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CADTH OPTIMAL USE REPORT

Axicabtagene Ciloleucel for Large B-cell Lymphoma: Implementation and Ethics Project Protocol

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

CAR	chimeric antigen receptor
CRS	cytokine release syndrome
CRES	CAR-related encephalopathy syndrome
EMA	European Medicines Agency
FACT	Foundation for the Accreditation of Cellular Therapy
FDA	US Food and Drug Administration
HSCT	hematopoietic stem cell transplant
HTA	health technology assessment
IEC	immune Effector Cells
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

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Protocol Amendment

Amendment	Page	Date Amended
Following Health Canada's issue of a Notice of Compliance for axicabtagene ciloleucel and publication of the final product monograph, the confirmed indication was used to inform a revision of the indication in the population eligibility criterion for the review — i.e., instances of "Non-Hodgkin lymphoma" were changed to "large B-cell lymphoma" throughout except for the Patients' and Caregivers' Experience Review, where the larger disease category of Non-Hodgkin lymphoma was retained.	All (including title page and all footers)	April 30, 2019

Background and Purpose

Axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy for several subtypes of B-cell non-Hodgkin lymphoma (NHL). It is approved for use by regulators in European Union[1] and the US,[2] and is pending approval from Health Canada. Where approved, it is indicated for patients with eligible subtypes of B-cell NHL who are relapsed or refractory (r/r), meaning patients whose cancer has returned or relapsed, sometimes more than once, or whose cancer has never gone into remission. This means that prior to receiving axicabtagene ciloleucel, patients would have undergone two or more lines of therapy including chemotherapy, immunotherapy, radiation therapy, or autologous hematopoietic cell transplant (HSCT).[3] Typically only non-curative treatment options remain for these relapsed and refractory patients.

CAR T-cell therapies are a new category of therapeutics that involve genetically modifying patients' own immune T cells to attack their cancer. Producing and delivering axicabtagene ciloleucel is a multi-stage procedure that takes several weeks. First, a patient's T cells are collected through a process called leukapheresis, typically an outpatient procedure taking three to four hours. For axicabtagene ciloleucel, patients' cells are then shipped through specialized transportation services to a manufacturing facility. There, the T cells are isolated, genetically modified, expanded (multiplied) in a process that takes between two to three weeks. In the meantime, patients face the potential of their condition deteriorating and some may undergo bridging chemotherapy to keep their condition stable. The modified cells are then cryopreserved and shipped back to the treating facility, and before reinfusion, patients undergo lymphodepletion, which is a short course of chemotherapy (five days) to eliminate competing lymphocytes. Once cells are received at the treating facility and patients have completed successful lymphodepletion, the cells are thawed and reinfused typically on an outpatient basis. Beginning at the time of reinfusion, patients are closely monitored by their clinical team and their family caregivers for early signs of potentially severe adverse events including cytokine release syndrome (CRS) and neurologic toxicities such as CAR-related encephalopathy syndrome (CRES). Should patients experience these adverse events, they can be life-threatening and may require lengthy treatment in intensive care. Patients and their caregivers stay close to the treating facility and are continued to be monitored for a minimum of four weeks post-infusion.

CAR T-cell therapies such as axicabtagene ciloleucel are resource intensive. Currently commercially available CAR T-cell therapies including axicabtagene ciloleucel are costly for health care payers, with axicabtagene ciloleucel being stated as costing US$373,000 US per infusion in the US.[4] This price reflects the cost of the therapy itself, and not the delivery of the therapy and management of adverse events. Ancillary costs associated with CAR T-cell therapies are estimated to be high because of it being a multi-stage therapy composed of numerous individual procedures, and because the costs associated with the intensive management of adverse events.[4]

This protocol is one part of a larger health technology assessment (HTA) to support evidence-based decision-making relating to the provision of axicabtagene ciloleucel in Canadian health care systems.[9] This protocol encompasses a plan to conduct an Implementation Analysis, an Ethics Review and Patient and Stakeholder Input to complement the larger HTA.

Policy Question

The full HTA will address the following policy question:

How should the provision of axicabtagene ciloleucel be structured for treating adults with eligible types of refractory or relapsed large B-cell lymphoma?

Objectives and Research Questions

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 axicabtagene ciloleucel for adults with eligible types of relapsed or refractory large B-cell lymphoma. The issues raised in this review will go beyond narrowly defined ethical concerns to encompass broader legal, social, and cultural considerations as well.

Two research questions will guide the Ethics Review:

1) What are the major ethical issues raised by the implementation of axicabtagene ciloleucel for adults with relapsed or refractory large B-cell lymphoma?
2) How might these issues be addressed?

Implementation Analysis

The purpose of the Implementation Analysis is to provide evidence-based information and analysis of implementation considerations in the provision of axicabtagene ciloleucel for adults with eligible types of relapsed or refractory large B-cell lymphoma, including travel, hospital stays, and health care resource utilization, to support Canadian jurisdictions with structuring the provision of axicabtagene ciloleucel.

The research objectives guiding the Implementation Analysis are:

1) To provide a detailed description of potential pathways of care for adult patients with eligible types of relapsed or refractory large B-cell lymphoma to receive axicabtagene ciloleucel, and the resources (e.g., health and human resources, training, organizational) needed to do so.
2) To provide an overview of feasibility and capacity considerations relating to the provision of axicabtagene ciloleucel 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).

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, with rationale provided.

Ethics Analysis

Methods of Inquiry

This review will use a two-step approach to identifying and describing potential ethical issues. Step One will be a review of the ethics, clinical, and health policy, and health services literature to identify existing ethical analyses of the implementation of axicabtagene ciloleucel. Step Two 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 will identify and assess unidentified ethical issues and possible solutions.

The approach of this review will be inductive and iterative, and will be responsive to results emerging from clinical, economic, and implementation reviews, including patients,' caregivers' and families, and stakeholders' perspectives. This may require additional targeted literature searches relating to 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 ethical, legal, and social issues related to the use of axicabtagene ciloleucel for adults with relapsed and refractory large B-cell lymphoma (Step One).

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

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

A methodological filter will be applied to limit retrieval to articles that are relevant to ethical issues. The search will be limited to English- or French-language documents published between January 1, 2008 and November 2018.

The initial search will be completed in November 2018. 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. Articles identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified before the completion of the stakeholder feedback period of the final report and offer new analytical insight.

Grey literature (literature that is not commercially published) will be identified by searching sources included in the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review (SR) repositories, and professional associations. Google 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.

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 axicabtagene ciloleucel in populations of interest (i.e., adults with relapsed or refractory large B-cell lymphoma)
- presents empirical research directly addressing an ethical issue arising in the implementation and use of axicabtagene ciloleucel
- explicitly identifies, but does not analyze or investigate empirically an ethical issue arising with the implementation and use of axicabtagene ciloleucel
- identifies broader ethical issues concerned with HTA and drug and technology access for axicabtagene ciloleucel.

In the second stage, full-text reports will be screened by a single reviewer and 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 of reviewing the 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 members of 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 description of a patient's 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

For Stage Two, the de novo analysis, the ethical issues identified, values described, and solutions proposed in the literature (Step One) 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. As appropriate, ethical theories and frameworks such as Hoffman's axiological approach for identifying ethical issues in an HTA[10] will be drawn on to identify and describe ethical issues related to the implementation of the therapy. Supplementary searches will be conducted in the case where ethical issues arise that can be further explored in other related or analogous literatures not captured during 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.

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 axicabtagene ciloleucel, as well as industry documents.

1) Subanalysis One: A rapid qualitative evidence synthesis of patients' and their caregivers' perspectives and experiences of advanced or terminal hematologic cancer and its treatment; to identify patient-important clinical outcomes, patient-centered 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 axicabtagene ciloleucel 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 axicabtagene ciloleucel from the Clinical, Economic, and Ethics Reviews of CADTH's assessment, from additional sources identified by stakeholders, and from the manufacturer implementation plan documents relating to site selection, training, and anticipated volumes of patients.

The Implementation Analysis will use data and analysis from each of these inputs to identify capacity and feasibility considerations for implementing access to and delivering axicabtagene ciloleucel using a framework approach.[11]

Subanalysis One: A Rapid Qualitative Evidence Synthesis of Patients' and Caregivers' Perspectives and Experiences

The goal of this subanalysis is to understand the context in which patients and their family and professional caregiver's experience relapsed and refractory large B-cell lymphoma and the context in which they would make decisions about and potentially receive axicabtagene ciloleucel. The research question guiding this subanalysis is:

What are the experiences and perspectives of patients and their family and professional caregivers members, about advanced or terminal hematologic cancer and its treatment and prognosis?

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. Appendix 1 presents the detailed search strategy.

Information related to patients,' family members' and providers' perspectives and experiences will be identified by searching the following bibliographic databases: MEDLINE (1946–)through Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–)through EBSCO, and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts are axicabtagene ciloleucel, lymphomas, hematologic cancers, and chimeric antigen receptor (CAR) T-cell therapy.

Methodological filters will be applied to limit retrieval to qualitative studies. The search will be limited to English- or French-language documents published between January 1, 2013 and November 2018.

The initial search will be completed in November 2018. 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. Studies identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified before the completion of the stakeholder feedback period of the final report and offer new analytical insight.

Grey literature (literature that is not commercially published) will be identified by searching sources included in the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review (SR) repositories, and professional associations. Google 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.

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 through 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 One

Sample	Patients with advanced or terminal hematologic cancer; family and professional 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 family and professional caregivers
Research Type	Studies using any qualitative methodology; mixed-methods studies with a qualitative 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 to analyze data relating to the perspectives and experiences of people with advanced or terminal hematologic cancers, and those of their families and clinical and non-clinical caregivers.[12] 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 so 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, and family member), across the pathway of care (i.e., decision-making, treatment, and outcome) to reveal the context in which axicabtagene ciloleucel will be delivered. 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 axicabtagene ciloleucel 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 axicabtagene ciloleucel for the treatment of adults with relapsed or refractory non-Hodgkin lymphoma at micro, meso, and macro levels are raised in the published literature on axicabtagene ciloleucel?

Literature Search Strategy

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

Published information relating to the implementation of axicabtagene ciloleucel will be identified by searching the following bibliographic databases: MEDLINE (1946–), Embase (1974–), the Cochrane Central Register of Controlled Trials through Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) through EBSCO, and PubMed. The search strategy will be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept is axicabtagene ciloleucel.

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

The initial search will be completed in November 2018. 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. Studies identified in the alerts and meeting the selection criteria of the review may be incorporated into the review if they are identified before the completion of the stakeholder feedback period of the final report and offer new analytical insight.

An additional search will be conducted for clinical practice guidelines, health technology assessments, systematic reviews, or meta-analyses. The main search concepts are non-Hodgkin lymphomas, and chimeric antigen receptor T-cell therapy. The search for non-Hodgkin lymphoma guidelines will be limited to English- or French-language documents published between January 1, 2016 and November 2018. The search for chimeric antigen receptor T-cell therapy guidelines, health technology assessments, systematic reviews, or meta-analyses will be limited to English- or French-language documents published between January 1, 2013 and November 2018. Conference abstracts will be removed from these search results.

Grey literature (literature that is not commercially published) will be identified by searching sources included in the Grey Matters checklist (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, systematic review (SR) repositories, and professional associations. Google will be used to search for additional Web-based materials. These searches will be supplemented through contact with appropriate experts

Eligibility Criteria

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

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 axicabtagene ciloleucel. Full-text of all remaining potentially eligible citations will then be screened for eligibility by one reviewer.

Data Analysis

A “best fit” framework approach to data analysis will be used.[12] Documents will be imported into NVivo 11 for data analysis. 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*.[13] 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 by one reviewer. Through team discussion, reviewers will reflect on the coding process, identify patterns appearing in the codes used, refine the set of codes, and identify if different codes are needed. Codes will be refined and organized into concepts and findings through ongoing and frequent discussions between the review team, 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 across the pathway of care, relating to the implementation of axicabtagene ciloleucel in Canadian health care systems. Results will be reported in narrative form.

Stakeholder and Patient Input

Stakeholder Input

CADTH will seek input from clinicians regarding the implementation of axicabtagene ciloleucel. Clinicians will use the standard *Clinician Input Template for CAR T-Cell Therapy Reviews* to submit their input. The template guides clinicians in providing key information such as: current treatment options for patients; eligible patient population; relevance of the therapy to clinical practice; the therapy’s place in treatment; and any companion diagnostic testing and additional information deemed relevant by the clinicians.

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 axicabtagene ciloleucel. Stakeholders will be recruited through clinical experts, CADTH's Implementation Support and Knowledge Mobilization team members, additional CADTH staff connections, and individuals identified through consultation. Telephone interviews will be approximately one hour in length and consist of open-ended questions.

Questions for stakeholders will be developed to probe and refine the findings from the rapid qualitative synthesis of the implementation literature. For example, questions may ask, from the perspective of the stakeholder, what are the barriers and supports for axicabtagene ciloleucel implementation in general, but also for a particular health care setting? Notes from interviews and results from surveys will be used to inform the Implementation Analysis.

Patient Input

CADTH will seek input from patient groups on behalf of adults with relapsed and refractory large B-cell lymphoma in relation to their experiences with the condition, of currently available treatment, and experiences and expectations of axicabtagene ciloleucel and CAR T-cell therapies. This information will be used to assess how well axicabtagene ciloleucel 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 CAR T-Cell Therapy Reviews* to submit their input. 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 axicabtagene ciloleucel *(*Information Gathering).
- A description of relapsed and refractory large B-cell lymphoma from a patient's perspective, including what impact the condition has on patients' and caregivers' day-to-day lives 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 how side effects are experienced and managed; 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 axicabtagene ciloleucel, including how they were able to access the therapy, benefits and side effects compared with other treatments, and any impact on families and caregivers (Experience With Drug Under Review).
- Anything else specifically related to axicabtagene ciloleucel that patient groups feel that CADTH reviewers or the expert committee should know.

Patient Group Input Submissions was received in November of 2018.

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.

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 any 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 axicabtagene ciloleucel from the Clinical, Economic, and Ethics Reviews of CADTH's full 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 in the implementation analysis.

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.[11]

The analysis will focus on describing implementation issues that arise in the context of providing access to and delivering axicabtagene ciloleucel 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 before 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)[11]

Charting will help to visualize the data across cases or themes; data will be sorted into charts based on key ideas or concepts, or they 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 considerations, across the pathways of care (i.e., referral, decision-making, treatment, outcome, follow-up) and by perspective (i.e., patient, provider, manufacture, purchaser). Mapping and interpretation will be supported by frequent discussion among researchers involved in all components of the implementation analysis and through larger team discussions.

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, as well as members of CADTH’s Health Technology Expert Review Panel.

Protocol Amendments

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

References

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Appendix 1: Literature Search Strategy — Patients' and Caregivers' Perspectives and Experiences

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE ALL
Date of Search:	November 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
.jw	Journal Word
.kf	Author keyword heading word (MEDLINE)
.nm	Name of Substance; used to search portions of chemical names
.ot	Original Title; includes any non-English titles in the original language

MULTI-DATABASE STRATEGY	
#	Searches
#	Searches
1	(axicabtagene ciloleucel* or Yescarta* or axi-cel or KTEC19* or KTE-C19*).ti,ab,ot,kf,hw,nm.
2	exp Lymphoma/
3	exp Hematologic Neoplasms/
4	(DLBCL or lymphoma* or lymphosarcoma* or lympho-sarcoma* or reticulosarcoma* or reticulo-sarcoma* or ((lymphatic* or reticulum-cell*) adj sarcoma*) or PMBCL).ti,ab,kf.
5	((lymphoid* or bcell* or b-cell* or tcell* or t-cell* or nonhodgkin* or non hodgkin* or hematologic* or haematologic*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metasta*)).ti,ab,kf.
6	Receptors, Antigen, T-Cell/
7	Antigens, CD19/
8	((chimeric antigen adj3 receptor*) or (chimeric* adj3 (immune* or immunoreceptor* or immuno-receptor*)) or ((artificial or chimeric or engineered or modif*) adj3 (Tcell* or T-cell* or Tlymphocyte* or T-lymphocyte*)) or (CAR adj3 T) or CAR therap* or CART cell* or anti CD19 or anti CD-19 or ((CD19 or CD-19) adj5 (antibod* or anti-bod* or antigen* or anti-gen* or immune* or immunotherap* or immuno-therap* or target* or therap* or Tcell* or T-cell*)) or CART19 or CART-19).ti,ab,kf.
9	or/1-8
10	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/
11	Interview/
12	interview*.ti,ab,kf.
13	qualitative.ti,ab,kf,jw.
14	(theme* or thematic).ti,ab,kf.
15	ethnological research.ti,ab,kf.
16	ethnograph*.ti,ab,kf.
17	ethnomedicine.ti,ab,kf.
18	ethnonursing.ti,ab,kf.
19	phenomenol*.ti,ab,kf.
20	(grounded adj (theor* or study or studies or research or analys?s)).ti,ab,kf.
21	(life stor* or women* stor*).ti,ab,kf.
22	(emic or etic or hermeneutic* or heuristic* or semiotic*).ti,ab,kf.
23	(data adj1 saturat$).ti,ab,kf.
24	participant observ*.ti,ab,kf.
25	(social construct* or postmodern* or post-structural* or post structural* or poststructural* or post modern* or post-modern* or feminis*).ti,ab,kf.
26	(action research or cooperative inquir* or co operative inquir* or co-operative inquir*).ti,ab,kf.
27	(humanistic or existential or experiential or paradigm*).ti,ab,kf.
28	(field adj (study or studies or research or work)).ti,ab,kf.
29	(human science or social science).ti,ab,kf.
30	biographical method.ti,ab,kf.
31	theoretical sampl*.ti,ab,kf.

MULTI-DATABASE STRATEGY	
#	**Searches**
32	((purpos* adj4 sampl*) or (focus adj group*)).ti,ab,kf.
33	(open-ended or narrative* or textual or texts or semi-structured).ti,ab,kf.
34	(life world* or life-world* or conversation analys?s or personal experience* or theoretical saturation).ti,ab,kf.
35	((lived or life) adj experience*).ti,ab,kf.
36	cluster sampl*.ti,ab,kf.
37	observational method*.ti,ab,kf.
38	content analysis.ti,ab,kf.
39	(constant adj (comparative or comparison)).ti,ab,kf.
40	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
41	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
42	(van adj manen*).ti,ab,kf.
43	(van adj kaam*).ti,ab,kf.
44	(corbin* adj2 strauss*).ti,ab,kf.
45	or/10-44
46	9 and 45
47	limit 46 to (yr="2013 -Current" and (english or french))
38	content analysis.ti,ab,kf.
39	(constant adj (comparative or comparison)).ti,ab,kf.
40	((discourse* or discurs*) adj3 analys?s).ti,ab,kf.
41	(heidegger* or colaizzi* or spiegelberg* or merleau* or husserl* or foucault* or ricoeur or glaser*).ti,ab,kf.
42	(van adj manen*).ti,ab,kf.
43	(van adj kaam*).ti,ab,kf.
44	(corbin* adj2 strauss*).ti,ab,kf.
45	or/10-44
46	9 and 45
47	limit 46 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:	November 2018
Keywords:	Included terms for lymphomas, hematologic cancers, or chimeric antigen receptor T-cell therapy
Limits:	English or French language 2013-current

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.