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Abbreviations

CAR	chimeric antigen receptor
CD	cluster of differentiation
CRS	cytokine release syndrome
DLBCL	diffuse large B-cell lymphoma
HTA	health technology assessment
NHL	non-Hodgkin lymphoma
NHS	National Health Service
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews

Background and Rationale

Clinical Need and Target Population

Lymphomas are blood cancers that develop in the lymphatic system and are divided into Hodgkin lymphoma and non-Hodgkin lymphomas (NHL). NHLs are categorized as B-cell, T-cell, or natural killer/T-cell lymphoma, depending on the cell implicated in the disease.[1,2] While B-cell NHLs display a wide range of clinical behaviours, there are several subtypes that have a roughly similar clinical course and are treated in a similar manner. These subtypes include diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. In Canada, NHL accounts for 83% of all cases of lymphomas.[1]

Among these different types of NHLs, DLBCL is an aggressive variant that is also the most common type of NHL.[1,3,4] Although it can occur at any age, DLBCL is the most commonly occurring subtype of NHL in adults,[5-8] accounting for 30% to 40% of all adult lymphomas in adults,[6,7,9,10] with an estimated annual incidence of around 10.2 per 100,000. DLBCL is relatively sensitive to chemotherapy, and the remission rate in patients who undergo first-line chemotherapy is approximately 50% to 70%.[8,11] However, 30% to 50% of patients experience relapse and 10% have refractory (i.e., non-responsive to first-line treatment) DLBCL.[8,11] If left untreated, the life expectancy of patients with relapsed or refractory DLBCL is three to four months.[11] Second-line (or salvage) therapy for DLBCL patients who do not respond to chemotherapy or who relapse after initial response usually involves a combination of drugs and may include combinations such as rituximab, dexamethasone, cytarabine, and cisplatin (i.e., R-DHAP); rituximab, ifosfamide, carboplatin, and etoposide phosphate (or R-ICE); rituximab, gemcitabine, cisplatin, and dexamethasone (or R-GDP); and others.[12] The objective response rate to salvage therapy has been reported to be 26% (7% complete response rate), with a median overall survival of 6.3 months.[8]

Primary mediastinal B-cell lymphoma affects mainly young women and has been reported to account for approximately 2% to 4% of all lymphomas.[1] Follicular lymphoma comprises 20% of new diagnoses of NHL, and has a long, indolent course. The majority of patients who die of follicular lymphoma die of transformed disease, with the follicular lymphoma transforming to DLBCL at a rate of 1% to 3% per year.[13] No data were identified on the incidence and prevalence of high-grade B-cell lymphoma, and relapsed and refractory cases of primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, or DLBCL arising from follicular lymphoma.

A range of standard treatments that include chemotherapy, immunotherapy, radiation therapy, and autologous stem cell transplantation are used as first-line or second-line therapies to treat the aggressive forms of B-cell lymphoma;[1,4,14] however, it has been reported that these treatments fail for an estimated 20% of patients.[4] Outside of approved CAR T-cell therapies, only palliative options are currently available for patients with NHL who do not respond to second-line therapy. The estimated overall survival for these patients is approximately six months.[4,12,14]

In this context, axicabtagene ciloleucel is a chimeric antigen receptor (CAR) T-cell therapy that has been approved by the FDA for use in "adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma."[15,16] As Health Canada approval for axicabtagene ciloleucel is pending, the final indication remains to be confirmed;

however, based on the available evidence and existing approvals for this therapy (i.e., by the FDA[17] and the European Union[18]), potentially eligible indications are these types of relapsed or refractory NHLs (hereafter collectively described as relapsed or refractory NHL): DLBCL, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.[3,18,19]

A Brief Overview of CAR T-Cell Therapy and Axicabtagene Ciloleucel

CAR T-cell therapy uses genetic engineering to alter a patient's own T cells to kill tumour cells. CARs are artificial receptors that redirect antigen specificity, activate T cells, and further enhance T cell function through their co-stimulatory component.[20] The current manufacturing process for commercial CAR T-cell therapy products involves using leukapheresis to harvest the patient's peripheral blood mononuclear cells, isolating the T cells, and sending them to a central facility where the DNA for the chimeric protein is inserted into the DNA of the patient's T cells using retrovirus vectors. The resulting CAR T cells are then cryopreserved and shipped back to the treating institution for infusion into the patient's bloodstream to fight the cancer.[12,21] An overview of the CAR T-cell therapy procedure is provided in Appendix 2. Currently, it takes approximately two to three weeks from leukapheresis to the time the CAR T cells are ready to be infused back into the patient. Before the infusion of the CAR T cells, the patients must undergo lymphodepleting chemotherapy to decrease the number of competing lymphocytes, which enhances the engraftment and survival of the genetically modified T cells.[12,22]

CAR T-cell therapies are associated with adverse events, such as the release of cytokines from the rapidly proliferating T cells (known as cytokine release syndrome [CRS]) and neurotoxicity.[12] CRS may present with various symptoms ranging from headache and nausea, to fever (as high as 41°C), low blood pressure (often refractory to fluid resuscitation), respiratory distress (or failure), or organ toxicity (e.g., liver or kidney dysfunction). Patients with CRS often require treatment in the intensive care unit, and the severity of CRS appears to be proportional to the tumour burden.[9,12,21] Neurotoxicity is commonly associated with headache, anxiety, tremors, delirium, aphasia, seizures, ataxia, hemiparesis, and encephalopathy.[12] As the cluster of differentiation 19 (CD19) antigen is also expressed on normal B-cells, CAR T-cell therapies will also eliminate normal mature and precursor B-cells (in addition to the targeted cancer cells); therefore, patients who receive CD19 CAR T-cell therapy are expected to develop B-cell aplasia, which may contribute to a higher risk of infection in these patients.[4,12,14,21] B-cell aplasia may continue for as long as CAR T-cells persist, and has been reported to be ongoing for more than three years.[12]

Axicabtagene ciloleucel is a second generation CAR T-cell therapy designed to target the CD19 antigen, which is expressed on the surface of B cells, including the malignant cells involved in the aggressive B-cell NHLs.[12] The CAR portion in axicabtagene ciloleucel is composed of an extracellular murine, anti-CD19, single-chain, variable fragment linked to intracellular CD28 and CD3-zeta co-stimulatory domains.[16] It is administered by intravenous infusion at a target dose of 2×10^6 CAR-positive viable T cells per kilogram of body weight, with a maximum of 2×10^8 CAR-positive viable T cells.[16,23] Prior to receiving the infusion of axicabtagene ciloleucel, patients undergo lymphodepleting chemotherapy, with three doses (one dose per day) of cyclophosphamide and fludarabine administered via infusion on the fifth, fourth, and third day before infusion of axicabtagene ciloleucel.[14,16,23] Evidence suggests lymphodepleting chemotherapy may improve the efficacy of CAR T-cell therapy

by promoting greater proliferation, expansion, function, and persistence of the implanted CAR T cells.[14]

Axicabtagene ciloleucel is the first CAR T-cell therapy to have received regulatory approval by the FDA in October 2017 for the treatment of adults with certain types of relapsed or refractory large B-cell lymphoma.[3] In August 2018, axicabtagene ciloleucel was granted approval in the European Union for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy.[18,24] The FDA requires that a CAR T-cell therapy be administered in a specially certified treatment centre, while the European Union approval recommends that it be performed in a qualified centre.[3,24] Axicabtagene ciloleucel is currently under review by Health Canada; [25] if approved, it would be the second CAR T-cell therapy approved in Canada joining tisagenlecleucel, which was approved by Health Canada in September 2018.[26] The National Institute for Health and Care Excellence issued a draft guidance in August 2018 recommending against the inclusion of axicabtagene ciloleucel in the UK's Cancer Drugs Fund, as the committee considered that there was a lack of data demonstrating the magnitude of benefit for axicabtagene ciloleucel compared with salvage chemotherapy, and that there was no plausible potential for the therapy to be cost-effective at its current cost.[27,28] On October 5, 2018, the National Health Service (NHS) England announced that it had reached an agreement with the manufacturer on the price of the product, allowing National Institute for Health and Care Excellence to approve the entry of axicabtagene ciloleucel into NHS England's Cancer Drugs Fund.[29,30] The price agreed upon was not made public. Axicabtagene ciloleucel is not currently approved in Canada and therefore a Canadian list price is not available; however, some publications have reported a list price of US$373,000 per unit in the US.[12,31,32] In addition to the cost of the product, costs associated with the administration of the therapy and management of its adverse effects are expected to be substantial.[31,32]

Whereas the adverse effects have been described as manageable (e.g., tocilizumab for CRS[22,23] and intravenous immunoglobulin for B-cell aplasia[4,12,14,21]) and not worse than the serious adverse events associated with chemotherapy in this patient population,[12] there is uncertainty about the long-term efficacy and harms of CAR T-cell therapies because of the absence of long-term follow-up data. Other considerations for the implementation of axicabtagene ciloleucel include the location's treatment centres, the need for travel and accommodation for patients and caregivers, and the proper capacity, expertise, and controls to manufacture and deliver the therapy.

Rationale for the Health Technology Assessment

Given that the cost of axicabtagene ciloleucel may be considerable, the uncertainty of the clinical benefit and long-term harms, and the potential for adverse events, there is a need to systematically evaluate the evidence for the use of axicabtagene ciloleucel for relapsed or refractory NHL prior to its implementation in Canada. Specifically, the clinical, cost-effectiveness, and budget impact of axicabtagene ciloleucel implementation, ethical issues relating to the provision of axicabtagene ciloleucel, and patients' and caregivers' perspectives need to be assessed and considered, and patient perspectives and preferences need to be addressed.

Policy Question

This health technology assessment (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 non-Hodgkin lymphoma?

Objectives

CADTH will conduct an HTA to assess the optimal use of axicabtagene ciloleucel for adults with relapsed or refractory NHL.

The purpose of this HTA is to provide evidence-based information in the areas of clinical effectiveness, health economics, patients' and caregivers' perspectives and experiences, and implementation and ethical issues to support decision-making in the jurisdictions concerning the structure and provision of axicabtagene ciloleucel therapy in Canada.

Each component of the HTA (i.e., Clinical Review, Economic Review, Patients' Perspectives and Experiences, Ethics Review, and Implementation Analysis) will be conducted individually and collaboratively. This protocol describes the Clinical Review.

The objective of this Clinical Review component is to assess the beneficial and harmful effects of axicabtagene ciloleucel for eligible types of relapsed or NHL in adults and to identify available evidence-based guidance for the use of axicabtagene ciloleucel in this population.

Research Questions for Clinical Review

The Clinical Review component of this HTA will address the policy question by exploring the following research questions:

1. What are the beneficial effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory non-Hodgkin lymphoma?
2. What are the harmful effects of axicabtagene ciloleucel for treating adults with eligible types of relapsed or refractory non-Hodgkin lymphoma?
3. What are the evidence-based clinical practice guidelines for the use of axicabtagene ciloleucel for the treatment of adults with eligible types of relapsed or refractory non-Hodgkin lymphoma?

Clinical Review Methods

The methodology for this review is guided by the criteria outlined in the checklist described in Assessing the Methodological Quality of Systematic Reviews II — or AMSTAR II — [33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.[34] The Clinical Review will be published in accordance with CADTH standards for Optimal Use reviews and relevant reporting guidelines such as the PRISMA statement[35] and the PRISMA harms checklist.[36]

The protocol for this systematic review was developed and written a priori based on information from an informal scoping review. The scoping review identified one trial with safety and efficacy data that was used for the approval of axicabtagene ciloleucel by the FDA in October 2017 and the European Union in August 2018.[19] Given the recent European Union approval of axicabtagene ciloleucel in August 2018, it is anticipated that there will be few, if any, other relevant HTAs or systematic reviews conducted following that date. Therefore, a *de novo* systematic review of all relevant published and unpublished primary clinical evidence will provide the most comprehensive evidence to address the research

questions. The protocol will be followed throughout the review process; if any amendments are required during the study, the reasons for changes will be recorded in a study file, the research registration with PROSPERO will be updated, and the final report will disclose any alterations. If necessary, a rescreening of the previous literature search, or an updated literature search, will be performed to capture additional data according to the amendments.

Literature Search Methods

The literature search will be performed by an information specialist using a peer-reviewed search strategy. See Appendix 1 for the detailed search strategy.

Published literature will be identified by searching the following bibliographic databases: MEDLINE (1946–), Embase (1974–), the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and the Health Technology Assessment database via Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1981–) via 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, NHL, and CAR T-cell therapy.

No methodological filters will be applied to limit the retrieval of the axicabtagene ciloleucel search by study type. This search will also not be limited by language or publication date. Methodological filters will be applied to limit the retrieval of the NHL and CAR T-cell therapy searches to clinical practice guidelines, HTAs, systematic reviews, or meta-analyses. The search for NHL publications will be limited to English- or French-language documents published between January 1, 2016 and November 2018. The search for CAR T-cell therapy publications will be limited to English- or French-language documents published between January 1, 2013 and November 2018.

The 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 that meet inclusion criteria of the review and offer new analytical insight may be incorporated into the review. Any studies identified after the manufacturer feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analyses conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching the websites of regulatory agencies (FDA and European Medicines Agency), clinical trial registries (US National Institutes of Health — clinicaltrials.gov and Canadian Partnership Against Cancer Corporation–Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts will be retrieved through a search of the Embase database and will not be limited by publication date. Abstracts from the American Society of Hematology (ASH), the American Society of Clinical Oncology (ASCO), the European Hematology Association (EHA), and the European Society for Medical Oncology (ESMO) will be searched manually for conference years not available in Embase.

Relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters) will also be searched, which includes the websites of HTA agencies, clinical guideline repositories, systematic review 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 and industry.

Study Design

This Clinical Review will include a *de novo* systematic review of published and unpublished primary clinical evidence to address the clinical effectiveness of axicabtagene ciloleucel (research questions 1 and 2). The analytical framework is provided in Appendix 2. Research question 3 will be addressed through a systematic review of clinical practice guidelines on the use of axicabtagene ciloleucel for the treatment of adults with relapsed and refractory DLBCL.

Study Eligibility Criteria

The pivotal and supportive studies provided by the manufacturer will be included in the systematic review. The eligibility criteria for the clinical research questions are listed in Table 1.

Table 1: Eligibility Criteria for Clinical Research Questions

Population(s)	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, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma[a] Subgroups of possible interest: number of previous lines of systemic therapy; type of lymphoma; cell of origin; age; sex; race; ECOG performance status; relapsed/refractory status; previous stem cell transplant; CAR T cell dose; conditioning chemotherapy; tumour burden at the time of therapy; stage of disease; histological; molecular; c-Myc mutations (double- or triple-hit); EBV-positive or -negative tumour status
Intervention(s)	Axicabtagene ciloleucel[b] (Gilead Sciences, Inc.)[c]
Comparator(s)	• Salvage chemotherapy • Other CAR T-cell therapies (e.g., tisagenlecleucel) • No comparator • No additional therapy
Outcome(s)	**Clinical Efficacy/Effectiveness Outcomes**: • Response/remission rate[d] (e.g., objective response/remission rate, complete, partial) • Survival (e.g., overall, event-free, progression-free) • Persistence of CAR T cells • Health-related quality of life and other patient-reported outcomes • The need for subsequent treatment(s) S**afety/Harms Outcomes**: • Mortality (e.g., treatment-related mortality, all-cause mortality) • Adverse events (AEs), serious adverse events (e.g., AEs ≥ Grade 3), withdrawal due to adverse event • Notable harms: CRS, B-cell aplasia, febrile neutropenia, neurological effects (e.g., hallucination, dysphasia), infections • Management of adverse effects • Frequency of manufacturing failure • Development of secondary malignancy • Hospitalization (e.g., hospital readmission, length of stay, admission to the ICU) **Evidence-Based Clinical Practice Guidelines**[e]
Study Design(s)	**Experimental or Observational Comparative and Non-comparative Primary Studies:** • Randomized controlled trials (RCTs) • Non-randomized controlled clinical trials • Single-arm studies • Cohort studies[f] • Case-control studies

	• Case series[f] • Indirect treatment comparisons, network meta-analyses **Exclusions:** • Case reports • Review articles • Editorials, letters, and commentaries **Evidence-Based Clinical Practice Guidelines[e]**

AEs = adverse events; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; EBV = Epstein-Barr virus; ECOG = Eastern Cooperative Oncology Group; ICU = intensive care unit; RCT = randomized controlled trial.

[a] Potentially eligible indications include patients with relapsed (i.e., returned) or refractory (i.e., no response to treatment) large B-cell lymphoma after two or more lines of systemic therapy. Studies that include patients with primary refractory disease (i.e., no response to first-line therapy) will be eligible for inclusion, but the evidence will be considered separately.

[b] A lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 is administered intravenously on the fifth, fourth, and third day before infusion of axicabtagene ciloleucel.

[c] Prescribing information indicates that the dose of axicabtagene ciloleucel is 2 × 10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells in approximately 68 mL.[15] Studies in which axicabtagene ciloleucel was administered at a different dose will be eligible for inclusion, but the evidence will be considered separately.

[d] "Response" and "remission" may be considered synonymous in the context of this review, in accordance with the National Cancer Institute's *Dictionary of Cancer Terms*[37] and the FDA's *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry*[38]

[e] "Clinical practice guidelines" are defined as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[39] Guidelines that are evidence-based (i.e., informed by supporting data or citations) and that were developed or endorsed at the national level (e.g., from national societies or federal governments) for non-Canadian guidelines, or at the national, provincial, or territorial level for Canadian guidelines, are eligible for inclusion.

[f] Cohort studies are defined as studies in which participants are compared based on whether or not they received an exposure; participants are studied prospectively or retrospectively.[40] Case series are defined as studies in which participants are sampled on the basis of the presence of an outcome, or of both an exposure and outcome.[41] For case series studies, a minimum sample size of five patients is required to be eligible for inclusion.[42]

Studies with mixed populations that include patients who do not meet the eligibility criteria will be included if separate results are reported for the eligible patients. Studies with mixed populations in which the results for the population are not reported separately will be included if at least two-thirds (i.e., 66% or more) of the population meets the eligibility criteria (cut-off point based on expert opinion), but results will be considered separately because of their indirect nature.

If multiple reports are identified for the same eligible study, we will include all reports from the study but will only extract the most current data. Publication status (e.g., abstracts) will not be a criterion for exclusion.

The reference lists of potentially relevant HTAs or systematic reviews identified by the literature search for the project will be reviewed, and primary studies that meet the inclusion criteria will be included in the review.

Position statements and consensus documents that do not make reference to evidence upon which the recommendations are based will not be included. For Canadian guidelines, national, provincial, or territorial guidelines will be eligible for inclusion. For non-Canadian guidelines, only national-level guidelines will be eligible for inclusion in order to facilitate their generalizability to the Canadian context. Guidelines that are explicitly applicable to a smaller jurisdiction or a specific facility will be excluded.

Literature Screening and Study Selection

Using the eligibility criteria outlined in Table 1, two reviewers will independently screen all titles and abstracts identified through the comprehensive literature searches. The checklist for level 1 screening is available in Appendix 4. Full-text articles of any abstracts and titles deemed potentially relevant by at least one reviewer will be retrieved for a second level of screening. The same reviewers will independently examine all full-text articles for inclusion in the review. The two reviewers will compare their chosen included and excluded studies; disagreements will be resolved through discussion until consensus is reached, or by a third reviewer, if necessary. The checklist for level 2 screening is available in Appendix 4.
A separate checklist for screening clinical practice guidelines is available in Appendix 4.

A list of included studies and guidelines will be sent to clinical content experts to ensure that no relevant evidence (published or unpublished) was missed. The selection process will be presented in a PRISMA flow diagram and a list of excluded reports will be provided with the reasons for exclusion.[35]

Data Extraction

Data extraction will be performed by one reviewer and independently checked for accuracy by a second reviewer. Disagreements will be resolved through discussion until consensus is reached or through adjudication by a third reviewer, if necessary. Data will be extracted directly into standardized tables created in Microsoft Word, which will be developed, piloted, and modified, as necessary.

For primary studies, information covering the following areas will be extracted, as well as other relevant information:

- description of the publication or source of data (e.g., first author's name, publication year, country where study was conducted, funding source, conflict of interest declarations, publication status)
- study characteristics (e.g., primary study objectives, study design, study setting, source of population, inclusion and exclusion criteria [e.g., age, sex, race, type of NHL], recruitment or sampling procedure, subgroup analyses of interest, statistical analysis methods including adjustment for confounders for non-randomized and observational studies)
- participant characteristics, separately for intervention and comparator groups, and/or subgroups if applicable (e.g., patient disposition [e.g., number of participants enrolled, included in analysis, withdrawn, with missing data, lost to follow-up, number of patients deemed eligible but never received treatment (e.g., conversion failure because of manufacturer, or due to progression of the disease)]; demographics and baseline characteristics; type of disease; Eastern Cooperative Oncology Group status; relapse or refractory status; prior treatment [e.g., chemotherapy or stem cell transplantation, details of bridging chemotherapy regimen])
- intervention characteristics (e.g., dose, number, and duration of cycles, treatment received prior to infusion)
- comparator characteristics (e.g., description of comparator, dose, route of administration, number and duration of cycles)
- outcome characteristics (e.g., definitions of outcomes, measurement method and properties [e.g., validity and reliability], unit of measurement, length of follow-up)
- results (e.g., measures of clinical effectiveness and safety, number of participants included in the analysis, number of participants with missing data).

For clinical practice guidelines, relevant information will be extracted, including:

- target population and intended users
- country of development
- details of the intervention and major outcomes considered
- details of the evidence collection, selection, synthesis, and quality assessment
- methods for developing and evaluating the recommendations
- key recommendations and their level of evidence.

Critical Appraisal of Studies

The critical appraisal of the included studies will be conducted independently by two reviewers. Disagreements will be resolved through discussion until consensus is reached, or through a third reviewer if necessary.

The critical appraisal will include a global assessment of the characteristics of the studies that contribute to the internal and external validity of the studies. The critical appraisal of the individual studies will be reported narratively, including a description of the strengths and weaknesses of each study. The results of the critical appraisal will be used to assess confidence in the results.

Internal validity is defined as "the extent to which the design and conduct of a study are likely to have prevented bias."[43] Criteria that will be considered while assessing the internal validity of the studies will include (but may not be limited to) whether the study was adequately powered, the appropriateness of the statistical analysis (e.g., multiplicity of testing), loss to follow-up, handling of missing data, and the validity of outcome measurements. External validity is defined as "the extent to which results provide a correct basis for generalizations to other circumstances."[43] An assessment of the external validity of the studies will include criteria such as whether the participants are representative of the population of interest, the generalizability of the treatment protocol to the Canadian context, whether the outcomes are considered clinically relevant and important to patients, relevance of the time points, appropriateness of the comparator group, and whether the length of the follow-up was sufficient. Other criteria that affect external validity may also be considered.

The quality of included clinical practice guidelines will be assessed using the *Appraisal of Guidelines for Research & Evaluation II* — or AGREE II — instrument.[39] Results of this assessment will be will be summarized in tabular form and reported narratively, including a description of the strengths and weaknesses of each guideline.

Data Analysis

The results of the informal scoping review demonstrated that there is limited available literature; therefore a narrative synthesis will be conducted. For the purpose of analysis, studies regarding the clinical effectiveness of axicabtagene ciloleucel (research questions 1 and 2) will be grouped by study design. For example, clinical trials (i.e., experimental design) will be analyzed separately from observational studies (e.g., cohort studies). Specifically, findings will be summarized within and across studies, including the direction and magnitude of any observed effects, trends, and deviations, and an assessment of the likelihood of clinical effectiveness (i.e., benefits or harms [i.e., safety]). Results for subgroups of interest (Table 1) will be described separately, if possible, depending on the availability of the data. The measurement properties of outcomes assessed subjectively or indirectly (e.g., scale measures) will be described in a supplemental appendix, along with a detailed description of the instrument or tool.

Specific recommendations will be described from evidence-based clinical practice guidelines for the effective use of axicabtagene ciloleucel for the treatment of adults with eligible types of relapsed or refractory NHL (research question 3).

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CADTH

Appendix 1: Literature Search Strategy

Clinical Search

OVERVIEW	
Interface:	Ovid
Databases:	EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment database Embase Ovid MEDLINE ALL **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	2018 November
Alerts:	Monthly search updates
Study Types:	Guidelines, health technology assessments, systematic reviews, or meta-analyses filters used
Limits:	None for Drug search CAR-T 2013-present; Indication 2016-present; English, French
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
.dq	Candidate Term Word (Embase)
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.nm	Name of Substance; used to search portions of chemical names
.ot	Original Title; includes any non-English titles in the original language
.pt	Publication type

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(axicabtagene ciloleucel* or Yescarta* or axi-cel or KTEC19* or KTE-C19*).ti,ab,ot,kf,kw,hw,nm.
2	1 use medall
3	1 use cctr
4	Axicabtagene Ciloleucel/
5	(axicabtagene ciloleucel* or Yescarta* or axi-cel or KTEC19* or KTE-C19*).ti,ab,kw,dq.
6	or/4-5
7	6 use oemezd
8	2 or 3 or 7
9	Receptors, Antigen, T-Cell/
10	Antigens, CD19/
11	((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.
12	or/9-11
13	12 use medall
14	Chimeric Antigen Receptor/
15	Chimeric Antigen Receptor T Cell/
16	Chimeric Antigen Receptor T Cell Immunotherapy/
17	CD19 Antigen/
18	((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,kw,dq.
19	or/14-18
20	19 use oemezd
21	13 or 20
22	limit 21 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
23	limit 22 to yr="2013 -Current" [Limit not valid in DARE; records were retained]
24	Lymphoma, Non-Hodgkin/
25	exp Lymphoma, B-Cell/
26	Lymphoma, Follicular/
27	(DLBCL or lymphoma* or lymphosarcoma* or lympho-sarcoma* or nonhodgkin* or non hodgkin* or reticulosarcoma* or reticulo-sarcoma* or ((lymphatic* or reticulum-cell*) adj sarcoma*) or PMBCL).ti,ab,kf.
28	((lymphoid* or mediastinal or mediastinum or bcell* or b-cell* or tcell* or t-cell*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metasta*)).ti,kf.
29	or/24-28
30	29 use medall
31	Nonhodgkin Lymphoma/
32	B Cell Lymphoma/
33	exp Diffuse Large B Cell Lymphoma/
34	Large Cell Lymphoma/
35	Lymphocytic Lymphoma/

MULTI-DATABASE STRATEGY	
#	**Searches**
36	Lymphosarcoma/
37	Follicular Lymphoma/
38	(DLBCL or lymphoma* or lymphosarcoma* or lympho-sarcoma* or nonhodgkin* or non hodgkin* or reticulosarcoma* or reticulo-sarcoma* or ((lymphatic* or reticulum-cell*) adj sarcoma*) or PMBCL).ti,ab,kw,dq.
39	((lymphoid* or mediastinal or mediastinum or bcell* or b-cell* or tcell* or t-cell*) adj3 (cancer* or neoplas* or carcinoma* or malignan* or tumor* or tumour* or metasta*)).ti,kw.
40	or/31-39
41	40 use oemezd
42	30 or 41
43	limit 42 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
44	limit 43 to yr="2016 -Current" [Limit not valid in DARE; records were retained]
45	1 or 4 or 5
46	45 use coch
47	45 use dare
48	45 use clhta
49	or/9-11,14-18
50	limit 49 to (english or french) [Limit not valid in CDSR,DARE; records were retained]
51	limit 50 to yr="2013 -Current" [Limit not valid in DARE; records were retained]
52	51 use coch
53	51 use dare
54	51 use clhta
55	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
56	(guideline* or standards or consensus* or recommendat*).ti.
57	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
58	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
59	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
60	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
61	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
62	or/55-61
63	meta-analysis.pt.
64	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
65	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
66	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
67	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
68	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
69	(handsearch* or hand search*).ti,ab,kf,kw.
70	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
71	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
72	(meta regression* or metaregression*).ti,ab,kf,kw.

MULTI-DATABASE STRATEGY	
#	**Searches**
73	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
74	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
75	(cochrane or (health adj2 technology assessment) or evidence report).jw.
76	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
77	(outcomes research or relative effectiveness).ti,ab,kf,kw.
78	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
79	(meta-analysis or systematic review).md.
80	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
81	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
82	umbrella review*.ti,ab,kf,kw.
83	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
84	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
85	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
86	or/63-85
87	62 or 86
88	23 and 87
89	44 and 62
90	8 or 46 or 47 or 48 or 52 or 53 or 54 or 88 or 89
91	remove duplicates from 90
71	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
72	(meta regression* or metaregression*).ti,ab,kf,kw.
73	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
74	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
75	(cochrane or (health adj2 technology assessment) or evidence report).jw.
76	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
77	(outcomes research or relative effectiveness).ti,ab,kf,kw.
78	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
79	(meta-analysis or systematic review).md.
80	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
81	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
82	umbrella review*.ti,ab,kf,kw.
83	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
84	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
85	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
86	or/63-85
87	62 or 86
88	23 and 87
89	44 and 62

MULTI-DATABASE STRATEGY	
#	**Searches**
90	8 or 46 or 47 or 48 or 52 or 53 or 54 or 88 or 89
91	remove duplicates from 90

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 axicabtagene ciloleucel, lymphomas, chimeric antigen receptor T-cell therapy
Limits:	None

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

Conferences and Meetings

American Society of Hematology (ASH)
http://www.hematology.org/

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

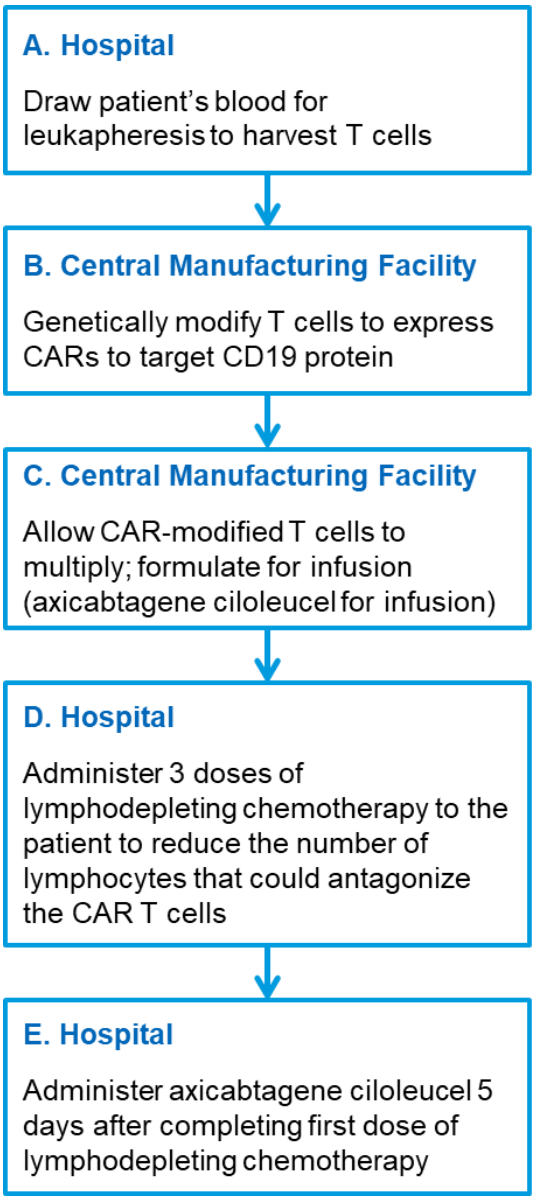
European Hematology Association (EHA)
https://ehaweb.org/

European Society for Medical Oncology (ESMO)
https://oncologypro.esmo.org/Meeting-Resources

Search: axicabtagene ciloleucel, Yescarta, axi-cel, KTE-C19, KTEC19, lymphomas, chimeric antigen receptor T-cell therapy

Appendix 2: Therapy Procedure Overview

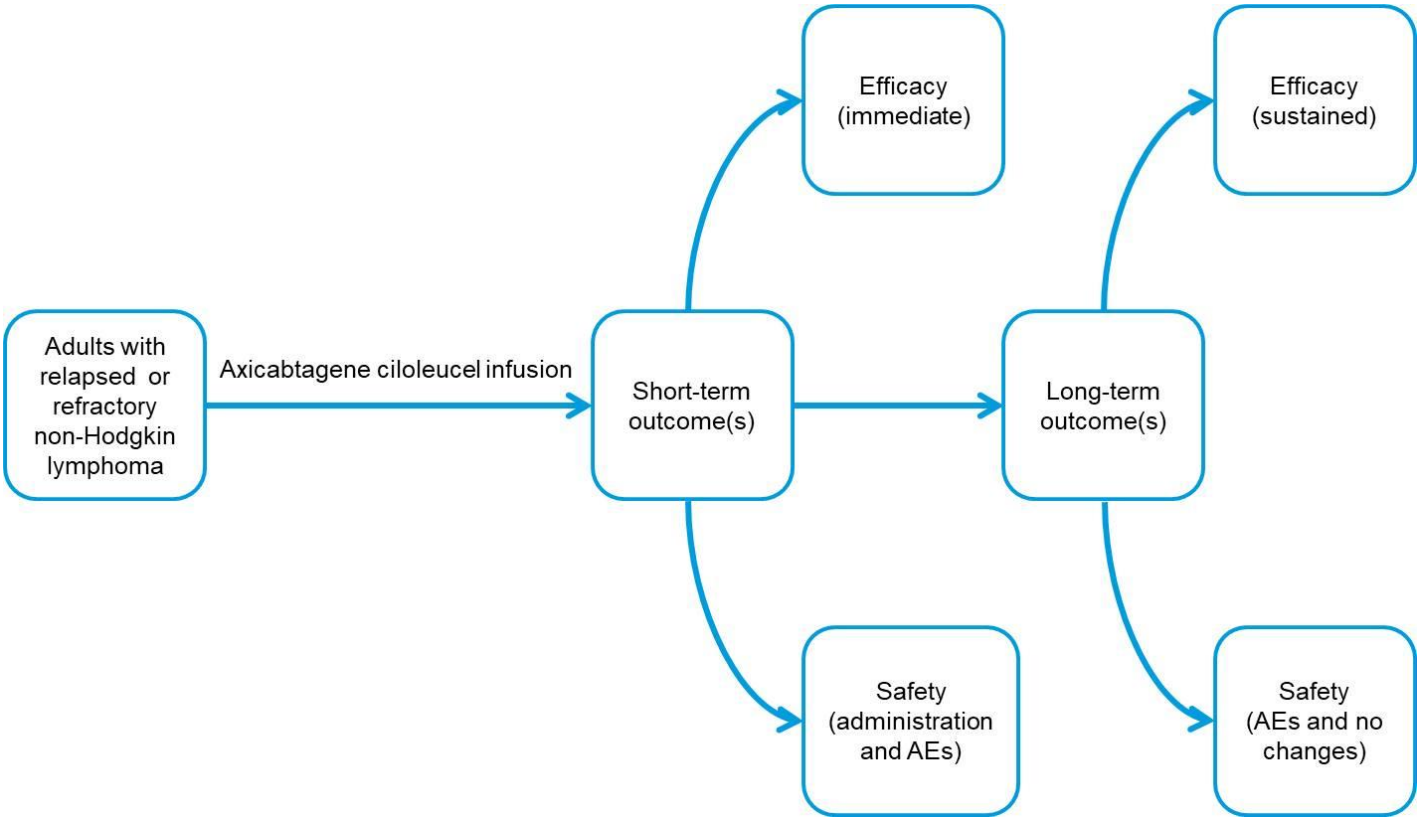
Figure 1: An Overview of Manufacturing and Administering CAR T-Cell (Axicabtagene Ciloleucel) Therapy



CAR = chimeric antigen receptor; CD19 = cluster of differentiation 19.

Appendix 3: Review Framework

Figure 2: Short- and Long-Term Review Framework After Axicabtagene Ciloleucel Infusion



Note: In this context "short-term" refers to six months or less, and "long-term" refers to more than six months and up to 24 months. Acute toxicities will be assessed at one month.

AEs = adverse events.

Appendix 4: Checklists for Screening References

Table 2: Level 1 Checklist for Screening Titles and Abstracts of Clinical Effectiveness Studies

Reviewer: _____ Date: _____			
Ref ID: **Author:** **Publication Year:**			
Did the study include:	**Yes (Include)**	**Unclear (Include)[a]**	**No (Exclude)**
A. The population of interest:			
Adults (mean age of 18 years or older) with any of the following types of histologically confirmed relapsed or refractory non-Hodgkin lymphoma:[b] • DLBCL, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	☐	☐	☐
Mixed population, including adults with eligible types of relapsed or refractory non-Hodgkin lymphoma (to be further considered at the full-text level)			
B. The intervention of interest:			
• Axicabtagene ciloleucel[c]	☐	☐	☐
C. The comparator(s) of interest:			
• Other CAR T-cell therapies (e.g., tisagenlecleucel)	☐	☐	☐
• Salvage chemotherapy	☐	☐	☐
• No comparator	☐	☐	☐
• No additional therapy			
D. Outcome(s) of interest:			
Clinical effectiveness outcomes (e.g., response rate, survival persistence of CAR T cells, health-related quality of life, patient-reported outcomes, hospitalization, and the need for subsequent treatment)	☐	☐	☐
Safety/harms outcomes (e.g., mortality, AEs, CRS, febrile neutropenia, B-cell aplasia, neurological effects including hallucination and dysphasia, infections, management of AEs, frequency of manufacturing failure, development of secondary malignancy)	☐	☐	☐
E. The study design(s) of interest:			
• RCTs	☐	☐	☐
• Non-randomized controlled trials • Single-arm studies	☐	☐	☐
• Cohort studies	☐	☐	☐
• Case-control studies	☐	☐	☐
• Case series	☐	☐	☐
• Indirect treatment comparisons, network meta-analyses	☐	☐	☐
F. Select for full-text review [d]	**Yes ☐**		**No ☐**

AE= adverse event; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; RCT = randomized controlled trial.

[a] "Unclear" means that the relevant information cannot be ascertained from the title or abstract.

[b] Potentially eligible indications include patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Studies that include patients with primary refractory disease (i.e., no response to first-line therapy) will be eligible for inclusion, but the evidence will be considered separately.

[c] Prescribing information indicates that the dose of axicabtagene ciloleucel is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL.[15] Studies in which axicabtagene ciloleucel was administered at a different dose will also be eligible for inclusion, but the evidence will be considered separately.

[d] The full-text article of any title or abstract will be retrieved for further review if the responses to all screening items are either "Yes" or "Unclear" by at least one of two independent reviewers.

Table 3: Level 2 Checklist for Screening Full-Text Articles and Clinical Effectiveness Study Reports

Reviewer: _____ **Date:** _____		
Ref ID: **Author:** **Publication Year:**		
Did the study include:	**Yes (Include)**	**No (Exclude)**
A. The population of interest:		
Adults (mean age of 18 years or older) with any of the following types of histologically confirmed relapsed or refractory non-Hodgkin lymphoma:[a] • DLBCL, primary mediastinal B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	☐	☐
Mixed population, including adults with eligible types of relapsed or refractory non-Hodgkin lymphoma, and results are reported separately for the eligible population	☐	☐
Mixed population, including adults with eligible types of relapsed or refractory non-Hodgkin lymphoma, but results are not reported separately. • There are sufficient numbers of eligible patients (66% or more) to include in the study, but results will be reported and discussed separately.		
B. The intervention of interest:		
• Axicabtagene ciloleucel[b]	☐	☐
C. A comparator of interest:		
• Other CAR T-cell therapies (e.g., tisagenlecleucel)	☐	☐
• Salvage chemotherapy	☐	☐
• No comparator	☐	☐
• No additional therapy		
D. Outcome(s) of interest:		
• Clinical effectiveness outcomes (e.g., response rate, survival persistence of CAR T cells, health-related quality of life, patient-reported outcomes, hospitalization, and the need for subsequent treatment)	☐	☐
• Safety/harms outcomes (e.g., mortality, AEs, CRS, febrile neutropenia, B-cell aplasia, neurological effects including hallucination and dysphasia, infections, management of AEs, frequency of manufacturing failure, development of secondary malignancy)	☐	☐
E. A study design of interest:		
• RCTs	☐	☐
• Non-randomized controlled trials • Single-arm studies	☐	☐
• Cohort studies	☐	☐
• Case-control studies	☐	☐
• Case series	☐	☐
• Indirect treatment comparisons, network meta-analyses	☐	☐
F. Notes:		
G. Selected for inclusion in the review [c]	**Yes** ☐	**No** ☐
H. Reason for exclusion	☐ Irrelevant population ☐ Irrelevant intervention	

Reviewer: _____ Date: _____		
Ref ID: **Author:** **Publication Year:**		
Did the study include:	**Yes (Include)**	**No (Exclude)**
	☐ Irrelevant comparator ☐ Irrelevant outcomes ☐ Irrelevant study design ☐ Other (specify):	

AE= adverse event; CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; RCT = randomized controlled trial.

[a] Potentially eligible indications include patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy. Studies that include patients with primary refractory disease (i.e., no response to first-line therapy) will be eligible for inclusion, but the evidence will be considered separately.

[b] Prescribing information indicates that the dose of axicabtagene ciloleucel is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL.[15] Studies in which axicabtagene ciloleucel was administered at a different dose will also be eligible for inclusion, but the evidence will be considered separately.

[c] Both reviewers must answer "Yes" to all questions for inclusion at the full-text level. If there is a discrepancy between the reviewers, disagreements will be resolved by discussion or with the involvement of a third reviewer, if necessary.

Table 4: Checklist for Screening Clinical Practice Guidelines

Reviewer: _____ Date: _____		
Ref ID: **Author:** **Publication Year:**		
Did the guideline include recommendations for:	**Yes (Include)**	**No (Exclude)**
A. The population of interest:		
• Adults (mean age of ≥ 18 years) with relapsed or refractory non-Hodgkin lymphoma	☐	☐
B. The intervention of interest:		
• Axicabtagene ciloleucel[a]	☐	☐
Was the guideline developed using a systematic approach with a clearly defined methodology? (e.g., literature search, Delphi process)		
If the guideline is Canadian, was the guideline endorsed at the national, provincial, or territorial level (e.g., federal or provincial government)? **For non-Canadian guidelines, was the guideline developed or endorsed at a national level (e.g., national society or federal government)?** **Guidelines that are explicitly applicable to a smaller jurisdiction or a specific facility will be excluded.**	☐	☐
Is the guideline "evidence-based" (i.e., informed by evidence as indicated by supporting data or citations)?	☐	☐
Selected for inclusion in the review [b]	**Yes ☐**	**No ☐**
Reason for exclusion	☐ Irrelevant population ☐ Irrelevant intervention ☐ Not national ☐ Not evidence-based ☐ Other (specify):	

[a] Potentially eligible indications indicates the dose of axicabtagene ciloleucel is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells in approximately 68 mL. Guidelines for axicabtagene ciloleucel administered at a different dose will be eligible for inclusion, but the recommendations will be reported separately.

[b] Both reviewers must answer "Yes" to all questions for inclusion at the full-text level. If there is a discrepancy between the reviewers, disagreements will be resolved by discussion or with the involvement of a third reviewer, if necessary.