

CADTH OPTIMAL USE REPORT

Tisagenlecleucel for B-Cell Acute Lymphoblastic Leukemia and Diffuse Large B-Cell Lymphoma — Project Protocol, Implementation and Ethics Section

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Background and Purpose

Implementation Analysis

Tisagenlecleucel is a new chimeric antigen receptor (CAR) T-cell therapy that may offer clinical benefit for adults with relapsed or refractory diffuse large B-cell lymphoma and children and young adults (25 years or younger) with relapsed or refractory acute lymphoblastic leukemia. It is a multi-stage procedure involving T-cell harvesting, transportation and storage, and manufacturing (which involves modifying the DNA of harvested T cells to include CARs), and then reinfusion. The purpose of this analysis is to support decision-making relating to the provision of tisagenlecleucel in Canadian health care systems.

Ethics Review

The purpose of the ethics review is to identify, describe, and provide guidance on key ethical considerations in the implementation and provision of tisagenlecleucel for adults with relapsed or refractory diffuse large B-cell lymphoma and children and young adults with relapsed or refractory acute lymphoblastic leukemia. The issues raised in this review necessarily go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations, as well. It is common in the ethics literature, across a broad range of health-related issues, to refer to ELSI —ethical, legal, and social issues— when addressing broader values and related considerations. While the primary emphasis here will be on ethical considerations, legal and social issues may also figure in the analysis.

Policy Question

This project will address 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?

Objectives and Research Questions

Implementation Analysis

The research objectives guiding this analysis are:

- 1) 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, and;
- 2) 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); via hospital or health care organizations such as regional health authorities (i.e., meso level); and at the provincial, territorial, and federal levels (i.e., macro level).

This analysis considers the use of tisagenlecleucel in the following populations:

- children and young adults with r/r-ALL
- adults with r/r-DLBCL.

When and where appropriate, these two populations will be explored separately, although there may be areas of overlap where a combined analysis is conducted.

Ethics Review

Two questions will guide this review:

- 1) 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?
- 2) How might these issues be addressed?

As appropriate, these two populations will be explored separately, although there may be areas of overlap where a combined analysis is conducted.

Methods

This protocol was written a priori and will be followed throughout the study process. Any deviations from the protocol will be disclosed in the final report.

Ethics Analysis

Methods of Inquiry

This review will use a two-step approach to identifying and describing potential ethical issues. The first step will be 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 is a *de novo* ethical analysis based on gaps identified in the literature review. This analysis will identify and assess the relative importance and strengths of existing ethical concerns and proposed solutions, and identify and assess unidentified ethical issues and possible solutions.

The approach of this ethical review will be inductive and iterative, and will be responsive to results emerging from clinical, economic, and implementation reviews, including patients' and stakeholders' perspectives. This may require additional targeted literature searches of theoretical ethics and applied ethical analyses of similar or related technologies (e.g., stem cell transplantation).

Review of the Ethics Literature

A review of the empirical and normative ethics literature will be 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 will be performed by an information specialist, using a peer-reviewed search strategy. The search strategy is available upon request. Additional searching may be required because of the iterative nature of the literature review.

Ethics-related information will be identified by searching the following databases: MEDLINE (1946–) via Ovid, PsycINFO (1806–) via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO, and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be tisagenlecleucel, chimeric antigen receptor T-cell therapy, and gene therapy as related to cancer.

Methodological filters will be applied to limit retrieval to studies related to ethical, legal, and social issues. The search will be limited to English- or French-language documents published since January 1, 2008. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>), which includes the websites of health technology assessment (HTA) agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Literature Screening and Selection

The selection of relevant literature will proceed in two stages. In the first stage, titles and abstracts of citations will be screened for relevance by a single reviewer. Articles that meet any of the following criteria will go on to the second stage and be retrieved for full-text screening:

- provides normative analysis of an ethical issue arising with the implementation and use of tisagenlecleucel in populations of interest (i.e., adults with DLBCL and children and young adults with ALL)
- presents empirical research directly addressing an ethical issue arising in the implementation and use of tisagenlecleucel in populations of interest
- explicitly identifies but does not analyze or investigate empirically an ethical issue arising with the implementation and use of tisagenlecleucel in populations of interest
- identifies broader ethical issues concerned with HTA and drug and technology access in children.

In the second stage, the full-text reports will be screened by a single reviewer and the selected reports will be verified by a second reviewer. Reports meeting any of the above mentioned criteria will be included in the analysis.

The goal in a review of ethics literature is to describe what arises as an ethical issue from a broad range of relevant perspectives. As such, the quality of normative analysis does not figure in the article selection criteria: any identification of an issue by the public, patients, health care providers, researchers, or policy-makers is of interest, whether presented through rigorous ethical argumentation or not. For example, academic ethicists may focus on certain issues because these relate to theoretical trends in their discipline, while an opinion piece by a clinical or policy leader, or a patient experience, may bring to the fore ethical questions neglected by academic ethicists but highly pertinent to the assessment of the technology in the relevant context. Despite the different standards of normative argumentation for each kind of report, the importance of the issues raised cannot be assessed solely by these standards and so literature cannot be excluded based on methodological standards.

Data Abstraction

For each included citation, bibliographic details (e.g., author, publication date, journal), potential ethical issues raised, and the report's conclusions (issues identified, values at stake identified through normative analysis, and solutions proposed, and their normative justification, if presented) will be extracted and summarized in a tabular format.

Analysis

At this stage, the ethical issues identified, values described, and solutions proposed in the literature will be evaluated using the methods of ethical (applied philosophical) analysis. This involves applying standards of logical consistency and rigour in argumentation, particularly where specific implications are identified and specific solutions advocated; responsiveness to important values of health care and health care policy in the field in which the technology is proposed for implementation; adequacy to the context for which the technology is being considered; and the representation of perspectives from diverse relevant communities, particularly attending to the possibility of the neglect of marginalized and vulnerable populations.

The proposed analysis will employ an axiological questions-based approach (described by Hofmann¹) to explore the issues identified, values described, and solutions proposed in the review to further clarify and uncover ethical issues relevant to decision-makers. This axiological approach applies 33 questions to explore a comprehensive set of overt and covert value issues relevant to the ethical assessment of health technologies. Issues identified and not addressed by the axiological approach will be highlighted, and supplementary searches will be conducted in case there are axiological questions that were not addressed by any of the identified issues in the initial search.

Summarizing and Presenting Results

Ethical issues are multidimensional. Their reporting can be organized procedurally (through a patient or clinical care continuum), structurally (through the levels of the health care system at which they emerge, as micro, meso, and macro level issues), according to the key values commonly identified in the literature, or according to the specific issues and concerns identified in the review and in communication with other review processes. The review will be organized according to whichever of these four frameworks best suits the results of the review and facilitates its use by decision-makers. It will be presented in a way that helps decision-makers better understand the ethical implications of the decisions and recommendations arrived at. Findings specific to children and young adults will be presented separately to allow for independent consideration.

Implementation Analysis

Overview of Approach

The implementation analysis will involve the synthesis of the findings from two subanalyses, patient and stakeholder input, and relevant information from the clinical, economic, and ethics reviews conducted as part of CADTH's assessment of tisagenlecleucel, as well as industry documents:

- 1) Subanalysis One: A rapid qualitative evidence synthesis of patients', families', and providers' perspectives and experiences of advanced or terminal hematologic cancer and its treatment; to identify patient-important clinical outcomes, patient-centred pathways and models of care, and treatment-related burdens for patients and their families.
- 2) Subanalysis Two: A rapid qualitative evidence synthesis of issues raised in the published literature relating to the implementation of tisagenlecleucel at micro, meso, and macro levels.
- 3) Patient and stakeholder input to inform and clarify findings from subanalyses and preliminary findings from the implementation analysis.
- 4) Information pertaining to the implementation and delivery of tisagenlecleucel from the clinical, economic, and ethics reviews of CADTH's assessment, from additional sources identified by stakeholders, and from manufacturer implementation plan documents relating to site selection, training, and anticipated volumes.

The implementation analysis will use data and analysis from of these inputs to identify capacity and feasibility considerations for implementing access to and delivering tisagenlecleucel using a framework approach.²

Subanalysis One: A Rapid Qualitative Evidence Synthesis of Patients', Families' and Providers' Perspectives and Experiences

The goal of this subanalysis is to understand the context in which patients, and their families and providers experience r/r-ALL or r/r DLCBL and the context in which they would make decisions about and potentially receive tisagenlecleucel. The research question guiding this subanalysis is:

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?

A rapid qualitative evidence synthesis will be conducted to address this question.

Literature Search Strategy

The literature search will be performed by an information specialist, using a peer-reviewed search strategy. The search strategy is presented in Appendix 1.

Information related to patient perspectives and experiences will be identified by searching the following bibliographic databases: MEDLINE (1946–), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via EBSCO and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concepts will be leukemia and lymphoma.

Methodological filters will be applied to limit retrieval to qualitative studies. The search will be limited to English- or French-language documents published since January 1, 2013.

Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching using the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>), which includes the websites of HTA agencies, clinical guideline repositories, systematic review repositories, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials.

Literature Screening and Study Selection

Retrieved citations from the literature search will be screened by one reviewer in DistillerSR according to predefined eligibility criteria. The full-text of all potentially eligible citations will be retrieved, and subsequently full-text screening will be conducted by two reviewers to determine final eligibility. Disagreements about eligibility will be resolved via discussion until consensus is reached.

Eligibility Criteria

Studies published in English or French that use qualitative data collection and analysis methods and are about the experiences of patients with advanced or terminal hematologic cancers, and their caregivers, will be eligible for this review. The following types of publications will be excluded: theses and dissertations, data presented in abstract form only,

book chapters, commentaries, case reports, and editorials. In addition, the following elements will render a study ineligible for inclusion: studies that are not focused on terminal or advanced cancer, studies on survivorship of cancer patients, studies on advance directives, studies that take place in health care systems dissimilar to Canada.

Table 1: Selection Criteria for Subanalysis

Sample	Patients with advanced or terminal hematologic cancer; family and clinical and non-clinical caregivers of patients with advanced or terminal hematologic cancer
Phenomena of Interest	Living with advanced or terminal hematologic cancer; experiences with specialized and/or last-resort treatment for advanced or terminal hematologic cancer; treatment burden associated with advanced or terminal hematological cancer; end-of-life decision-making
Design	Qualitative studies of any design (e.g., phenomenology, grounded theory, qualitative description)
Evaluation	Patients' perspectives and experiences with advanced or terminal hematologic cancers, and those of their families and clinical and non-clinical caregivers
Research Type	Studies using any qualitative methodology; mixed-methods studies with qualitative a component

Data Extraction

Bibliographic details — including the country and funding of the research team, the description of participants, the research methods used, and the research question(s) — will be extracted into structured forms in DistillerSR. Data extraction forms will be piloted by two reviewers until both reviewers agree that consistency is reached. The remaining data extraction will be completed by a single reviewer.

Data Analysis

Data describing the characteristics of included studies and of included participants will be summarized and presented in tabular form.

A “best fit” framework approach to data analysis will be used.³ Articles will be imported into NVivo 11 for data analysis. Two reviewers will begin by coding documents, line by line, using an initial set of codes based on the research questions. This set of codes will focus on identifying key concepts and topics related to patients’, caregivers’, and families’ experiences and perspectives of their conditions; of its treatment; of outcomes of interest; and of treatment burden and expectations. An initial set of articles will be coded independently by the two reviewers, who will then meet to discuss and reflect on the coding process and coding patterns, and refine the codes if needed. The reviewers will discuss if consistency in coding is achieved and if the remaining included articles will be coded by a single reviewer. If consistency has not been achieved, a second set of articles will be coded, with a subsequent meeting to discuss the process. Codes will be refined and organized into concepts and findings through ongoing and frequent discussions between the reviewers, supported by the use of diagramming and memoing. The goal will be to create categories that describe the perspectives, and experiences by perspective (i.e., patient, caregiver, family member), across the pathway of care (i.e., decision- making, treatment, outcome) to reveal the context in which tisagenlecleucel will be delivered.

Because of the anticipated differences between the experiences and interaction with the health care system, separate analyses will be conducted for adults with r/r-DLBCL and children and young adults with r/r-ALL. Results will be reported in narrative and in tabular form.

Subanalysis Two: A Rapid Qualitative Evidence Synthesis of Implementation Issues

The aim of this subanalysis is to identify implementation considerations (e.g., feasibility and capacity issues) relating to implementing tisagenlecleucel at micro, meso, and macro levels, as described in the published literature. The research question guiding the analysis is:

What issues relating to the feasibility and capacity for implementing tisagenlecleucel for the treatment of children and young adults with r/r-ALL and adults with r/r-DLBCL at micro, meso, and macro levels are raised in the published literature on tisagenlecleucel?

Document Searching

The literature search will be performed by an information specialist, using a peer-reviewed search strategy. The search strategy is available upon request.

Implementation-related information will be identified by searching the following bibliographic databases: MEDLINE (1946–) via Ovid, Embase (1974–) via Ovid, the Cochrane Central Register of Controlled Trials via Ovid, CINAHL (1981–) via EBSCO, Scopus, and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH, and keywords. The main search concept will be tisagenlecleucel (Kymriah).

No methodological filters will be applied to limit the retrieval by study type. The search will not be limited by language or publication date.

An additional search will be conducted for clinical practice guidelines. The main search concepts will be leukemia, lymphoma, and CAR T-cell therapy. The search for lymphoma and leukemia guidelines will be limited to English- or French-language documents published since January 1, 2016. The search for CAR T-cell therapy guidelines will be limited to English- or French-language documents published since January 1, 2013. Conference abstracts will be removed from the search results.

Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching the *Grey Matters* checklist (<https://www.cadth.ca/grey-matters>), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, public perspective groups, and professional associations. Google and other Internet search engines will be used to search for additional Web-based materials.

Eligibility Criteria

English- or French-language documents that explicitly describe feasibility and capacity considerations relating to the implementation and delivery of tisagenlecleucel will be eligible for this review. All documents that have a primary focus or substantive discussion about

tisagenlecleucel, at any level of the health care system, will be eligible regardless of publication type, although conference abstracts will be excluded. Eligibility criteria may be refined, as necessary, to ensure a data-rich and relevant set of included documents; finalized inclusion criteria will be documented in the final report.

Selection of Documents

Titles and abstracts of retrieved citations will be screened by a single reviewer in DistillerSR. First-level screening will exclude all citations that are not primarily about or include substantive discussion about tisagenlecleucel. Full text of all remaining potentially eligible citations will then be screened by one reviewer using the eligibility criteria.

Data Extraction

Data extraction forms will be piloted by two reviewers until both reviewers agree that consistency is reached. The remaining data extraction will be completed by a single reviewer. Data extraction will include bibliographic details of included documents including country and funding of authors, research question or aim, and document type (e.g., editorial, HTA document).

Data Analysis

Data describing the characteristics of included studies and of included participants will be summarized and presented in tabular form.

A “best fit” framework approach to data analysis will be used.³ Documents will be imported into NVivo 11 for data analysis. Two reviewers will begin by coding documents, line by line, using an initial set of codes based on the domains of the Integrate-HTA Context and Implementation of Complex Interventions (CICI) Framework.⁴ These codes will focus on identifying the implicit and explicit feasibility and capacity considerations at micro, meso, and macro levels of health care systems.

An initial set of documents will be coded independently by the two reviewers, who will then meet to discuss and reflect on the coding process, identify patterns appearing in the codes used, refine the set of codes, and identify if different codes are needed. The reviewers will discuss if consistency in coding is achieved and if the remaining included documents will be coded by a single reviewer. If consistency has not been achieved, a second set of documents will be coded, with a subsequent meeting to discuss the process. Codes will be refined and organized into concepts and findings through ongoing and frequent discussions between the reviewers, supported by the use of diagramming and memoing. The goal will be to develop categories that describe the breadth of issues related to feasibility and capacity considerations by level, and by condition and population, and across the pathway of care, relating to the implementation of tisagenlecleucel in Canadian health care systems. Results will be reported in narrative and in tabular form.

Stakeholder and Patient Input

Stakeholder Input

Interviews or surveys may be conducted with stakeholders (e.g., clinicians, nurses, support staff, administrators, and decision-makers) who have been or may become involved in the delivery or provision of tisagenlecleucel. Stakeholders will be recruited through clinical experts, CADTH’s Implementation Support and Knowledge Mobilization program, additional

CADTH staff connections, and individuals identified through consultation. Audio-recorded telephone interviews will be approximately one hour in length and consist of open-ended questions.

Based on the findings from the implementation literature review, questions for stakeholders will be developed to complement and address perceived gaps in the literature. For example, questions may ask: from the perspective of the stakeholder, what are the barriers and supports for tisagenlecleucel implementation in general, but also for specific groups of people or settings? More specific questions may arise from previous consultations and based on the information found in the literature review. Notes from the interviews and verbatim pieces of text will be used to inform the implementation analysis.

Patient Input

CADTH will seek input from children and young adults with r/r-ALL and from young adults and adults with r/r-DLBCL including experiences of the condition, of currently available treatment, and experiences and expectations of tisagenlecleucel. This information will be used to assess how well tisagenlecleucel might address current gaps in care and provide insight into how it may meet the needs and preferences of patients, and their caregivers and families.

Patient groups will use the standard *Patient Input Template for CADTH CDR and pCODR Programs* to prepare their submissions. The template guides patient groups in providing key information such as:

- how and when the perspectives were gathered: patient groups share whether data were gathered in Canada or elsewhere; demographics of the respondents; and the number of patients, caregivers, and individuals with experience with tisagenlecleucel (Information Gathering)
- a description of ALL and DLBCL from a patient's perspective, including how their condition impacts patients' and caregivers' day-to-day life and quality of life (Disease Experience)
- a description of how well patients and caregivers are managing their cancer with currently available treatments including benefits seen, and side effects experienced and their management; CADTH will also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines) (Experiences With Currently Available Treatments)
- patients' views on what outcomes should be considered when evaluating new therapies (Improved Outcomes)
- patients' experiences with tisagenlecleucel including how they were able to access the therapy, benefits and side effects compared to other treatments, any impact on families and caregivers (Experience With Drug Under Review)
- anything else specifically related to tisagenlecleucel that patient groups feel that CADTH reviewers or the expert committee should know.

Patient group input was received in June 2018 to allow CADTH to incorporate patient-important outcomes and issues important to patients into the protocol and the review. For childhood and young adult with r/r-ALL, a joint submission was received from the Ac²orn – Advocacy for Canadian Childhood Oncology Research Network, with collaboration from the Leukemia & Lymphoma Society of Canada (LLSC) and Ontario Parents Advocating for

Children with Cancer (OPACC). For adults with r/r-DLBCL, a patient input submission was received by Lymphoma Canada.

Interviews with representatives of patient groups who submitted patient input may be conducted to clarify issues raised in the submissions. Any clarifying information received during the interviews will be included in a summary of patient input, which will become part of the final report and used to guide the implementation analysis.

Patient input submissions will be summarized in the final report and the full patient input submissions from all groups will be included as an appendix.

The summary and the full patient input submissions will be shared with the full research team and members of the CADTH Health Technology Expert Review Panel, and used to guide the implementation analysis and in the committee's deliberations. The full patient input submissions will be included as an appendix in the final report. The name of the submitting patient group and all conflict of interest information will be included in the posted patient group submission; however, the name of the author, including the names of an individual patient or caregivers and other identifying details, will be redacted before posting to the CADTH website.

Additional Information Sources

Information pertaining to the implementation and delivery of tisagenlecleucel from the clinical, economic, and ethics reviews of CADTH's assessment, from additional sources identified by stakeholders, and from manufacturer implementation plan documents relating to site selection, training, and anticipated volumes, will be reviewed and considered.

Implementation Analysis

The findings from the two subanalyses, patient and stakeholder input, and information from other sections of this HTA (i.e., ethics, economics, and clinical) will be synthesized using a framework approach.²

The analysis will focus on describing implementation issues that arise in the context of providing access to and delivering tisagenlecleucel across pathways of care and across levels of the health care system.

Data Analysis

A framework approach involves a five-stage process of data analysis: familiarization, indexing, charting, mapping, and interpretation.

Stage 1: Familiarization

Familiarization involves gaining an understanding of the breadth, richness, diversity, and range of stakeholders, perspectives, and types of data and findings before any sorting or categorizing. This process is akin to the qualitative approach of immersion in the data, which enables the research team to be oriented and versed in the breadth of available material prior to analysis. Familiarization will be done through team discussion, and through the conduct of the subanalyses and patient and stakeholder input. During the process of familiarization, researchers will aim to draw out initial ideas and concepts through diagramming, memoing, and discussion.

Stage 2: Identifying a thematic framework

This stage will involve returning to the key concepts and ideas that started emerging during the familiarization stage, and setting up a framework with which the data will be sorted for analysis. The framework will be guided by the research objectives and allow for implementation issues to be mapped across the pathway of care, by levels of implementation (i.e., micro, meso, macro), and by stakeholder perspectives (e.g., patient, provider and health care system, regulator, manufacturer).

Stage 3: Indexing

This stage involves applying the framework to the results of both subanalyses, and to patient and stakeholder input and additional information from other sections of the HTA. Attention will be paid to who raised the issue, the potential implications of the issue, and potential solutions.

More than one concept or idea can be applied to a piece of text or single passage to allow full exploration of the relationship of themes within the data. While applying a framework involves using research judgment to explore the meaning and significance of the data, indexing provides transparency to this process. During indexing, changes may be made to the framework to improve its clarity and relevance to research objectives.

Stage 4: Charting

The process of charting involves the visualization of the data as a whole set. Richie and Spencer describe charts as such: “Charts are devised with headings and subheadings which may be drawn from the thematic framework, from a priori research questions, or according to considerations about how best to present and write up the study. (p182)²ⁿ”

Charting will help to visualize the data across cases or themes; data will be sorted into charts based on key ideas or concepts, or will be sorted based on the type of source data. This process will aid in comparing and contrasting key findings across data types and sources (e.g., literature, stakeholder interviews, and clinical findings).

Findings from each of the subanalyses, patient and stakeholder input, and information from other sections of the HTA will be mapped onto this framework, progressing through the steps of indexing and charting using memoing and diagramming.

Stage 5: Mapping and interpretation

This stage involves mapping and interpreting the analytic results of the previous stages to describe the implementation issues, including feasibility and capacity, across the pathways of care (i.e., referral, decision-making, treatment, outcome, follow-up) and by perspective (i.e., patient, provider, manufacture, purchaser). This also means attending to the differences between conditions and between populations. Mapping and interpretation will be supported by frequent discussion among researchers involved in all components of the implementation analysis and through larger team discussion.

Reporting

Results of the implementation analysis will be presented using tables and diagrams, where appropriate. The full synthesis will be reported narratively and will incorporate feedback provided from manufacturers, stakeholders, and patient groups, and CADTH expert committees.

Protocol Amendments

If amendments to the protocol are required at any time during the study, reasons for changes will be recorded and reported in the final report.

References

1. Hofmann B. Toward a procedure for integrating moral issues in health technology assessment. *Int J Technol Assess Health Care*. 2005;21(3):312-318.
2. Richie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman A, Burgess R, eds. *Analysing qualitative data*. London: Routledge; 1994.
3. Booth A, Noyes J, Flemming K, et al. Guidance on choosing qualitative evidence synthesis methods for use in health technology assessments of complex interventions. [place unknown]: Integrate-HTA; 2016: <https://www.integrate-hta.eu/wp-content/uploads/2016/02/Guidance-on-choosing-qualitative-evidence-synthesis-methods-for-use-in-HTA-of-complex-interventions.pdf>. Accessed 2018 Jul 27.
4. Pfadenhauer L, Rohwer A, Burns J, 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.

Appendix 1: Literature Search Strategy — Patient Perspectives and Experiences Search

OVERVIEW

Interface:	Ovid
Databases:	Ovid MEDLINE ALL Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 13, 2018
Alerts:	Monthly search updates
Study Types:	Qualitative studies
Limits:	English-or French-language publications 2013 to present

SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type

MULTI-DATABASE STRATEGY

Search Strategy

#	Searches
1	exp Lymphoma, Large B-Cell, Diffuse/
2	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/
3	Hematologic Neoplasms/
4	(lymphoma* or leukemia* or leukaemia* or childhood ALL or DLBCL).ti,ab,kf.
5	((hematologic* or haematologic* or hematopoietic or blood or lymphoid or b cell* or t cell* or nonhodgkin* or non hodgkin*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metastas*)) .ti,ab,kf.
6	or/1-5
7	exp Empirical Research/ or Interview/ or Interviews as Topic/ or Personal Narratives/ or Focus Groups/ or exp Narration/ or Nursing Methodology Research/ or Narrative Medicine/
8	Interview/
9	interview*.ti,ab,kf.
10	qualitative.ti,ab,kf,jw.
11	(theme* or thematic).ti,ab,kf.
12	ethnological research.ti,ab,kf.
13	ethnograph*.ti,ab,kf.
14	ethnomedicine.ti,ab,kf.
15	ethnonursing.ti,ab,kf.
16	phenomenol*.ti,ab,kf.
17	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
18	(life stor* or women* stor*).ti,ab,kf.
19	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
20	(data adj1 saturat\$).ti,ab,kf.
21	participant observ*.ti,ab,kf.
22	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
23	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
24	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
25	(field adj (study or studies or research or work)).ti,ab,kf.
26	(human science or social science).ti,ab,kf.
27	biographical method.ti,ab,kf.
28	theoretical sampl*.ti,ab,kf.
29	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
30	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
31	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
32	((lived or life) adj experience*).ti,ab,kf.
33	cluster sampl*.ti,ab,kf.
34	observational method*.ti,ab,kf.
35	content analysis.ti,ab,kf.

MULTI-DATABASE STRATEGY

Search Strategy

- 36 (constant adj (comparative or comparison)).ti,ab,kf.
 37 ((discourse* or discours*) adj3 analys?s).ti,ab,kf.
 38 (heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
 39 (van adj manen*).ti,ab,kf.
 40 (van adj kaam*).ti,ab,kf.
 41 (corbin* adj2 strauss*).ti,ab,kf.
 42 or/7-41
 43 6 and 42
 44 limit 43 to (yr="2013 -Current" and (english or french))

OTHER DATABASES

PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
CINAHL (EBSCO Interface)	Same keywords and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for EBSCO platform.

Grey Literature

Dates for Search:	June 2018
Keywords:	Included terms for tisagenlecleucel, leukemia, lymphoma, chimeric antigen receptor T cell therapy
Limits:	2013 to present

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (<https://www.cadth.ca/grey-matters>) were searched:

- Health Technology Assessment Agencies
- Clinical Trial Registries
- Regulatory Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals