Canada's Drug and
Health Technology Agency

CADTH Health Technology Review

Thrombopoietin Receptor Agonists as Second-Line Treatment in Children With Ongoing Immune Thrombocytopenia — 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.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**.

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Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
HTA	Health Technology Assessment
ITP	immune thrombocytopenia
RCT	randomized controlled trial
TPO RA	thrombopoietin receptor agonists

Introduction and Rationale

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelets and an increase in bleeding risk due to increased platelet destruction and impaired platelet production.[1-4] It was previously called *idiopathic thrombocytopenic purpura*, but is no longer considered to be an idiopathic disease.[4,5] The specific cause of ITP is unknown but may be a mix of genetic and environmental factors.[6] In addition, not all patients will experience bleeding symptoms such as purpura.[6]

Primary ITP is defined as isolated thrombocytopenia, that is peripheral blood platelet count below 100 × 10^9/L, in the absence of other causes or disorders that may be associated with thrombocytopenia.[1] The disorder falls into one of the following 3 disease groups according to disease duration:[1]

- newly diagnosed ITP – active disease duration of 0 to 3 months
- persistent ITP – active disease duration of 3 to 12 months, including those patients not reaching spontaneous remission or not maintaining complete response of therapy
- chronic ITP – ongoing, active disease lasting longer than 12 months.

ITP differs between the adult and pediatric populations. Spontaneous remission, which occurs when there is an improved platelet count in the absence of ongoing or recent therapy, may be observed in around 70% of children according to various studies,[7,8] which is significantly more frequent than in the adult population (5% of adults achieve spontaneous remission at 6 months, 49% at 12 months, and 30% at 24 months).[7,8]

ITP has a reported incidence rate varying between 2 and 5 per 100,000 children per year according to various epidemiological studies around the world.[9] Bleeding symptoms are often present, including severe bleeding (such as in the gastrointestinal tract or in the brain) in approximately 20% of children.[7,10]

Newly diagnosed pediatric patients with no or minor bleeding may undergo observation according to the *American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia*[11] and the *2019 International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia.*[5] In the presence of non–life threatening mucosal bleeding or bleeding that has an impact on quality of life, first-line therapy is a short course (up to 7 days) of corticosteroids. For patients with ITP who are unresponsive or have a contraindication to taking corticosteroids, other first-line therapies include IV immunoglobulin and anti-D immunoglobulin.[11] In pediatric patients who do not respond to first-line treatment (platelet count below 50 x 10^9/L),[5] guidelines recommend the use of thrombopoietin receptor agonists (TPO-RAs), that is eltrombopag or romiplostim.[5,11]

Considering the balance of benefits and harms, costs, patient preference and feasibility, the American Society of Hematology suggests the use of TPO-RAs rather than rituximab, which would be considered a subsequent-line therapy.[5,11] Issues such as the scarcity of evidence led to this recommendation being conditional, based on very low certainty in the evidence of effects.[11] Based on the body of evidence, the guideline panel concluded that the potential benefits of TPO-RAs were high, especially with regard to the reduction of bleeding events and reduction or discontinuation of corticosteroids. Additionally, the risks of

TPO-RAs were considered low, with a high value placed on avoiding immunosuppression in children.[11] The importance of avoiding immunosuppression in the pediatric population was also emphasized by the clinical experts consulted by CADTH for this review. For example, the clinical experts mentioned the issue of delay in standard immunization schedule with the use of immunosuppressive therapies, which became even more serious in clinical practice during the recent COVID-19 pandemic.

Other options for subsequent-line therapy include azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, and the vinca alkaloids; however, guidelines such as that of the American Society of Hematology did not prioritize a review of these drugs due to limited availability of data, a lack of direct comparisons, and large variability in outcome measures.[11] The clinical experts consulted by CADTH also confirmed that there is only a limited role for immunosuppressants in children with ITP in clinical practice.

CADTH previously undertook at the request of the jurisdictions a health technology assessment (HTA) to review the comparative effectiveness and cost-effectiveness of treatments for ITP in adults after failure of first-line therapies. In adults, the American Society of Hematology acknowledges the lack of a universal optimal second-line treatment option and suggests individualizing treatment choices based on patient characteristics, frequency and intensity of bleeding episodes, patient values and preferences, as well as cost.[11] In this context, a systematic review aimed to inform decision-making regarding which drugs should be used in adults who failed first-line therapy.

Among the stakeholder feedback received, CADTH was approached to conduct an evidence review in the pediatric population as well. Before being authorized to access a TPO RA, children who require second-line pharmacotherapy may be required, in some jurisdictions, a trial of another drug such as rituximab, which does not align with the 2019 American Society of Hematology and International Consensus Report guidance on treatment for children with ITP described above.[5,11] Of note, only eltrombopag has a Health Canada indication in children with ITP;[12] romiplostim holds an indication in adult patients but Health Canada has not authorized an indication for pediatric use.[12] Consistent with reimbursement review requirements, only eltrombopag has been reviewed by CADTH, which was in 2011, with the final recommendation that eltrombopag not be listed due to the fact that, despite significant benefits on relevant outcomes compared to placebo (i.e., platelet response, any bleeding events, use of rescue and quality of life), the cost of eltrombopag per quality-adjusted life-year compared with standard of care in adults refractory to first-line therapies greatly exceeded conventional standards for cost-effectiveness.[13]

Therefore, CADTH will perform a systematic review assessing the efficacy of TPO-RAs (i.e., eltrombopag and romiplostim) and other relevant drugs identified by the jurisdictions, that is rituximab for children with ITP who have failed first-line therapies. For jurisdictions, knowing the level of evidence for, and efficacy of TPO-RAs compared with each other and with other standard treatment options will add to what is currently known and may help inform decision-making regarding the reimbursement of these drugs with potential budget impact implications.

Project Scope and Protocol Development

The final scope of this HTA project was informed by feedback received from stakeholders and patient group(s) following publication of the CADTH HTA on the comparative effectiveness and cost-effectiveness of treatments for ITP in adults after failure of first-line therapies. In addition, CADTH jurisdictional clients were involved in the protocol review process.

Objectives

CADTH will undertake a HTA to review the clinical effectiveness and safety of TPO-RAs eltrombopag and romiplostim as second-line treatments in pediatric patients with ITP when compared to current second-line drugs.

Deliverables

This protocol document provides research questions and methods for a clinical systematic review. The planned deliverable is a Science Report that includes a clinical evaluation.

This protocol document provides research questions and methods for a clinical systematic review. A budget impact assessment (BIA) tool may also be considered, in consultation with the requestor, if an economic evaluation is not feasible.

Policy Questions

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 questions:

- In children with ongoing active ITP, what is the overall body of evidence supporting the use of TPO-RAs (i.e., eltrombopag and romiplostim) and rituximab after failure of first-line therapies?
- Based on the level and quality of clinical evidence, should the reimbursement of TPO-RAs come earlier in the treatment sequencing for children with ongoing active ITP, rather than having to try a course of rituximab before being able to access eltrombopag or romiplostim?

Research Questions

The project will address the following research question:

- What is the clinical efficacy and safety of TPO-RAs (i.e., eltrombopag and romiplostim) and rituximab for children with ITP who have failed first-line therapies?
- What is the comparative clinical efficacy and safety of TPO-RAs (i.e., eltrombopag and romiplostim) and rituximab for children with ITP who have failed first-line therapies?

Methods

Clinical Review

The systematic review protocol was developed a priori and is registered in the PROSPERO international prospective registry of systematic review.[14] The protocol is reported according to the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)[15] with consideration for advancements in the PRISMA 2020 statement.[16]

Literature Search Methods

An information specialist will perform the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[17]

Published literature will be identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase 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 be comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts will be developed based on the elements of the PICOS framework and research questions. The main search concepts will be pediatrics, immune thrombocytopenia, and eltrombopag, romiplostim, or rituximab. The following clinical trials registries will be searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization'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).

No filters will be applied to limit the retrieval by study type. Retrieval will not be limited by publication date or by language. Conference abstracts will be excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search will be completed in April 2023. Regular alerts to update the search will be run until project completion.

Grey literature (literature that is not commercially published) will be identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search are the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google will be used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches will be supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

Eligibility Criteria

Inclusion and Exclusion Criteria

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

Table 1: Selection Criteria

Criteria	Description
Population	Pediatric patients (<18 years) with ongoing, active ITP who have failed first-line treatment (i.e., observation, corticosteroids, IVIG or anti-D immunoglobulin)

Interventions[a]	Question 1 (clinical efficacy) and Question 2 (comparative clinical efficacy):
	• eltrombopag (Revolade)
	  ○ 25 mg orally once daily (starting dose) in patients < 6 years of age
	  ○ 50 mg orally once daily (starting dose) in patients ≥ 6 years of age
	  ○ The dose may be increased to a maximum of 75 mg once daily
	• romiplostim (Nplate)
	  ○ 1 to 3 mcg /kg subcutaneous injection once weekly (starting dose)
	  ○ Dose adjustments of 1 mcg /kg/week to achieve and maintain a platelet count ≥ 50 x 10^9/L (maximum dose of 10 mg/kg)
	• rituximab (including biosimilars)
	  ○ 375 mg/m^2 IV infusion once weekly for 4 weeks.

Comparators[b]	Question 1 (clinical efficacy): • Placebo Question 2 (comparative clinical efficacy): • Eltrombopag • Romiplostim • Rituximab (including biosimilars)
Outcomes	**Efficacy outcomes**[1]**:** • Bleeding events (i.e., clinically significant bleeding events, bleeding assessment tools) • Platelet count response (i.e., complete response, time to complete platelet response) • HRQoL (i.e., measured with an assessment tool validated in pediatric ITP) • Function (i.e., measured with an assessment tool validated in pediatric ITP) • Need for rescue medication (e.g., IVIG, corticosteroids, platelet transfusions) **Harms outcomes:** • Adverse events[c] • Serious adverse events[c] • Withdrawal due to adverse events • Mortality • Notable harms: immunological toxicity (e.g., infections), myelofibrosis

Criteria	Description
Study design	Published phase II, phase III, and phase IV RCTs If no RCTs are available to adequately inform a particular comparison: Nonrandomized controlled trials and comparative prospective cohort studies.

FACIT = Functional Assessment of Chronic Illness Therapy – Fatigue subscale; FACT-Th6 = Functional Assessment of Cancer Therapy – Thrombocytopenia; HRQoL = health-related quality of life; ITP = immune thrombocytopenia; ITP-PAQ = Immune Thrombocytopenic Purpura Patient Assessment Questionnaire; IVIG = intravenous immunoglobulin; MEI-SF = Motivation and Energy Inventory – Short-Form; RCT = randomized controlled trial; SF-36v2 = Short-Form 36 Health Survey, Version 2.

Note: Relevant comparisons do not include different doses of the same drug.

a Only eltrombopag has a Health Canada indication in children with ITP.[12] Romiplostim holds an indication in adults with ITP; Health Canada has not authorized an indication for pediatric use.[18] Rituximab does not have a Health Canada indication for ITP.[19]

b Health Canada recommended dosage for pediatric ITP or clinically relevant dosage based on expert advice or on relevant ITP Guidelines.

C Reported as a composite outcome, that is the total numbers and proportions of patients with adverse events or serious adverse events.

The following will be considered when selecting studies for inclusion:

- For research question 1 (clinical efficacy), evidence will be sought from placebo-controlled RCTs. CADTH discourages the use of informal, naive, indirect comparisons (i.e., observational comparisons across the results of separate trials or groups of trials), because they do not preserve the within-trial randomization. Such comparisons are likely to be affected by bias and confounding.
- For research question 2 (comparative clinical efficacy), direct head-to-head evidence from RCTs will be sought first, since well-designed and conducted 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 evidence will include the following:
  - Placebo-controlled RCTs, that is evaluating 1 of the interventions or 1 of the comparators under review compared to placebo. If possible, CADTH will conduct a meta-analysis; if there are reasons precluding meta-analysis (e.g., heterogeneity across the publications), a narrative review will be conducted.
  - If no placebo-controlled RCTs are available for any given outcome-comparison, then nonrandomized controlled trials (nRCTs) and comparative prospective cohort studies will be considered for inclusion if they evaluate one of the interventions versus 1 of the comparators under review in the targeted population. To be considered prospective, comparative cohort studies must have clearly defined a hypothesis prior to the enrolment of patients and collection of outcomes data (i.e., registry studies will be excluded).
- 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).
- 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.
- Drug regimens eligible for inclusion in the systematic review for interventions and comparators are those that have been approved by Health Canada for ITP or are considered clinically relevant based on expert advice or on the major ITP Guidelines.[5,11]

- All relevant instruments and timepoints 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 and identified explicitly on the excluded studies list.
- 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 1 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 risk of bias or generalizability; therefore, studies reporting findings only though these means of publication will not be included in the systematic review. However, we will report on ongoing trials registered in clinicaltrials.gov at the time the final report for this project is published.

Study Selection

Before screening begins, 2 reviewers will conduct a pilot round by independently screening 50 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.

Once reviewers are satisfied with their understanding of the selection criteria, the 2 reviewers 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 2 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 reasons for exclusion, will be recorded and reported. Reference lists of included studies and relevant systematic reviews identified during screening will be screened following the same selection process. Due to resource constraints, reviewers will not routinely attempt to retrieve further information from study investigators in cases where a study's eligibility for inclusion cannot be ascertained from the report and the study will be excluded.

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 prior to 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, reviewers will independently extract data from 2 to 3 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 involvement of a third reviewer if required.

Relevant information to be extracted will include details of the study characteristics (study design, enrolment dates, length of follow-up, funding source), population (number randomized, setting and region, inclusion and exclusion criteria, baseline characteristics), intervention and comparator (dose, route of administration, timing and frequency, description of co-interventions, adherence), outcomes (definitions and assessment methods, details of any scales used, timing of assessment) as well as relevant results (number randomized, analysis perspective; for example, intention to treat [ITT], analysis method, within and between-group results), and conclusion regarding the outcomes listed in Table 1. Where possible, data reporting on the ITT effect will preferentially be extracted. 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 (https://apps.automeris.io/wpd/). Extracting data from graphs and figures using software is more efficient, accurate, and reliable relative to manual extraction.[20,21]

Where multiple variations of the same outcome are reported in the included studies, we will collect the most clinically relevant definitions and timepoints for each outcome (based on clinical expert input, where needed), which will facilitate later synthesis of the findings. Wherever possible we will prioritize data reported according to established definitions as suggested by Rodeghiero and colleagues (2009).[1]

If data are not reported for an outcome, no assumption will be made about its presence or absence. Due to resource constraints, reviewers will not routinely contact authors of included studies to clarify any information or retrieve missing information.

Risk of Bias Assessment

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

- Outcome-level risk of bias of relevant randomized controlled trials (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).[22] This assessment tool facilitates the evaluation of potential

biases across 5 domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, 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).[23] This tool was chosen for ease of comparison to assessment of 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. A judgment of low, moderate, serious, or critical risk of bias will be assigned for each domain. The overall risk of bias of each study will be rated and designated based on the domain-level assessments. 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.

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, to ensure a mutual understanding of the tool and methodological intricacies across studies. 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 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, and if required from the protocols and registrations.

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 significant aspects of study methodology (study design, intervention, and comparator; selection, allocation and disposition of patients; outcome 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 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. 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

Prior to embarking on synthesis, we will tabulate the characteristics of the included studies, using standardized terminology and similar summary measures when possible, and present these in a table with accompanying textual summary. We will then chart the available studies and consider which are similar

enough in their PICO (including the time point of outcome measurement) elements to be grouped in the synthesis.

The data synthesis method will depend on the included studies and may consist of pairwise meta-analyses 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) prior to pooling. In the case that pairwise meta-analyses are feasible, studies will be pooled using the DerSimonian and Laird random effects models in RevMan Web.[24] Random effects approaches are generally considered most reasonable (vs. fixed effects) as they incorporate the assumption that studies are measuring heterogeneous but related effects.[25] Hazard ratios will be extracted (or computed)[26] for time-to-event data and will be pooled using the generic inverse-variance approach.[25] In the case of rare events (<1% event rate, e.g., for rare harms), the Peto odds ratio[27] will be considered in order to provide a less biased effect estimate.[28]

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. Hazard ratios and their 95% CIs will be reported for time-to-event outcomes. 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. For meta-analyses of binary outcomes, we will compute absolute effect estimates and present these as natural frequencies (e.g., per 1,000 patients) for ease of interpretation using standard formulas.[29]

If data required for meta-analysis are not reported by individual studies, these will be computed or calculated using other statistics presented in the reports based on available guidance;[30] suitable imputations (e.g., medians for means, missing standard deviations [SDs]) may be considered as needed.[25] If studies report on an outcome in a way that cannot be incorporated in a meta-analysis, their findings will be presented alongside the meta-analysis and compared to the pooled estimate of effect. Where possible, we will report within-study subgroup data for the prespecified population subgroups of interest. Additionally, we will explore heterogeneity within meta-analyses using between-study subgroup analyses, and interpret these carefully using available guidance.[31] When appropriate, sensitivity analyses will be performed to assess the robustness of the findings (e.g., for variability in risk of bias or study design across studies, differing outcome definitions) by removing studies from the analysis and checking whether the effect estimate differs. If any pooled analysis contains 10 or more studies of varying size,[32] small study bias will be investigated by visually inspecting funnel plots for asymmetry and using the Egger's regression test [33] or another appropriate test based on the summary measure of effect used in the analysis [32].

In the event that the included studies are deemed too heterogenous to combine statistically (e.g., differences in methods, outcome measures), the findings will be synthesized narratively considering the guidance by Popay et al.,[34] and the rationale for not pooling will be provided. We will begin by developing a preliminary

synthesis which will include organizing the studies by direction and size of effect. We will then explore within- and between-study relationships and consider factors (including the a priori subgroups) that might have influenced the direction and magnitude of observed effects. We will explore the robustness of the findings (e.g., considering the risk of bias of contributing studies) and draw a single final conclusion about our best estimate of the size and direction of the anticipated effect across studies.

Conclusions will be drawn for each outcome-comparison based on informal appraisals of the certainty of evidence, informed by elements of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[35] 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 one study contributes evidence for a comparison-outcome), the generalizability (or applicability) of the findings, and publication bias.

Opportunities for Stakeholder Feedback

Patient Engagement

CADTH involves patients, families, and patient groups to improve the quality and relevance of our assessments, ensuring that those affected by the assessments have an opportunity to contribute to them. CADTH has adopted a Framework for Patient Engagement in HTA. The framework includes Standards for Patient Involvement in Individual HTAs and is used to support and guide our activities involving patients and patient groups.

For this HTA on pediatric ITP, the belief that individuals who have experience with ITP have knowledge, perspectives, and experiences that are unique and contribute to essential evidence for HTA will guide our patient engagement activities.

Engagement Activities

CADTH will engage with patient group(s) who have experience with pediatric ITP. During the development of the protocol, the patient group(s) will be invited to discuss pediatric ITP and share their perspectives on the disease and the impact on patients and families. Upon completion of the protocol, patient group(s) will be sent the PICO table and asked to share their thoughts, particularly on the outcomes of greatest interest to patients. Upon completion of the report, patient groups will be invited to provide feedback and comment on the relevance of the findings to patients and families in Canada.

Stakeholder Feedback

Stakeholder feedback will be solicited at key steps throughout the systemic review process. As such, stakeholders will be given the opportunity to provide feedback on the draft included studies list and the draft

report, 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 review, reasons for changes and timing during the review will be recorded in a study file and subsequently reported in the PROSPERO record and 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

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Limits:

- 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
.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#	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
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term

Syntax	Description
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq=#	Requires terms to occur # number of times in the specified fields
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

Multidatabase Strategy

1. Purpura, thrombocytopenic/ or purpura, thrombocytopenic, idiopathic/
2. ((autoimmune* or immun* or idiopathic* or purpur*) adj2 thrombocytop*).ti,ab,kf.
3. (Werlhof* disease* or morbus werlhof*).ti,ab,kf.
4. ITP.ti,ab,kf.
5. or/1-4
6. Pediatrics/ or Hospitals, Pediatric/ or Intensive Care Units, Pediatric/ or Adolescent/ or exp Child/ or exp Infant/ or Pediatric Nursing/ or Child, Hospitalized/ or Adolescent, Hospitalized/
7. (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf.
8. (pediat* or paediat* or child* or adolescen* or juvenile*).jw.
9. or/6-8
10. (TPO RA* or TPORA* or thrombopoietin receptor agonist*).ti,kf.
11. (eltrombopag* or revolade* or promacta* or alvaiz* or DDL701 or DDL 701 or SB497 115 or SB 497 115 or SB 487115 or SB497115 or SSS20 or SSS 20 or ETB115 or ETB 115 or S56D65XJ9G).ti,ab,kf,rn,nm,hw,ot.
12. (romiplostim* or Nplate* or romiplate* or AMG531 or AMG 531 or GN5XU2DXKV).ti,ab,kf,rn,nm,hw,ot.
13. Rituximab/
14. (rituximab* or mabthera* or Rituxan* or GP2013 or GP 2013 or IDEC102 or IDEC 102 or "PF 05280586" or PF05280586 or RG105 or RG 105 or IDEC C2B8 or IDECC2B8 or truxima* or riximyo* or ruxience* or CTP10 or CT P10 or blitzima* or riabni* or ritemvia* or rituenza* or rixathon* or 4F4X42SYQ6).ti,ab,kf,rn,nm,hw,ot.

15. or/10-14
16. and/5,9,15
17. 16 use medall
18. Thrombocytopenic purpura/ or idiopathic thrombocytopenic purpura/
19. ((autoimmune* or immun* or idiopathic* or purpur*) adj2 thrombocytop*).ti,ab,kf,dq.
20. (Werlhof* disease* or morbus werlhof*).ti,ab,kf,dq.
21. ITP.ti,ab,kf,dq.
22. or/18-21
23. exp pediatrics/ or pediatric hospital/ or pediatric intensive care unit/ or exp adolescent/ or exp child/ or exp pediatric nursing/
24. (child* or infant* or baby or babies or newborn* or newborns or neonate or neonates or neonatal or preemie? or infancy or paediatric* or pediatric* or toddler* or girl? or boy? or kid? or teen or teens or teenage* or youngster? or youth* or preteen* or adolescent* or adolescence or preschooler* or pre-schooler* or nursery school* or daycare* or school age? or (months adj2 age) or (month? adj2 old) or preadolescen* or juvenile* or prepubescen* or prepubert* or pre-pubescen* or pre-pubert* or pre-adolescen*).ti,ab,kf,dq.
25. (pediat* or paediat* or child* or adolescen* or juvenile*).jx.
26. or/23-25
27. (TPO RA* or TPORA* or thrombopoietin receptor agonist*).ti,kf.
28. *Eltrombopag/
29. (eltrombopag* or revolade* or promacta* or alvaiz* or DDL701 or DDL 701 or SB497 115 or SB 497 115 or SB 487115 or SB497115 or SSS20 or SSS 20 or ETB115 or ETB 115).ti,ab,kf,dq.
30. *Romiplostim/
31. (romiplostim* or Nplate* or romiplate* or AMG531 or AMG 531).ti,ab,kf,dq.
32. *Rituximab/
33. (rituximab* or mabthera* or Rituxan* or GP2013 or GP 2013 or IDEC102 or IDEC 102 or "PF 05280586" or PF05280586 or RG105 or RG 105 or IDEC C2B8 or IDECC2B8 or truxima* or riximyo* or ruxience* or CTP10 or CT P10 or blitzima* or riabni* or ritemvia* or rituenza* or rixathon*).ti,ab,kf,dq.
34. or/27-33
35. and/22,26,34
36. 35 use oemezd
37. conference abstract.pt.
38. 36 not 37
39. or/17,38
40. remove duplicates from 39

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 | eltrombopag, romiplostim, pediatric ITP]

WHO ICTRP

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

[Search terms -- eltrombopag, romiplostim, pediatric ITP]

Health Canada's Clinical Trials Database

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

[Search terms -- eltrombopag, romiplostim, pediatric ITP]

EU Clinical Trials Register

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

[Search terms -- eltrombopag, romiplostim, pediatric ITP]

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 -- eltrombopag, romiplostim, pediatric ITP]

Grey Literature

Keywords: eltrombopag, romiplostim, pediatric ITP

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 will be 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.