questionnaires before your family member is randomized into either group.

You will be asked to complete questionnaires at 2 weeks, 1 month, and 3 months after your family member's transplant or CAR T-cell therapy.

If you agree, we may contact you again at 6-12 months after your family member's transplant or CAR T-cell therapy and ask you to complete questionnaires at those times.

STUDY PROCEDURES

Questionnaires

You will be provided with some questionnaires; the type of questionnaires and the timing of when we will ask you to complete them are explained below. Each questionnaire will take about 5-10 minutes to complete.

The information you provide is for research purposes only and will remain strictly confidential. Some of the questions are personal; you may choose not to answer them.

Even though you may have provided information on a questionnaire, these responses will not be reviewed by individuals not involved in this study, e.g., your health care practitioner/team. If you would like them to know this information, please bring to their attention.

The questionnaires include:

The Quality of Life in Life-Threatening Illness – Family Carer Version 2 (QOLLTI-Fv3). This questionnaire asks questions about your quality of life. We will ask you to complete this questionnaire before you are randomized and then 2 weeks, 1 month, and 3 months after your family member's transplant or CAR T-cell therapy.

The Perception of Treatment and Prognosis Questionnaire (PTPQ) is a questionnaire that asks questions about treatment expectations, the importance and helpfulness of knowing about prognosis, the preferences for information about treatment, and the satisfaction with quality of information provided regarding prognosis and treatment. We will ask you to complete this questionnaire before you are randomized and then again at 3 months after your family member's transplant or CAR T-cell therapy.

WHAT ARE THE POTENTIAL RISKS FROM PARTICIPATING IN THIS STUDY?

It is expected that participation in this study will be associated with minimal risk and not any greater than what would be expected in your regular experience as a caregiver for someone undergoing hematopoietic stem cell transplantation or CAR T-cell therapy. It is possible that you may be exposed to the following risks and inconveniences:

- You may feel uncomfortable emotion or feel upset talking about your experiences.
- Inconvenience due to time commitment

To reduce these risks, the following steps will be taken:

- You do not have to answer any question(s) you do not wish to answer. There are no right or wrong answers, we are seeking your opinion and insights. If at any time you find the discussion or sharing of your experiences upsetting, you are welcome to stop completing the questionnaires.
- Support is available through the Department of Psychosocial Resources at the Tom Baker Cancer Centre. It is offered free of charge to all patients and their family members. Please call [redacted] if you need to speak with someone.
- The meetings with research team members will occur at times that are convenient to you and your family member and will occur via phone or Zoom.

A Data and Safety Monitoring Board (DSMB), an independent group of experts, will be reviewing the data throughout the conduct of the study to ensure continuing participant safety as well as scientific validity and quality of the research.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Participation in this study may or may not be of personal benefit to you.
We hope that the information learned from this study can be used to improve the quality of life and experiences of people who undergo blood stem cell or bone marrow transplantation or CAR T-cell therapy and the care provided to their family caregivers. The findings from this study will be used by the Alberta Blood and Marrow Transplant Program and nationally to improve the care provided to other Canadians undergoing blood stem cell, bone marrow transplantation, or CAR T-cell therapy. Some people may find it helpful to talk about their experiences and concerns. Overall, it is hoped that this study will help improve the patient and family caregiver experience.

WHAT ARE MY RESPONSIBILITIES AS A STUDY PARTICIPANT?

If you choose to participate in this study, you will be expected to:

- Complete the questionnaires described above

HOW LONG WILL I BE PARTICIPATING IN THIS STUDY?

You will be participating in the study until 3 months after your family member's transplant or CAR T-cell therapy. If you agree, the researchers may contact you at 6 and 12 months after your family member's transplant or CAR T-cell therapy to ask you to complete the same questionnaires.

WILL THERE BE ANY LONG-TERM FOLLOW-UP INVOLVED WITH THIS STUDY?

We would like to contact you at 6 months and 12 months after your family member's transplant or CAR T-cell therapy to complete the questionnaires. Do you agree to someone from the research team contacting you at 6 months and 12 months after your family member's transplant or CAR T-cell therapy?

☐ Yes ☐ No Participant's Initials: __________

CAN I CHOOSE TO LEAVE THIS STUDY EARLY?

You can choose to end your participation in this research (called early withdrawal) at any time without having to provide a reason. If you choose to withdraw early from the study without finishing the intervention, procedure or follow-up, you are encouraged to contact the study team.

You may be asked questions about your experience with the study.

Information that was recorded before you withdrew will be used by the researchers for the purposes of the study, but no additional information will be collected after you withdraw your permission. If you do not want the information collected by the researchers before you withdrew to be used, you can request that the researchers not use your information.

HOW WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study team will only collect the information they need for this study. You will be given a unique study identification number that will be used in place of your name.

Authorized representatives of the following organizations may look at your identifiable study records at the site where these records are held for quality assurance purposes and/or to verify that the information collected for the study is correct and follows proper laws and guidelines:

- The Health Research Ethics Board of Alberta – Cancer Committee, which oversees the ethical conduct of this study

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during the study will be published in medical or nursing journals and presented to the medical and nursing community at meetings. Research results will be published on the University of Victoria Library's site 'UVic Space'.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your identifiable information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information. Study data will be stored on the University of Victoria's secure server; this network storage is hosted solely in Canada.

WILL MY HEALTHCARE PROVIDER(S) BE INFORMED OF MY PARTICIPATION IN THIS STUDY?

Your family doctor/health care provider will not be informed by the study team that you are taking part in the study. You can choose to let your family doctor/health care provider know, if you like. If you are undecided, the principal investigator can discuss this with you.

WILL THERE BE ANY COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

Participation in this study will not involve any additional costs to you or your private health care insurance.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the principal investigator.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form, you do not give up any of your legal rights against the hospital, investigators, sponsor, involved institutions for compensation or their agents, nor does this form relieve these parties from their legal and professional responsibilities.

IS THERE CONFLICT OF INTEREST RELATED TO THIS STUDY?

Alberta Health Services is receiving financial payment from the Alberta Cancer Foundation to cover the cost of conducting this study. The researchers at this centre will not receive any direct benefit for conducting the study.

WHERE CAN I FIND ONLINE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on www.clinicaltrials.gov/ct2/show/NCT05190653. This website will not include information that can identify you. You can search for this website at any time.

WHO DO I CONTACT FOR QUESTIONS?

If you have questions about taking part in this study, you should talk to the principal investigator or co-investigator. These person(s) are:

Reanne Booker	[redacted]
Name	Telephone
Kelli Stajduhar	[redacted]
Name	Telephone

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta – Cancer Committee at:

Telephone: 780-423-5727

Toll Free: 1-877-423-5727

SIGNATURES

Part 1 - to be completed by the potential participant.

	Yes	**No**
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits of taking part in this study?	☐	☐
Do you understand the risks of taking part in this study and the risks of becoming pregnant or fathering a child during this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand the alternatives to participating in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason and without affecting your future health care?	☐	☐
Do you understand who will see your records, including health information that identifies you?	☐	☐
Do you understand that by signing this consent form you are giving us permission to access your health information and specimens if applicable?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Have you had enough opportunity to ask questions and discuss this study?	☐	☐

By signing this form I agree to participate in this study.

Signature of Participant

PRINTED NAME

Date

<u>Part 2</u> - to be completed by the study team member who conducted the informed consent discussion. Only compete this section if the potential participant has **<u>agreed</u>** to participate.

I believe that the person signing this form understands what is involved in the study and has freely decided to participate.

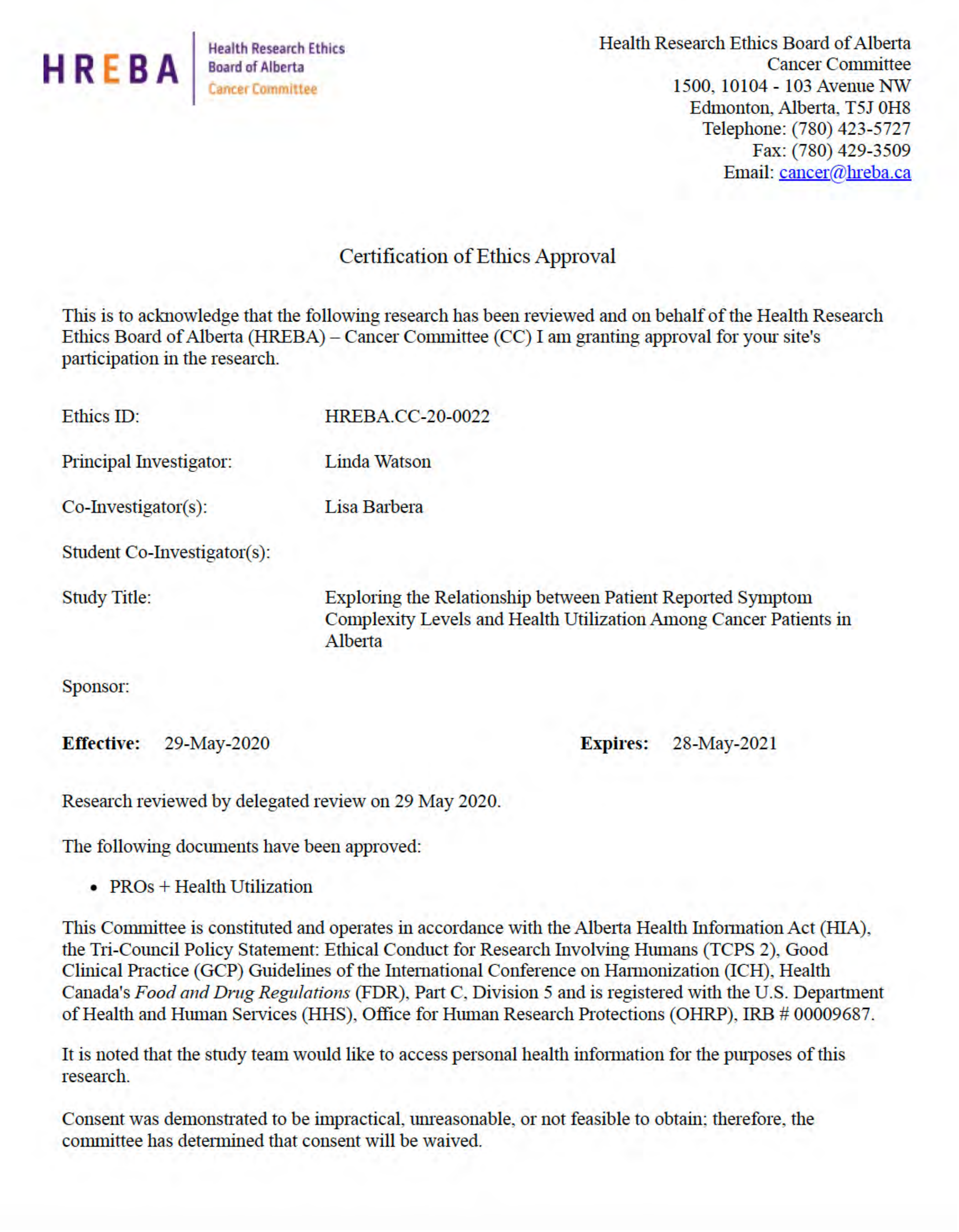
Signature of Person Conducting the Consent Discussion	PRINTED NAME	Date

You will be given a copy of this signed and dated consent form prior to participating in this study.

Appendix I

Chapter 6: Symptoms, symptom profiles, and healthcare utilization in patients with hematologic malignancies in a Canadian province: a retrospective cohort study and latent class analysis

Ethics Certificate



HREBA | Health Research Ethics Board of Alberta
Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Certification of Ethics Approval

This is to acknowledge that the following research has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC) I am granting approval for your site's participation in the research.

Ethics ID:	HREBA.CC-20-0022
Principal Investigator:	Linda Watson
Co-Investigator(s):	Lisa Barbera
Student Co-Investigator(s):	
Study Title:	Exploring the Relationship between Patient Reported Symptom Complexity Levels and Health Utilization Among Cancer Patients in Alberta
Sponsor:	

Effective: 29-May-2020 **Expires:** 28-May-2021

Research reviewed by delegated review on 29 May 2020.

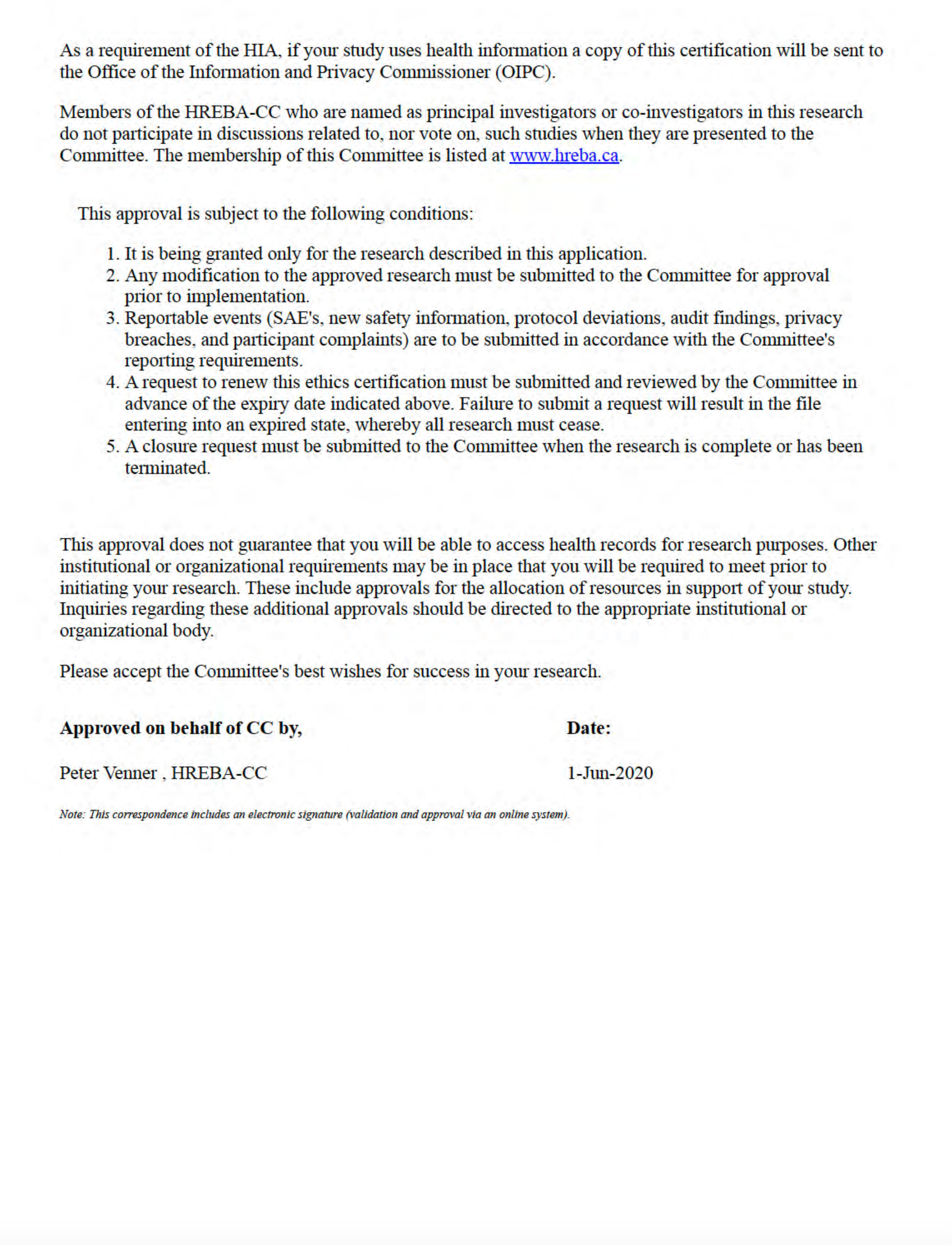
The following documents have been approved:

- PROs + Health Utilization

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 00009687.

It is noted that the study team would like to access personal health information for the purposes of this research.

Consent was demonstrated to be impractical, unreasonable, or not feasible to obtain; therefore, the committee has determined that consent will be waived.



As a requirement of the HIA, if your study uses health information a copy of this certification will be sent to the Office of the Information and Privacy Commissioner (OIPC).

Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

This approval is subject to the following conditions:

1. It is being granted only for the research described in this application.
2. Any modification to the approved research must be submitted to the Committee for approval prior to implementation.
3. Reportable events (SAE's, new safety information, protocol deviations, audit findings, privacy breaches, and participant complaints) are to be submitted in accordance with the Committee's reporting requirements.
4. A request to renew this ethics certification must be submitted and reviewed by the Committee in advance of the expiry date indicated above. Failure to submit a request will result in the file entering into an expired state, whereby all research must cease.
5. A closure request must be submitted to the Committee when the research is complete or has been terminated.

This approval does not guarantee that you will be able to access health records for research purposes. Other institutional or organizational requirements may be in place that you will be required to meet prior to initiating your research. These include approvals for the allocation of resources in support of your study. Inquiries regarding these additional approvals should be directed to the appropriate institutional or organizational body.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by,	**Date:**
Peter Venner , HREBA-CC	1-Jun-2020

Note: This correspondence includes an electronic signature (validation and approval via an online system).

HREBA Health Research Ethics Board of Alberta Cancer Committee

Health Research Ethics Board of Alberta
Cancer Committee
1500, 10104 - 103 Avenue NW
Edmonton, Alberta, T5J 0H8
Telephone: (780) 423-5727
Fax: (780) 429-3509
Email: cancer@hreba.ca

Modification of Ethics Approval

This is to acknowledge that the modification to the research indicated below has been reviewed and on behalf of the Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC), I am pleased to advise that approval has been granted.

Ethics ID:	HREBA.CC-20-0022_MOD6
Principal Investigator:	Linda Watson
Co-Investigator(s):	Lisa Barbera
Student Co-Investigator(s):	
Study Title:	Exploring the Relationship between Patient Reported Symptom Complexity Levels and Health Utilization Among Cancer Patients in Alberta
Sponsor:	

Effective: 4-Apr-2023 **Expires:** 3-Apr-2024

Modification reviewed by delegated review on 11 August 2023.

The following documents have been approved:

- Modified Protocol (clean), Aug 10 2023, August 10, 2023

This Committee is constituted and operates in accordance with the Alberta Health Information Act (HIA), the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), Good Clinical Practice (GCP) Guidelines of the International Conference on Harmonization (ICH), Health Canada's *Food and Drug Regulations* (FDR), Part C, Division 5 and is registered with the U.S. Department of Health and Human Services (HHS), Office for Human Research Protections (OHRP), IRB # 00009687.

Members of the HREBA-CC who are named as principal investigators or co-investigators in this research do not participate in discussions related to, nor vote on, such studies when they are presented to the Committee. The membership of this Committee is listed at www.hreba.ca.

Please note that the approval of this modification does not change the effective or expiry dates of this study as indicated above.

Please accept the Committee's best wishes for success in your research.

Approved on behalf of CC by,	**Date:**
Raul Urtasun, HREBA-CC	11-Aug-2023 10:41 AM

Appendix J

Chapter 6: Symptoms, symptom profiles, and healthcare utilization in patients with hematologic malignancies in a Canadian province: a retrospective cohort study and latent class analysis

Supportive Care Medications, Cohort C

alprazolam (n=1)
amitriptyline (n=10)
bupropion (n=5)
buspirone (n=1)
cannabidiol (n=1)
celecoxib (n=3)
citalopram (n=15)
clonazepam (n=6)
codeine (n=19)
cyclobenzaprine (n=10)
diclofenac (n=6)
duloxetine (n=14)
escitalopram (n=11)
fentanyl (n=7)
fluoxetine (n=1)
gabapentin (n=50)
haloperidol (n=1)
hydromorphone (n=95)
indomethacin (n=1)
ketorolac (n=2)
lorazepam (n=18)
methadone (n=3)
methotrimeprazine (n=1)
midazolam (n=1)
mirtazapine (n=29)
morphine (n=17)
naproxen (n=10)
nortriptyline (n=2)
oxycodone (n=10)
oxycodone/acetaminophen (n=4)
paroxetine (n=4)
pregabalin (n=21)
sertraline (n=8)
temazepam (n=2)
topiramate (n=1)
tramacet (n=22)
tramadol (n=5)

trazodone (n=20)
Tylenol #3 (n=31)
Tylenol #4 (n=1)
venlafaxine (n=8)