

CADTH OPTIMAL USE REPORT

Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma: Ethics and Implementation Report

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Abbreviations

ALL	acute lymphoblastic leukemia
CAR	chimeric antigen receptor
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
EMA	European Medicines Agency
FACT	Foundation for the Accreditation of Cellular Therapy
HSCT	hematopoietic stem cell transplant
HTA	health technology assessment
IEC	immune effector cells
NCA	national coverage analysis
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
r/r	Relapsed and/or refractory

Executive Summary

Background

Tisagenlecleucel (marketed as Kymriah by Novartis) is the first chimeric antigen receptor (CAR) T-cell therapy to be approved in Canada. Following a Priority Review, Health Canada approved tisagenlecleucel on September 5, 2018 for adult patients with refractory/relapsed diffuse large B-cell lymphoma (r/r DLBCL) and pediatric and young adult patients with refractory/relapsed B-cell acute lymphoblastic leukemia (r/r B-cell ALL).¹

As part of a health technology assessment (HTA) of tisagenlecleucel, CADTH conducted an Implementation Analysis and an Ethics Review to support Canadian jurisdictions with structuring the provision of tisagenlecleucel.

Ethics Review

Methods

A review of the empirical and normative ethics literature was conducted to identify literature relevant to the identification and analysis of the potential ethical, legal and social issues related to the use of tisagenlecleucel for adults with DLBCL and children and young adults with ALL.

Summary of Findings

Tisagenlecleucel is a first-in-class CAR T-cell therapy for the treatment of r/r ALL and r/r DLBCL. Given continuing uncertainty concerning clinical and economic evidence, from an ethics perspective it is best understood as an experimental therapy. This means striking a balance between the protection of vulnerable persons and the promotion of therapeutic benefit. Key ethical considerations include: i) balancing safety and efficacy, both short and long-term; ii) addressing barriers or limitations on equitable access, including geographic constraints, manufacturing and processing constraints, patient selection, and age as a criterion for access; and iii) considering the total cost of tisagenlecleucel, including its affordability at both the health system and patient levels. These considerations underline the importance of informed choice and consent in treatment decision-making as well as recognition of psychological and emotional benefits and burdens. There may also be legal questions associated with the ownership of the genetically modified T cells. Clinical and policy implications shed light on how some of these concerns may be addressed in practice and illuminate considerations for the implementation of tisagenlecleucel.

Implementation Analysis

Methods

The analysis involved the synthesis of information and results from several sources including: patient and stakeholder input; relevant information from the Clinical, Economic, and Ethics reviews conducted as part of the broader CADTH assessment; industry documents; a rapid qualitative evidence synthesis of patients' and caregivers' perspectives and experiences of advanced or terminal hematologic cancer; and a rapid qualitative evidence synthesis of implementation issues relating to tisagenlecleucel.

Summary of Findings

Deciding how to provide access to tisagenlecleucel, an expensive and novel therapy with limited long-term evidence of clinical effectiveness, safety and cost, is a challenge. Decisions-makers must determine how to structure access to tisagenlecleucel — in terms of selecting sites, supporting patient travel and short-term relocations to sites, and anticipating how the access might or should develop. Concerns about geographic inequalities and the potential for inequities in access loom large. Eligibility criteria should be developed that allow for appropriate patient selection and that anticipates clinician and patient challenges that may arise when applied. Evidentiary uncertainty around long-term clinical effectiveness and safety provides an unsteady footing for regulatory agencies and payers upon which to make decisions, especially as this therapeutic area is likely to evolve and expand in terms of approved indications and therapies.

Background and Purpose

Tisagenlecleucel (marketed as Kymriah by Novartis) is the first chimeric antigen receptor (CAR) T-cell therapy to be approved in Canada. Following a Priority Review, Health Canada approved tisagenlecleucel on September 5, 2018 for adult patients with refractory/relapsed diffuse large B-cell lymphoma (r/r DLBCL) and pediatric and young adult patients with refractory/relapsed B-cell acute lymphoblastic leukemia (r/r B-cell ALL).¹

CAR T-cell therapies involve collecting a patient's own immune cells (T cells) and genetically altering the collected cells to express a chimeric antigen receptor, which in the case of tisagenlecleucel is CD19. Once reinfused back into the patient, the CAR T-cells attach to the cancer cells because of the modified receptor and attack the cancer cells.

Manufacturing and infusion of tisagenlecleucel involves multiple steps. First, patients must be stable enough to undergo leukapheresis, a process by which their white blood cells are collected to make the product. Patients' blood is then handled through rigorous procedures for freezing, packaging, labelling, and shipping through specialized courier to the manufacturer's centralized facility in the US. At the centralized manufacturing facility, the T cells are processed, genetically modified using lentiviruses, expanded, washed, then frozen, packed, and shipped back to the treating facility. As the processing can take between three to four weeks, patients often receive bridging chemotherapy. Once the manufactured product is received by the treating facility, patients undergo lymphodepleting chemotherapy to prepare them for subsequent reinfusion. Patients are monitored post-infusion for potentially serious adverse events including cytokine release syndrome (CRS) and neurologic symptoms associated with T cell expansion and activity.

This therapy is currently indicated for patients whose cancer is relapsed or refractory (r/r). These are children, adolescents, young adults, and adults who have relapsed, perhaps more than once, or whose cancer never went into remission. They typically are given a prognosis of months, often after a long treatment journey, sometimes in the order of years. In a medically fragile state, they face ongoing deterioration in their health.

As part of a health technology assessment (HTA) of tisagenlecleucel, CADTH conducted an Implementation Analysis and an Ethics Review to support Canadian jurisdictions with structuring the provision of tisagenlecleucel. The purpose of the Implementation Analysis is to provide evidence-based information and an analysis of implementation considerations, including travel, hospital stays, and health care resource utilization and costs, to support Canadian jurisdictions with structuring the provision of tisagenlecleucel. The purpose of the Ethics Review is to identify, describe, and provide guidance on how to address the major ethical issues raised by the implementation of tisagenlecleucel for adults with DLBCL and children and young adults with ALL. Clinician Input and Patient Input were also collected to inform this assessment.

Policy Question

The analyses reported here inform the following policy question:

How should the provision of tisagenlecleucel for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (r/r ALL) and adults with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) be structured?

Ethics Review

Objectives and Approach

Ethical principles can serve as a guide to assessing and implementing new therapies such as tisagenlecleucel. Common ethical principles include:

- Promoting overall net benefit to individual patients through access to safe and effective therapies (beneficence) and minimizing risk of harm (non-maleficence).
- Respecting the importance of informed and voluntary patient choice (autonomy).
- Ensuring a fair distribution of benefits and burdens across affected patients (equity).
- Protecting the public from harm (non-maleficence) and fostering public confidence in the health system (accountability).
- Promoting the responsible use of health resources based on the best available evidence (stewardship).

It is common in an ethical analysis to consider ethical issues as well as broader legal and social issues (referred to as ELSI). While the primary emphasis of this Ethics Review is on ethical issues arising, legal and social issues are also considered in the analysis.

Principles of procedural justice are also important in health policy, particularly where there may be competing ethical principles, reasonable disagreement about how different principles ought to be balanced or prioritized, or uncertainty in the policy context. The “accountability for reasonableness” framework outlines five conditions of a legitimate and fair decision-making process toward publicly defensible decisions and support for decision-maker accountability.²

Table 1: Accountability for Reasonableness Framework

Relevance	Decisions should be based on reasons (i.e., evidence, principles, values, and arguments) that fair-minded people can agree are relevant under the circumstances.
Publicity	Decisions processes should be transparent and decision rationales should be publicly accessible.
Revision	There should be opportunities to revisit and revise decisions in light of further evidence or arguments, and there should be a mechanism for resolving disputes.
Empowerment³	There should be efforts to optimize effective opportunities for participation in priority setting and to minimize power differences in the decision-making context.
Enforcement	There should be a leadership commitment to ensure that the first four conditions are met.

The findings of the Ethics Review illustrate the relevance of these principles to the proposed implementation of tisagenlecleucel, including where more than one principle may be in conflict or it may need to be balanced and where considerations of procedural justice may be relevant.

Two research questions guided the Ethics Review:

- What are the major ethical issues raised by the implementation of tisagenlecleucel for adults with r/r DLBCL and children and young adults with r/r ALL?
- How might these issues be addressed?

The Ethics Review used a two-step approach to identify and describe potential ethical issues. The first step was a review of the ethics, clinical, and health policy and health

services literature to identify existing ethical analyses of the implementation of the technology. The second step was a *de novo* ethical analysis based on gaps identified in the literature review. The Ethics Review approach was inductive and iterative, and was responsive to results emerging from the clinical, economic and implementation reviews, including patients' and stakeholders' perspectives. A review of the empirical and normative ethics literature was conducted to identify literature relevant to the identification and analysis of the potential ELSI issues related to the use of tisagenlecleucel for adults with DLBCL and children and young adults with ALL. The literature search was performed by an information specialist, using a peer-reviewed search strategy. Further details are available in the published protocol.

Ethics Review Findings

Tisagenlecleucel as “Experimental Therapy”

Tisagenlecleucel holds promise as a last-chance therapy for patients with refractory or relapsed B-cell ALL and DLBCL. While tisagenlecleucel has demonstrated high potential for benefit, it is also associated with high risks due to short-term toxicity as well as a high degree of uncertainty about long-term effectiveness and harms.⁴ Several authors have drawn attention to the “hype” surrounding CAR T-cell therapy,⁵⁻⁹ which has been described by one author as a form of “experimental therapy” that blurs the line between research and clinical care.¹⁰ Given this, the ethical status of tisagenlecleucel may be examined from both a research ethics and a clinical ethics paradigm; the former focusing on the protection of vulnerable persons and the latter focusing on the promotion of therapeutic benefit.¹¹

Implementing tisagenlecleucel involves balancing distinct ethical imperatives of protecting vulnerable persons from harm (non-maleficence), while also guarding against paternalism and respecting patients as autonomous decision-makers capable of deciding to pursue a therapy that comes with risk (respect for persons, autonomy), and enabling patients to access potentially beneficial therapies (beneficence). Jecker et al. describe therapeutic benefit as existing along a continuum “from the complete uncertainty associated with standard research, to an intermediate stage where evidence of benefit mounts and reaches a peak, to a final stage of clearly demonstrated benefit that is sufficient to gain approval for clinical applications” (p. 393).¹¹ Furthermore, they argue that patients may have greater ethical claims to accessing therapies if evidence of therapeutic benefit mounts. As is discussed subsequently, the evidentiary uncertainty surrounding tisagenlecleucel's safety, effectiveness, and cost-effectiveness shapes many key ethical considerations related to its implementation.

Key Ethical Considerations

2.1 *Balancing Safety and Effectiveness*

A primary ethical consideration for implementing tisagenlecleucel, as with any therapy, is determining how to weigh therapeutic risks and benefits.¹² Although available evidence indicates that tisagenlecleucel has demonstrated significant benefit to some patients,⁴ its risk profile is ethically relevant in three key respects. First, tisagenlecleucel has known, severe adverse events that can occur within several weeks of administration. Second, there is uncertainty surrounding tisagenlecleucel's long-term safety and efficacy.⁴ Third, patients eligible for tisagenlecleucel are at high risk of serious health decline or death without treatment, so the risks associated with treatment remain relative to the known risks of the

patient's untreated condition.^{6,13} Among the references included in this review, there is no expert consensus concerning what constitutes an ethically justifiable or appropriate balance of risks and benefits when using tisagenlecleucel for the treatment of r/r ALL or DLBCL. Some authors have highlighted the value of a therapy that is both life- and quality-of-life-preserving, even in the face of significant risks such as severe CRS.^{9,14} This is echoed in the patient group input submissions (Summary of Patient Input) and other consultations with patients.¹³ Moreover, patients report assessing the risks and benefits associated with tisagenlecleucel in comparison to the risks and benefits of previous or alternative treatments, such as chemotherapy or stem cell transplants, which also bear serious risks (Summary of Patient Input).^{6,13}

Considering whether a therapy offers net benefit over harm in the long-term also has implications for both patients and the public. Evidentiary uncertainty about the therapy's long-term impact on safety and efficacy presents a barrier to effectively protecting present and future patients from harm. Evidentiary uncertainty also limits accurate cost-effectiveness assessments, which are used to support stewardship and public accountability in resource allocation. Evidence generating measures, such as active post-market surveillance, are necessary to inform clinical and policy decision-making that serve the interests of patients and the public.^{7,12}

2.2 Access

There are several ethical considerations associated with accessing tisagenlecleucel. Four commonly cited access concerns include: i) geographic constraints on access, ii) manufacturing and processing constraints on supply, iii) patient selection, and iv) age as a criterion for access. These concerns underline ethical tensions between safety and equity (geographic constraints), timely access and quality control (constraints on supply), patient need and procedural fairness (patient selection), and equal need and fair chances (age as a criterion for access).

2.2.1 Geographic Constraints

It has been proposed that tisagenlecleucel will be administered at a limited number of treatment centres in a limited number of provinces equipped with the resources and highly trained clinical staff required to properly administer the therapy, manage potential adverse events, and ensure safe treatment (Implementation Analysis). While this may foster safety in the provision of tisagenlecleucel, patients and caregivers who live remotely from these treatment centres will bear a disproportionate burden in accessing care compared with others patients and caregivers.^{7,12,15-17} As noted both in published literature and the Implementation Analysis under Patient Specific Considerations Relating to Access, some patients and caregivers face additional costs associated with travel, lodging, and absence from work, as well as psychological burdens associated with spending time away from family and communities, especially during a time of need (Appendix 1: Patients' and Caregivers' Perspectives and Experience Review).^{13,15,16,18} Moreover, patients are required to remain within close proximity of the treatment facility for a minimum of four weeks (during the period in which the risk of severe adverse events is highest), and then require follow-up care at multiple points over the subsequent year (Implementation Analysis). These geographic constraints and the duration of treatment together place additional burdens on patients and caregivers who live far away from treatment facilities (Implementation Analysis). When the ability to pay for treatment is a barrier to access, existing inequities in access to health care resources and outcomes are exacerbated.^{12,18,19} Hence, the geographic location of treatment centres illuminates not only an ethical tension between minimizing harm (non-

maleficence) and ensuring equitable access; it may also act as a barrier to access for some patients who are unable to shoulder the out-of-pocket costs associated with travel and short-term relocation.

2.2.2 Constraints on Supply

T cell collecting, manufacturing, and delivery processes may present additional barriers to access. As tisagenlecleucel is manufactured individually for each patient, supply is limited by access to highly trained personnel and facilities capable of collecting cells, shipping and handling the cells, administering the therapy, and managing potential adverse events (Implementation Analysis).^{6,18,20} This could have significant implications for patient outcomes given a limited treatment window, i.e., patients must be sick enough to be eligible for treatment but well enough to wait between two and four weeks while their T cells are processed for infusion.^{6,20,21} Some authors flagged additional concerns about possible off-label use for CAR T-cell therapy, which could introduce production delays for currently approved products and indications.²² With potentially limited resources for collecting, processing, and reinfusing patients' modified T cells, the demand for tisagenlecleucel may exceed supply. On the one hand, this underlines the need for efficient and high-quality production processes. On the other hand, supply constraints may entail setting priorities among patients for access to tisagenlecleucel.

2.2.3 Patient Selection

Considerations of distributive and procedural justice may arise if the demand for tisagenlecleucel exceeds manufacturing and administration capacities. Jecker et al. have proposed a set of selection criteria for prioritizing patient participation in CAR T-cell clinical trials.¹¹ First, they recommend setting a minimum threshold of expected benefit sufficient to justify the potential risk of harm (beneficence). Next, among eligible patients, they recommend giving priority to the sickest patients in order to save the most lives and improve the well-being of the worst-off (equity). Finally, in the absence of ethically salient criteria to prioritize remaining participants, they recommend using a fair procedure (e.g., random lottery) to give each patient a fair opportunity to be selected (procedural fairness). While the appropriateness of these criteria within a therapeutic context requires further consideration, Jecker et al.'s assertion that patients are entitled to a fair selection process is translatable to clinical contexts where there is an analogous need for just criteria for prioritizing access to limited therapies.

It may be the case that if evidence of tisagenlecleucel's benefit increases, there ought to be a shift in criteria from prioritizing the sickest patients (saving lives) to prioritizing patients who are most likely to benefit from therapy (promoting better outcomes and maximizing overall therapeutic impact).¹¹ Unguru et al. present curability, prognosis, and the drug's incremental significance to a patient's outcomes as guiding principles in their ethical framework for allocating scarce, life-saving pediatric cancer drugs.²³ Moreover, as patients with greater disease burden are more likely to experience severe CRS,²⁴ earlier treatment may be preferable to help mitigate toxicity.⁶ Whatever criteria may be chosen, fairness suggests the importance of a common set of selection criteria to ensure consistency across similar patients and to alleviate decision-making burden from clinicians.²³

2.2.4 Age as a Criterion for Access

Age is sometimes proposed as a criterion for prioritizing access to CAR T-cell therapy. It has been argued, for example, that pediatric and young adult patients should be prioritized on the grounds of giving them fair access to a full lifespan ("fair innings").¹¹ However, in the

case of last-chance therapy, it can be argued that medical need may be more appropriate than age as a criterion for access.²² In practice, it may also be difficult to apply the age criterion consistently (Implementation Analysis). On the one hand, there is variability among different clinical trials in the age range of children and young adults; on the other hand, age cut-offs may not be clinically relevant, e.g., is a patient who is 25 years and one month of age clinically distinctive from a patient who is 24 years and 11 months of age?²² In the case of r/r ALL, all patients — regardless of age — are similar in that they have limited or no other treatment options available.

2.3 Cost

The high cost of tisagenlecleucel is commonly identified as an ethical challenge for individual patients, clinicians, and health system funders.^{5-7,12,14,15,17,19,20,25} Although it is possible that price negotiations may reduce the cost of CAR T-cell therapy products, the total cost of CAR T-cell therapy is likely to remain high for the foreseeable future. Moreover, the total cost of tisagenlecleucel's is not limited to costs associated with the collection, manufacturing, and administration; the total cost includes pre- and post-infusion treatment costs and extra-therapeutic costs, such as travel and lodging, borne by patients and their caregivers.¹⁵ As noted in the Economic Review, the total costs of tisagenlecleucel exceed the costs that were factored into the manufacturer's cost-effectiveness assessments.^{26,27} Funding highly expensive and last-chance therapies, such as tisagenlecleucel, is sometimes defended with reference to a "rule of rescue," by which society might have an obligation to provide available, beneficial treatment to patients who face severe or terminal illness and have run out of therapeutic options.²⁸ However, at the policy level, tisagenlecleucel's high cost presents an ethical challenge related to the opportunity cost of funding some benefits but not others and the fair distribution of burdens and benefits.^{7,8,19,25} Limit-setting is necessary within budgetary constraints and raises questions about ethically appropriate criteria for constraining and prioritizing access to tisagenlecleucel based on resource availability (e.g., monetary, human resources, etc.) and other health resource demands, including forgone benefits elsewhere in the health care system⁸ as well as considerations of long-term sustainability. Moreover, as the first CAR T-cell therapy licensed in Canada, public trust for CAR T-cell therapies may depend on how tisagenlecleucel is implemented. Procedural justice in decisions about new therapies (e.g., whether to publicly fund tisagenlecleucel, eligibility criteria) can contribute to sustaining public trust.^{8,17,20}

2.4 Informed Choice About Treatment Options

Evidence gaps about safety and efficacy underline the importance of informed consent processes, on the one hand, and the need for clinical aids to assess patient-level risk and suitability for tisagenlecleucel, on the other. Patients describe tisagenlecleucel as offering "hope for the hopeless," conferring greater benefits or lower risks than treatment alternatives, such as bone marrow transplant (Summary of Patient Input), or "hope for a cure" (p. 3) where no alternatives previously existed, and hope for a treatment with fewer side effects compared with chemo-radiation and stem cell transplant therapies.¹³ Patients also describe a "fear of the unknown" (p. 3) about long-term efficacy and safety, in particular, possible neurotoxicity and its long-term impact on quality of life¹³ — a theme similarly observed in the Patients' and Caregivers' Preferences and Experiences Review (Appendix 1). However, several authors noted concerns about the unique vulnerability of patients with few therapeutic options who may pursue high-risk treatment in a context of "false promises" if benefits are overstated or harms are understated.^{7,8,15,25,29,30} Nevertheless, it is important to be wary of paternalism and recognize that patients are capable of making autonomous, rational decisions to pursue high-risk therapies.^{8,29} Some have argued that the term "cure"

ought to be eschewed or used with caution to prevent misleading or promoting false hope for patients given that the long-term clinical effectiveness of CAR T-cell therapies are unknown.⁵ Considerations about patient vulnerability and autonomy draw attention to the importance of establishing robust informed consent and education strategies for patients and caregivers.^{8,15,25,29-31} As one patient advocate argued, patient education and anticipatory guidance is essential in setting expectations related to potential benefits and risks, especially when hype exceeds available evidence.³² The need for a balanced presentation of potential benefits and risks was emphasized by several authors.^{7,15,25,32}

Consenting to treatment is best understood as an ongoing and iterative process. Given that tisagenlecleucel involves a lengthy pre- and post-infusion process with many individual procedures, it has been recommended that consent processes are accompanied by continuous education and discussion with patients and caregivers to allow them to express concerns and make informed choices.³³ For children, parents will be involved in consenting to treatment, so appropriate educational supports are required to facilitate family-based discussions. Depending on their maturity, minors may have a more active role in the consent process. However, it is generally argued that capacity to consent ought to be assessed on a case-by-case basis to facilitate patient assent, or consent where appropriate, and that this should be supported by age-appropriate educational materials and advanced directives.^{21,33,34} Caregivers describe being unprepared for how sick their loved one may become after receiving CAR T-cell therapy (Summary of Patient Input) or for dealing with any side effects.^{5,13} This underscores the importance of patient and caregiver education as constitutive of informed consent and effective treatment.³³

Existing clinical guidelines also recommend that patients should be informed that, even in the event that CAR T-cells are manufactured successfully, infusion remains contingent on the patient's continued clinical eligibility.²¹ In developing consent processes, it will be necessary to consider the extent to which patients ought to be informed and provide consent related the use of their health information or the use and knowing the status of their cells in the event of non-reinfusion (e.g., due to death or product failure).^{5,13,32} A further consideration will be to determine who should be responsible for patient and caregiver education within the health care system (e.g., clinicians, health administrators, etc.), including at transitions of care.

2.5 Beyond Clinical Harms and Benefits

In addition to the clinical harms and benefits associated with tisagenlecleucel and associated medical procedures, patients who undergo intensive and lengthy treatment and their caregivers are likely to face emotional and/or psychological burdens. Treatments that have serious side effects or require long-term hospitalization may contribute to emotional and psychological harms, including post-traumatic stress, for both patients undergoing the treatment as well as caregivers and family who witness severe side effects and are involved in caring for ill patients, often over long periods of time.^{13,33} Moreover, appropriate education and open communication with patients and caregivers throughout treatment can contribute to the safety and psychological well-being of patients.³¹ Some authors also identified societal benefits and harms emphasizing, for example, the importance of fostering and maintaining public trust and pursuing overall benefit through mechanisms such as post-market surveillance of long-term safety and effectiveness, fair decision-making processes, and public reporting.^{8,12}

2.6 Legal Considerations

There is a paucity of legal scholarship and litigation relevant to the ethical considerations of tisagenlecleucel or CAR T-cell therapies, likely because they remain nascent technologies. Litigation related to CAR T-cell therapies is thus far confined to intellectual property disputes between manufacturers in the US.³⁵ Similarly, legal scholarship on CAR T-cell therapy is primarily confined to intellectual property issues, including defining CAR T-cell therapy as a genetic therapy,^{36,37} or ownership and commodification of cells in pre-market research.³⁸ As tisagenlecleucel involves the creation of genetically modified T cells using a proprietary method, questions remain about who owns the modified cells — the patient whose T-cell have been modified, the health system, or the manufacturer — and at what point ownership is transferred; what happens to the modified T cells if a patient is no longer eligible for or dies prior to reinfusion; and for what purposes and under what conditions may any remaining modified T cells be used.

In the absence of legal scholarship, it is possible to look to the ethics literature on biobanking to identify legal and ethical concerns that may arise with respect to tisagenlecleucel. In biobanking, the primary ethical concerns about ownership of tissues or genetic material emphasize human dignity (related to identity and consent), benefit sharing (related to potential consequences of ownership, including financial and intellectual), and trust (related to the perceived intentions and trustworthiness of the owner).^{39,40} For tisagenlecleucel, considerations of human dignity may raise questions about the ownership of specimens (e.g., do genetically modified T cells belong to patients?) and its implications for consent (e.g., the extent to which patients can dictate the use of modified cells, obligations to keep patient apprised of research conducted using their cells, etc.). The ownership of cells can also constrain the extent and nature of the benefits (therapeutic, financial, or intellectual) that patients, the public, and the manufacturers accrue from the cells. Finally, ownership of biospecimens also relates to patient and public trust, which relates to legitimacy. Empirical research about biobanking with Canadian cancer patients suggests that patients place greater trust in public institutions, such as hospitals or research institutes, than for-profit companies,⁴⁰ signally that measures may need to be taken by private manufacturers in order to secure patient trust, particularly if the manufacturer has ownership of the biospecimens.

Clinical and Policy Implications

Clinical Implications

A number of clinical implications emerged through the Ethics Review. This included key strategies to address or mitigate the risks associated with using tisagenlecleucel in a clinical context. These focused on the need for:

- Patient and caregiver education, including what to expect before, during and after the treatment and how to manage potential adverse events.
- Health care provider education to support their role in caring for patients and responding to caregiver needs.
- Effective communication with patients to support informed choice (e.g., use of translators, age-appropriate language and materials).
- Informed consent based on balanced presentation of benefits/risks and an iterative process of shared decision-making.

- Consideration of the impact of CAR T-cell therapy on caregivers as well as patients (e.g., financial costs, psychological and emotional support, time commitment).

Policy Implications

The Ethics Review also identified policy implications relevant to the system-level implementation of tisagenlecleucel and the broader public. These focused on the need for legitimate and fair priority-setting and allocation processes, including the selection of treatment sites and the requirement of expert trained staff in these sites. Owing to high evidentiary uncertainty about the safety and efficacy of tisagenlecleucel, it is widely recognized that concerted post-licensing surveillance measures are required to gather long-term effectiveness and safety data.⁷ Evidence generating measures are in the public interest, but are also resource intensive, which will be an important factor in implementation design. Finally, clear and transparent communication with the general public about the benefits and risks associated with CAR T-cell therapy will be important to mitigate “hype” that may unduly affect clinical and policy decisions.^{5,31,32}

Limitations

The ethics literature concerning tisagenlecleucel in particular and CAR T-cell therapy in general is limited. Literature identifying ethical issues pertaining to pediatric populations is especially sparse. Similarly, there is little legal scholarship describing tisagenlecleucel and the use of CAR T-cell therapies. As a result, this Ethics Review draws both on a systematic review of existing literature and an original ethical analysis, which has included references to related bodies of ethics literature to identify additional ethical issues that may arise in the implementation of tisagenlecleucel.

Implementation Analysis

Objectives and Approach

The Implementation Analysis was guided by two research objectives:

- To provide a detailed description of potential pathways of care for patients to receive tisagenlecleucel, and the resources (e.g., health and human resources, training, organizational) needed to do so.
- To provide an overview of feasibility and capacity considerations relating to the provision of tisagenlecleucel at the level of the individual patient and provider (i.e., micro level), hospital or health care organization such as health authority or region (i.e., meso level) and the provincial, territorial, and federal levels (i.e., macro level).

The analysis involved the synthesis of information and results from several sources including: patient and stakeholder input; relevant information from the Clinical, Economic, and Ethics reviews conducted as part of the broader CADTH assessment; industry documents; a rapid qualitative evidence synthesis of patients', families', and providers' perspectives and experiences of advanced or terminal hematologic cancer, and a rapid qualitative evidence synthesis of implementation issues relating to tisagenlecleucel. The data and results from these sources were synthesized using a framework approach.⁴¹ Further details about the a priori methods are detailed in a published protocol.⁴² The analysis takes a pan-Canadian perspective on issues around structuring the provision of tisagenlecleucel.

Implementation Findings

The findings are presented by three interconnected themes — access, eligibility, and evidentiary uncertainty. Access refers to the models through which health care systems and clinicians might provide access to eligible patients. Eligibility refers to both the development of eligibility criteria by health care systems and the process of applying those criteria at the patient level. Evidentiary uncertainty describes areas identified as containing evidence gaps that pose challenges to structuring access to tisagenlecleucel. Issues related to access, eligibility, and evidentiary uncertainty can manifest at all stages of the process of manufacturing and delivering tisagenlecleucel.

6. Access

6.1 Proposed Model of Access

Two key features of tisagenlecleucel affect how access to it may be structured: its safety profile (i.e., the risk of severe adverse events, specifically CRS), and the specialized clinical skills and health care resources needed to treat severe adverse events. Taken together, these two features have led other regulatory jurisdictions (FDA, EMA) to limit access to tisagenlecleucel to approved or certified sites.

In the US, the FDA has provided regulatory approval for tisagenlecleucel (for both adult and pediatric indications) with a Risk Evaluation and Mitigation Strategies (REMS) requirement.⁴³ The REMS specify that the manufacturer only deliver tisagenlecleucel in sites that have completed manufacturer training and have two doses of tocilizumab per patient receiving tisagenlecleucel on hand, a key medicine for the treatment of severe CRS.⁴⁴ The

manufacturer is also to audit sites on an annual basis to ensure their continued compliance with training and certification requirements.⁴⁴ Additional pharmacovigilance requirements are also specified by the FDA and are discussed in [Section 8.3 Long-term Uncertainties](#).

In the European Union, the EMA has approved tisagenlecleucel with a Risk Management Plan that includes a controlled distribution program.⁴⁵ Similar to the FDA, the EMA has required that the manufacturer only deliver tisagenlecleucel through qualified sites that have undergone manufacturer training and have four doses of tocilizumab per patient receiving tisagenlecleucel on hand.⁴⁵ As with the FDA, the EMA specifies additional pharmacovigilance requirements, discussed in [Section 8.3 Long-term Uncertainties](#).

In Canada, regulatory decisions by Health Canada are guided by the Food and Drug Act, with a Notice of Compliance indicating that a therapeutic product that conforms to those regulations and is thus approved in Canada for market access.⁴⁶ Under a Notice of Compliance, no further post-market studies or risk management plans are formally required by Health Canada.⁴⁶

Differences in the regulatory frameworks and scope between jurisdictions (i.e., Canada, the US, and the European Union) can account for differences in the regulatory decisions. Given the division of responsibility for health care between federal and provincial and territorial governments in Canada,⁴⁶ it falls to provinces and territories to determine how to structure access to tisagenlecleucel for the indications for which it is approved.

Elsewhere, (currently for r/r B-cell ALL in UK, r/r B-cell ALL and r/r DLBCL in the US), the model of access being proposed involves rolling out the delivery of tisagenlecleucel through a limited number of qualified sites. Sites able to deliver tisagenlecleucel will be accredited by the Foundation for the Accreditation of Cellular Therapy (FACT) to perform hematopoietic stem cell transplants (HSCT) and/or meet the new standards for immune effector cells (IEC), and will require certification from the manufacturer specific to tisagenlecleucel.⁴³ The manufacturer will provide training which includes a number of important dimensions, including ordering, cell collection, handling and shipping with the chain of identity, and therapy use including management of adverse effects.^{44,47}

Given the medical fragility of patients, the multi-stage process of administering tisagenlecleucel, and the potential for life-threatening adverse events, the process of delivering tisagenlecleucel involves intensive clinical and ancillary resources.⁴⁸ Situating the therapy within HSCT centres opens up access to multidisciplinary clinical teams with experience and resources for apheresis, cell handling and shipping reinfusion, and monitoring and treating adverse events including CRS, all of which are necessary for the delivery of tisagenlecleucel.^{21,48,49} Further, selecting those sites which have achieved voluntary FACT HSCT or IEC ensures sites have the resources and training to deliver immune cellular therapies such as CAR T-cell therapies. These resources include the ability to handle the complex scheduling logistics, ensure that the chain-of-identity of the project is maintained, pharmacy training to ensure availability of specialized drugs to manage severe adverse events (notably tocilizumab for CRS), and long-term patient follow-up in registries.^{48,50}

A centralized model of access may facilitate building clinician, site, and manufacturer experience with delivering tisagenlecleucel as a commercial product.¹³ This model of access may build capacity and evidence for managing adverse events, and support the long-term evaluation of clinical effectiveness and economic impact by facilitating data collection.¹³ Further, consolidating experience with tisagenlecleucel may assist with the identification of

additional clinical and site needs for the effective and efficient delivery of tisagenlecleucel before its widespread diffusion. For instance, it may facilitate refinements in processes and allow for the identification of additional resources (e.g., improved capacity through staffing and training considerations, opportunities for efficiency through collaboration) across the process of delivering tisagenlecleucel. Through ongoing collaboration and communication across clinicians, sites, and the manufacturer, opportunities for developing best practices in the effective and efficient delivery of tisagenlecleucel in Canadian health care settings may be maximized.

6.2 Challenges with a Centralized Model of Access

Despite the potential advantages of a centralized model of access to tisagenlecleucel, it could introduce several implementation challenges. In Canada, a key challenge is how to ensure access to tisagenlecleucel across Canadian health care systems. Given the potential clinical benefit that tisagenlecleucel provides to this patient population, Canadians will likely expect to have the opportunity to access this therapy no matter where they live (Section 2.2 Access of Ethics Review).

Under the current model of access, FACT accreditation is often seen as central component of providing access, again for assuring the necessary resources for the safe administration of tisagenlecleucel.^{48,50} Currently five provinces have FACT accredited HSCT centres: British Columbia, Alberta, Manitoba, Ontario, and Quebec, leaving five provinces (Saskatchewan, New Brunswick, Prince Edward Island, Nova Scotia, Newfoundland and Labrador) and all three territories unable to deliver tisagenlecleucel according to proposed manufacture requirements.⁵¹ This raises the issue of how to provide access across provinces and territories and the potential for geographic inequalities in access (Section [2.2.1 Geographic Constraints in the Ethics Review](#)).

A centralized model of access would likely come with the expectation or promise that accredited sites will provide access to tisagenlecleucel to populations beyond their typical HSCT catchment areas. Those provinces without an access site may be required to enter into reciprocal billing arrangements. These may become complex should the process of delivering tisagenlecleucel (i.e., assessment, apheresis, bridging chemo, lymphodepletion, reinfusion, monitoring and follow-up) be funded by different sources (e.g., provincial health plans, cancer agencies, global hospital budgets).

Further, these expectations would require sites to assess their capacity and anticipate what portion of their catchment area will be eligible for tisagenlecleucel, and how many additional patients they could reasonably receive. Site specific capacity factors (including equipment availability, in-patient and outpatient treatment and clinical space, and staffing) may limit the ability to meet the demands of other provinces and territories, introducing inequalities in access to tisagenlecleucel. Increasing existing capacity, by either optimizing current resource use or by increasing available resources, may enable sites to meet the treatment needs of both out-of-catchment tisagenlecleucel patients and within-catchment HSCT and tisagenlecleucel patients. Selecting sites with the greatest capacity to accept patients outside of their catchment may minimize geographic inequalities in access to tisagenlecleucel. Access concerns due to capacity limitations and geographic inequalities perhaps could be managed with arrangements and agreements for out-of-country treatment to the US.

Whatever the model of access, the addition of a novel resource intensive treatment such as tisagenlecleucel will pose challenges to the existing capacity of HSCT centres. In recent

years, capacity issues relating to HSCT centres have been raised in the Canadian media, specifically in Ontario for adults requiring HSCT,⁵² leading to additional resources being made available. Stakeholder consultations and [Clinician Input Submissions \(Appendix 4\)](#) identified numerous points where capacity issues were already strained. These included human resources, specifically the availability of apheresis nursing staff, laboratory technicians for the processes of preserving, packaging and shipping cellular products, and multidisciplinary nursing staff for the monitoring and management of adverse events. Facilities and capital resources such as in-patient and outpatient treatment and clinician space and apheresis machines also place constraints on sites' capacity.

Adding to the challenges faced by sites is the likely increase in both the number of eligible patients due to anticipated expansion of the indications for which tisagenlecleucel is approved ([Clinician Input Submission Appendix 4](#)) and the likely increase in the number of CAR T-cell therapies approved for use in Canada. While a centralized model for clinical care is not unique or new, the proposed manufacturer certification of sites is, and poses a challenge. In the US where there are currently two CAR T-cell therapies on the market for diffuse large B-cell lymphoma (tisagenlecleucel and axicabtagene ciloleucel), approximately half of those sites delivering CAR T-cell therapies are delivering both products.⁵³ These sites have reported capacity and feasibility issues with being certified by more than one manufacturer, both in terms of start-up and ongoing auditing, and in adhering to multiple but slightly different protocols.⁵³ Decisions around the use of multiple products at sites could also have implications in the future if and when more CAR T-cell therapies are granted regulatory approval for use in Canada.

6.3 Potential Development of Models of Access

With increased clinical and health care service experience with tisagenlecleucel and a larger body of evidence on clinical effectiveness, ancillary costs, and the management of adverse effects, models of access have the potential to evolve. Two particular features of access provide opportunities to shift: expanding the number of centres able to deliver tisagenlecleucel through redistributing certification and oversight from manufacturers to professional associations, and shifting care from an in-patient to an outpatient model. Anticipating potential changes may facilitate such changes through early communication between all stakeholders and appropriate resource planning.¹³

A key opportunity to increase the number of centres able to deliver tisagenlecleucel would be to consider if FACT accreditation is a suitable requirement within Canada and, if so, identify geographical and population needs, and the sites able to meet those needs. Within Canada, Health Canada has regulatory oversight of HSCT centres under the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (CTO Regulations).⁵⁴ Compliance with the CTO Regulation is often described by Canadian transplant specialists as equivalent to or exceeding the standards assured through FACT HSCT accreditation. This option would allow Health Canada to maintain oversight of the delivery of tisagenlecleucel and enable all transplant sites within Canada to access the therapy.

As most of the provinces without FACT-accredited sites do have bone marrow transplant or stem cell transplant centres (Saskatchewan, New Brunswick, Nova Scotia, Newfoundland),⁵⁵ this option could open up access in most provinces, with the exception of Prince Edward Island and the territories. However, it may be prudent to undertake a detailed comparison of the CTO regulatory framework and the objectives of CAR T-cell specific standards (e.g., IEC) before shifting or assuming oversight. For example, ensuring the appropriate number of

doses of tocilizumab are at the infusion site, at the time of infusion, may be out of scope for the CTO Regulations, but remains a critical consideration in the delivery of tisagenlecleucel.

An alternative strategy to increasing access to tisagenlecleucel would be through increasing the number of FACT-accredited sites in Canada. To become FACT accredited, centres need to meet a variety of conditions including set volumes of patients (for example, 10 patients in the 12 months before accreditation), and have a variety of health and human resources (e.g., an active and well-staffed quality improvement program/office with stable funding that is specific to transplant and cellular therapy).⁵⁶ These and other conditions are likely challenging for smaller centres to meet, thus some consideration to balancing the benefits of accreditation with the resource expenditure (and potential additional infusion of resources needed to seek and maintain accreditation) is required if additional sites would need to be FACT accredited. The recent development of FACT IEC standards provides an alternative to FACT HSCT accreditation: these standards cover the key training and capacity considerations necessary for the delivery of CAR T-cell therapies outside of HSCT units.^{50,57} It may be possible to explore FACT IEC accreditation in locations that currently do not have FACT HSCT accreditation and in those that have the capacity and resources to deliver tisagenlecleucel outside of transplant units. Shifting oversight for CAR T-cell therapy sites from manufacturers to a third party, such as FACT or Health Canada, may also address potential challenges faced by the delivery of multiple CAR T-cell therapies.⁵⁸ As more products receive regulatory approval, such an approach might help to develop standardized non-product specific protocols for the delivery of CAR T-cell therapies, including tisagenlecleucel. Expanding geographic access of tisagenlecleucel in the future is also possible given the feasibility of delivering tisagenlecleucel on an outpatient basis.⁵⁸ Influences on the location of infusion include site-specific consideration (e.g., existing processes and resources to deliver stem cell transplant (SCT) on an outpatient basis, access pathways to intensive care unit, emergency department capacity, clinician preferences) and patient-specific factors (e.g., indication and burden of illness and treatment).^{13,58} If delivered on an outpatient basis, patients and their caregivers would need to remain within short proximity of the treating facility for a period of four to eight weeks. As an outpatient, patients can be monitored for fever, which would be the first indication of the onset of CRS at which point they would be admitted to hospital as an in-patient.²¹ Based on the current clinical evidence of safety, an outpatient basis for delivery may be more feasible for r/r DLBCL than r/r B-ALL, as patients with r/r DLBCL may experience a lower proportion of serious adverse events than with patients with r/r B-ALL.⁵⁹ Regional access on an outpatient basis would depend on clinician comfort, which would likely increase in time with more evidence and experience, as well as the further development of algorithms for the treatment of adverse events.

There will be a need for tisagenlecleucel delivery sites to have access to tocilizumab. This medication is currently indicated for a number of forms of arthritis,⁶⁰ but has been found to be effective in the management of CRS.⁶¹ In the US, the FDA has mandated that tisagenlecleucel delivery sites have a minimum of two doses on hand for each patient receiving the therapy and has approved tocilizumab for the treatment of CRS.⁴³ In the EMA, this number of doses per patient is four.⁴⁵ Within Canada, as it is not indicated for the management of CRS associated with CAR T-cell therapies, its use by delivery sites would be off-label, which may affect mechanisms for how it is reimbursed.

6.4 Patient specific considerations for access

When considering designing and funding services to deliver tisagenlecleucel to patients, the issue of timely access arises. In order for tisagenlecleucel to be effective, patients have to

be healthy enough and able to undergo lymphodepletion and be otherwise eligible for tisagenlecleucel. Given the length of time between the collection of patients' cells and the return of the manufactured product, once approved for treatment, timely access throughout the entire pathway of care will maximize opportunities to deliver effective treatment.⁶²

As a highly specialized cancer service being delivered through a centralized model, travel and short-term stays will likely be part of patients' journey to access tisagenlecleucel. Receiving tisagenlecleucel will likely involve travel for assessment, apheresis, short-term relocation (minimum of four to eight weeks) for reinfusion and monitoring of adverse events, and for short-term follow-up.

The impact of travel and relocation on patients and their caregivers can be multidimensional.⁴⁹ As described in the patient group input submissions and the Patients' and Caregivers' Perspectives and Experiences Review (Appendix 1), the act of travel itself can be physically exhausting, particularly given eligible patients are medically fragile. Travel and short-term relocation is associated with economic costs with direct and indirect patient and family-borne costs including transportation, lodging, and food. Additionally, many patients and families have to keep two households running with reduced income due to leave of absences from work. These economic burdens can add to stress and tension in families already experiencing a health crisis (Appendix 1).

Beyond economic concerns, travel and relocation can be disruptive for patients and caregivers due to being physically distant from family and support networks. This disruption can be accentuated when patients and caregivers are unfamiliar or unaccustomed to the new city and urban environs, which can add further stress and challenges. Moreover, patients and caregivers are forced to forge new relationships with health care providers at the delivery site, raising challenges with building trusting and communicative relationships in the short term (Appendix 1).⁴⁹ Given the long period of post-infusion monitoring, it may be difficult for patients who feel as though they have clinically improved to be compelled to stay near the treatment site and not return to their home, their family, and their clinical and personal support networks.

At the same time, many of those who would be travelling for tisagenlecleucel may have already experienced the need to travel for care, given the geographic dispersion of the population in many of the provinces and territories. For them, travel for care is routine or expected. For some patients, travel is associated with the perception of accessing high-quality innovative care, with urban centres seen as being able to provide better care due to the availability of greater resources. Further, the findings of the Patients' and Caregivers' Perspectives and Experiences Review suggest that transitioning from highly specialized care to local treatment centres can be challenging for some patients who feel that they are losing access to the highest quality care (Appendix 1).

Existing resources that support travel and relocation for care may be leveraged to support patients' and caregivers' travel for the process of receiving tisagenlecleucel. Aid in logistics, including securing and financing appropriate lodging during relocation becomes particularly important if tisagenlecleucel is delivered on an outpatient basis and may help retain patients for the full duration of the post-infusion monitoring period, particularly if connected to a peer support network.

Given the conditions for which patients will be receiving tisagenlecleucel therapy and the potential for serious adverse events, patients' psychosocial needs will likewise also need to be supported (Ethics Review and Appendix 1). Accounts of clinicians' experiences with CAR

T-cell therapies for r/r B-cell ALL suggest that patients' non-clinical needs can be supported in a variety of ways, including by drawing on and augmenting existing travel and relocation supports (e.g., making arrangements and providing funding), and providing access to psychological and social supports (e.g., social workers, peer support networks), and building clear and trusting relationships with clinical staff.²¹

7. Eligibility

7.1 Developing eligibility criteria

Developing and communicating eligibility criteria for tisagenlecleucel is a central implementation challenge. Eligibility criteria would serve to define which patients were likely to benefit from the therapy and which patients would be able to access it. As such, eligibility criteria can be understood as one mechanism for allocating this resource intensive therapy.

Several considerations arise when considering the development and description of eligibility criteria. These include (but are not limited to):

- The indications for which tisagenlecleucel is approved by Health Canada.
- Characteristics of patients most likely to benefit clinically from tisagenlecleucel, based on available clinical evidence.
- Physician judgment and professional autonomy.
- Communication of eligibility criteria and processes including to individual patients, their families, and patient groups, and referring physicians.
- Ways to account for newly emerging clinical evidence.
- And ethical considerations including fairness in their application.

Each of these considerations will be briefly described in turn, except for ethical concerns which are described in the [Ethics Review](#). In general, decision-makers and clinicians may wish to consider ways to develop clear, transparent, and robust criteria that maximize the likelihood of clinical benefit, minimize the risk of harms, account for clinician judgment and autonomy, are consistent with regulation and manufacturer considerations, and are acceptable to a breadth of stakeholders.

Tisagenlecleucel has currently received regulatory approval in Canada for two indications: pediatric and young adult patients three to 25 years of age with B-cell acute ALL who are refractory, have relapsed after allogeneic SCT or are otherwise ineligible for SCT, or have experienced a second or later relapse; and adult patients (≥ 18 years) with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.⁶³ The product monograph also details contraindications to tisagenlecleucel including prior central nervous system involvement.⁶³

Consultations with clinical experts highlighted two reasons for clinician support for eligibility criteria that select patients that most resemble the patient populations of the supporting clinical trials for tisagenlecleucel.²¹ First, clinicians felt that mimicking trial criteria means that one is selecting patients from those populations in which evidence of effectiveness has been assessed. Second, because of the proportion of patients who may experience serious adverse events,⁵⁹ clinicians felt it may be best to limit the use of tisagenlecleucel to those populations who have an unmet need, similar to those who were enrolled in supporting

clinical trials. Thus, eligibility criteria that mimic clinical trial eligibility criteria would be intended to both maximize benefits as well as to minimize harms.

However, two eligibility criteria — age and relapse — may be challenging to operationalize or implement. As age is part of the approved indication, any treatment of patients outside of listed age ranges would be off label and thus be potentially ineligible for reimbursement. Consultation with clinical experts suggested that in some cases, the approved age ranges may be challenging, particularly as there are no perceived biological reasons for not treating someone with the therapy on the edges of the age boundaries (i.e., 26 years of age versus 25). Moreover, based on conversations with patient groups, there will likely be a push to secure access for patients outside of the currently approved age ranges and late stage criteria. (Additional ethical issues associated with age as an eligibility criteria are discussed in the [Ethics Review](#)). While the manner in which tisagenlecleucel is ordered and manufactured means that the manufacturer could play a role to limit off-label use, including requiring adherence to the indicated age ranges, it is clear that multiple views exist on the acceptability of using age limits as an eligibility criterion.

Similar challenges arise when considering what is meant by “relapsed.” For instance, in the clinical trials for r/r B-cell ALL a threshold of 25% leukemic lymphoblasts was used as a measure of relapse.⁵⁹ The rationale is such that in patients with B-cell ALL who have had prior allogeneic SCT or a prior relapse, greater than 25% leukemic lymphoblasts suggests that the patient is going to have a full relapse. Some consulted clinicians felt it could make more sense to initiate therapy immediately upon early signs of relapse, particularly given the speed at which the disease progresses and the need for timely therapy in order for it to be effective, in addition to the potential for reduced toxicity in the event of reduced disease burden for adults with DLBCL.⁶⁴ Taken together, the issues surrounding age and relapse point to the importance of considering the role of clinical judgment and physician autonomy in developing eligibility criteria.

Whatever the criteria, the decision-making behind developing eligibility criteria and how they are applied will benefit from being transparent, evidence-based, and consistent. Individual patients and patient groups are waiting for evidence that supports the use of tisagenlecleucel earlier in the clinical pathway ([Patient Group Input Submissions Appendix 3](#)). Further, some patients have expressed a desire to know that all clinicians of potentially eligible patients will have knowledge and potential access, not just those already seeking care or residing near delivery sites. Ongoing clinical trials will provide additional evidence about the use of tisagenlecleucel in other indications, and clinical experience with the therapy will likely contribute to understanding which patients have the potential to benefit the most. A priori processes for considering additional evidence as it becomes available may aid in the development and refinement of robust criteria. Further, communication with patient groups, professional associations, referring sites, and physicians may aid in improving uptake and acceptance of eligibility criteria. Ensuring information about the availability of tisagenlecleucel and about processes and criteria for referral will facilitate physicians accessing the treatment for their patients, particularly for those not affiliated with an access site.

7.2 Challenges in Applying Eligibility Criteria

Once eligibility criteria are established, sites and treating physicians will need to apply those criteria to referred patients. Clinician judgment and autonomy arise again as important considerations, as referred patients are typically medically fragile and have already undergone extensive treatment. Given the aggressiveness of patients' cancers, their

eligibility status may change before access to treatment is possible. Ongoing clinical evaluation may need to balance those who are sick enough with advancing disease that they are most likely to benefit and yet not so sick that they are unable to endure treatment.²⁰

In the event that referrals to sites exceed capacity, there may be the need to triage patients across the pathway of receiving tisagenlecleucel. Decisions regarding the triaging of patients may best take place at the level of the site, where the clinician can make real-time assessments of patients' readiness for treatment and the availability of treatment. It is unlikely there will be any ability to triage individual patients at the point of manufacturing, thus triaging will likely fall exclusively to the delivery site. The potential for continuing assessment of eligibility and triaging highlights the potential need for short-term relocation for out-of-town and out-of-province patients.

7.3 Patient Specific Considerations for Eligibility

As with access, processes for determining individual patients' eligibility need to be efficient.⁶²

Patients, once eligible, will need to wait to receive the manufactured product after leukapheresis. The estimated waiting period of three to four weeks is stressful and challenging, as even with bridge chemotherapy, patients' conditions may continue to advance. This waiting period may become even more difficult to bear should there be manufacturing failures. Site administrators and physicians could alleviate some burden by developing protocols for how to handle manufacturing failures, including whether to recollect and reorder cells, depending on the reason for the failure. Site administrators and physicians might also consider exploring with the manufacturer if and how access to tisagenlecleucel that is manufactured out-of-specification (e.g., made with a leukapheresis product or a final manufactured product that did not meet the manufacturer's standards of cell quality or quantity standards) may be able to be delivered through the interim Managed Access Program.⁶⁵ Clear communication with patients from the initiation of therapy that eligibility does not guarantee treatment, or effect, is important. Similarly, in the event of triaging or changes in eligibility status, communication with patients and caregivers about treatment options and its timing are welcomed by patients and their caregivers.

8. Evidentiary Uncertainty

8.1 Decision-Making with Uncertainty

The limited available evidence about the long-term effectiveness and safety are a key challenge when implementing tisagenlecleucel.¹³ This is all the more given its resource intensity, both in terms of the anticipated high purchase price per patient and health care resource use relating to the pathway of care. Additional evidence supporting tisagenlecleucel's long-term clinical outcomes and economic impact may improve decision-makers' ability to make evidence-based decisions about access. In the interim, exploiting opportunities to build a flexible and adaptable approach to implementing tisagenlecleucel may support appropriate resource allocation as new evidence becomes available. Further, decision-makers who will be providing access to tisagenlecleucel will also likely face additional decisions about access to other CAR T-cell therapy products, including those that use decentralized manufacturing^{66,67} and off-the-shelf allogenic CAR T-cell therapies.⁶⁸

In many jurisdictions where tisagenlecleucel has received regulatory approval, reimbursement decisions are still under way. In England, the National Health Services announced on September 5, 2018 that tisagenlecleucel for pediatric r/r B-cell ALL would be reimbursed through the Cancer Drugs Fund.⁶⁹ In November 2018, tisagenlecleucel received

support from the National Institute for Health and Care Excellence (NICE) for reimbursement for r/r ALL, provided the managed access agreement is followed.⁷⁰ The managed access agreement includes arrangements with the manufacturer that makes tisagenlecleucel available to the National Health Services at a discount.⁷⁰ For adults with r/r DLBCL, draft guidance from NICE recommends against reimbursement for r/r DLBCL on the basis of the absence of evidence comparing it with salvage chemotherapy, it not meeting the criteria for being a life-extending treatment at the end of life, and that estimates of its cost-effectiveness are outside of the threshold for reimbursement (final guidance is to be issued in November of 2018).⁷¹ In the US, reimbursement of tisagenlecleucel is currently inconsistent across private plans.⁷² In the public insurance system, UnitedHealthcare, a provider of Medicare Advantage insurance, has requested that the Centers for Medicare and Medicaid Services (CMS) perform a national coverage analysis (NCA) of CAR T-cell therapies for cancer.⁷³ The National Coverage Analysis may recommend a National Coverage Designation (that is, uniform reimbursement across all Medicare and Medicaid plans) or recommend that reimbursement decisions are left to the discretion of individual insurance plans.⁷⁴ UnitedHealthcare requested the NCA on the basis of their assessment of the (limited) evidence on clinical effectiveness and the high costs (direct and ancillary) of CAR T-cell therapies, leading to the worry that smaller plans would be priced out of the competition, which could result in unequal access to these therapies.⁷³ The CMS decision may involve a number of dimensions that Canadian jurisdictions may also consider. These include limiting which sites can deliver CAR T-cell therapies, and assigning a Coverage with Evidence Development designation that requires further outcome data be collected in order to be reimbursed.⁷⁴

Pricing and reimbursement approaches being discussed with regard to tisagenlecleucel attempt to account for the challenges of paying for costly therapies in the context of evidentiary uncertainty. In terms of payment models, the approaches most commonly discussed in relationship to tisagenlecleucel are outcome-based models of payment and indication-specific approaches to pricing.^{5,13,17,72,74} Outcome-based models provide manufacturers' payment upon an a priori agreed-upon clinical outcome, or reimbursement to payers if the outcome is not achieved. For tisagenlecleucel, the manufacturer has been reported as proposing that payment be provided only when there has been a response to treatment (no residual disease) at one month.^{17,72,75} Outcomes-based payment is a form of risk sharing between payers and manufacturers where there remains uncertainty about clinical effectiveness. However, given limited evidence about the association between response at one month and sustained remission,^{5,13,59} and the uncertainty of the durability of remission in general,¹³ some have recommended the use of other time points including three-months⁵ or one-year outcomes¹³ as more clinically meaningful. Moreover, an important limitation of outcome-based payment is that it only addresses direct costs for purchasing tisagenlecleucel; health care systems still assume the risk for ancillary costs such as intensive care unit stays for the management of severe adverse events.⁷² A careful and consistent selection of clinical outcomes is required in order to assure payers receive value for money and that payers assume reasonable risks.

Indication-specific pricing for tisagenlecleucel is another approach to value-based pricing, which accounts for differences in the clinical effectiveness of a therapy by indication.^{5,13} It has been reported that the manufacturer is open to considering indication-specific pricing for tisagenlecleucel,⁵ with the anticipation of a higher price for r/r B-cell ALL than r/r DLBCL given its higher clinical effectiveness.^{5,13} However, differences in pricing by indication do not entirely address the issue of the overall cost of delivering tisagenlecleucel for payers.

8.2 Treatment Uncertainties

Uncertainty remains with the long-term safety and effectiveness of tisagenlecleucel.^{13,59} As the durability of remission remains to be seen, uncertainty exists about whether it is a “definitive therapy” or a bridge to HSCT once a patient is in remission.⁷⁶ Part of this uncertainty depends on the persistence of the infused CAR T-cells and whether they act as a constant anti-cancer presence, or if they are successful at eliminating all cancer and thus no longer play a role ([Clinician Input Appendix 4](#)). The issue also relates to the potential for prolonged B-cell aplasia, where patients need long-term intravenous immunoglobulin (IVIG) therapy as long as their modified T cells persists.⁵⁹ Depending on the mechanism by which tisagenlecleucel induces remission (constant presence versus total one time elimination), it raises the question of how long patients need their modified T cells,⁷⁶ or if they should be removed to enable the development of healthy B cells.

Additionally, there is the potential to move tisagenlecleucel to earlier in the treatment trajectory before HSCT,^{62,76} in particular as evidence of its effectiveness mounts ([Ethics Review](#)). Evidence is needed to support decision-making around how tisagenlecleucel might fit elsewhere into the trajectory of care and in relation to other available therapies.¹³

A final area of treatment uncertainty arises from the fact that tisagenlecleucel would be manufactured commercially for the first time for Canadian markets. As a new process, there may be initial hurdles with scaling up production of tisagenlecleucel. For example, in the US, the manufacturer has reported challenges with manufacturing a product for DLBCL that meets specifications, particularly due to cell variability associated with the condition and due to commercial products having high-quality control standards.⁷⁷ Additionally, the manufacturer has established an interim Managed Access Program for out-of-specification products,⁶⁵ suggesting that the manufacturer anticipates a certain rate of manufacturing failures.

8.3 Long-Term Uncertainties

Given the existing uncertainties, long-term follow-up studies for clinical effectiveness and safety have been required by other jurisdictions (FDA, EMA).^{44,45} As a result, the manufacturer is conducting one observational study (registry). The study will enrol treated patients and collect data on clinical effectiveness and safety outcomes over the planned long-term follow-up of 15 years.^{43,45} The registry is to be hosted by the Center for International Blood and Marrow Transplant Research and will involve the manufacturer providing annual safety reporting. The registry will be used to monitor measures of effectiveness, serious adverse events, and other safety concerns related to immunogenicity and mutagenicity.^{58 13}

Limitations

The purpose of the Implementation Analysis was to provide information and analysis about structuring the provision of tisagenlecleucel in Canadian jurisdictions. The review identified resources needed and capacity issues arising across the process of delivering tisagenlecleucel; however, it should be recognized that the perspectives of other non-physician health professionals and staff involved in procedures and processes needed for the delivery of CAR T-cell therapies were neither directly sought nor considered. As a result, there may be areas of resource constraint or additional implementation considerations beyond those identified by this analysis. Furthermore, this review included and combined an analysis of both indications for tisagenlecleucel. Health care systems for treating childhood

and adult patients with cancer differ in a variety of ways, including influences on access and delivery such as policy landscape, funding sources, geographic diffusion, and capacity constraints. The detailed ways in which these influences may interact with the provision of tisagenlecleucel should be further reflected on in light of the findings of this analysis. Lastly, although effort was made in keeping this analysis up-to-date, as the regulatory approval and implementation of tisagenlecleucel as well as other CAR T-cell therapies is active and ongoing in Canada and in other jurisdictions, analyses regarding the optimal delivery of tisagenlecleucel may not reflect current practice.

Appendix 1: Patients' and Caregivers' Perspectives and Experiences Review

Research Approach and Question

Tisagenlecleucel is a chimeric antigen receptor (CAR) T-cell therapy approved for use in the treatment for children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia and adults with relapsed or refractory diffuse large B-cell lymphoma in Canada.¹ As part of CADTH's larger health technology assessment of tisagenlecleucel, a rapid qualitative evidence synthesis was conducted to understand patients', their family members', and their health care providers' perspectives and experiences related to receiving tisagenlecleucel. Given the novelty of the tisagenlecleucel and CAR T-cell therapy, it was anticipated that there would be no qualitative research specifically on tisagenlecleucel or on CAR T-cell therapy. The research question was thus broadened to explore the pathway of care in which patients' eligible for tisagenlecleucel find themselves and the treatment of advanced or end-of-life hematologic cancers. Direct experience with tisagenlecleucel was gathered through [patient group input submissions \(Appendix 3\)](#).⁴²

As such, the research question guiding this review was:

What are the experiences and perspectives of patients, their family members and their health care providers regarding advanced or terminal hematologic cancer in relation to treatment and health care?

Further details about the methods can be found in an a priori published protocol.⁴² In brief, the literature search was performed by an information specialist using a peer-reviewed search strategy. Articles published in English or French that used qualitative data collection and analysis methods to investigate the experiences of patients with advanced or end-of-life hematologic cancers and their family members and health care providers were eligible for this review. A "best fit framework" approach to data analysis was used.⁷⁸ Eligible articles were imported into NVivo 11⁷⁹ for data analysis, with the goal of creating categories that comprehensively describe the perspectives and experiences of patients, family members, and providers across the pathway of care (i.e., diagnosis, decision-making, treatment, and outcome) in which tisagenlecleucel will be offered and delivered.

Summary of Evidence

Quantity of Research Returned Though Search

The details of citation screening and article selection are presented in Figure 1 using the PRISMA⁸⁰ flowchart. A total of 2,143 citations were identified through the initial literature search. After first level screening of titles and abstracts by a single reviewer, 2,111 citations were excluded and 32 articles were retrieved for full-text review by two independent reviewers. Of these 32 articles, 15 were excluded for the following reasons: non-relevant population (n = 4); non-relevant phenomena (n = 6); non-relevant study design (n = 4); and ineligible publication type (n = 1). Seventeen publications were included in this review, seven of which used the same data set but reported on a different objective and findings.⁸¹⁻

⁸⁷ Thus, this review includes 17 publications representing 11 unique studies.

Summary of Publication Characteristics and Participants

Publication Characteristics

Table 1 describes the characteristics of the 17 included publications. Of the 17 included publications, eight of the represented studies were conducted in Australia,⁸¹⁻⁸⁸ three in the US,⁸⁹⁻⁹¹ two in the UK,^{92,93} and one each in France,⁹⁴ Japan,⁹⁵ Sweden,⁹⁶ and Malta.⁹⁷

As reported by study authors, the study designs used across the included publications were: descriptive qualitative (n = 7),⁸¹⁻⁸⁷ phenomenology (n = 2),^{93,97} grounded theory (n = 1),⁹⁴ constructivist grounded theory (n = 1),⁹⁵ or “qualitative” without further details (n = 1).⁸⁸ Authors of five publications did not report on the study design.^{89-92,96}

Fifteen publications indicated collecting data through interviews alone,^{81-87,90-97} one through focus groups alone,⁸⁹ and one with a mixture of focus groups and interviews.⁸⁸ Twelve publications indicated using purposive sampling,^{81-90,93,97} one sampled through primary physician referrals,⁹⁵ one noted identifying participants through a patient database at a supra-region cutaneous T-cell lymphomas clinic,⁹² another noted identifying participants through “clinical databases,”⁹¹ and two did not report sampling methods.^{94,96}

In terms of the research objectives, seven publications explored the experiences of patients from rural and remote areas who had to relocate or travel for treatment, and the various dimensions of the impact of travel and relocation on themselves and their family members.⁸¹⁻⁸⁷ Three publications focused on exploring end-of-life communication, one from health care providers’ perspectives,⁹⁴ one from patients’ perspectives,⁹⁵ and one from both patients’ and providers’ perspectives.⁹⁶ Five publications explored the provision of end-of-life care, three from providers’ perspectives,^{89,90,97} one from patients’ perspectives,⁸⁸ and one from the perspective of bereaved family caregivers.⁹² Two publications explored the experiences of patients with hematologic cancer, one from the perspectives of patients,⁹³ and another that included the perspectives of patients and family caregivers.⁹¹

Participant Characteristics

Participant characteristics from the 11 unique included studies are detailed in Table 2. The study populations varied and included a range of patients, family members or caregivers, and health care providers.

Three studies described in nine publications included patients only,^{81-88,93} one study included both patients and caregivers,⁹¹ and one other included both patients and health care providers.⁹⁶ A total of 40 family members or caregivers^{91,92,95} and 111 health care providers^{89,90,94,96} were included across eight of the 11 included studies. One study with seven publications included 45 patients,⁸¹⁻⁸⁷ and four others included an additional 90 patients,^{88,91,93,96} to make a total of 135 included patients.

Of those including family members or other caregivers, one study reported an age range of 37 to 65 years,⁹¹ another indicated a range of 20 years or older,⁹⁵ with the third indicating ranges of 42 years or younger and 66 years or older.⁹² Within the seven publications including study data from the same 45 patients, the age ranged between 18 to 70 years.⁸¹⁻⁸⁷ In the four remaining studies that included patients, the ages ranged from 22 to 80 years.^{88,91,93,96}

While patients' conditions varied across studies, all were focused on individuals with hematologic malignancies. Condition severity tended to be focused on relapsed or refractory hematologic malignancies at the end of life.^{88,91,93,96} Condition severity for participants included across the seven publications sharing the same study data was not reported.⁸¹⁻⁸⁷

Results

Treatment Burden Associated with Travel

Travelling was largely linked with the need to go to a metropolitan hospital for specialized hematologic cancer care. Patients and their caregivers described the ways in which travel disrupted their lives: travel is time consuming, costly, and dislocates patients and their caregivers from their social networks and economic activities.

One of largest disruptions entails the time it takes to travel for access to specialist treatment. Depending on where an individual lives and their treatment plan, patients and their caregivers could spend a few hours to a few days travelling. For some, it is even necessary to temporarily relocate.^{81,82} In either case, patients expressed the physical, emotional, and financial burdens any amount of travel could add to an already tenuous situation. Pulling them, and their caregivers, away from families, jobs and other support networks can feel isolating and risks loss of income due to time off work.^{82,84} One participant who had relocated for 15 months noted her emotional devastation, "I want to be with family. And that was a big trade-off last year being away from them. Missing out on their lives, you know." (p. 346)⁸² Rural property owners with livelihoods in agriculture noted a particular "shock to the system"^{81,83} as their treatment at larger metropolitan hospitals distanced them from their farms and prevented them from keeping up with their work.

Economic Costs of Travel

Aside from the potential indirect costs associated with travel (e.g., time off work or school), direct costs can significantly add to treatment burden. These include doubling up on living expenses for family members remaining at home (e.g., two grocery bills, daycare, long distance telephone calls),^{82,85,86} travel costs for family caregivers, and additional costs of a short-term stay in an unfamiliar metropolitan area. Often, when patients are unable to work due to their illness and lack a source of finances, the extra costs of travel contribute to the downward spiral of financial hardship for patients and their families.^{83,85} Faced with the potential of having to mortgage their farms due to the cumulative financial burdens of treatment costs, travel cost and the inability to work their land, one patient from rural Australia noted they would rather keep their property than continue treatment.⁸³ Compared with patients that are financially compromised, patients that can afford to travel to metropolitan areas were reported to be less concerned with the costs of travel.⁸⁶

Relocation and Transfer of Care

The disruptions associated with travel are amplified for those who require relocation for treatment. Here, the financial burden was reported to mount, with increasing long absences from work (resulting in reduced income).⁸³ Depending on from where people are relocating, patients and their family caregivers can find themselves in an unfamiliar metropolitan environment and uprooted from their social support networks, inducing further isolation during the difficult time of receiving care for patients' advanced cancer.⁸¹ Without access to their social support, patients struggled with coping with treatment and their illnesses.⁸¹ In some cases, family caregivers are no longer able to stay with patients due to financial responsibilities, leaving the patients feeling even more alone in their struggle to cope.⁸¹

Throughout the processes of short-term travel or longer bouts of necessary relocation, patients became acutely attuned to the ways in which health care systems distribute resources across geographic regions. As patients tend to relocate to larger metropolitan hospitals because their own local hospital(s) lack the resources (e.g., human, equipment), required for specialized cancer care, some patients have expressed distrust of treatment provided outside of metropolitan areas due to the perception that urban hospitals are able to provide superior, more innovative care.⁸⁴ Some patients and caregivers also reported being hesitant to return to local hospitals for care afterwards because they forged connections with metropolitan hospital care providers and thus were unwilling to re-adapt to a new care environment closer to home.⁸⁴

Benefits of Local Treatment

Keeping the difficulties associated with relocation and travel in mind, patients stressed the convenience of access to treatment in local hospitals. According to one participant, local treatment affords more time to focus on one's own well-being and that "The more time you can spend at home, it really boosts your morale and drive to get better..."⁸¹ While this boost to morale could certainly be self-contained, the ability to remain immersed within one's support network throughout the course of treatment was also emphasized.⁸¹ Additionally, local treatment was reported to allow those patients who either are, or could become, financially compromised to access treatment without layering additional stress on an already tenuous situation.⁸²

With local treatment, patients who are financially compromised are still able to access treatment locally due to the reduced costs of travel. In response to being asked about the importance of local treatment and not having to travel, one patient replied: "Oh, yes, financially because of my situation. I don't know how I would pay for all that [travelling to Brisbane for treatment] and what I would do with my kids. Yes, it has been great."⁸²

Patients often had to tap into medical benefits or take unpaid sick leave when travelling for care. For some patients, local care meant a reduced need to take time of work. One patient described the difference as follows:

My oncologist I use [sic] to see him at [town] when he started the visiting service to [town] every six months and of course that stopped after a while. Look I'll be honest about that when I was seeing [doctor] in [town] it was half an hour run and it was easy and I could see him at 2 o'clock and that's the thing about Brisbane you have to take the whole day off work and they're never on time. That's the thing you have to use a sick day then. But when they're closer to you in the [regional] area you can take a half day off from work. So, yeah, it is good when you can see them in a regional area. (p. 346)⁸²

A final benefit patients felt of local care was the ability to be close to their support network throughout the course of treatment. For example, another patient when describing the benefits of local care stated: "Immensely, yes [would prefer to be treated locally]... Not 400 km away from your support network. It was just great to be at home during treatment. . . . Yes, that would be the most important thing... to spend as much time at home and with your support group that you can."⁸¹

Some patients reported that a significantly shorter travel time would allow them to allocate their time to boost morale and to focus on their health.⁸⁴ For instance, when speaking to the benefits of treatment in a regional hospital rather than needing to travel all the way to a metropolitan hospital, some individuals noted combining these shorter trips with recreational or business activities as a way of normalizing their lives.⁸²

Treatment, Palliative Care, and End-of-Life Discussions

In those studies focused on health care providers' perspectives, conversations around treatment decision-making at the end of life could be influenced by characteristics of both the patient (e.g., condition severity, age) and the type of health care provider (e.g., nurse, hematologic oncologist, solid-tumour oncologist).^{90,97} For instance, one nurse working the hematology oncology unit in Grech et al.'s⁹⁷ study noted encouraging younger patients to pursue treatment "against all odds," while simultaneously questioning whether the same pursuit among older populations would really be in the patient's best interest. Whether found with a desire that younger patients "should still have a life ahead of them,"(p.241)⁹⁷ seeing their own family members in their younger patients, or a general sense of hope that treatment would be more successful, this sentiment was echoed across several other studies.^{89,94,96,97} Even where concern for overtreatment in younger patients was expressed, one physician noted they would only withdraw or advise against treatment if "dead sure about it."(p. 301)⁹⁶

In some cases, physicians shared paternalistic perspectives in which they attempt to protect their patients through probing conversations, non-verbal communication, or avoiding end-of-life discussions altogether.^{94,96} Thus, physicians appeared to struggle with their roles and the credibility of the patient-provider relationship: many care providers perceived end-of-life discussions to be incompatible with the responsibility of "saving" the patient from death and boosting a patient's morale.⁹⁴ In addition, some physicians reported viewing a patient's impending death with guilt and as a symbol of "professional failure."⁹⁴

While patients generally noted faith in their health care provider's ability to make the best treatment decisions and initiating end-of-life discussions, there were those who felt they may have asked more questions or chosen a different path had they understood their prognosis better or felt heard by their health care provider.^{92,95} For both those who trusted and those who felt unprepared, responses seemed to stem from the uncertainty surrounding their illness due to the "invisible" nature of hematologic malignancies.⁹⁵ Those trusting their care providers assumed them to be expert authorities, and thus the need for certainty is placed in care providers as expert authorities on health.

Similarly, it is important to note the psychological burden, for some, of being on "death's door."(p. 92)⁹³ Some of the participants in this study described the difficulty of always being on call and alert for their partner, for example, watching to see if there were dramatic changes in temperature. This constant vigilance played out in a psychological toll, with heightened awareness of signs and signals of a changing condition. However, this experience was not uniform. In one study by Hoff and Hermeren,⁹⁶ some patients noted that aside from wanting to be involved in decision-making, they also wanted to know where they stood and the status of their prognosis. In other words, decision-making was important but perhaps not an end in itself — patients wanted know their prognosis as part of consultations.

Limitations

The limitations of this qualitative evidence synthesis on patients' and caregivers' perspectives and experiences around advanced and terminal hematological cancer largely relate to the use of rapid review methods. The resulting analysis is largely descriptive of the data and findings of the included studies; no comparative analyses across studies were conducted due to time constraints. Similarly, as no quality appraisal was conducted, the relative strengths and limitations of the included studies were not explicitly accounted for in the findings. The absence of included studies that explored the experiences and perceptions of children and young adults with advanced or terminal cancer meant that population-specific analyses were not possible, and so the analysis reveals little of their unique perspectives and experiences.

Figure 2: Study Selection Flow Diagram — Patients’ and Family Members’ Perspectives and Experiences Review

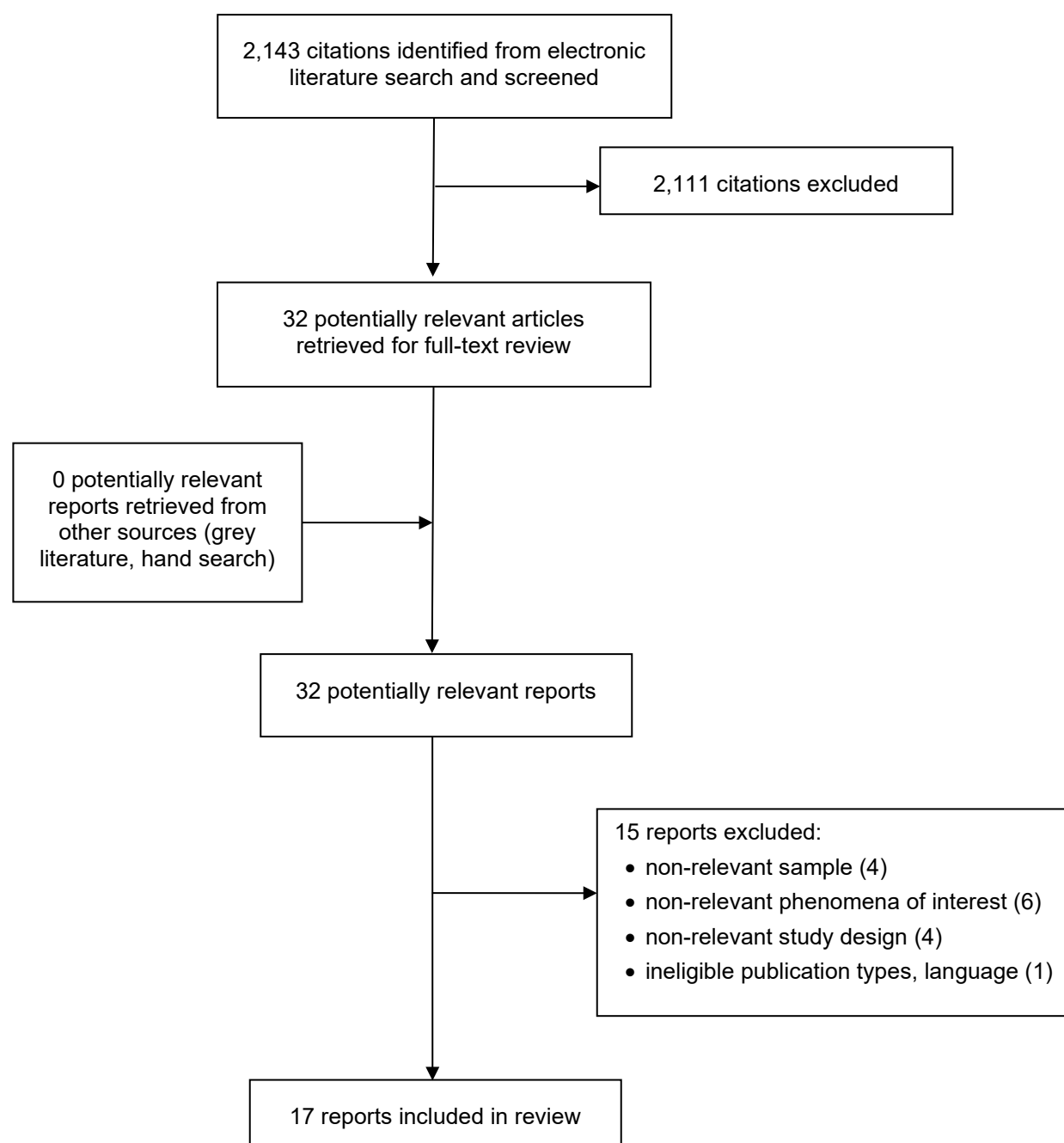


Table 1: Characteristics of Included Publications

First Author, Publication Year, Country	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection (type; sampling method)
Orlowska, 2018, ⁹² UK, Dimbleby Cancer Care	NR	To explore experiences of bereaved caregivers of patients' cutaneous T-cell lymphoma up to and beyond the death	15 family members	Bereaved relatives of patients that had cutaneous T-cell lymphoma as the primary or secondary cause of death	Semi-structured interviews; identified from patient database at supra-region cutaneous T-cell lymphoma clinic
Prod'homme, 2018, ⁹⁴ France, NR	Grounded theory	To explore hematologists' perspectives of end-of-life discussions with patients with recurring hematologic cancer	10 hematologists	Hematologic specialist members of the European Cooperator Group located in one of the four study sites	In-depth semi-structured interviews; NR
Horinuki, 2018, ⁹⁵ Japan, Policy-Based Medical Service Foundation	Constructivist grounded theory	To explore experiences of persons with hematological malignancies in communicating with health care professionals	14 family members	Bereaved family members 20 years or older who were the primary caregiver of a patient who died in acute care ward within 2 month to the past two years	Interviews; primary physician referrals
McGrath, 2016, ⁸⁶ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To provide evidence on the financial impact of relocating for hematological treatment and its contribution to poverty	45 patients	Patients with hematologic malignancies that needed to travel or relocate for specialist care	In-depth interviews; purposive sampling
Odejide, 2014, ⁸⁹ US, NR	NR	To determine how hematologic oncologists identify the end-of-life phase of a disease, to identify factors that characterize factors initiating end-of-life care, and to examine perspectives on current end-of-life care	20 hematologic oncologists	Hematologic oncologists eligible if they had at least 25% of their time attending to patients and provided longitudinal care for adult patients with blood cancers	Focus groups; purposeful sampling

First Author, Publication Year, Country	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection (type; sampling method)
McGrath, 2016, ⁸⁴ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To explore experiences and preferences of regional, rural and remote hematologic cancer patients in travelling for specialist care	45 patients	Patients with hematologic malignancies who needed to travel or relocate for specialist care	In-depth interviews; purposive sampling
McGrath, 2015, ⁸² Australia, Leukaemia Foundation of Queensland, Senior Research Fellowship	Descriptive qualitative	To explore the economic and psychosocial aspects of relocating for specialized hematologic cancer treatment in patients	45 patients	Patients with hematologic malignancies who needed to travel or relocate for specialist care	In-depth interviews; purposive sampling
McGrath, 2017, ⁸⁷ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To examine findings on referrals for financial assistance for hematologic patients who need to relocate for specialist care	45 patients	NR	In-depth interviews; purposive sampling
Dunn, 2016, ⁹³ UK, Guys and St Thomas' Foundation Trust	Phenomenological	To explore lived experiences of patients undergoing allogeneic stem cell transplant for hematologic cancer	15 patients	Patients >18 who could communicate in English and had undergone allogeneic stem cell transplant between 3 months and one year prior	Semi-structured interviews; purposive sampling
McGrath, 2016, ⁸⁵ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To understand out-of-pocket costs for patients with hematologic cancers in relocating for specialist treatment	45 patients	NR	In-depth interviews; purposive sampling
McGrath, 2015, ⁸³ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To provide findings on issues impacting rural property owners who need to travel to metropolitan areas for specialist care for	45 patients	NR	In-depth interviews; purposive sampling

First Author, Publication Year, Country	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection (type; sampling method)
		hematologic cancer			
McGrath, 2015, ⁸¹ Australia, Leukaemia Foundation of Queensland	Descriptive qualitative	To explore experiences of relocating for specialist care for patients with hematologic malignancies	45 patients	NR	In-depth interviews; purposive sampling
LeBlanc, 2015, ⁹⁰ US, National Palliative Care Research Center, National Center for Advancing Translational Sciences, University of Pittsburgh Department of Medicine	NR	To explore differences in referral practices and perspectives of palliative care among hematologic oncologists and solid-tumour oncologists	23 hematologic oncologists 43 solid-tumour oncologists	NR	In-depth semi-structured interviews; purposive sampling
Hoff, 2014, ⁹⁶ Sweden, Lund University, Sodalitium Majus Lundense, Foundation of Birgit and Sven Hakan Ohlsson	NR	To identify challenges in communicating with patients about imminent death	7 patients 10 hematologists	NR	Repeated interviews with patients, interviews with clinicians; NR
Loggers, 2014, ⁹¹ US, Grant CA 098486	NR	To explore the effect of pre-transplant discussions on mortality risk and advance care planning on survivors' or caregivers' confidence of medical team, commitment of medical team to help patient through transplant, personal hope that patient would survive	18 patients "survivors" 11 bereaved caregivers	English speaking adults ≥ 21 free of major, uncontrolled psychiatric illness Stem cell transplant survivors had to have received their transplants 6-12 months before Caregivers' of patients who had a transplant 6-12 months before and died within 6 months of the transplant	Interviews; "identified via clinical databases"

First Author, Publication Year, Country	Study Design	Study Objectives	Sample Size	Inclusion Criteria	Data Collection (type; sampling method)
McGrath, 2013, ⁸⁸ Australia, Leukemia Foundation of Queensland	Qualitative design	To provide findings on perceptions and experiences about end-of-life care for patients with hematologic cancer	50 patients	Adults with a hematologic malignancy who were at least one year post-diagnosis	Open-ended interviews, focus groups; purposive sampling
Grech, 2018, ⁹⁷ Malta, NR	Phenomenological	To explore experiences of nurses providing end-of-life care for patients with hematologic malignancies	5 nurses from one hematologic oncology unit	Nurses presently working at the hematologic oncology unit and having more than one year of experience working in that unit	In-depth semi-structured interviews; purposive sampling

NR = not reported.

Table 2: Characteristics of Study Participants

First Author, Publication Year	Sample Size	Sex (% Male)	Age (Range in Years)	Conditions	Severity of Conditions, Special Population
Orlowska, 2018 ⁹²	15 family members	33%	Under 42 to older than 66	Cutaneous T-cell lymphoma	NA; family members of patients who died
Prod'homme, 2018 ⁹⁴	10 hematologists	40%	33-56	Myeloma, lymphoma; myeloproliferative disease; acute myeloid lymphoma, allograft	NA; health care providers working with patients at the end of life
Horinuki, 2018 ⁹⁵	14 family members	NR	Older than 20	Hematological malignancies	NA; family members of patients who died
McGrath, 2016 ⁸¹⁻⁸⁷	45 patients	44%	18-70	Hodgkin disease; non-Hodgkin lymphoma; acute myeloid leukemia; acute lymphoblastic leukemia; acute promyelocytic leukemia; chronic myeloid leukemia; chronic lymphocytic leukemia; myeloma; myelodysplastic syndrome; myeloproliferative neoplasm-essential thrombocythemia; hemolytic anemia	NR; Patients from rural and remote areas
Odejide, 2014 ⁸⁹	20 hematologic oncologists	75%	NA	Leukemia; lymphoma; myeloma; hematologic malignancies	NA; Health care providers working with patients at the end of life
Dunn, 2016 ⁹³	15 patients	60%	22-68	Hodgkin lymphoma; acute myeloid lymphoma; acute lymphoblastic lymphoma; aplastic anemia; myelofibrosis; myelodysplastic syndrome; lymphoma; peripheral T-cell lymphoma	Patients undergoing stem cell transplant; NR
LeBlanc, 2015 ⁹⁰	23 hematologist-oncologists 43 solid-tumour oncologists	Hematologist oncologists: 70% Solid-tumour oncologists: 65%	NR	NA	NA; Health care providers working in palliative care

First Author, Publication Year	Sample Size	Sex (% Male)	Age (Range in Years)	Conditions	Severity of Conditions, Special Population
Hoff, 2014 ⁹⁶	7 patients 10 hematologists	Patients: 43% Hematologists: 70%	Patients: 37-80 Hematologists: NR	Malignant hematological disease	Patients at the end of life; Health care providers whose patients are at the end of life
Loggers, 2014 ⁹¹	18 patient “survivors” 11 caregivers	Patients: 44% Caregivers: 18%	Patients: 33-67 Caregivers: 37-65	Acute myeloid leukemia; acute lymphoblastic leukemia; lymphoma; multiple myeloma; chronic myelogenous leukemia; other	NR; Stem cell transplant survivors and bereaved caregivers
McGrath, 2013 ⁸⁸	50 patients	52%	22-77	Multiple myeloma, lymphoma, leukemia, and other	End of life
Grech, 2018 ⁹⁷	5 nurses	0%	25-55	NA	NA; Health care providers to patients at the end of life

NR = not reported; NA = not applicable

Appendix 2: Summaries of Clinician and Patient Input

Summary of Clinician Input Submission

Clinician Input was received for r/r DLBCL in June 2018 and summarized by CADTH staff. The full Clinician Input Submission can be found in Appendix 4 and was used to inform the Implementation Analysis.

Description of Clinicians who Submitted Input

Ten clinicians from across Canada completed the CADTH pan-Canadian Oncology Drug Review (pCODR) program's Clinician Input Submission for tisagenlecleucel, a CD19 chimeric antigen T-cell therapy (CAR T-cell therapy). There was representation from seven provinces, with two clinicians each from Quebec, Manitoba, and Saskatchewan, and one clinician each from Alberta, British Columbia, Ontario, and Newfoundland and Labrador. Two clinicians (one from Quebec and one from Ontario) had experience with tisagenlecleucel; the remaining eight clinicians had no experience with the therapy. As for clinical speciality, eight clinicians self-identified their speciality as "hematology/oncology," one clinician stated hematology, and one clinician stated their speciality was oncology.

Overview of Need and Place in Therapy

In response to current treatments for adult patients with r/r DLBCL, the clinicians described how there are few options available and how this is a population with a high unmet treatment need. Currently, standard treatment for patients is non-curative therapies (e.g., radiation therapy, oral chemotherapy, intravenous chemotherapy). This is a group of patients who have utilized all of their therapy options (including autologous stem cell transplant, allogeneic stem cell transplant, non-curative, and experimental therapies). The submitting clinicians considered CD19 CAR T-cell therapy to be "essential treatment" for patients with r/r DLBCL.

There is a great deal of expectation for CD19 CAR T-cell therapy to be the standard of care for patients for whom no further curative treatment options exist and the potential for it to provide long-term disease control. Submitting clinicians felt that clinical trials are needed to determine the superiority of tisagenlecleucel compared with other therapies, but if these trials are favourable, this therapy could replace salvage chemotherapy and allogeneic stem cell transplants earlier in the disease trajectory.

It is expected that patients will be sent to expert centres (not further specified) to determine their eligibility for treatment, due to their prolonged disease state and the potential toxicity of CAR T-cell therapies. Some patients may not be eligible for tisagenlecleucel because of contraindications or disease progression, but this proportion was not known by the submitting clinicians (due to a lack of data at the time of the submission).

Regarding eligibility, treatment with tisagenlecleucel requires immunohistochemistry testing to determine whether there is CD19 expression on tumour. It was noted that this is routine testing that could be performed on archival tissue, meaning a new biopsy before CD19 CAR T-cell therapy would not be required if there had been a biopsy expressing CD19 at some point following first and second-line therapy.

Additional Comments

The clinician submission noted that patients are currently being referred to centres in the US to get treatment and receiving provincial funding for this — though this causes inevitable delays and travel is burdensome to patients and caregivers. CAR T-cell therapy was considered as analogous to stem cell transplants by the clinicians submitting input, and the current capacity issues relating to this stem cell transplant are likely to apply to CAR T-cell therapies (i.e., number of eligible patients and lack of resources to provide timely treatment).

Summaries of Patient Group Input Submissions

Patient Input Submissions were received and summarized by CADTH staff in June 2018. Interviews with representatives with patient groups were conducted in July and August of 2018 to ask clarifying questions and for additional detail. The original patient group input submissions can be found in [Appendix 3](#) and were used to inform the Implementation Analysis

Patient Input for r/r B-cell ALL

Description of Patient Groups Who Submitted for r/r B-cell ALL

For the indication of r/r B-cell ALL in children and young adults, a joint submission was received from the Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), with collaboration from Leukemia and Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for Children with Cancer (OPACC). Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers (<http://www.curesforourkids.com/>). The mission of the Leukemia & Lymphoma Society of Canada (LLSC) is to cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families (<http://www.llscanada.org/>). Ontario Parents Advocating for Children with Cancer (OPACC) is a leading voice and expert resource for families and organizations navigating the childhood cancer journey (<http://www.opacc.org/>).

Patients' and Caregivers' Experiences of r/r B-cell ALL

For children and young adults with r/r B-cell ALL, their experience of their condition is intimately bound with its treatment. These patients have already undergone diagnosis and frontline treatment for their ALL which can span months to years. At the point of being diagnosed with r/r B-cell ALL, children and young adults are already often experiencing challenges to their emotional well-being, social and cognitive development, educational involvement, and abilities to be physically and socially active due to their previous cancer treatments.

Having cared for their ill child for potentially many years, caregivers of children and young adults with r/r B-cell ALL face many challenges. These include emotional stress, relationship difficulties, and health problems. Caregivers often described already dealing with the financial burden of caring for an ill child, including travel costs and the inability to continue working while their child was receiving treatment. Further burdens fall onto the other children in families, who deal with the emotional toll of having an ill sibling and the absences of their parent(s) as they care for their ill sibling.

It is worth noting that young adults with r/r B-cell ALL, face a unique set of challenges. Often they can find themselves navigating transitions across health care systems (from children to

adult). Depending on their personal circumstances, particularly their relationships to their families, can face dealing with fewer financial resources and be forced to make decisions about relationships, school, and work that have profound effects on their future lives.

Patients' and Caregivers' Experiences with Current Treatments for r/r B-cell ALL

At the point of relapse, families are exhausted from the struggle and upheaval of caring for a child with ALL. The physical, social, economic and emotional challenges patients and their caregivers face are exacerbated by the disappointment that prior treatment was unsuccessful and the realization that more invasive, aggressive treatment is needed. Children are often weak from the disease and initial treatment. Parents describe the distress they feel at the idea of extending or restarting treatment, using words such as lost, fearful, and helpless. Caregivers describe feeling that physicians did not know what to do next. Treatment options are limited, and some patients need to make decisions about whether to participate in a clinical trial.

Families found the treatment for relapsing disease to be more difficult and complicated than initial therapies. Some parents described these treatments as torture and poison for their children. They describes these therapies are more challenging in terms of their side effects, and given that patients' journey of care was long, families struggled to continue to care for their ill child and to maintain the household.

Patients' and Caregivers' Expectations for Tisagenlecleucel for r/r B-cell ALL

Patient input included the perspectives of caregivers of nine pediatric patients who received tisagenlecleucel for r/r B-cell ALL through clinical trials. One respondent was a parent of a child who died after enrolment but before they received tisagenlecleucel.

Respondents felt that it offered "hope for the hopeless" with significantly lower risks and more promising results than stem cell transplants.

Most patients had to travel long distances either by plane or by car for treatment and have short-term stays away from home. Caregivers described the additional difficulties of temporary relocation, and the challenges of being away from home and their families. Some families noted many costs associated with tisagenlecleucel including automobile expenses (e.g., parking, gas, mileage, and car rental), food for parents and child when away from home, accommodations (e.g., Ronald McDonald House, apartment rental, hotel), travel (e.g., airfares), medications and other costs such as professional accountant to do taxes to claim as many costs as possible.

Overall, side effects were described as tolerable and as easier than previous treatments. Few patients experienced cytokine release syndrome and only one described it as a very serious side effect, resulting in a near fatal drop in blood pressure. In another case, low white blood cell count was reported as leading to infections and an extended hospital stay.

Caregivers described tisagenlecleucel as "life changing" and that the child was now cancer free or without evidence of disease, and now living a life that was "nearly normal," with the child now at home and playing and able to act like a kid. Caregivers who responded expressed their positive views of CAR T-cell therapy as a treatment for r/r B-cell ALL and potentially as a frontline therapy for ALL through language such as having "amazing potential," being a "miracle," as the "best breakthrough," and "the future of treatment."

The perspectives of patients with r/r B-cell ALL who died after receiving and/or caregivers who are grieving the death of child and were unable to participate are not represented in the Patient Input submissions received by CADTH. The experiences of these patients and their families may not be reflected in the input received.

Summary of Patient Input for r/r DLBCL

Description of Patient Groups who Submitted Input for r/r DLBCL

For the indication of r/r DLBCL, a patient group input submission was received from Lymphoma Canada. Lymphoma Canada is Canada's only national organization focused entirely on lymphoma. Lymphoma Canada provides education materials, peer and caregiver support groups, and advocacy on behalf of patients. Lymphoma Canada also funds Canadian research (<https://www.lymphoma.ca/about-us>).

Patients' Experiences of r/r DLBCL

Patients' experiences of r/r DLBCL centres on their prior treatments. Patients with r/r DLBCL have undergone one or more first-line therapies (chemotherapy, radiation and stem cell transplants) and possibly many years of cancer treatment. Their prior diagnosis and treatments affected their physical, emotional, and mental health in a multiplicity of ways.

Physically, patients undergoing treatment for DLBCL treatment experienced a host of side effects, and reported finding fatigue, nausea/vomiting, "chemo brain", and hair loss the most difficult to tolerate.

Patients described the stress of life with DLBCL as living with fear, anxiety, depression, brain fog, fatigue, and having difficulties sleeping. Patients' and their families' financial well-being was strained the patient borne costs of treatment and reduction in ability to work. In addition to being unable to work and sometimes having to give up their career, often times a partner or other family member also had to leave work or reduce their hours in order to act as a caregiver. Those patients whose children were still at home struggled to fulfill the family's responsibilities.

Patients' Experiences with Current Treatments for r/r DLBCL

Treatment also had a significant and negative impact on many respondents' ability to work, travel and participate in daily activities because of fatigue, side effects, number of clinic visits, infusion time, number and frequency of infections, and infusion reaction. The absence from work or school for treatment also adds a serious financial burden to some patients and their families.

Patients' Expectations for Tisagenlecleucel for r/r DLBCL

When respondents to the patient group survey were asked to prioritize outcomes of new therapies, the vast majority of respondents felt "longer survival" and "longer remission" than that offered by current therapies were the most important. Also, 49% of respondents said they would choose a treatment with potentially serious side effects if recommended by their doctors, with another 49% choosing "I'm not sure" and only 3% saying "no," suggesting that patients with DLBCL are willing to tolerate negative side effects of therapies.

CAR T-cell therapies and tisagenlecleucel represent a last resort for many of these patients, and should they achieve remission, a chance to live for longer with less side effects. Of the

nine respondents who had a CAR T-cell therapy to treat their cancer, two patients from Canada who had tisagenlecleucel reported being in remission.

Patients expressed a range of views of the tolerability of side effects, with one comparing it as easier than autologous stem cell transplant, while another describing it as a very difficult treatment. None of the respondents reported experiencing the potentially fatal toxicities, including cytokine release syndrome and neurological toxicities that are known side effects of CAR T-cell therapy treatment. Costs associated with travel were noted as being a substantial concern, as they included having to travel for initial assessment, for cell collection, and for infusion, then monitoring. Patient-borne costs are a negative dimension of the treatment burden associated with patients' access to tisagenlecleucel.

The perspectives of patients with r/r DLBCL who died after receiving treatment and were unable to participate are not represented in the patient group input submissions received by CADTH. The experiences of these patients may not be reflected in the input received.

Appendix 3: Patient Input Submissions for Tisagenlecleucel for Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma

Patient group input submissions were received from the following patient groups.

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn),
Leukemia and Lymphoma Society of Canada (LLSC) and
Ontario Parents Advocating for Children with Cancer (OPACC)

Lymphoma Canada

CADTH received patient group input for this review on or before June 20, 2018

The views expressed in each submission are those of the submitting organization or individual; not necessarily the views of CADTH or of other organizations.

While CADTH formats the patient input submissions for posting, it does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no personal information is included in the submission. The name of the submitting patient group and all conflict of interest information are included in the posted patient group submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Tisagenlecleucel (Kymriah) CAR T-Cell Therapy (Novartis)
Name of the Patient Group	Childhood Acute Lymphoblastic Leukemia
Author of the Submission	Advocacy for Canadian Childhood Oncology Research Network (Ac2orn), Leukemia and Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for Children with Cancer (OPACC)

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)

Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers.

<http://www.curesforourkids.com/>

Leukemia and Lymphoma Society of Canada (LLSC)

The mission of the Leukemia & Lymphoma Society of Canada (LLSC) is: Cure leukemia, lymphoma, Hodgkin's disease and myeloma, and improve the quality of life of patients and their families.

<http://www.llscanada.org/>

Ontario Parents Advocating for Children with Cancer (OPACC)

OPACC will be the leading voice and expert resource for families and organizations navigating the childhood cancer journey.

<http://www.opacc.org/>

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

Information was gathered through one survey, provided in both English and French and jointly created by Ac2orn, LLSC and OPACC. The survey was created and made available to respondents in March 2018 and closed in June 2018. Four one-on-one interviews were also conducted.

An online survey was posted using Survey Monkey in both French and English and distributed by Ac2orn, LLSC, and OPACC through various social media channels and directly by email. The survey asked for input from patients and families who were treated for childhood leukemia, and who may or may not have had experience with CTL019.

There were 115 responses to the English survey, with 59 complete responses. There were three responses to the French survey. There were a total of 10 respondents with direct experience with CTL019.

The majority of respondents identified the location of their primary residence as Ontario (96 responses). Quebec (6 responses), Alberta (4 responses), and British Columbia (3 responses), Nova Scotia (2 responses) and Saskatchewan (2 responses) were also

represented. There was one response from the US and one response from an international respondent. Overall, the survey respondents were Ontario- centric; however, there was representation from across Canada overall.

The majority of respondents were the parent of the patient (104 responses). Five respondents were the actual patients, two respondents were an immediate family member of the patient, one respondent identified as the legal guardian of the patient, and four respondents stated "other."

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Pre-Diagnosis:

Children diagnosed with leukemia varied at their age of diagnosis. The following is the breakdown for the respondents by prevalence from most to least:

1. 2 years old
2. 3 years old
3. 10 to 14 years old
4. 4 years old
5. 5 years old
6. 8 years old
7. 15 years or older
8. 6 years old
9. Younger than 1 year of age
10. 9 years old
11. 1 year old
12. 7 years old

The main symptoms experienced prior to diagnosis included low energy level, pain, fevers, bruising, weight loss or gain, headaches, nausea and vomiting, skin changes, constipation, and other side effects.

Indirect treatment side effects and impact on quality of life included (in order from most prevalent to least prevalent):

1. Changes to physical activity
2. Eating challenges
3. Mental health and overall happiness
 - Withdrawn from normal activities and engagement with family and friends
4. Anxiety
5. Educational development
 - Not able to attend school
 - Scattered thinking and delayed cognitive development
6. Social development

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers. Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

Experiences with Frontline Therapy:

Diagnosis:

Post initial diagnosis and during frontline therapy, the following treatments were experienced, listed in the order of most common to least:

1. chemotherapy
2. maintenance therapy
3. high-dose chemotherapy
4. radiation
5. surgery
6. steroid treatment
7. stem cell transplant
8. immunotherapy.

Direct treatment-related side effects and their impact (in order from most prevalent to least):

1. Neutropenia (low white blood cell counts)
2. Hair loss
3. Movement/ability to take part in physical activities
4. Fevers
5. Nausea
6. Pain
7. Vomiting
8. Constipation
9. Neuropathic pain
10. Organ damage
11. Impact to eye-sight

Respondents also commented on issues relating to steroid treatment with mood changes and anxiety, and mobility changes with paralysis and muscle stiffening.

Many respondents commented on both the negative and positive aspects of frontline treatments:

“Negative: - major weight loss (20 kg) – mouth sores - paralysis - reactions (rashes, inflamed hands) - weakness in extremities of hands and feet - weakness in legs (lost the ability to walk) - infections due to low neutrophil counts - nausea and reflux - back pain from lumbar punctures Positive: - gained an new perspective - became more appreciative.”

“I liked how **most of her treatment was done as a day patient** limiting how often she had to sleep in the hospital. She did have some planned an unplanned admissions, but for the most part, treatment was done in the day hospital or with oral medication at home.”

“**Very difficult.** Nausea, vomiting, severe weight loss, fatigue, falls, muscle pain, hair loss twice, bruising, general pain, stress/fear, loneliness, isolation, inability to run or do normal kid activities.”

"Frontline treatment is **very hard**. Positive experience was all of the care team was great at explaining and offering different avenues of support for all of us as a family and not just for our child. Negative experiences is the process as a whole, the actual experience is hard. Being away from home I think was the most difficult part."

"MRD negative after 4 weeks, 3 years 4 months of treatment, several admissions due to fever, almost no vomiting or discomfort. Moods changes due to steroids. Leg movement impacted and required physiotherapy. **Difficulty administering some home medications** due to age, frequency of meds, amount of and taste of meds. Increased lethargy throughout treatment."

"Frontline was very difficult. **In-patient days during frontline totalled 232 days**. Exhaustion for both the patient and the caregiver. The negatives are as follows: - side effects of treatment, including but not limited to: blood clots, steroid induced diabetes, broken bones, neurotoxicity from IT MTX, seizures, vision issues, severe mucositis, weight loss, steroid induced rage, lumbar puncture headaches, severe anxiety around procedures. There was also some cognitive/mental regression as she was out of school for a full year. Social regression also. Mentally, physically and emotionally draining. Caregiver's inability to continue to work. Positives were minimal. She has managed to stay in remission thus far and for that we are grateful. Our experiences with the nursing staff at our hospital has been nothing but incredible. There has been little extra costs incurred by our family as a result of treatment."

"It was **very scary and heartbreaking** to watch your child get so sick from the chemo and not have any options."

"The worst side effects for my child was kidney function problems early in treatment that was resolved with albumin transfusion, and an extreme sensitivity to Vincristine that led to much smaller doses than called for on study but still caused neuropathy and foot drop that later needed double Achilles surgery and **still causes problems five years post-treatment**. Best experiences were with staff and professionals at [hospital]."

Difficulties in Accessing Treatment:

For almost all of the respondents, accessing treatment was not an issue. Most respondents were able to receive care at a major centre; however, there were two comments from respondents about living in a rural area which required a long drive into the primary care hospital. Most respondents spoke very positively about their primary care hospital and the treatment that they received. One respondent noted: "Access to health care services and therapy we're more readily available. We unfortunately had move to the US after a year if treatment and health care services are not as readily available and not as good as Ontario!"

Respondents did comment on challenges for caregivers and their inability to continue working while their child was on treatment. The following comments were noteworthy:

"Mentally, physically and emotionally draining. Caregiver's **inability to continue to work**."

"Life was a big struggle, and we just did it. But I (the dad) had some weight gain, and some depression which linger to this day, as well as employment difficulties from being out of the job market at an advanced age (nearing 60 this year). **We are impoverished, and don't have good job prospects**; the mom and dad are separating, which stems partially from the relationship difficulties of constant stress in caring for our child."

"1 parent took an **unpaid leave of absence** to handle treatment and care. Hospital stays required 24 hour supervision by a parent making the maintenance of life and home very difficult, including parenting of other children."

"**Our family has a whole had a lower quality of life and struggled financially**, socially and our general health all together."

Difficulties in Receiving Treatment:

Some respondents mentioned issues with receiving treatment. For example, two respondents commented on the challenges with the formulation of medications:

"It had its ups and downs. We finally had to **change from oral suspension to pills as our son could not tolerate the suspensions and consistently vomited following having to consume the large dosages as required**. The steroids

changed our son into being a very angry boy, very quickly and all the pokes and prods made for one very anxious and nervous and defiant child.”

“He was too young to take pills, **so we ground it up and he had to swallow it.** He avoided it lots, and was prone to heavy drama, especially when he was on steroids.”

In general, one respondent noted “difficulty administering some home medications due to age, frequency of meds, amount of and taste of meds.”

Experiences with Relapsed Therapies:

For relapsed leukemia, respondents noted that they have tried the following therapies (listed from most to least prevalent):

1. Chemotherapy
2. Radiation
3. Bone Marrow Transplant
4. Immunotherapy

The following were the most common patient reported side effects experienced with treatments for relapse therapies:

1. Low platelets
2. Hair loss
3. Low white blood cell count
4. Fatigue
5. Nausea
6. Vomiting
7. Low red blood cell count
8. Infections
9. Diarrhea
10. Constipation
11. Allergic reactions
12. Mobility changes
13. Respiratory and breathing issues
14. High and low blood pressure

Respondents provided comments about their experiences with relapsed leukemia:

“It was **3 1/2 years of torture.** Told the BEST kind of Leukemia to have was ALL B Cell. Constant challenges such as, how to pick him up without hurting him. Feeding tubes, diarrhea, fevers. Too many antibiotics as a regimen.”

“2nd relapse treatment **highly complicated** with viral and bacterial infections. High amounts and variety of antifungal, antibacterial, antibiotic meds used. There are too many challenges to list here, but include financial, organizational, emotional, and of course medical.”

“There really was **no set treatment plan.** No one knew what to do once the first round of chemo was ineffective & the cancer actually grew, we did a trial treatment that they found....we felt lost, helpless and completely let down by the medical world.”

“The first relapse gave us the ability to get into remission with use of intense chemo and radiation. It is **scary how much poison has been tossed into his body under the guise of chemo.** Radiation of his skull is obviously another large concern. He was unable to walk due to infections and needed a wheel chair and walker for months for mobility. He is behind in reading and writing. His joints have limited range.”

“Spent **longer time in hospital** and as such child developed some behaviour issues that were difficult to manage at times.”

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Respondents provided a great deal of insight into the challenges faced when in frontline treatment for leukemia. The most common theme in the majority of the comments provided was the challenge of isolation due to the risk of their child getting an infection because of low white blood cell counts. Respondents commented on the changes to their daily life, being separated from family, not being able to engage in public events, their child not attending school regularly, changes in relationships with family and friends, and being away from home. The following are some comments provided by respondents which illustrate these points:

"The treatment requires a lot of time spent at hospital and away from normal childhood activities. My son had many extreme side effects so **missed lots of school hence was isolated from friends** for most of the first two years of treatment. He also reacted physically and mentally to the drugs, including medication induced psychosis. Once he returned to attending more school he routinely missed a week at a time due to fever and other symptoms if he caught a cold."

"Being a teenager at school having cancer **became difficult to fit in**. Loss of extracurricular sports due to low platelets. Hospitalized many times due to side effects of treatment. Isolation."

"We were in the hospital so much and apart from my husband and our other son. We felt isolated from the rest of the world. **We would finally get to go home and then didn't know how to be at home**. Just when we were getting used to home life, we'd be admitted again."

"It's difficult to identify whether our son experiences some of the more common side effects as he is unable to verbalize what is happening. As a parent, this life is devastating for reasons that don't need explanation. **Time spent admitted to hospital is extremely depressing**. Time spent as an outpatient makes you feel like an outsider knocking on the window wanting attention."

"My quality of life has deteriorated to the level of needing my parents to push me in a wheel chair, my mom helps me with my personal hygiene. **I have had to give up going to College.**"

When making decisions about a new cancer treatment, the most important factors that respondents consider are (from most to least prevalent):

1. quality of life
2. physician recommendation
3. possible impact on the disease
4. outpatient treatment
5. closeness to home
6. family recommendation
7. religious considerations.

The survey asked "if you did not have CTL019 treatment, but would consider it – why would you be willing to tolerate the side effects? If you did have CTL019 treatment, why were you willing to tolerate the side effects from CTL019 treatment?"

"If treatment has better chance at saving life (or same) and it means there is weeks or months of treatment rather than years of treatment that causes severe physical and mental disabilities we would be **willing to try**."

"If relapse happened, and CTL019 was the best option, we would be willing to try it. **As bad as the side effects are, the outcome would be worth it.**"

"Yes I **would be willing to help my daughter tolerate the side effects** if it would significantly increase remission and survival."

“All treatment comes with side effects. If the first protocol didn't do the trick we would find it difficult to go through it again rather than try something else.”

“We would have done anything we could.”

“Would depend on success rate on cure whether to tolerate side effects.”

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families. How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared with any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

In choosing the CTL019 therapy, respondents noted that there weren't many options available to them when they were facing a second or greater relapse. CTL019 offered a last hope, and respondents felt that it offered significantly lower risk than going forward with a bone marrow transplant.

“It is an easy choice when you don't have a lot of options. Early signs of this treatment were very strong. The only other remote option was a bone marrow transplant by a third party donor. The complications associated with BMT are extreme, severe and he had been through a lot at that point. The fact that he relapsed twice in the cerebral spinal fluid did not guarantee that BMT would work.”

“Wanted anything other than a bone marrow transplant. It has been exciting to be a part of a clinical trial with so much amazing potential. Even though his T cells haven't persisted, he has been healthy and in remission for 6 months.”

Access to CTL019 for ALL:

10 patients received the treatment through a clinical trial (all patients were from Ontario except one from Saskatchewan). An additional respondent stated that “access was denied by OHIP. We proceeded with cell collection but my daughter's sample was not enough to qualify for CAR T.” The majority of respondents (8) stated that it was either normal, not difficult or not difficult at all to access the CTL019 treatment. Three respondents stated that it was difficult or extremely difficult to access the CTL019 treatment. The following are comments from respondents:

“We were VERY VERY lucky. The clinical trial at Sainte-Justine had just opened. It was and continues to be a miracle.”

“The main obstacle was getting provincial funding for the treatment since it was out of province. This was mostly impacting our doctors, not us. There was significant anxiety about whether approval would be granted.”

“The challenge was in getting my son's body in a state that it could generate enough t cells to qualify and also, rid his body of numerous infections, complications that resulted from the relapse: bacterial blood infections, flesh infections.”

“We had to make sure she qualified to have it done, so that was stressful with the not knowing, but thankfully she qualified.”

“Travelling to Toronto from Saskatchewan for collection of T cells. Time and expense. Also since the treatment was offered in Philadelphia there is time away from work, kids miss school, no family or friends, and cost [incurred] is a lot.”

Six respondents had to travel a long distance by airplane and to another county to receive treatment, with five respondents travelling from Ontario to the US and one respondent travelling from Saskatchewan to the US. Three respondents had to travel long distances by car within their home province. One respondent had to travel by airplane within their home country and one respondent was able to access the treatment at their home hospital.

In terms of access, one respondent eloquently noted: “This is the future of treatment for relapsed or refractory ALL. If I had to pay out of pocket and CAR T was twice the cost of a bone marrow transplant, I would choose CAR T every time.”

Experience With CTL019:

“Today is day 40 post CAR T, so it hasn't been that long since she received her T cells. The first hard part was the waiting at the beginning to see if she qualified, because she couldn't be given any chemo until we found out. The second hard part was waiting for the cells to come back so she could receive them. She had to wait 2.5 months, so not bad compared to other cases. During that time she pretty much lived in the hospital because she became sick so often, and she required so many blood transfusions. She had a maintenance schedule of chemo while waiting for her cells. Things became so much better after she received her T cells. She handled everything so well. She did receive one fever after the first week, but it was for only about 24 hours on and off. As of the time of me completing this form, she has not experienced any of the severe reactions that may happen. On day 30 post CAR T, my daughter had a bone marrow biopsy which has shown that she is in remission. I feel that it is still a bit too early to answer question 20 as it has only been 40 days, but so far CTL019 has eliminated her disease with no relapse. She no longer needs hemoglobin or platelet transfusions on a regular basis and she looks and feels great.”

Benefits Compared With Other Treatments:

Respondents made the following comments about the benefits of the CTL019 therapy:

“My son had only a very mild reaction and spent only one night as in-patient due to fever. We needed a reinfusion at 7 months due to returning B cells. To sum it up, my son asked why we couldn't have just done this in the first place (instead of the original treatment). **So far his quality of life is much improved and his physical condition is nearly normal again after almost 8 years.**”

“Excellent. It's remarkable to see the **CAR T-cell therapy transform my son's health**. In one month he went from being very ill to his old self....just a skinnier version. The medical team was kind, caring, and had a great deal of experience. Felt like we were in very good hands.”

“**Compared to front line treatment, CAR T-cell therapy is a much more pleasant experience.** Although there is still a significant investment in time, much of the inconvenience that we experienced centered around being away from home more than the actual therapy itself. There were no serious complications.”

“Amazing! Finally **Hope given to the hopeless**. We are the patients really with no hope and CAR T-cell [therapy] has given us incredible hope when essentially there was none. His complications were very limited. He spent one night in hospital with a fever. He was a bit dizzy and a bit absent for a bit but we could not be happier with these results. **HOPEFULLY** this can someday become front line treatment and children (and adults) won't need to be tortured endlessly in the future!”

“**Amazing.** We were well taken care of and everyone was wonderful.”

Disadvantages:

For those respondents who had the CTL019 therapy, many stated that a significant amount of expenses were covered by the pharmaceutical company; however, other respondents noted many costs associated with the CTL019 treatment. These included:

1. Automobile expenses (e.g., parking, gas, mileage, car rental)
2. Food (e.g., for parents and child when out of the hospital)
3. Accommodations (e.g., Ronald McDonald House, apartment rental, hotel)
4. Travel (e.g., airfares)
5. Medications
6. Other (e.g., professional accountant to do taxes to claim as many costs as possible)

“We've spent a total of 13 weeks in Philadelphia since the end of September 2017. Loss of wages and time away from home.”

Only one respondent noted their child becoming very sick: "Pretty good although they should tell you, you WILL be so sick that you will end up in intensive care. They tell you that you might.... you WILL!"

Impact of Advantages and Disadvantages:

Respondents noted the positive impact CTL019 has had on their child's disease:

"**1.5 years cancer free** - the longest time frame cancer free since he was 3 - he is now 11."

"Eliminated the disease for **9+ months and counting**."

"**Eliminated disease**, but CAR T cells have lost persistence requiring two additional infusions."

"After six months **Still MRD negative** but B cells returned."

Respondents who received CTL019 treatment were overwhelmingly positive about the therapy and its advantages (100%) and expressed how it has changed their lives for the better:

"Too early to tell. We have been told that we will be trained to give our daughter an immunoglobulin injection, so that will be different. But we have already had to learn so much during the past 5.5 years of her cancer experiences that this will just be one more thing. **We would learn how to do anything to keep her healthy.**"

"This treatment has **exceeded my expectations**. If successful or available at a first-line treatment, I would highly encourage it to others."

"**Life changing!!** My son is healthy right now even though the future is uncertain. It's truly and medical miracle."

"We were able to **regain a higher degree of normalcy** than we would have had we stayed on the normal course of chemo treatment. Being part of the trial and having to be away from our home city for an extended period was a challenge, but overall the general level of anxiety around the leukemia challenge has gone down significantly."

"**POSITIVE!!** This is the **best breakthrough in medicine since penicillin**. Please do not deprive those people that really have no other options. My child is enjoying being a child - imagine that!"

"It worked, life is rather normal again and **back to being a kid!!**"

"It has **improved our quality of life significantly**. Only issue is living with the anxiety that he could relapse."

Side Effects of CTL019:

Cytokine Release Syndrome:

Most respondents did not experience this side effect or classified it as a manageable or minor side effect. One respondent classified it as a very serious side effect.

Low White Blood Cell Count, Low or High Blood Pressure, Fever, Nausea/Vomiting, Pain:

One or two respondents classified the above side effects as very serious or serious. The majority of respondents classified the above side effects as manageable, minor, or did not experience.

"Appetite and weight loss, neutropenia and low counts that were slow to recover. After second infusion same but neutropenia lead to fever due to Parainfluenza 3 and PJP pneumonia with long hospital stay."

"Severe drop in blood pressure during CRS nearly killed my son. We were very VERY lucky."

Dizziness, Confusion, Headache, Low Platelet Count, Low Red Blood Cell Count, Count, and Sleepiness:

Manageable side effects but most did not experience those listed above.

"Poor appetite was hardest. Needed to keep him hydrated and eating. He also truly felt like crap. Not much made him feel better but his symptoms weren't severe."

"Some sleepiness and fever but nothing we hadn't done before. We experienced no Unexpected issues."

Comparison to Previous Therapies:

50% of respondents who received CTL019 states that they strongly agreed that CTL019 improved their quality of life. The other 50% of respondents stated that they were "neutral" about this statement.

"It has **saved my son's life**: no question about it."

"**Physical recovery has been steady**. Energy level much higher. Personal demeanour much more positive."

"You may take for granted your child laughing, running, playing. Those of us that have suffered endlessly with our children take great joy in so many things that many take for normal and don't appreciate. **This treatment has given my son a "normal" life for the first time in 6.5 years**. He is enjoying life without endless medications and doctor's appointments. This treatment means that a child can just be a child. Imagine that! The treatment may stop working tomorrow and I would be grateful for the gift of the past 1.5 of a 'normal' child."

"CAR T has been, so far and almost two years post-infusion, successful and **less disruptive than the previous treatments** which included chemotherapy and radiation both in-patient and outpatient."

"Traditional treatment for ALL is an incredibly long grind (3.5 years for boys) with an incredible amount of scary poisons pumped into a young body that will have lifelong effects. CAR T-cell **Immunotherapy holds hope not only for those without any options** for to the future children with the hope that someday, this will be the first-line of attack for ALL cancer diagnosis. The amount of suffering it will save children, parents, family, and friends - there is **HOPE!!!**"

Most respondents who received CTL019 felt that the treatment was significantly less challenging than what they have otherwise experienced for ALL. One respondent felt "neutral" on this question and one respondent felt that it was "more challenging" than other ALL treatments.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?
- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

Not Applicable.

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

For patients and families who have received CAR T-cell therapy, specifically CTL019, this treatment has given them improved quality of life, more time to live, and an opportunity to achieve remission. For the respondents to the survey who have experienced CTL019 therapy, this treatment has also provided hope and an opportunity for their child to be a kid again.

"I didn't know much about treatment of childhood cancers prior to our son's diagnosis but am **pleased to live in a country where access to treatment was readily available**. The fact that I had medical benefits to cover the cost of most drugs helped tremendously. Even the cost of anti-nausea drugs can be prohibitive for some. I had to "fight" for sick benefits for myself in this time of family crisis."

"The treatments for ALL are 40 or 50 years old with horrible impacts during treatment, for years of recovery and then the lifelong impacts. **We can do better with new treatments and children deserve better**. Please help kids access the newer, better treatments with less effects."

"I hope that through genetic coding, researchers will figure out who will relapse anyway with chemo and bone marrow transplant (my son had BMT before CAR T) so that they can spare patients the agony of relapse and the adverse effects of chemo, radiation and BMT and go straight to CAR T. **CAR T is a miracle**."

"It is far too harsh on their little bodies. Our son already has kidney and liver issues. This doesn't leave much confidence for the future. Our 2 year old has been tortured and will continue to be for 3 years. **There's got to be a better way**."

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Childhood Cancer Canada provided Ac2orn with the use of their Survey Monkey account to administer the English survey. They only provided access to Survey Monkey and Ac2orn did all of the English survey set-up and analysis.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Antonia Palmer, Novartis CAR T-Cell Consultation Meeting, Info gathering for patient materials, February 2018	x			
Nadine Prevost (LLSC), Novartis CAR T-Cell Consultation Meeting, Info gathering for patient materials, February 2018. Partnerships for patients programs			x	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Antonia Palmer
 Position: Co-Founder
 Patient Group: Ac2orn
 Date: June 11, 2018

Name: Nadine Prevost
 Position: Senior Manager, Community Engagement
 Patient Group: Leukemia & Lymphoma Society of Canada
 Date: June 16, 2018

Name: Sarai Porretta
 Position: Administrative Coordinator
 Patient Group: OPACC
 Date: June 11, 2018

Patient Input Template for CADTH CDR and pCODR Programs

Name of the Drug and Indication	Tisagenlecleucel for relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
Name of the Patient Group	Lymphoma Canada

1. About Your Patient Group

www.lymphoma.ca

2. Information Gathering

Lymphoma Canada (LC) conducted two anonymous online surveys of diffuse large B-cell lymphoma (DLBCL) patients from April 18 to June 15, 2018. Links to the surveys were sent through email to patients registered on the LC database. The links were also made available through LC Twitter and Facebook accounts, Canadian and American Cancer Society message boards, Facebook groups organized for lymphoma patients and survivors, and international lymphoma organizations' own contacts. The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into surveys so respondents were asked questions only relevant to them. Open-ended responses to surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

Overall, 107 patients provided input. Of patients who provided their demographic information (Tables 1 and 2), 90% live in Canada, 62% are female, 53% are ≥ 60 years old, 33% are 40 to 59 years old and 14% are < 40 years old.

Table 1: Country of survey respondents (107 respondents)

Respondents	CANADA	US	Other	Skipped	Total
Patients <u>with</u> tisagenlecleucel experience	2	3	0	4	9
Patients <u>without</u> tisagenlecleucel experience	85	5	2	6	98

Table 2: Gender and age of survey respondents

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	skipped	Female	Male	Skipped
Patients <u>with</u> tisagenlecleucel experience	0	1	1	3	4	3	2	4
Patients <u>without</u> tisagenlecleucel experience	2	11	31	48	6	57	35	6

3. Disease Experience

Symptoms of DLBCL that most commonly affected respondents' quality of life at diagnosis (98 respondents) were fatigue or lack of energy (72%), enlarged lymph nodes (49%), drenching night sweats (37%), unexplained weight loss (28%), loss of appetite (25%), flu-like symptoms (18%), and persistent cough (18%). Other symptoms affecting quality of life for ≥ 10% of respondents included itching, chest pain and trouble breathing.

Respondents were asked which aspects of their life have been **NEGATIVELY** impacted by DLBCL. Notably, 56% and 42% indicated that DLBCL had a negative impact on their ability to work or attend to family obligations, respectively. Additional responses are summarized in Table 3.

Table 3: Effect of DLBCL on day-to-day life of patients (95 respondents)

Aspect of life NEGATIVELY impacted by DLBCL	# of respondents	% of respondents
Ability to work	53	56%
Family obligations	40	42%
Personal image	36	39%
Intimate relations	27	28%
None of these	23	24%
Friendships	21	22%
Ability to attend school	2	2%

The majority of respondents (85%) also reported that their quality of life has been negatively affected by mental and emotional problems associated with their disease or treatments (Table 4).

Table 4: Impact of DLBCL on patients' mental and emotional well-being (98 respondents)

Symptom	# of respondents	% of respondents
Fear of disease recurrence	66	67%
Memory loss	41	41%
Anxiety/worry	38	38%
Problems concentrating	37	38%
Difficulty sleeping	28	29%
Loss of sexual desire	25	26%
Stress of diagnosis	18	18%
Depression	17	20%
None of these	15	15%

As described by four patients:

"[Fear of disease recurrence] is very high and consumes a lot of my thought process almost every day. Even after two years since my chemo treatments finished and I had a complete response."

"I retired early due to memory loss, lack of concentration, and ongoing depression."

"It affected our personal lives my husband had to stay home from work to help me. We had no income. Very stressful. Our community did a couple benefits which helped us pay our bills. Big life changer for sure."

"I was an avid exerciser and have difficulty walking right now. The cancer is in my pelvis; it's a sizable tumour and limits my movements. In the last year I have sold my businesses and am now retired. I could not manage business, family, daily activities. There were times I had brain fog or chemo brain, not good for decision-making. I try to do daily activities, laundry, cooking etc. The trial I am on right now has given me more fatigue, so I rest more than ever."

4. Experiences With Currently Available Treatments

Ninety-six (96) respondents provided information about their experience with DLBCL treatments. All respondents had received at least one line of treatment or were undergoing first-line treatment for DLBCL, 46% had received more than one line of treatment, and 5% had received three or more lines of treatment. The most commonly reported first-line treatment (84% of respondents) was the chemoimmunotherapy regimen R-CHOP. Of those who received more than one line of treatment (44 respondents), 25% had undergone an autologous stem cell transplant and 5% had undergone an allogeneic stem cell transplant.

Side effects of current treatments: The most common side effects respondents experienced during their DLBCL treatments are listed in Table 5.

Table 5: Side effects from treatment (96 respondents)

Side effect	% of resp.	Side effect	% of resp.	Side effect	% of resp.
Hair loss	92%	Mouth sores	47%	Trouble breathing	23%
Fatigue	86%	Thrombocytopenia	35%	Cough	22%
Memory problems or confusion	73%	Infections	35%	Other	22%
Neutropenia	67%	Anemia	32%	Loss of menstruation	19%
Nausea	61%	Diarrhea	27%	Irregular heartbeat	16%
Constipation	50%	Pain	27%	Viral reactivation	7%
Peripheral neuropathy	50%	Skin rashes/severe itching	23%	Bowel obstruction	7%

When asked which side effects they found most difficult to tolerate, respondents most often reported fatigue (32/80; 40%), nausea/vomiting (15/80; 19%), chemo brain (13/80; 16%), and hair loss (8/80; 10%). Eighty (80) respondents provided responses to this question.

Impact of treatments on quality of life: When asked about the impact of various aspects of treatment on daily living (on a scale of 1 – 5, where 1 = No impact and 5 = significant negative impact), respondents noted that treatment-related fatigue and other side effects had the most significant impact on their quality of life (Table 6).

Table 6: Impact of treatment on quality of life (96 respondents)

Treatment aspect	Weighted average	Significant negative impact (rating = 4-5)	Number of responses
Fatigue	3.8	63%	95
Side effects	3.6	57%	93
# of clinic visits	2.4	22%	93
Infusion time	2.4	21%	92
# of infections	2.4	24%	91
Infusion reaction	2.4	21%	92
Frequency of infections	2.2	21%	92

Treatment also had a very significant impact on many respondents' ability to work, travel and participate in daily activities (Table 7).

Table 7: Impact of treatment on daily living (95 respondents)

Activity	Weighted average	Significant negative impact (rating = 4-5)	Number of responses
Work	4.0	61%	94
Travel	3.9	64%	94
Activities	3.9	69%	94
Intimate relations	3.3	45%	92
Family	2.9	36%	91
Friendships	2.5	23%	93
School	2.1	6%	85

As reported by three respondents:

"I needed to make extra visits to emergency or to the clinic between treatments as a result of fever. Eventually I was given Neupogen injections after treatments to keep my white blood cells at a better level (these were daily in my home for several days - impact, had to be home)"

"Learning to not to push myself with physical activity, i.e., yard work, house renos etc.

Not taking on extra duties at work, and possibly retiring early in age"

"There is always some stress getting time off work to attend check-ups with oncologist. I am tired after work so I do very little during the work week to make sure I will have enough energy for my job."

When asked about the financial implications of treatment, almost half of respondents from Canada (40/85; 47%) reported that their absence from work or school impacted them financially.

As reported by two respondents:

"Had to give up a new career and job to have treatment"

"I was unable to continue working so I had to retire early, and therefore I lost my salary and health benefits"

Additional financial costs for respondents living in Canada are reported in Table 8.

Table 8: Financial implications of treatment for DLBCL patients in Canada (85 Canadian resp.)

Financial impact	% of respondents	Number of respondents
Absence from work or school	47%	40
Cost of medications	33%	28
None	24%	20
Travel	13%	11
Other	13%	11
Accommodation	8%	7
Drug administration supplies	4%	3
Clinical trial charges	0%	0

5. Improved Outcomes

Patient preferences: Respondents were asked to rate, on a scale of 1 -5 (1 = not important; 5 = extremely important), the importance of various factors regarding a new drug or therapy for DLBCL. "Longer survival" and "longer remission" than current therapies were rated as the most important outcomes for a new therapy (Table 9). "Fewer side effects" was rated as the least important outcome, overall.

Table 9: Treatment preferences (94 respondents)

Treatment outcome or factor	Rating = 5 (Extremely important)	Weighted average	Number of responses
Longer survival	90%	4.9	94
Longer remission	87%	4.8	94
Better quality of life	77%	4.6	94
Fewer side effects	55%	4.1	94

Respondents were also asked if they would choose a treatment with known side effects, potentially serious, if their doctor recommended it was the best option for them. Of the 94 respondents who answered this question, 49% selected "Yes," while only 3% selected "No." The remaining 49% of respondents selected "I'm not sure." Furthermore, 42% of respondents would be willing to tolerate potential side effects if the benefits were short term, while only 7% were not.

6. Experience With Drug Under Review

Nine respondents from Canada and the US reported that they had been treated with CAR T-cell therapy for diffuse large B-cell lymphoma. Most patients received CHOP +/- R as their first-line of treatment. All but one of the respondents were diagnosed from 2014 to 2016 and treated with CAR T-cell therapy between 2015 and 2018 (the lone exception was diagnosed in 2011 and treated in 2012). Two patients received tisagenlecleucel (Kymriah), one received KTE-C19 (Yescarta), two received JCAR017, and four did not specify what type of CAR T-cell therapy they had received. All of the respondents received CAR T-cell therapy through a clinical trial. Four patients are currently in remission, one remains in treatment with CAR T-cell therapy and four patients did not indicate their current status. Patients who provided demographic information are profiled below:

- A male patient from Ontario (50 to 59 years old) was interviewed. He was diagnosed in 2014 and treated with CHOP +/- R, followed by CHEOP +/- R, GCVP +/- R, DHAP +/- R and radiation therapy. The patient indicated that he had exhausted the available lines of treatment prior to his enrolment in the clinical trial. He began CAR T-cell therapy (CTL019) in July 2016 and has been in remission for one to two years. He commented that: *"I did not experience any significant adverse effects from the treatment."*
- A female patient from the US (70 to 79 years old) was diagnosed in 2016. She was treated with CHOP +/- R, followed by GemOx +/- R, cisplatin, ibrutinib + buparlisib and high-dose methotrexate. She was treated with CAR T-cell therapy (JCAR017) beginning in March 2018 and is newly in remission. She was admitted to hospital four days prior to the infusion and remained for five weeks, due in part to a C. difficile infection.
- A male patient from the US (60 to 69 years old) was diagnosed in 2015. He was treated with CHOP +/- R, followed by lenalidomide +/- rituximab and HDT + auto-SCT. He was treated with CAR T-cell therapy (JCAR017) beginning in May 2017 and has been in remission for six months to one year. He suffered from skin issues related to his therapy that lasted for more than two months. He remarked that *"I was supposed to be dead last April. I couldn't walk 5 feet. After CAR T therapy, I am now in remission and I just golfed 18 holes. Life is good."*
- A female patient from Canada (20 to 29 years old) was diagnosed in 2015. She was previously treated with CHOP +/- R and began CAR T-cell therapy (CTL019) in June 2017. She is currently in remission.

- A female patient from the US (60 to 69 years old) was diagnosed in 2011. She began CAR T-cell therapy (KTE-C19) in 2018 and remains in treatment.

Side Effects: Neutropenia was the most commonly reported side effect of CAR T-cell therapy followed by decreased appetite, cytokine release syndrome, and febrile neutropenia. Only one patient required hospitalization to manage side effects due in part to a *C. difficile* infection and one patient reported side effects that lasted longer than two months (skin issues).

Quality of Life: Five respondents answered a question asking them to rate the impact of different aspects of their CAR T-cell therapy on a scale of 1 (no negative impact on my life) to 5 (significant negative impact on my life). None of the weighted averages for these responses was higher than 3 and only 1 of 5 respondents gave a rating > 3 for any aspect of CAR T-cell therapy, suggesting that CAR T-cell therapy had a reasonably benign effect of their quality of life.

Table 10: Impact of CAR T-Cell Therapy on Patients' Lives (5 respondents)

Aspect of CAR T-Cell Therapy	Weighted Average
Number of clinic visits	2.8
Travel to treatment centre	2.8
CAR T-cells infusion	2.6
Short-term side effects of treatment	2.5
Activity level	2.5
Treatment-related fatigue	2.5
Lasting side effects of treatment	2.0
Leukapheresis	1.8

As reported by one patient:

"For all intents and purposes, despite having reviewed and discussed all of the potential side effects with respect to the CAR T-cell therapy program, the experience was fairly uneventful. I did not experience any significant adverse effects from the treatment." (Male, 50-59, Ontario)

Recommend CAR T-Cell Therapy: When asked to describe the positive and negative effects of CAR T-cell therapy, patients provided these two responses:

"Nothing negative, but the cost for travel. It was so much easier than the auto stem cell transplant." (Male, 60 to 69, US).

"Positive, in that it removed the cancer. But it was a very difficult treatment." (Female, 70 to 79, US).

When asked if they would recommend CAR T-cell therapy to other DLBCL patients based on their own experience, patients answered:

"After 25 days I am cancer free, so that was worth it, since nothing else worked." (Female, 70 to 79, US).

"I would recommend it to any patient with relapsed DLBCL." (Male, 60 to 69, US).

7. Companion Diagnostic Test

CD19 CAR T-cell therapy requires expression of CD19 on the tumour cells. Hematologists and oncologists with knowledge of CAR T-cell therapy and experience treating DLBCL indicated that this is a routine test that can be performed on archival biopsy tissue using readily available laboratory testing and would not need to be performed on new tissue prior to the initiation of CAR T-cell therapy.

8. Anything Else?

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR T-cell therapy experience and wrote the "Experience with Drug Under Review" section of the submission.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

Adam Waiser, an independent consultant, helped promote the patient surveys, analyzed the survey data for patients with CAR T-cell therapy experience and wrote the "Experience With Drug Under Review" section of the submission.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	Check Appropriate Dollar Range			
	\$0 to 5,000	\$5,001 to 10,000	\$10,001 to 50,000	In Excess of \$50,000
Novartis			X	
Gilead			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Elizabeth Lye

Position: Scientific Advisor

Patient Group: Lymphoma Canada

Date: June 20, 2018

Appendix 4: Clinician Input Submission — Original Submission



pan-Canadian Oncology Drug Review Registered Clinician Input on a Drug Review

February 2018

Before completing this template, be sure to register with the pCODR program. Please visit <https://www.cadth.ca/pcodr/registration> for information about the registration process.

1. Information about the Registered Clinician

Name of the drug and indication: tisagenlecleucel for relapsed or refractory DLBCL

Name of registered clinician: Dr. John Kuruvilla

Title: Chair of the Scientific Advisory Board, Lymphoma Canada

Specialty (if applicable): Hematology

Province: Ontario

Membership: Lymphoma Canada

Phone: 416 946 2821

Email: john.kuruvilla@uhn.ca

1.1 If this is a joint clinician submission, please list the names of the other clinicians, their title and specialty (if applicable). Please note all clinicians listed must also register with CADTH.

Dr. Isabelle Fleury, Hematologist, Hôpital Maisonneuve-Rosemont (Has experience with drug under review)

Dr. Graeme Fraser, Associate Professor, Department of Oncology, McMaster University, Hematology/Oncology (Has experience with drug under review)

Dr. Kerry Savage, Associate Professor, University of British Columbia and Oncologist at British Columbia Cancer (BCC). (No experience with drug under review)

Dr. Jean-Francois Larouche, Hematologist/Oncologist, CHU de Québec (No experience with drug under review)

Dr. Mark Bosch, Director of Hematology at the Saskatchewan Cancer Agency (No experience with drug under review)

Dr. Mohamed Elenary, Medical Director of Blood and Marrow Transplant Program, Saskatchewan Cancer Agency, Hematology/Oncology (No experience with drug under review)

Dr. Mona Shafey, Clinical assistant professor at the Foothills Medical Centre & University of Calgary, Hematology/Oncology (No experience with drug under review)

Dr. Pamela Skrabek, Chair of the Provincial Lymphoproliferative Disease Site Group, CancerCare Manitoba, Hematology/Oncology (No experience with drug under review)

Dr. Versha Banerji, Senior Scientist, CancerCare Manitoba, Hematology/Oncology (No experience with drug under review)

Before completing this template, be sure to register with the pCODR program. Please visit <https://www.cadth.ca/pcodr/registration> for information about the registration process.

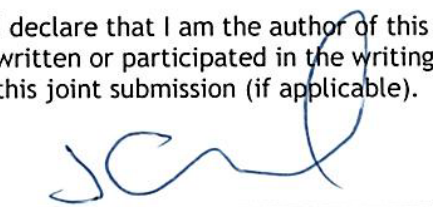
Dr. Joanne Hickey, Assistant Professor, Memorial University, Hematology/Oncology (No experience with drug under review)

1.2 Do you have experience with prescribing the drug under review?

☐ Yes ☒ No Note: 2 clinicians (I. Fleury and G. Fraser) have experience with the drug under review.

1.3 Confirmation of Authorship

I declare that I am the author of this submission and to confirm that no other parties have written or participated in the writing of the submission, except for those named above in this joint submission (if applicable).



Signature



Date (YYYY/MM/DD)

2 Key Questions for Clinician Input

2.1 Current Treatment(s) for this Type of Cancer

- Please list the current standard treatment(s) you use for the defined patient population in the funding request.

Patients in this setting are typically managed palliatively. Most of these patients have not responded to aggressive chemotherapy and are no longer candidates for curative approaches, such as autologous stem cell transplantation (ASCT). The other group in this patient population consists of patients who have developed disease progression post-ASCT. Current treatment strategies include radiation therapy, palliative chemotherapy (either oral strategies such as prednisone, etoposide, cyclophosphamide or IV treatments such as gemcitabine, vinblastine etc.). Clinical trials are also prioritized when available. A selected group of patients would potentially be considered for allogeneic stem cell transplantation (Allo-SCT). These patients typically require chemosensitive disease and need to be younger age (up to 70 years) which no significant medical comorbidities and an available donor.

Before completing this template, be sure to register with the pCODR program. Please visit <https://www.cadth.ca/pcodr/registration> for information about the registration process.

2.2 Eligible Patient Population

- In your opinion, does the patient population in the funding request meet the needs in the clinical practice setting? Is there any population/sub-population where you specifically want to use this drug?
- Can the inclusion and exclusion criteria of the clinical trial be applied in clinical practice?
- Please describe which patient population would you prescribe the new drug under review if it becomes available and which patient population would you prescribe current treatments?
- Please briefly explain your rationale.

The funding request represents a population with an extremely high unmet need; one for which we currently have no effective therapies. The inclusion/exclusion criteria are typical characteristics routinely evaluated in clinical practice. An historical population with similar criteria were identified in an international collaboration with Canadian participation as having consistently poor OS (median 6.4 months) with currently available salvage therapies (Crump SCHOLAR-1, Blood 2017). It is important to note that this population would have utilized all potential available therapies including both ASCT and allo-SCT, along with conventional palliative and experimental therapies. The largest patient group in the review was from Canada.

If CD19 CAR-T cell therapies are available in this indication, it is very likely that ALL potential patients included in the funding request will be considered for this treatment. CD19 CAR-T cell therapy appears to offer an unprecedented benefit over other standard and experimental treatments currently available in this indication. Given the potential for prolonged disease control and significant toxicity, the majority of these patients will be sent to expert centres for evaluation regarding potential candidacy for this treatment. It is expected that a proportion of patients (unknown at this time due to lack of data) would not ultimately receive the therapy (or have the CAR-T cell product manufactured) if they were deemed ineligible for medical issues or if their disease tempo precluded this type of treatment.

2.3 Relevance to Clinical Practice

- In your opinion, how important would it be to have this new treatment (e.g., must have, nice to have, doesn't add anything to currently available therapy)? Is there an unmet need? How or when would you use the new treatment?
- Have you prescribed the new treatment for the indication being reviewed (e.g., through clinical trials, manufacturer's access program, private drug insurance)? How is the new treatment, in your clinical opinion, different than currently available treatments with respect to efficacy, safety and tolerability?

Before completing this template, be sure to register with the pCODR program. Please visit <https://www.cadth.ca/pcodr/registration> for information about the registration process.

Important Note: Scientific published references are not required, as pCODR has access to current scientific literature through the manufacturer's submission and a rigorous, independent literature search.

CD19 CAR-T therapy is now an essential treatment for patients with DLBCL who have exhausted all curative treatment options. There is an extremely high unmet need in DLBCL (the most common lymphoma - the 6th most common cancer in Canada) for potentially curative treatment in this setting. With a typical median survival of approximately 6 months with available therapies, the potential to transform care in this setting is unprecedented.

Unfortunately, CAR-T cell trials have been largely limited to the US for initial clinical trial populations. There are a limited number of patients that have had therapy in Canada - centres involved in these clinical trials (multiple companies with patient accrued) have included the Vancouver General Hospital, Juravinski Cancer Centre and Hopital Maisonneuve Rosemont.

2.4 Sequencing and Priority of Treatments

- Please describe how the new treatment could be sequenced with current treatment(s), if appropriate.
- In your opinion, in the event that the drug under review becomes available for funding in your jurisdiction, would the new treatment be a replacement of current treatment(s) or another option?

Currently, CD19+ CAR-T would be considered standard of care in patients who are no longer eligible for curative treatment (ie beyond second-line therapy). In patients eligible for additional aggressive treatment strategies, this would clearly become a new standard in the palliative setting, given the potential for long-term disease control. It is very likely that this would displace potential allo-SCT in this setting given the favourable results in terms of disease control and lack of meaningful late effects given current follow-up.

Randomized controlled trials will determine the potential superiority of CAR-T in the second-line curative setting. CD19+ CAR-T cells could replace salvage chemotherapy and ASCT if this generation of clinical trials is positive.

2.5 Companion Diagnostic Testing

- If companion diagnostic testing is required for the new drug, is the test available in your jurisdiction? Is it funded by your jurisdiction? What concerns, if any, do you have on the test and turn-around time for test results? Are there specific considerations to a testing algorithm that you think would be important to share with the pCODR Expert Review Committee?

Before completing this template, be sure to register with the pCODR program. Please visit <https://www.cadth.ca/pcodr/registration> for information about the registration process.

CD19 CAR-T cell therapy requires expression of CD19 on tumour - this is a routine study that can be performed on tissue using immunohistochemistry. It would be very reasonable to require demonstration of the target on archival tissue. As anti-CD19-based therapy is not routine, it is highly unlikely that CD19 negative disease would arise through standard therapy and thus it would not be important to ensure a new biopsy is collected to document CD19 status immediately prior to therapy if a biopsy expressing CD19 has been performed at sometime following primary therapy.

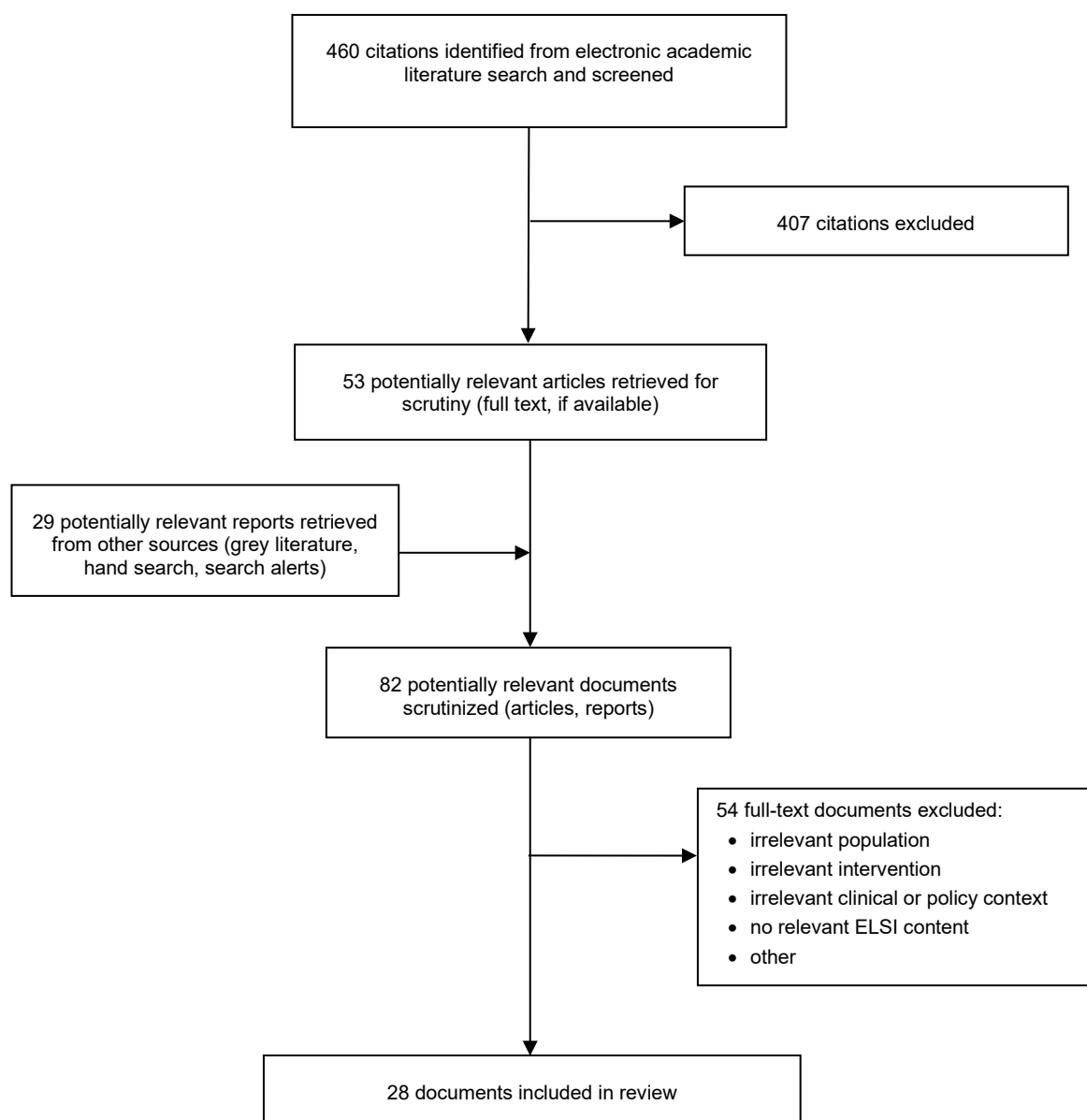
3 Additional Information

Please provide any additional information that would be helpful to pCODR. This could include suggestions for improving the clinician input process, indicating whether the questions are clear, etc.

There are clear implications for patient care in Canada in the short term. Patients are being considered for referral to expert centres in the United States with reimbursement being potentially provided by provincial funders. This is clearly costly and imperfect patient care as it places a huge burden for patients and their caregivers for travel and will introduce inevitable delays.

Given the potential to cure the disease, the advent of CAR-T cell therapy is analogous the stem cell transplantation in hematologic malignancies. This has become a challenging issue across the provinces given the numbers of patients in Canada potentially eligible for these types of treatments and the lack of resources to provide these therapies in a timely manner within the country.

Appendix 5: Study Selection Flow Diagram — Ethics Review



Appendix 6: Table of Literature Included – Ethics Review

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Atilla E, Kilic P, Gurman G. Cellular therapies: Day by day, all the way. <i>Transfus Apheresis Sci.</i> 2018 Apr;57(2):187-196. ⁷	Turkey	Review	CAR T-cell therapy as experimental therapy – hype Balancing safety and effectiveness Access – location of treatment sites Cost – affordability Informed choice	Discusses general ethical issues related to safety and unknown risks, access to therapy limited by available treatment sites, affordability to health systems and patients, and post-market surveillance of cellular therapies, including CAR T-cell therapy. Notes specific ethical issues related to clinical trials including patient and data confidentiality, consent, decisional vulnerability of patients with severe illness and few options, and importance of honest communication about the benefits and risk of treatment to mitigate hype.
Bach PB, Giralt SA, Saltz LB. FDA Approval of Tisagenlecleucel: Promise and complexities of a \$475 000 cancer drug. <i>JAMA.</i> 2017;318(19):1861-1862. ⁵	US	Opinion	CAR T-cell therapy as experimental therapy - hype Balancing safety and effectiveness Cost - affordability	Discusses the importance of mitigating hype of CAR T-cell therapy and not overstating benefits and understating harms in clinical encounters and media to ensure appropriate use of CAR T-cell therapy in clinical practice. Argues in favour of making tisagenlecleucel available only at institutions with expertise managing severe toxicities (e.g., hematopoietic cell transplantation) to minimize harms. Argues that total costs should be reported, inclusive of costs associate with pre- and post-infusions, treatment for severe side effects, etc. Raises concern about long-term affordability of CAR T-cell therapy if extended to other tumour types in the future.
Carvalho M, Sepodes B, Martins AP. Regulatory and scientific advancements in gene therapy: State-of-the-art of clinical applications and of the supporting European Regulatory Framework. <i>Front Med (Lausanne).</i> 2017;4:182. ¹⁴	Portugal, EU	Review	Cost – barrier to patient access, affordability	Identifies inequities in patient access related to patient-level affordability. Suggests current high cost may be offset by potential long-term benefits resulting in reduced health system utilization.
Chimeric antigen receptor T-cell therapy for B-cell cancer: Effectiveness and value - Final evidence report. Boston (MA):	US	Technology Assessment Report – patient perspectives	Balancing safety and effectiveness Cost Informed choice about treatment options	Reports findings of consultation with patients and caregivers about tisagenlecleucel. Describes how patients with no other options hoped therapy would offer a cure and perceived to be less toxic than alternative treatments; how

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Institute for Clinical and Economic Review (ICER); 2018: https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf Accessed 2018 Oct 29. ¹³			Beyond clinical harms and benefits	patients also expressed fear of the unknown related to limited evidence, not knowing if they would experience a serious side effect, and uncertainty associated with long-term side effects (especially neurological). Stresses the importance of detailed patient education regarding what to expect. Patients incurred various non-medical costs associated with treatment (accommodation, taking time off work, etc.) “but they felt that they had no choice; parents, in particular, spoke of doing anything for their child with leukemia.” Notes that both patients and caregivers experience distress associated with experiencing or witnessing severe side effects and that emotional and psychological support are required to mitigate the post-traumatic stress following treatment and the emotional toll of cancer.
Cossu G, Birchall M, Brown T, De Coppi P, Culme-Seymour E, Gibbon S, Hitchcock J, Mason C, Montgomery J, Morris S, Muntoni F, Napier D, Owji N, Prasad A, Round J, Saprai P, Stilgoe J, Thrasher A, Wilson J. <i>Lancet</i> Commission: Stem cells and regenerative medicine. <i>Lancet</i> 2018; 391:883–910. ⁸	UK	Primary research and review; normative analysis	Balancing safety and effectiveness Informed choice about treatment options Beyond clinical harms and benefits Policy implications	Raises concern about how hope of cure and false promises may exacerbate patient vulnerability underling the importance of informed consent and efforts to support patient autonomy to make life choices and at the same time avoiding unjustified paternalism. Argues that consideration of benefits and risk not limited to direct benefits/risks at patient level, but also broader population level considerations, including distributive justice, opportunity costs associated with providing these benefits, and trust in health care systems. Emphasizes principles of procedural justice (e.g., transparency) to protect patients, maintain public trust, and enable social licences for emerging technologies.
Couzin-Frankel J. For experimental cancer therapy, a struggle to ensure supply keeps up with demand. <i>Science</i> 2017; https://www.sciencemag.org/news/2017/06/experimental-cancer-therapy-struggle-ensure-supply-keeps-demand Accessed 2018 Nov 26. ²²	US	Editorial	Access – constraints on supply, patient selection, age	Addresses ethical issues associated with supply of CAR T-cell therapy, including how to fairly allocate supply and what factors should be considered in allocating resources. Notes potential impact on supply of ‘off-label’ use. Identifies difficulty of balancing meeting sickest patients’ needs and keeping other patients stable enough to be eligible for treatment. Raises question about age-based selection criteria (“If Novartis’s product is approved for leukemia patients up to 28 years old, say, and you have a

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
				28.1-year-old, does that mean you can't treat them?")
Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. <i>N Engl J Med</i> . 2015;372(3):279-286. ²⁹	US	Primary research; normative analysis	Informed choice about treatment options	Addresses difficulty of respecting patient autonomy and supporting informed consent in the context of evidentiary uncertainty and information asymmetries associated with investigational drugs. Cautions against paternalism because patients are rational actors capable of making decisions based on their own risk-benefit thresholds. Argues for greater deference to patient autonomy when the stakes are highest (i.e., imminent or likely death).
de Lima Lopes G, Nahas GR. Chimeric antigen receptor T cells, a savior with a high price. <i>Chin Clin Oncol</i> . 2018;7(2):21. ²⁰	US	Opinion	Access – barriers based on cost to patients and time delays Cost – affordability, transparency, clinician role	Discusses cost of CAR T-cell therapy as an ethical issue with a number of dimensions: high cost of CAR T-cell therapy potentially justified if it offers a cure; affordability (including for total costs, i.e., hospital, supportive, and outpatient treatment) as potential barrier to access for patients; duration of reimbursement approval processes as potential barrier to access for patients whose health status declines to point of clinical ineligibility while waiting for approval; need for greater transparency about pricing given public investment into R&D. Asserts that physicians should be aware of costs in clinical decision-making to help mitigate inefficient or wasteful health care spending.
Ertl HCJ, Zaia J, Rosenberg SA, June CH, Dotti G, Kahn J. Considerations for the clinical application of chimeric antigen receptor T cells: observations from a Recombinant DNA Advisory Committee symposium held June 15, 2010 (vol 71, pg 3175, 2011). <i>Cancer Res</i> . 2011;71(12):4325-4325. ³⁰	US	Commentary	CAR T-cell therapy as experimental therapy	Describes ethical dilemma in balancing societal benefit in knowledge creation and potential for therapeutic benefit in design of early phase research involving CAR T-cells. Address challenge of accurate disclosure of risks and benefits and appropriate informed consent involving seriously ill patient-subjects with few therapeutic options.
Fernandez C. CAR T cells: A drive to the future of cancer treatment. <i>Impact Ethics</i> . 2017. https://impactethics.ca/2017/08/31/car-t-cells-a-drive-to-the-future-of-cancer-treatment/ . Accessed 2018	Canada	Blog – ethical analysis	CAR T-cell therapy as experimental therapy - hype Informed choice Cost – patient and system-level affordability	Identifies two key ethical challenges related to CAR T-cell therapy: i) over-promising the benefits of a new therapy and ii) justice. Argues for caution in discussing benefits/risks, including lack of evidence on long-term effects, with patients and caregivers faced with limited treatment options. Raises concerns about financial

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Nov 2. ²⁵				implications of CAR T-cell therapy on patients and caregivers, opportunity costs of expanded use beyond current indications, and competing health priorities in short and long term.
Gumer JM. A new frontier in the fight against cancer (that is, for those who can afford it): The approval and cost of CAR T-cell therapies. <i>Voices in Bioethics</i> . 2018. http://www.voicesinbioethics.net/voices-in-bioethics/the-approval-and-cost-of-car-t-cell-therapies Accessed 2018 Nov 2. ¹⁹	US	News	Cost – patient-level affordability	Identifies financial burden on patients may exacerbate existing inequities in ability to pay for health care.
Hammer MJ, Eckardt P, Barton-Burke M. Informed consent: A clinical trials perspective. <i>Oncol Nurs Forum</i> . 2016;43(6):694-696. ⁹⁸	US	Case analysis	CAR T-cell therapy as experimental therapy – research ethics paradigm	Identifies the Belmont Principles (respect for persons, beneficence, and justice) as relevant ethical tenets for participation in gene therapy clinical trials and studies. Raises concern about whether marginalized people with poor access to health care will have a chance to benefit and whether some patients will be better informed than others based on education level.
Hayden MA. The burgeoning “biorights movement:” Its legal basis, what’s at stake, and how to respond. <i>Boston Coll Law Rev</i> . 2018;59(5):1775. ³⁸	US	Primary research; legal analysis	Legal considerations	Describes trend of individuals refusing to contribute biological materials for research purposes without monetary compensation.
Holmes H. Barriers to patient access to CAR T-cell therapy in the community setting. 2018; https://www.journalofclinicalpathways.com/news/barriers-access-standards-toxicity-management-car-t-therapy-community-setting Accessed 2018 Nov 26. ¹⁶	US	Interview	Access – location of treatment centres	Describes constraints on access due to limited number of treatment centres, which may be justified on grounds of ensuring appropriate management of toxicity but has implications for patient access.
Imbach KJ, Patel A, Levine AD. Ethical considerations in the translation of CAR T-cell therapies.	US	Primary research; normative analysis	Balancing safety and effectiveness Access – geographic constraints	Identifies ethical issues associated with CAR T-cell therapy across the various stages of development and implementation—from pre-clinical to post-market. Claims

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
<i>Cell Gene Ther Insights</i> . 2018;4(4):295-307. ¹²			Cost Policy implications	that minimizing harm to research participants and patients is a challenge that cuts across the various stages of the therapeutic life cycle. Identifies challenge of managing patient and public expectations and minimizing hype, which involves balancing the benefits of excitement (e.g., increased awareness and funding) with the actual uncertainty around the long-term effectiveness. Raises concern about potential exacerbation of health inequities based on cost of treatment and location of treatment centres. Underlines importance of studying safety and effectiveness in order to preserve public trust.
Jecker NS, Wightman AG, Rosenberg AR, Diekema DS. From protection to entitlement: selecting research subjects for early phase clinical trials involving breakthrough therapies. <i>J Med Ethics</i> . 2017;43(6):391-400. ¹¹	US	Primary research; normative analysis	CAR T-cell therapy as experimental therapy – clinical and research ethics paradigms Access – patient selection, age	Characterizes breakthrough therapies such as CAR T-cell therapy as existing between therapy and research. Argues that while individuals may not be entitled to receive an experimental therapy, they are entitled to a fair selection process and protection from risks. Proposes selection criteria for prioritizing clinical trial participants for CAR T-cell (ALL). Discuss additional selection criteria such as age based on a fair-innings argument. Argues that as evidence of therapeutic benefit increases, obligations of justice shift from protection from harm to ensuring fair access to benefits, which may mean modification of selection criteria.
Jecker NS, Wightman A, Rosenberg A, Diekema D. Breakthrough immunotherapies seem like a dream come true for children with leukemia. 2017; https://blogs.bmj.com/medical-ethics/2017/04/18/breakthrough-immunotherapies-seem-like-a-dream-come-true-for-children-with-leukemia/ Accessed 2018 Nov 26. ⁹⁹	US	Blog – ethical analysis	CAR T-cell therapy as experimental therapy – clinical and research ethics paradigms	Proposes that, with respect to breakthrough therapies, benefit should be understood as a continuum from complete uncertainty about benefit to clearly demonstrated benefit. Argues that as evidence of benefit increases, the ethical claim for access increases. Outlines a framework for prioritizing access along the continuum -- earlier in the continuum, priority to those with greatest medical need to justify risk of participation and later in the continuum, priority to those most likely to benefit on basis of available evidence.
Kimmelman J. Ethics of cancer gene transfer clinical research. <i>Methods Mol Biol</i> . 2009;542:423-445. ¹⁰⁰	Canada	Primary research; normative analysis	CAR T-cell therapy as experimental therapy Informed choice	Discusses cancer gene therapies, primarily in the context of early-stage clinical trials. Discusses ethical importance of managing public expectations about breakthrough therapies as well as participant expectations for the purpose of informed consent.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Kodish E. "What's in a name?" CAR-T gene therapy. <i>Hastings Center Report</i> . 2017;47(6). ¹⁰	US	Opinion	CAR T-cell therapy as experimental therapy	Describes CAR T-cell therapy as an example of "experimental therapy" (or alternatively, "therapeutic research") characterized by "high risk, high reward" and "high cost" at the intersection of research and therapy.
Kuehn BM. The promise and challenges of CAR-T gene therapy. <i>JAMA</i> . 2017;318(22):2167-2169. ⁶	US	News article	CAR T-cell therapy as experimental therapy Balancing safety and effectiveness Access – constraints on supply, patient selection Cost – system-level and long-term effects	Discusses the hope and hype surrounding CAR T-cell therapy and patient willingness to accept severe side effects (toxicities) for potential benefit. Raises a concern about impact of production time-lines on patient outcomes. Cites a physician claiming that treating patients earlier in the course of cancer may help minimize CRS. Describes systems-level impacts (e.g., insufficient ICU beds if such therapies became widely available). Suggests that CAR T-cell therapy may be cost-effective and reduce future costs if it proves to be curative.
Levine AD. Revolutionary new cancer therapies come with big risks. Drug makers must be prepared. 2017; https://www.statnews.com/2017/11/08/car-t-cancer-death-pharma-companies/ Accessed 2018 Nov 08. ¹⁰¹	US	Opinion	Balancing safety and effectiveness	Argues for restraint in expanding CAR T-cell therapy "too far and too fast" given evidentiary uncertainty and risk. Recommends giving priority to meeting needs of worst-off patients (i.e., those for whom there are no other options not those with earlier-stage cancers who have a wider array of options), ensuring there are processes in place to address risks, developing educational materials for patients, and coordinating with patient advocacy groups on communications.
Lowenstein PR. A call for physiopathological ethics. <i>Mol Ther</i> . 2008;16(11):1771-1772. ³⁴	US	Editorial	Balancing safety and effectiveness Access - age Informed choice	Argues that need to balance protection from undue risk with consideration of potential forgone benefits if novel therapies are not made available to patients who could experience the greatest benefit. Discusses informed consent and assent for pediatric patients, including that rigid implementation of age of consent ought not be barriers to access to novel and experimental therapies.
Madden DL. From a patient advocate's perspective: Does cancer immunotherapy represent a paradigm shift? <i>Curr Oncol Rep</i> . 2018;20(1):8. ³²	US	Review	CAR T-cell therapy as experimental therapy Informed choice – patient education Beyond clinical harms and benefits	Cautions against hype and discusses need for transparent and realistic reporting of research findings and clear, accurate and balanced education and discussion with patients about both benefits and risks.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Maschke KJ, Gusmano MK, Solomon MZ. Breakthrough cancer treatments raise difficult questions. <i>Health Aff (Millwood)</i> . 2017;36(10):1698-1700. ¹⁵	US	Commentary	Balancing safety and effectiveness Access – geographic constraints Cost Informed choice about treatment options	Notes that many patients without alternative therapeutic options are willing to undergo investigational treatments that bear serious risk of harm. Underlines importance of informed consent and open communication about the risk-benefit profile. Argues that post-licensing monitoring of side effects is required especially for drugs approved through priority review mechanisms. Also argues that access to therapy needs to be balanced with safety in determining treatment locations (i.e., equipped to manage toxicities); however, raises concern about treatment costs (including informal costs to patients and families who must travel to receive treatment) and impact on sustainability of health care systems. To ensure patient can receive therapy in facilities that are equipped to do so.
McConville H, Harvey M, Callahan C, Motley L, Difilippo H, White C. CAR T-cell therapy effects: Review of procedures and patient education. <i>Clin J Oncol Nurs</i> . 2017;21(3):E79-E86. ³³	US	Primary research and review; empirical analysis	Informed choice Beyond clinical harms and benefits	Describes consent as ongoing process and importance of iterative education of patients and caregivers to inform decision-making and consent. Identifies need for appropriate education processes and materials for pediatric patients. Links education to safety and psychological well-being of patients and caregivers. Identifies role of anticipatory guidance in reducing stress and anxiety for patients and caregivers. Underlines impact of treatment on caregivers and need to address the caregiver needs/concerns.
Mullin E. Gene therapy could make cancer care more unequal, and this map shows why. 2018; https://www.technologyreview.com/s/609890/gene-therapy-could-make-cancer-care-more-unequal-and-this-map-shows-why/ . Accessed 2018 Nov 2. ¹⁸	US	Editorial	Access – geographic constraints	Addresses implications of risk mitigation in limiting number of treatment centres with expertise in managing side effects, including burden on sick patients to travel long distances to receive care and exacerbation of existing health inequities (e.g., cancer patients in rural US states have poorer health outcomes). Also notes limited supply of clinicians with relevant expertise and argues that, in the immediate term, priority should be given to safety considerations over access considerations.
Prasad, V. Immunotherapy: Tisagenlecleucel – the first approved CAR T-cell therapy: implications for payers and policy makers. <i>Nat Rev Clin Oncol</i> .	US	Opinion	Access – geographic constraints, patient selection Cost	Identifies four policy considerations for tisagenlecleucel: (1) cost and the lack of transparency around pricing; (2) cost to payers, including total costs beyond just the therapy itself; (3) access, including whether all eligible patients will have access given that the limited number of treatment facilities

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
2018;15(1):11-12. ¹⁷				may introduce geographic constraints (including if some patients are not stable enough to travel to treatment facilities); (4) implications for non-pediatric or young adult patient populations, including that CAR T-associated toxicities, especially CRS, appear more concerning in older populations and thus limit extrapolating evidence from younger patient populations.
Sherkow JS, Contreras JL. Intellectual property, surrogate licensing, and precision medicine. <i>IP Theory</i> . 2018;7(2):Article 1. ³⁷	US	Legal Analysis	Legal considerations	Analyzes challenges associated with intellectual property, and surrogate licensing in particular, in the context of research and development of precision medicines, including tisagenlecleucel.
Sherkow JS, Zettler PJ, Greely HT. Is it 'gene therapy'? <i>J Law Biosci</i> . 2018;lsy020-lsy020. ³⁶	US	Legal Analysis	Legal considerations	Presents a legal definition of gene therapy, including CAR T- cell therapy, for clinical and regulatory clarity.
Unguru Y, Fernandez CV, Bernhardt B, Berg S, Pyke-Grimm K, Woodman C, et al. An ethical framework for allocating scarce life-saving chemotherapy and supportive care drugs for childhood cancer. <i>J Natl Cancer Inst</i> . 2016;108(6):1. ²³	US	Primary research; normative analysis and framework	Access – patient selection	Outlines an ethical framework for the allocation of scarce life-saving chemotherapy and supportive care drugs for pediatric cancers. Propose a two-step allocation process: i) minimize waste, and ii) prioritize access based on maximizing total benefit. Notes the value of an ethical framework in minimizing bias across clinicians and addressing distress experienced by clinicians faced setting priorities among patients in need.
Yeager AJ. CAR-T in the courts patent disputes bring immunotherapy technology and patent review process into focus Genetic Engineering and Biotechnology News 2017; https://www.genengnews.com/gen-exclusives/car-t-in-the-courts/77900974 . Accessed 2018 Nov 26. ³⁵	US	News article	Legal considerations	Describes ongoing intellectual property litigation related to CAR T-cell technologies between researchers and manufacturers in the US.

Citation	Country	Method	Topic	Claims (normative analysis); results (empirical ethics)
Zheng P-P, Kros JM, Li J. Approved CAR T-cell therapies: ice bucket challenges on glaring safety risks and long-term impacts. <i>Drug Discov Today</i> . 2018;23(6):1175-1182. ⁹	Netherlands, China	Opinion	CAR T-cell therapy as experimental therapy - hype Balancing safety and effectiveness	Focuses on current evidentiary uncertainty, particularly related to long-term effectiveness and long-term side effects or future harms. Identifies problem of overstated benefits and understated harms, especially in the media. Raises importance of considering both life-saving and quality of life-preserving measures in medicine, which may be especially important for caring for children and young adults, and question of physician's obligation to patients in balancing life-saving and quality of life efforts. Recommends ethical deliberation involving patients, physicians and other relevant stakeholders to find the balance.

References

1. Novartis Pharmaceuticals Canada Inc. Novartis receives Health Canada approval of its CAR-T cell therapy, Kymriah™ (tisagenlecleucel). 2018 Sep 6; <https://www.novartis.ca/en/news/media-releases/novartis-receives-health-canada-approval-its-car-t-cell-therapy-kymriah>. Accessed 2018 Oct 30.
2. Daniels N, Sabin JE. *Setting limits fairly : Can we learn to share medical resources?* New York (NY): Oxford University Press USA; 2002.
3. Gibson JL, Martin DK, Singer PA. Priority setting in hospitals: Fairness, inclusiveness, and the problem of institutional power differences. *Social Science & Medicine*. 2005;61(11):2355-2362.
4. Tisagenlecleucel for B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma. (*CADTH Optimal use report*). Ottawa (ON): CADTH; 2018.
5. Bach PB, Giral SA, Saltz LB. FDA approval of tisagenlecleucel: Promise and complexities of a \$475 000 cancer drug. *JAMA: Journal of the American Medical Association*. 2017;318(19):1861-1862.
6. Kuehn BM. The promise and challenges of CAR-T gene therapy. *JAMA*. 2017;318(22):2167-2169.
7. Atilla E, Kilic P, Gurman G. Cellular therapies: Day by day, all the way. *Transfus Apheresis Sci*. 2018;57(2):187-196.
8. Cossu G, Birchall M, Brown T, De Coppi P, Culme-Seymour E, Gibbon S, et al. Lancet Commission: Stem cells and regenerative medicine. *The Lancet*. 2018;391(10123):883-910.
9. Zheng P-P, Kros JM, Li J. Approved CAR T cell therapies: ice bucket challenges on glaring safety risks and long-term impacts. *Drug Discovery Today*. 2018;23(6):1175-1182.
10. Kodish E. "What's in a name?" CAR-T gene therapy. *Hastings Center Report*. 2017;47(6).
11. Jecker NS, Wightman AG, Rosenberg AR, Diekema DS. From protection to entitlement: selecting research subjects for early phase clinical trials involving breakthrough therapies. *J Med Ethics*. 2017;43(6):391-400.
12. Imbach KJ, Patel A, Levine AD. Ethical considerations in the translation of CAR-T cell therapies. *Cell and Gene Therapy Insights*. 2018;4(4):295-307.
13. Chimeric antigen receptor T-cell therapy for B-cell cancers: Effectiveness and value - Final evidence report. Boston (MA): Institute for Clinical and Economic Review (ICER); 2018: https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf. Accessed 2018 Feb 27.
14. Carvalho M, Sepodes B, Martins AP. Regulatory and scientific advancements in gene therapy: State-of-the-art of clinical applications and of the supporting European Regulatory Framework. *Front Med (Lausanne)*. 2017;4:182.
15. Maschke KJ, Gusmano MK, Solomon MZ. Breakthrough cancer treatments raise difficult questions. *Health Aff (Millwood)*. 2017;36(10):1698-1700.
16. Holmes H. Barriers to patient access to CAR-T therapy in the community setting. 2018; <https://www.journalofclinicalpathways.com/news/barriers-access-standards-toxicity-management-car-t-therapy-community-setting>. Accessed 2018 Nov 26.
17. Prasad V. Immunotherapy: Tisagenlecleucel - the first approved CAR-T-cell therapy: implications for payers and policy makers. *Nat Rev Clin Oncol*. 2018;15(1):11-12.
18. Mullin E. Gene therapy could make cancer care more unequal, and this map shows why. 2018; <https://www.technologyreview.com/s/609890/gene-therapy-could-make-cancer-care-more-unequal-and-this-map-shows-why/>. Accessed 2018 Nov 2.
19. Gumer JM. A new frontier in the fight against cancer (that is, for those who can afford it): The approval and cost of CAR T-cell therapies. *Voices in Bioethics*. 2018. <http://www.voicesinbioethics.net/voices-in-bioethics/the-approval-and-cost-of-car-t-cell-therapies>. Accessed 2018 Nov 2.
20. de Lima Lopes G, Nahas GR. Chimeric antigen receptor T cells, a savior with a high price. *Chin*. 2018;7(2):21.
21. Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nature Reviews Clinical Oncology*. 2018.
22. Couzin-Frankel J. For experimental cancer therapy, a struggle to ensure supply keeps up with demand. *Science* 2017; <https://www.sciencemag.org/news/2017/06/experimental-cancer-therapy-struggle-ensure-supply-keeps-demand>. Accessed 2018 Nov 26.
23. Unguru Y, Fernandez CV, Bernhardt B, Berg S, Pyke-Grimm K, Woodman C, et al. An ethical framework for allocating scarce life-saving chemotherapy and supportive care drugs for childhood cancer. *Journal of the National Cancer Institute*. 2016;108(6):1.
24. Maude SL, Frey N, Shaw PA, Aplenc R, Barrett DM, Bunin NJ, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *New England Journal of Medicine*. 2014;371(16):1507-1517.
25. Fernandez C. CAR-T cells: A drive to the future of cancer treatment. *Impact Ethics*. 2017. <https://impactethics.ca/2017/08/31/car-t-cells-a-drive-to-the-future-of-cancer-treatment/>. Accessed 2018 Nov 2.
26. Economic review report (DLBCL) In: Tisagenlecleucel for B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma. (*CADTH optimal use report*) Ottawa (ON): CADTH; 2018.
27. Economic review report (ALL) In: Tisagenlecleucel for B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma. (*CADTH optimal use report*) Ottawa (ON): CADTH; 2018.

28. Brock DW. Ethical and value issues in insurance coverage for cancer treatment. *The Oncologist*. 2010;15(Supplement 1):36-42.
29. Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. *New England Journal of Medicine*. 2015;372(3):279-286.
30. Ertl HCJ, Zaia J, Rosenberg SA, June CH, Dotti G, Kahn J. Considerations for the clinical application of chimeric antigen receptor T cells: observations from a Recombinant DNA Advisory Committee symposium held June 15, 2010 (vol 71, pg 3175, 2011). *CANCER RESEARCH*. 2011;71(12):4325-4325.
31. Kimmelman J. Ethics of cancer gene transfer clinical research. *Methods Mol Biol*. 2015;1317:263-285.
32. Madden DL. From a patient advocate's perspective: Does cancer immunotherapy represent a paradigm shift? *Curr Oncol Rep*. 2018;20(1):8.
33. McConville H, Harvey M, Callahan C, Motley L, Difilippo H, White C. CAR T-cell therapy effects: Review of procedures and patient education. *Clinical Journal of Oncology Nursing*. 2017;21(3):E79-E86.
34. Lowenstein PR. A call for physiopathological ethics. *Mol Ther*. 2008;16(11):1771-1772.
35. Yeager AJ. CAR-T in the courts patent disputes bring immunotherapy technology and patent review process into focus *Genetic Engineering and Biotechnology News* 2017; <https://www.genengnews.com/gen-exclusives/car-t-in-the-courts/77900974>. Accessed 2018 Nov 26.
36. Sherkow JS, Zettler PJ, Greely HT. Is it 'gene therapy'? *Journal of Law and the Biosciences*. 2018;lsy020-lsy020.
37. Sherkow JS, Contreras JL. Intellectual property, surrogate licensing, and precision medicine. *IP Theory*. 2018;7(2):Article 1.
38. Hayden MA. The burgeoning "biorights movement": Its legal basis, what's at stake, and how to respond. *Boston College Law Review*. 2018;59(5):1775.
39. Hawkins AK, O'Doherty KC. "Who owns your poop?": Insights regarding the intersection of human microbiome research and the ELSI aspects of biobanking and related studies. *BMC Medical Genomics*. 2011;4(1):72-72.
40. Master Z, Claudio JO, Rachul C, Wang JCY, Minden MD, Caulfield T. Cancer patient perceptions on the ethical and legal issues related to biobanking. *BMC Medical Genomics*. 2013;6(1):8-8.
41. Richie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, eds. *Analysing qualitative data*. London (GB): Routledge; 1994.
42. Tisagenlecleucel for B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma - Project protocol, Implementation and ethics section (CADTH Optimal use report vol.8, no.3b). Ottawa (ON): CADTH; 2018: https://cadth.ca/sites/default/files/pdf/OP0538_Tisagenlecleucel_for_B-Cell_Protocol.pdf. Accessed 2018 Nov 2.
43. U. S. Food and Drug Administration. KYMRIAH (tisagenlecleucel). 2018 Apr 13; <https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm>. Accessed 2018 Sep 27.
44. Novartis Pharmaceuticals Corporation. Risk Evaluation and Mitigation Strategy (REMS) Document: Kymriah (tisagenlecleucel) REMS Program. 2018: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Kymriah_2018_05_01_REMS_Full.pdf. Accessed 2018 Nov 14.
45. Committee for the Medicinal Products for Human Use. Assessment Report: Kymriah (tisagenlecleucel). (*European public assessment report*). London (GB): European Medicines Agency; 2018: https://www.ema.europa.eu/documents/assessment-report/kymriah-epar-public-assessment-report_en.pdf. Accessed 2018 Nov 14.
46. Health Canada. How drugs are reviewed in Canada. 2015; <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html>. Accessed 2018 Feb 27.
47. Butera S. CAR-T: trailblazing the path from clinical development to the clinic. *Gene Ther*. 2018;25(3):163-164.
48. Buechner J, Kersten MJ, Fuchs M, Salmon F, Jäger U. Chimeric antigen receptor-T cell therapy: Practical considerations for implementation in Europe. *HemaSphere*. 2018;2(1):e18.
49. Callahan C, Baniewicz D, Ely B. CAR T-cell therapy: Pediatric patients with relapsed and refractory acute lymphoblastic leukemia. *Clinical Journal of Oncology Nursing*. 2017;21(2 Suppl):22-28.
50. Maus MV, Nikiforow S. The why, what, and how of the new FACT standards for immune effector cells. *J Immunother Cancer*. 2017;5(36).
51. Foundation for the Accreditation of Cellular Therapy. FACT accredited institutions: Canada. 2018; http://accredited.factwebsite.org/?_sft_country=canada. Accessed 2018 Oct 10.
52. Zlomislic D. Plea from dying teen: Please help. 2016; https://www.thestar.com/life/health_wellness/2016/04/23/plea-from-dying-teen-please-help.html. Accessed 2018 Oct 10.
53. Dearment A. CAR-T therapies face logistical bottleneck as market set to see major growth. 2018; <https://medcitynews.com/2018/10/car-t-therapies-face-logistical-bottleneck-as-market-set-to-see-major-growth/?rf=1>. Accessed 2018 Oct 10.
54. Health Canada. Guidance document for cell, tissue and organ establishments - Safety of human cells, tissues and organs for transplantation. 2018; <https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/regulatory-initiatives/cells-tissues-organs/guidance-document-safety-human-cells-tissues-organs-transplantation/document.html#a2.6>. Accessed 2018 Nov 14.
55. Canadian Blood and Marrow Transplant Group. Blood and marrow transplant centres. 2018; <https://www.cbmtg.org/page/BMTCentres>. Accessed 2018 Oct 10.

56. Foundation for the Accreditation of Cellular Therapy. Cellular therapy accreditation eligibility. 2014; <http://www.factwebsite.org/cteligibility/>. Accessed 2018 Oct 10.
57. Foundation for the Accreditation of Cellular Therapy. Immune effector cell standards <http://www.factwebsite.org/iecstandards/>. Accessed 2018 Nov 1.
58. Tice J, Walsh J, Otuonye I, Chapman R, Kumar V, Seidner M, et al. Chimeric antigen receptor T-cell therapy for B-cell cancers: effectiveness and value. *Inst Clin Econ Rev*. 2017;1-120.
59. Tisagenlecleucel for acute lymphoblastic leukemia and diffuse large B-cell lymphoma - Clinical section. (CADTH Optimal use report). Ottawa (ON): CADTH; 2018.
60. PrACTEMRA® tocilizumab (20 mg/mL concentrate solution for infusion; 162 mg/0.9 mL solution for injection) [product monograph]. Mississauga (ON): Hoffman-La Roche Limited; 2017: https://pdf.hres.ca/dpd_pm/00041855.PDF. Accessed 2018 Oct 10.
61. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy - assessment and management of toxicities. *Nat Rev Clin Oncol*. 2018;15(1):47-62.
62. Chow VA, Shadman M, Gopal AK. Translating anti-CD19 CAR T-Cell therapy into clinical practice for relapsed/refractory diffuse large B-Cell lymphoma. *Blood*. 2018;18:18.
63. PrKymriah™ (tisagenlecleucel) cell suspension in infusion bag, 2.0 x 10⁶ to 6.0 x 10⁸ CAR-positive viable T-cells, for intravenous use [product monograph]. Dorval (QC): Novartis Pharma Canada Inc; 2018 Sept 5.
64. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J*. 2014;20(2):119-122.
65. International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH GCP). Managed Access Program (MAP) to provide access to CTL019, for ALL or DLBCL patients with out of specification leukapheresis product and/or manufactured tisagenlecleucel out of specification for commercial release. 2018; <https://ichgcp.net/clinical-trials-registry/NCT03601442>. Accessed 2018 Oct 18.
66. Harrison RP, Ruck S, Rafiq QA, Medcalf N. Decentralised manufacturing of cell and gene therapy products: Learning from other healthcare sectors. *Biotechnol Adv*. 2018;36(2):345-357.
67. Levine BL, Miskin J, Wonnacott K, Keir C. Global manufacturing of CAR T cell therapy. *Mol Ther Methods Clin Dev*. 2017;4:92-101.
68. Chung K. Toward off-the-shelf adoptive T cell therapies. *Sci Transl Med*. 2017;9(386), 2017 04 19.).
69. NHS England. NHS England announces groundbreaking new personalised therapy for children with cancer. 2018 Sep 5; <https://www.england.nhs.uk/2018/09/nhs-england-announces-groundbreaking-new-personalised-therapy-for-children-with-cancer/>. Accessed 2018 Nov 1.
70. Final appraisal document: Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years. London (GB): National Institute for Health and Care Excellence; 2018: <https://www.nice.org.uk/guidance/gid-ta10270/documents/final-appraisal-determination-document>. Accessed 2018 Nov 24.
71. Appraisal consultation document: Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies. London (GB): National Institute for Health and Care Excellence; 2018: <https://www.nice.org.uk/guidance/gid-ta10269/documents/appraisal-consultation-document>. Accessed 2018 Nov 1.
72. GlobalData Healthcare. Outcome-based contracts viable for Kymriah, but US payers still unsure. 2018 Jul 30; <https://www.pharmaceutical-technology.com/comment/outcome-based-contracts-kymriah/>. Accessed 2018 Nov 1.
73. Formal request for national coverage analysis for CAR T-cell therapies for cancer. Minnetonka (MN): UnitedHealth Care; 2018: <https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id291.pdf>. Accessed 2018 Nov 1.
74. Bach PB. National coverage analysis of CAR-T therapies — Policy, evidence, and payment. *New England Journal of Medicine*. 2018;379(15):1396-1398.
75. Novartis Pharmaceuticals Canada Inc. Novartis receives first ever FDA approval for a CAR-T cell therapy, Kymriah(TM) (CTL019), for children and young adults with B-cell ALL that is refractory or has relapsed at least twice. 2017 Aug 30; <https://www.novartis.com/news/media-releases/novartis-receives-first-ever-fda-approval-car-t-cell-therapy-kymriah-tm-ctl019> Accessed 2018 Nov 1.
76. Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol*. 2018;15(1):31-46.
77. Novartis has production hiccup for Kymriah CAR-T therapy. 2018 Jul 19; <http://www.biopharminternational.com/novartis-has-production-hiccup-kymriah-car-t-therapy-0>. Accessed 2018 Oct 18.
78. Pfadenhauer L, Rohwer A, Burns J, Booth A, Lysdahl KB, Hofmann B, et al. Guidance for the assessment of context and implementation in health technology assessments (HTA) and systematic reviews of complex interventions: the context and implementation of complex interventions (CICI) framework. [place unknown]: Integrate-HTA; 2016: <https://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-for-the-Assessment-of-Context-and-Implementation-in-HTA-and-Systematic-Reviews-of-Complex-Interventions-The-Co.pdf>. Accessed 2018 Jul 27.
79. NVivo qualitative data analysis Software. (Version 10). Victoria (AU): QSR International Pty Ltd; 2012: <https://www.qsrinternational.com/nvivo/home>. Accessed 2018 Oct 11.
80. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34.

81. McGrath P. Findings on family issues during relocation for hematology care. *Oncol Nurs Forum*. 2015;42(3):E250-256.
82. McGrath P. Overcoming the distance barrier in relation to treatment for haematology patients: Queensland findings. *Aust Health Rev*. 2015;39(3):344-350.
83. McGrath P. 'You never leave work when you live on a cattle property': Special problems for rural property owners who have to relocate for specialist treatment. *Aust J Rural Health*. 2015;23(5):286-290.
84. McGrath P. Haematology patients' desire to access metropolitan hospital expertise. *Aust Health Rev*. 2016;40(3):251-256.
85. McGrath P. 'The bills that were coming in...': out of pocket costs during relocation for specialist treatment for haematological malignancies. *Support Care Cancer*. 2016;24(7):2893-2903.
86. McGrath P. Financial distress during relocation for treatment of a hematological malignancy: Findings for social work. *Soc Work Health Care*. 2016;55(4):265-279.
87. McGrath P. Financial assistance for patients who relocate for specialist care in hematology: Practical findings to inform nursing supportive care. *Nurs Forum*. 2017;52(1):55-61.
88. McGrath P. End-of-life care in hematology: update from Australia. *J Soc Work End Life Palliat Care*. 2013;9(1):96-110.
89. Odejide OO, Salas Coronado DY, Watts CD, Wright AA, Abel GA. End-of-life care for blood cancers: a series of focus groups with hematologic oncologists. *J Oncol Pract*. 2014;10(6):e396-403.
90. LeBlanc TW, O'Donnell JD, Crowley-Matoka M, Rabow MW, Smith CB, White DB, et al. Perceptions of palliative care among hematologic malignancy specialists: a mixed-methods study. *J Oncol Pract*. 2015;11(2):e230-238.
91. Loggers ET, Lee S, Chilson K, Back AL, Block S, Loberiza FR. Advance care planning among hematopoietic cell transplant patients and bereaved caregivers. *Bone Marrow Transplant*. 2014;49(10):1317-1322.
92. Orlowska D, Selman LE, Beynon T, Radcliffe E, Whittaker S, Child F, et al. 'It's a traumatic illness, traumatic to witness': a qualitative study of the experiences of bereaved family caregivers of patients with cutaneous T-cell lymphoma. *Br J Dermatol*. 2018;16:16.
93. Dunn E, Arber A, Gallagher A. The immediacy of illness and existential crisis: Patients' lived experience of under-going allogeneic stem cell transplantation for haematological malignancy. A phenomenological study. *Eur J Oncol Nurs*. 2016;21:90-96.
94. Prod'homme C, Jacquemin D, Touzet L, Aubry R, Daneault S, Knoops L. Barriers to end-of-life discussions among hematologists: A qualitative study. *Palliat Med*. 2018;32(5):1021-1029.
95. Horinuki F, Noguchi-Watanabe M, Takai Y, Yamahana R, Ohno N, Okada S, et al. The experience of persons with hematological malignancy when communicating with health care professionals. *Qual Health Res*. 2018;28(3):479-490.
96. Hoff L, Hermeren G. Identifying challenges to communicating with patients about their imminent death. *J Clin Ethics*. 2014;25(4):296-306.
97. Grech A, Depares J, Scerri J. Nurses' experiences providing end-of-life care to adults with hematologic malignancies. *Journal of Hospice & Palliative Nursing*. 2018;20(3):237-244.
98. Hammer MJ, Eckardt P, Barton-Burke M. Informed consent: A clinical trials perspective. *Oncol Nurs Forum*. 2016;43(6):694-696.
99. Jecker NS, Wightman A, Rosenberg A, Diekema D. Breakthrough immunotherapies seem like a dream come true for children with leukemia. 2017; <https://blogs.bmj.com/medical-ethics/2017/04/18/breakthrough-immunotherapies-seem-like-a-dream-come-true-for-children-with-leukemia/>. Accessed 2018 Nov 26.
100. Kimmelman J. Ethics of cancer gene transfer clinical research. *Methods Mol Biol*. 2009;542:423-445.
101. Levine AD. Revolutionary new cancer therapies come with big risks. Drug makers must be prepared. 2017; <https://www.statnews.com/2017/11/08/car-t-cancer-death-pharma-companies/>. Accessed 2018 Nov 08.