Canada's Drug and
Health Technology Agency

CADTH Health Technology Review

Alemtuzumab, Cladribine, Fingolimod, Natalizumab, and Rituximab as First-Line Treatment in Adults With Highly Active Relapsing Multiple Sclerosis — 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

BIA	budget impact analysis
CNS	central nervous system
DMT	disease-modifying therapy
HTA	health technology assessment
ITC	indirect treatment comparison
MS	multiple sclerosis
NMA	network meta-analysis
nRCT	nonrandomized controlled trial
RCT	randomized controlled trial

Introduction and Rationale

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS).[1] Symptoms of MS are thought to result from demyelination, a process in which the immune system recognizes self cells and tissues within the CNS and orchestrates an inflammatory response that damages or destroys them. These cells and tissues include myelin, which is the insulating substance that wraps around the axons (i.e., the nerve fibres in the white matter of the CNS). The immune reaction may also damage the axons themselves and the oligodendrocytes (i.e., the CNS cells responsible for making myelin). Damaged myelin, or demyelination, forms scar tissue that is called sclerosis, which gives the disease its name.[1]

The inflammation, demyelination, and neurodegeneration associated with MS distort or interrupt the nerve impulses that are transmitted to and from the brain and spinal cord, resulting in several possible symptoms that vary from one individual to another, as well as over time for any given individual.[1] The different symptoms, associated with different areas of CNS inflammation, may include muscle weakness, spasticity, dizziness, tingling or reduced sensations, visual disturbances, bladder and bowel dysfunction, mental and physical fatigue, and cognitive impairment.[2]

The diagnosis of MS relies on clinical, imaging, and laboratory findings.[3,4] There are no symptoms, physical findings, or laboratory tests that can, by themselves, determine if a person has MS. The long-standing McDonald criteria[3] are used for diagnosing MS; the current version of MS diagnostic criteria requires evidence of damage in at least 2 separate areas of the CNS to confirm dissemination in space, evidence that confirms dissemination in time (which can be done at a single time point of onset), and ruling out other possible causes. In addition, imaging evidence and cerebrospinal fluid findings should be consistent with demyelinating disease.[3,4]

Relapsing MS is the most common disease course, being the phenotype identified in approximately 85% of patients upon MS diagnosis.[5] Relapsing MS is characterized by clearly defined attacks of new or increasing neurologic symptoms, followed by periods of relative stability, and partial or complete recovery. Relapsing MS was previously called relapsing-remitting MS, which was confusing to patients because, as there is no cure for MS, patients can never be considered in remission or cured. The natural course of relapsing MS includes periods where all symptoms may disappear, or where only some symptoms will continue and become permanent, but despite clinical inactivity, the disease unfortunately remains. Subclinical new inflammatory activity can be detected with routine MRIs during periods of remission as evidence of inadequate treatment response and/or risk of future disability.

While the MS phenotypes themselves have been well characterized, a subgroup of patients with relapsing MS who have an active, aggressive disease course and rapid disability accumulation remains difficult to define.[6] One observational study conducted in British Columbia using 3 different sets of definitions found that 4% to 14% of patients with MS had what was described as an aggressive

MS.[7] This type of disease presentation is associated with poor prognosis and outcomes over a relatively short period of time.[4,6] Previous efforts described severe or aggressive MS in patients with highly active relapsing disease who experience frequent and severe relapses, rapid worsening, and high inflammatory and neurodegenerative activity.[6] More specifically, the Canadian MS Working Group proposed a list of factors to identify highly active or aggressive MS that is based on 4 domains (relapse frequency, relapse severity, relapse recovery, and MRI).[4] This system suggests intensifying treatment if a major level of concern is present in any domain, or if a minor level of concern is present in any 2 domains.[4]

There is no curative treatment available for MS, and the current therapeutic strategy is aimed at reducing the risk of relapse and progression of disability.[4,8] The Canadian MS Working Group recommends early treatment (i.e., during the inflammatory phase of the disease), in order to provide optimal clinical benefit and alter the rate of progression.[4] Various disease-modifying therapies (DMT) with different mechanisms of action have been approved by Health Canada to treat MS, with the aim of suppressing or modulating the dysregulated immune system, limiting CNS inflammation, and preventing relapses and new lesions. Overall, they include various beta interferon products, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, alemtuzumab, fingolimod, natalizumab, ocrelizumab, ofatumumab, ozanimod, and siponimod. Although it doesn't hold a Health Canada indication for MS, rituximab is used in clinical practice, according to the clinical experts consulted by CADTH, and its use was supported by the Institute for Clinical and Economic Review (ICER) in its MS evidence report.[9]

The recommendations from the Canadian MS Working Group identified the first-line treatments approved for relapsing MS: 5 injectable drugs (glatiramer acetate, 3 formulations of interferon-beta-1a, and interferon-beta-1b) and 2 oral drugs (teriflunomide and dimethyl fumarate).[4] Five additional DMTs available in Canada are considered to be of high efficacy by the Canadian MS Working Group and are generally reserved for patients with a poor response or tolerability with a first-line drug (i.e., escalation treatment strategy);[4] these are fingolimod, cladribine, natalizumab, alemtuzumab, and ocrelizumab. However, the Canadian MS Working Group considers these drugs to be initial treatment options for patients with high disease activity, aggressive disease presentation, or rapidly evolving symptoms at onset, as these patients are at significant risk of worsening of early disability.[4] An increasing number of neurologists in clinical practice, according to the clinical experts consulted by CADTH, are preferring the treatment strategy of initiating high efficacy therapies early for the right patients, instead of following the traditional escalation treatment strategy. Despite the Canadian MS Working Group recommendations for patients with high disease activity, the strategy of initiating traditional first-line treatments, with the possibility of switching to another disease-modifying drug if necessary, is still typically used for many of these patients with relapsing MS.

This project was initiated at the request of Ontario, where a clinician working group of MS experts has approached the health ministry to request changes to the provincial reimbursement criteria for natalizumab and cladribine in order to align with the Canadian MS Working Group recommendations and to allow their use as first-line options in patients presenting with highly active relapsing MS. Experts in

other jurisdictions have also done the same. The rationale provided by the clinicians is that earlier use of higher efficacy treatments for patients presenting with high disease activity, more aggressive disease, or rapidly evolving MS at onset could prevent irreversible damage to the nervous system that may result from the current traditional sequential escalation approach that requires trial, failure, or intolerance to other options. Members of the Formulary Working Group indicated that alemtuzumab, fingolimod, and rituximab would also be of interest, but not other drugs that most drug plans fund as first-line treatment for relapsing MS (e.g., ocrelizumab).

During the project scope process, CADTH identified 1 published systematic review (Huisman et al. [2016])[8] of fingolimod and natalizumab in patients with active disease. Since then, additional randomized controlled trials (RCTs) have been published that evaluate the use of both of these drugs, as well as alemtuzumab and cladribine, in this patient population;[10-14] therefore, CADTH will perform a Health Technology Assessment (HTA) that aims to inform jurisdictional decision-making for reimbursement purposes.

Project Scope and Protocol Development

To inform the final scope of this HTA project, and following review with CADTH jurisdictional clients, a Proposed Project Scope was posted to the CADTH website for stakeholder feedback. Patient-group input was also solicited. The feedback received from stakeholders and 1 patient group was considered when developing the protocol.

Objectives

CADTH will undertake an HTA to review the clinical effectiveness, safety, and cost-effectiveness of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab relative to current first-line drugs for adults with highly active relapsing MS.

Deliverable

The following deliverable is planned:

- a Science Report (including a clinical evaluation and an economic evaluation if feasible).

This protocol document provides research questions and methods for a clinical systematic review. Jurisdictions have expressed interest in an economic evaluation assessing the cost-effectiveness of alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab as first-line treatments in adults with highly active relapsing MS. However, based on the Project Scope, it is uncertain if there will be enough clinical evidence to populate an economic model. Therefore, a staged approach to this HTA will be taken wherein the feasibility of an economic evaluation will be assessed based on the findings of the clinical systematic review. If an economic evaluation is deemed feasible, a priori detailed methods will be

appended and provided as an amendment to this protocol. Should sufficient evidence be identified, an existing health economic model developed by CADTH may be adapted for this purpose. A budget impact assessment tool may also be considered, in consultation with the requestor, if an economic evaluation is not deemed feasible.

Policy Question

The jurisdictions will be making local decisions regarding the public funding of drugs. To assist them in these decisions, the systematic review will focus on the following policy question:

- Should alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab be used as first-line treatments in adults with highly active relapsing MS?

Research Question

The project will address the following research question:

- What is the clinical efficacy and safety of alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab as first-line treatments in patients with highly active relapsing MS when compared to drugs currently used as first-line treatment in adults with highly active relapsing MS?

Methods

Clinical Review

Literature Search Methods

An information specialist will develop and conduct a literature search for clinical studies using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist.[15] The complete search strategy is presented in Appendix 1.

Published literature will be identified by searching the following bibliographic databases: MEDLINE via Ovid, Embase via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. All Ovid searches will be run simultaneously as a multifile search. Duplicates will be removed using Ovid deduplication for multifile searches, followed by manual deduplication in Endnote. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be relapsing multiple sclerosis and alemtuzumab, natalizumab, cladribine, fingolimod, or rituximab. The following clinical trials registries will be searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

CADTH-developed search filters will be applied to limit retrieval to HTAs, systematic reviews, meta-analyses or network meta-analyses, and RCTs. The RCT study design filter will be used in the search for included studies, while additional filters (HTAs, systematic reviews, meta-analyses, and network meta-analyses) will be used to retrieve background or supplementary information. Additional search filters may be included if insufficient results are identified in the initial search. Retrieval will not be limited by publication date but will be limited to the English or French language. Conference abstracts will be excluded from the search results.

The initial search will be completed in spring 2023. Regular alerts will update the database literature searches until the publication of the final report. The clinical trials registries search will be updated before completion of the stakeholder feedback period. Studies meeting the selection criteria of the review and identified in the alerts before completion of the stakeholder feedback period will be incorporated into the analysis of the final report. Any studies that are identified after the stakeholder feedback period will be described in the discussion, with a focus on comparing the results of these new studies with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) will be identified by searching sources listed in relevant sections of the Grey Matters: A Practical Tool For Searching Health-Related Grey Literature reference,[15] which includes the websites of regulatory agencies, HTA agencies, clinical guideline repositories, systematic review repositories, patient-related groups, and professional associations. Google will be used to search for additional internet-based materials. These searches will be supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate. The grey literature search will be updated before completion of the stakeholder feedback period. See Appendix 1 for more information on the grey literature search strategy.

Eligibility Criteria

Introduction and Rationale

Prespecified selection criteria for inclusion of studies in this systematic review are presented in Table 1. All included studies must meet all the eligibility criteria.

Table 1: Selection Criteria

Criteria	Description
Population	DMT-naive adults with highly active relapsing MS Subgroups according to: • age at diagnosis (e.g., 18 years to < 50 years; ≥ 50 years) • time since diagnosis (to account for disease duration) • EDSS score (e.g., < 3; 3 to < 6; ≥ 6) • MRI activity at baseline

Criteria	Description
Interventions	• Alemtuzumab (Lemtrada) 12 mg/day IV infusion for 5 consecutive days for the first treatment course, then 12 mg/day for 3 consecutive days administered 12 months later • Cladribine (Mavenclad) 3.5 mg/kg orally over 2 years, administered as 1 treatment course of 1.75 mg/kg per year • Fingolimod (Gilenya; generics) 0.5 mg orally once daily • Natalizumab (Tysabri) 300 mg IV infusion every 4 weeks • Rituximab (including biosimilars) 500 mg IV infusion every 6 months
Comparators	Relapsing MS first-line therapies:[a] • glatiramer acetate • interferon-beta-1a • interferon-beta-1b • teriflunomide • dimethyl fumarate • ocrelizumab • ofatumumab
Outcomes	Efficacy outcomes • Relapse (e.g., relapse rate, relapse-free rate, time to relapse) • Disability progression (including time to progression) or improvement • Function (e.g., MSFC score, including T25-FW or 9-HPT individual scores) • Imaging outcomes (e.g., MRI brain lesions, MRI brain volume, spinal cord imaging) • Cognitive outcomes (e.g., MSNQ, PASAT 3, SDMT) • Symptoms (e.g., fatigue, cognition, mobility, visual disturbance) • HRQoL (e.g., MSWOL-54, MSQLI, MS-QLQ27) • Instrumental activities of daily living (e.g., absenteeism, presentism, employment status) **Harms outcomes** • Adverse events • Serious adverse events • Withdrawal due to adverse events • Mortality • Notable harms: injection-related reactions, opportunistic infections, serious infections, progressive multifocal leukoencephalopathy, lymphopenia, neutropenia, malignancies
Study designs	Published phase II, phase III, and phase IV RCTs If no RCTs are available to adequately inform the research question: Nonrandomized controlled trials and comparative prospective cohort studies

9-HPT = 9 Hole Peg Test; DMT = disease-modifying therapies; EDSS = Expanded Disability Status Scale; HRQoL = health-related quality of life; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSNQ = Multiple Sclerosis Neuropsychological Questionnaire; MSQLI = Multiple Sclerosis Quality of Life Inventory; MS-QLQ27 = 27-item Multiple Sclerosis Quality of Life Questionnaire; MSWOL-54 = Multiple Sclerosis Quality of Life-54; PASAT 3 = 3-second Paced Auditory Serial Addition Task; RCT = randomized controlled trial; SDMT = Symbol Digit Modality Test; T25-FW = Timed 25-Foot Walk.

[a] Health Canada–recommended dosage for MS or clinically relevant dosage based on expert advice or on the Canadian MS Working Group guidelines.

The following will be considered when selecting studies for inclusion:

- The systematic review will include RCTs with a head-to-head comparison between 1 of the interventions (alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab) and 1 of the comparators (glatiramer acetate, interferon-beta-1a, interferon-beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, and ofatumumab) in the targeted population of DMT-naive patients with highly active relapsing MS. Full texts of titles or abstracts describing potentially relevant studies in a wider patient population will be retrieved for assessment and included in the systematic review if appropriate subgroup results are reported. Direct evidence from RCTs will be sought first, since well-designed RCTs allow for causal inferences to be drawn with greater certainty compared with nearly any other study type.
- If no such head-to-head RCTs can be identified for any given outcome comparison, then supplemental literature searches will be performed to identify additional relevant evidence. These will include:
    - Placebo-controlled RCTs will be identified for the purpose of performing indirect treatment comparison(s) (ITC[s]), specifically Bucher ITCs. As such, RCTs will be considered for inclusion if they evaluate 1 of the interventions under review (alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab) or 1 of the drugs currently used as first-line treatment in adults with highly active relapsing MS compared to placebo, in the targeted population of patients with highly active relapsing MS who are DMT-naive. Additional selection criteria will be used if necessary to keep the number of included studies manageable and to adequately inform the research question, with caution taken so that decisions made will not compromise the quality of the systematic review (i.e., introduce bias). Placebo-controlled trials that cannot be used in Bucher ITCs will not be eligible for inclusion.
    - Nonrandomized controlled trials (nRCTs) and comparative prospective cohort studies will be considered for inclusion if they evaluate 1 of the interventions (alemtuzumab, natalizumab, cladribine, fingolimod, and rituximab) versus 1 of the comparators (glatiramer acetate, interferon-beta-1a, interferon-beta-1b, teriflunomide, dimethyl fumarate, ocrelizumab, and ofatumumab) in the targeted population of DMT-naive patients with highly active relapsing MS for any given outcome comparison. Additional selection criteria will be used if necessary to keep the number of included studies manageable and to adequately inform the research question, with caution taken so that decisions made will not compromise the quality of the systematic review (i.e., introduce bias). To be considered prospective, the comparative cohort studies must have clearly defined a hypothesis before the enrolment of patients and collection of outcomes data (i.e., registry studies will be excluded).
- To avoid excluding potentially relevant evidence, there will not be a prespecified definition for highly active relapsing MS. Disease definitions from the studies will be used and assessed

individually for relevance to the Canadian relapsing MS clinical setting. According to the clinical experts consulted for this review, highly active (also called aggressive) disease is associated with features that put a patient at high risk of disability; these include a high number of or frequent relapses, an MRI indicative of high activity, and situations where another relapse may be devastating (e.g., in patients who did not recover well from a prior relapse). Studies of wider populations will only be included if findings can be isolated for treatment-naive patients with highly active relapsing MS (e.g., in subgroup analyses). The clinical experts will be consulted when there is uncertainty about whether the population investigated in any study would qualify as having highly active disease.

- Drug regimens eligible for inclusion in the systematic review for interventions and comparators are those that have been approved by Health Canada for MS or are considered clinically relevant based on expert advice or major clinical guidelines such as the Canadian MS Working Group guidelines.[4]
- All relevant instruments and time points for outcome measurements will be eligible for inclusion.
- This review will be limited to studies reported in English or French, as CADTH has the capacity for reviewing in both languages. Due to resource limitations, studies reported in other languages will be excluded.
- In the event that multiple reports are identified for the same study, they will all be included and cited; however, only unique data will be extracted without duplication and the reports will be considered as a single study in the analysis. The first complete report of a study will be identified as the primary report, while subsequent reports will be referred to as associated reports. Abstracts, conference proceedings, or results posted on clinicaltrials.gov will not be considered a complete report, as they typically do not provide sufficient information to properly assess study quality or generalizability; therefore, studies reporting findings only through these means of publication will not be included in the systematic review.

Study Selection

Before screening, 2 reviewers will conduct a pilot round by independently screening 100 randomly selected articles in duplicate, after which they will meet to resolve disagreements. Additional pilot rounds will be run as needed; for example, if there are major disagreements or changes to the selection criteria. Pilot testing will be repeated before each screening stage (i.e., for direct comparative evidence from RCTs, placebo-controlled RCTs, and direct comparative evidence from nRCTs and prospective observational studies).

Once both of the reviewers are satisfied with their understanding of the selection criteria, they will independently screen the titles and abstracts of all the citations retrieved from the literature search for relevance to the clinical research question in Microsoft Excel workbooks. Full texts of titles or abstracts

that are judged to be potentially relevant by at least 1 reviewer will be retrieved and independently assessed by both reviewers for possible inclusion based on the predetermined selection criteria outlined in Table 1. The 2 reviewers will then compare their chosen included and excluded studies; disagreements at the full-text level will be discussed until consensus is reached. If consensus cannot be reached, a third reviewer will be consulted. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) flow chart.[16] Studies excluded at the full-text screening stage, along with the reasons for their exclusion, will be recorded and reported. Reference lists of included studies and relevant systematic reviews that are identified during screening will be screened following the same selection process. Reviewers will not attempt to retrieve further information from study investigators in cases where a study's eligibility for inclusion cannot be ascertained from the report.

A list of studies selected for inclusion in the systematic review will be posted to the CADTH website for stakeholder review for 10 business days. Feedback and any additional studies identified for potential inclusion will be reviewed following the previously outlined process. Studies meeting the selection criteria for the review that are identified through alerts before the completion of the stakeholder feedback of the draft report will be incorporated into the analysis. Relevant reports identified once reaching the stakeholder feedback period will be described in the discussion, with a focus on comparing their results with those obtained from the synthesis of earlier reports included in the review.

Data Extraction

All relevant data will be extracted directly into a standardized data abstraction form, which will be part of a review-specific Microsoft Excel workbook. The form will be piloted before beginning full data extraction to ensure that it is usable and that it completely and reliably captures the items of interest, while avoiding redundancies. In the pilot round, the reviewers will independently extract data from 2 to 3 of the included studies, then meet to resolve disagreements through discussion and by referring to the source publications of interest. Additional pilot rounds will be run as needed, until reviewers are satisfied with the contents and usability of the form.

Formal data extraction will be performed by 1 reviewer and independently checked for accuracy and completeness by a second reviewer. Any disagreements in the assessment of these data will be resolved through discussion until consensus is reached, or through the involvement of a third reviewer, if required.

Relevant information to be extracted will include details of the study characteristics, methodology, population, intervention, and comparator, as well as relevant results and conclusions regarding the outcomes and the subgroups of interest listed in Table 1. All numerical data, including data presented in text or in figures, will be extracted. For data available only in unlabeled graphs or figures, the reviewers will independently extract the data using WebPlotDigitizer software. Extracting data from graphs and figures using software is more efficient, accurate, and reliable than manual extraction.[17,18] If data are not

reported for an outcome, no assumption will be made about its presence or absence. Reviewers will not contact the authors of the included studies to clarify any information or retrieve missing information.

Risk of Bias and Critical Appraisal

The reviewers will use the following risk of bias assessment, according to the study design of the included studies:

- Outcome-level risk of bias of relevant RCTs, based on the effect of assignment to the intervention (i.e., intention-to-treat effect), will be assessed using the Cochrane Risk of Bias tool, version 2 (RoB 2).[19] This assessment tool facilitates the evaluation of potential biases across 5 domains: the randomization process, deviations from intended interventions, missing outcomes data, measurement of the outcomes, and selection of the reported results. A judgment of low risk of bias, some concerns regarding the risk of bias, or high risk of bias will be assigned for each domain. The overall risk of bias of each trial will be rated and designated using the same terminology based on the domain-level determinations. Where possible, attempts will be made to predict the direction of the potential bias. A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.
- Outcome-level risk of bias in nonrandomized studies, if included, will be assessed using the Risk Of Bias In Non-Randomized Studies – Interventions tool (ROBINS-I).[20] This tool was chosen for ease of comparison in assessing the risk of bias in RCTs. ROBINS-I facilitates the assessment of the risk of bias across 7 domains: confounding, selection bias, measurement of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Risk of bias per domain per study will be assessed and used to assign an overall judgment to each study; that is, whether they are of low, moderate, serious, or critical risk of bias, or whether no information is provided. Where possible, attempts will be made to predict the direction of the potential bias. A rationale will be provided for decisions about the risk of bias for both the domain-level and overall assessments.

To ensure a mutual understanding of the tool and methodological intricacies across studies, all reviewers involved in the risk of bias assessment will independently pilot the selected tools across 2 to 3 studies and meet to resolve disagreements. After piloting, risk of bias will be evaluated in duplicate by 2 independent reviewers. Any disagreement in the risk of bias for the domain-level and overall assessments will be resolved through discussion, with the involvement of a third reviewer if consensus cannot be reached. Information necessary to evaluate the risk of bias will be obtained from the published reports.

In addition to the risk of bias, a critical appraisal of individual studies will also be performed independently by 2 reviewers using a standardized table. The critical appraisal will include an internal validity assessment, which will be based on 4 large aspects of study methodology (study design,

intervention, and comparator; selection, allocation, and disposition of patients; outcomes measurement; and statistical analysis), as well as a generalizability assessment of the findings (i.e., patient population, choice of outcomes, treatment regimen, and length of follow-up). Throughout the critical appraisal process, reviewers will include clinical input from the experts consulted by CADTH for this review.

Studies will not be excluded from the systematic review based on the results of the risk of bias assessment or critical appraisal. However, the critical appraisal results and how they affect study findings will be used to inform the assessment of the certainty in the body of evidence for each outcome comparison.

Data Analysis and Synthesis

The data analysis will depend on the included studies and may consist of pairwise meta-analyses, Bucher ITC(s), or synthesis without meta-analysis (i.e., narrative synthesis). The CADTH team will consider the clinical and methodological heterogeneity of the relevant studies (i.e., with respect to methodology, outcomes [measurement, timing], and populations) before pooling or undertaking ITCs. In the case that pairwise meta-analyses are feasible, studies will be pooled using the DerSimonian and Laird random effects models in RevMan Web.[21] Random effects approaches are generally considered most reasonable (versus fixed effects) as they incorporate the assumption that studies are measuring heterogeneous but related effects.[22] In the case of rare events (< 1% event rate, such as for rare harms), the Peto odds ratio[23] will be considered to provide a less biased effect estimate.[24] Evidence from RCTs and nRCTs will be pooled separately from observational studies. Risk ratios or rate ratios between groups and their 95% confidence intervals (CIs) will be reported for dichotomous data or counts, respectively. When there are 0 events for at least 1 of the interventions groups, the risk difference with 95% CI will be reported. The mean difference with 95% CI will reported for continuous outcomes when all data are collected using the same measurement tool, or the standardized mean difference and 95% CI when different tools have been used to measure a similar construct. In the case that direct comparative evidence is not available from RCTs for any comparison outcome, the reviewers will consider comparing the intervention and comparator treatments indirectly via the methods described by Bucher et al.[25] When there are no interaction effects between covariates describing various subgroups of patients (e.g., different eligibility criteria in different studies) and the magnitude of the treatment effect, and the sample size is large, effect estimates from Bucher ITCs can be unbiased.[25]

If data required for meta-analysis are not reported by individual studies, they will be computed or calculated using other statistics presented in the reports based on available guidance;[25] suitable imputations (e.g., medians for means, missing standard deviations) may be considered as needed.[22] Heterogeneity will be investigated via prespecified subgroups. When appropriate, sensitivity analyses will be performed (e.g., for variability in risk of bias or study design across studies, differences in adherence rates) by removing studies from the analysis and checking whether the effect estimates

differ. If any pooled analysis contains 10 or more studies of varying size,[26] small study bias will be investigated by visually inspecting funnel plots for asymmetry and via the Egger's regression test.[27]

In the event that the included studies are deemed too heterogenous to combine or compare via ITCs (e.g., differences in populations, methods, outcome measures), the findings will be synthesized narratively following the guidance by Popay et al.,[28] and the rationale for not pooling will be provided. In this case, within-study and between-study relationships will be evaluated and the findings related to the direction and magnitude of observed effects, trends, and deviations will be discussed by outcome comparison.

Certainty of Evidence and Drawing Conclusions

Conclusions will be drawn for each outcome comparison based on informal appraisals of the certainty of evidence. The following criteria will be considered: the risk of bias of the contributing studies, the precision of the effect estimates, the consistency of the evidence (in cases where more than 1 study contributes evidence for a comparison outcome), and the generalizability (or applicability) of the findings.

Opportunities for Stakeholder Feedback

Stakeholders have been previously given the opportunity to comment on the proposed project scope that informed this protocol.

Moving forward, stakeholder feedback will be solicited at key steps throughout the systematic review process. CADTH will follow the *Framework for Patient Engagement in Health Technology Assessment*, which includes standards for patient involvement in individual HTAs and is used to support and guide activities involving patients and patient groups.

As such, stakeholders will be given the opportunity to provide feedback on the draft included studies list, the draft report, and the recommendations, if applicable. Unpublished data identified as part of the feedback process may only be included if the source of data is in the public domain.

Areas for Potential Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. 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.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Cochrane Central Register of Controlled Trials (CCTR)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: Spring 2023

Alerts: Monthly search updates until project completion

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; guidelines; overview of reviews; randomized controlled trials; controlled clinical trials

Limits:

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 2: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
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
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word

Syntax	Description
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multi-Database Strategy

1. Alemtuzumab/
2. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,ot,hw,rn,nm.
3. Natalizumab/
4. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,ot,hw,rn,nm.
5. Cladribine/
6. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,ot,hw,rn,nm.
7. Fingolimod Hydrochloride/
8. (fingolimod* or gilenia* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,ot,hw,rn,nm.
9. Rituximab/
10. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or "hlx 01" or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,kw,ot,hw,nm,rn.
11. or/1-10
12. Multiple Sclerosis, Relapsing-Remitting/
13. (RRMS or RMS).ti,ab,kf.

14. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
15. or/12-14
16. 11 and 15
17. 16 use medall
18. 16 use cctr
19. *alemtuzumab/
20. (alemtuzumab* or campath* or lemtrada* or mabcampath* or HSDB8177 or HSDB-8177 or LDP03 or LDP-03 or remnig* or bxt1523 or bxt-1523 or LDP103 or LDP-103 or qz402673 or qz-402673 or mabkampat*).ti,ab,kf,dq.
21. *natalizumab/
22. (natalizumab* or tysabri* or antegren* or HSDB8174 or HSDB-8174 or an100226 or an-100226 or bg0002 or bg-0002 or dst356a1 or dst-356al or pb006 or pb-006).ti,ab,kf,dq.
23. *cladribine/
24. (cladribin* or cladarabin* or biodribin* or intocel* or leustat* or litak* or litax* or mavenclad* or movectro* or mylinax* or BRN0624220 or BRN-0624220 or CCRIS9374 or CCRIS-9374 or HSDB7564 or HSDB-7564 or NSC105014* or NSC-105014* or RWJ26251 or RWJ-26251).ti,ab,kf,dq.
25. *fingolimod/
26. (fingolimod* or gilenya* or imusera* or inzolfi* or fty720 or fty-720 or tdi132 or tdi-132).ti,ab,kf,dq.
27. *rituximab/
28. (rituximab* or Rituxan* or Truximab* or MabThera* or Mab Thera* or Truxima* or blitzima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or ritucad* or riximyo* or truxella* or halpryza* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or "hlx 01" or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or rtxm83 or rxtm 83 or ibi301 or ibi 301 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDEC-C2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,dq.
29. or/19-28
30. exp Multiple sclerosis/ and (relapse/ or remission/ or (relaps* or remit*).ti,ab,kf,dq.)
31. (RRMS or RMS).ti,ab,kf.
32. ((ms or multiple scleros*) adj3 (relaps* or remit*)).ti,ab,kf.
33. or/30-32
34. 29 and 33
35. 34 use oemezd
36. (conference abstract or conference review).pt.
37. 35 not 36
38. 17 or 37
39. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.

40. Randomized Controlled Trial/
41. exp Randomized Controlled Trials as Topic/
42. "Randomized Controlled Trial (topic)"/
43. Controlled Clinical Trial/
44. exp Controlled Clinical Trials as Topic/
45. "Controlled Clinical Trial (topic)"/
46. Randomization/
47. Random Allocation/
48. Double-Blind Method/
49. Double Blind Procedure/
50. Double-Blind Studies/
51. Single-Blind Method/
52. Single Blind Procedure/
53. Single-Blind Studies/
54. Placebos/
55. Placebo/
56. Control Groups/
57. Control Group/
58. (random* or sham or placebo*).ti,ab,hw,kf.
59. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
60. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
61. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
62. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
63. allocated.ti,ab,hw.
64. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
65. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
66. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
67. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
68. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
69. (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
70. or/39-69
71. (systematic review or meta-analysis).pt.
72. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/

73. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
74. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
75. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
76. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
77. (handsearch* or hand search*).ti,ab,kf.
78. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
79. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
80. (meta regression* or metaregression*).ti,ab,kf.
81. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
82. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
83. (cochrane or (health adj2 technology assessment) or evidence report).jw.
84. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
85. (outcomes research or relative effectiveness).ti,ab,kf.
86. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
87. [(meta-analysis or systematic review).md.]
88. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
89. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
90. umbrella review*.ti,ab,kf.
91. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
92. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
93. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
94. or/71-93
95. 70 or 94
96. 38 and 95
97. 18 or 96
98. remove duplicates from 97
99. limit 98 to (english or french)

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS]

Grey Literature

Search dates: Spring 2023

Keywords: alemtuzumab, natalizumab, cladribine, fingolimod, rituximab, relapsing multiple sclerosis, relapsing-remitting multiple sclerosis, RMS, RRMS

Limits: none

Updated: Search will be updated prior to the completion of stakeholder feedback period

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

The complete search archive of sites consulted for this report will be available on request.