CADTH Health Technology Review

Treatment of Adult Patients With Immune Thrombocytopenia After Failure of First-Line Therapies: Project Protocol

PROSPERO Registration Number: Submitted, registration not yet received.
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Abbreviations

HTA    health technology assessment
ITP    immune thrombocytopenia
IVIG   intravenous immunoglobulin
NMA    network meta-analysis
QALY   quality-adjusted life-year
TPO-RA thrombopoietin receptor agonist
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. It was previously called idiopathic thrombocytopenic purpura; however, it is no longer considered an idiopathic disease and some patients may not experience bleeding such as purpura (skin hemorrhage). Primary ITP is characterized by isolated thrombocytopenia (peripheral blood platelet count < $100 \times 10^3$/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. ITP falls into 3 disease groups: newly diagnosed ITP (0 to 3 months), persistent ITP (3 to 12 months), and chronic ITP, which is defined as ongoing, active disease at 12-month follow-up.

ITP has an incidence rate of 5 per 100,000 to 10 per 100,000 children per year and 3.3 per 100,000 adults per year. It occurs predominantly in women with a female to male ratio of 2:1. At diagnosis, 90% of children and 69% of adults will have bleeding symptoms. The bleeding will be severe (e.g., bleeding in the gastrointestinal tract or in the brain) in 20% of children and in approximately 10% of adults. The mean platelet count at presentation is $18.1 \times 10^3$/L for children and $25.4 \times 10^3$/L in adults. More than 30% of adults and approximately 4% of children will present with 1 or more comorbid conditions.

The cause of ITP is unknown; there may be genetic and/or environmental risk factors (such as infections with Helicobacter pylori, hepatitis C virus, or HIV). A family history of thrombocytopenia is seen in 2% of children and 3% of adults. Spontaneous remission occurs when there is an improved platelet count in the absence of ongoing or recent therapy. Spontaneous remission occurs in 70% and 45% of children and adults, respectively, at 6 months and in 71% and 49% of children and adults, respectively, at 12 months. Among those with chronic ITP, 28% of children and 30% of adults achieve remission at 24 months.

First-line therapies considered are intravenous immunoglobulin (IVIG), corticosteroids, and anti-D immunoglobulin. The American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia recommends a short course of corticosteroids as first-line treatment in newly diagnosed adult patients with a platelet count of < $30 \times 10^3$/L and no or minor mucocutaneous bleeding. An update to the International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia was published in 2019. For newly diagnosed adult patients, the report suggests administering a short course of corticosteroids. For those patients who are unresponsive or have a contraindication to corticosteroids, IVIG or anti-D immunoglobulin may be used. Thrombopoietin receptor agonists (TPO-RA) (e.g., romiplostim, eltrombopag) or rituximab are not recommended as initial treatments.

Second-line therapies are considered when patients do not respond to first-line therapies. In adult patients with ITP for 3 to 12 months (persistent ITP) who are corticosteroid-dependent or unresponsive to corticosteroids, the guidelines recommend treating with a TPO-RA (romiplostim, eltrombopag) or rituximab. For adult patients with chronic ITP (duration greater than 12 months), the guidelines recommend 1 of 3 treatment modalities: TPO-RA (romiplostim, eltrombopag), rituximab, or splenectomy. The choice of treatment will depend on patient preferences, such as whether they prefer a durable response, to avoid long-term medication, or to avoid surgery. These recommendations are all based on evidence of low to very low quality. Refractory ITP is characterized by non-response to splenectomy or relapse after surgery, with a high risk of bleeding that requires continued...
treatment. Recommended subsequent treatments include eltrombopag, avatrombopag, romiplostim, fostamatinib (a spleen tyrosine kinase inhibitor), rituximab, or surgery (splenectomy to be performed only after 12 months to 24 months from diagnosis), all of which, the international working group states, have robust evidence.

The American Society of Hematology guidelines do not provide recommendations on drugs that may be used as second-line treatments, including azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone mycophenolate mofetil, and the vinca alkaloids, because of limitations of the current evidence (small sample sizes of studies and heterogeneous patient populations).

The federal, provincial, and territorial public drug plans have requested an evaluation on the comparative evidence of available treatments for adults with ITP who have already received first-line therapies (i.e., corticosteroids, IVIG, and/or anti-D immunoglobulin) and the place in therapy of splenectomy.

Project Scope and Protocol Development

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

Objective

CADTH will undertake a Health Technology Assessment to review the effectiveness and cost-effectiveness of treatments for ITP in adults after failure of first-line treatments. A secondary objective will be to determine the place in therapy of splenectomy.

Deliverables

The following deliverables are planned:

- a Science Report, including a clinical evaluation and an economic evaluation
- a budget impact analysis may be considered, in consultation with the requestor, if an economic evaluation is not deemed feasible.

Policy Questions

The following policy questions will be addressed by this project:

1. What treatment(s) should be used in adult patients with immune thrombocytopenia who have failed first-line treatments?
2. What is the place in second-line therapy of splenectomy in adult patients with immune thrombocytopenia?
Research Questions

The project will address the following research questions. Details on the specific interventions and outcomes are included in Table 1 (Selection Criteria).

1. What is the efficacy and safety of therapies in adult patients with immune thrombocytopenia who have failed first-line treatments?

2. What is the efficacy and safety of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RA [romiplastim, eltrombopag, avatrombopag]) in adult patients with immune thrombocytopenia?

3. What is the cost-effectiveness of therapies in adult patients with immune thrombocytopenia who have failed first-line treatments?

4. What is the cost-effectiveness of splenectomy compared with second-line therapies (rituximab, fostamatinib, or TPO-RA [romiplastim, eltrombopag, avatrombopag]) in adult patients with immune thrombocytopenia?

Methods

Clinical Review

Literature Search Methods

The literature search for clinical studies will be performed by an information specialist using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist. The complete search strategy is presented in Appendix 1.

Published literature will be identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and the Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid. All Ovid searches will be run simultaneously as a multi-file search. Duplicates will be removed using Ovid deduplication for multi-file 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 ITP and rituximab, fostamatinib, TPO-RA (romiplastim, eltrombopag, avatrombopag), or splenectomy. 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, and the European Union Clinical Trials Register.

CADTH-developed search filters will be applied to limit retrieval to health technology assessments (HTAs), systematic reviews, meta-analyses or network meta-analyses, and randomized controlled trials or controlled clinical trials. 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 summer 2021. 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 checklist**,11 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.

**Data Source**

The primary source of data will be those published or in the grey literature. All stakeholders will be given the option of identifying and providing additional data.

**Eligibility Criteria**

**Study Selection**

Two reviewers will independently screen titles and abstracts for relevance to the clinical research questions. Full texts of potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the pre-determined selection criteria (Table 1). The 2 reviewers will then compare their chosen included and excluded studies; disagreements will be discussed until consensus is reached. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

**Inclusion and Exclusion Criteria**

Drug regimens eligible for inclusion in the review are those that have been approved by Health Canada for ITP or are considered of clinical relevance based on expert advice or international clinical practice guidelines. Therapies of interest to this review are presented in Table 1.
### Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Population** | Adult patients with ongoing, active ITP who have failed first-line treatments  
Subgroups of interest:  
• adult patients with chronic ITP (> 12 months)  
• adult patients with persistent ITP (between 3 to 12 months)  
• adult patients who have previously failed at least 1 second-line therapy |
| **Interventions** | • Rituximab<sup>a,b</sup>  
• Eltrombopag  
• Romiplostim  
• Fostamatinib  
• Avatrombopag  
• Splenectomy |
| **Comparators** | • Above interventions against each other  
• IVIG  
• Immunosuppressants (azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone)  
• Corticosteroids  
• Placebo and/or standard of care |
| **Outcomes**    | Clinical effectiveness:  
• platelet count response  
• time to platelet response  
• bleeding events  
• emergency department visits  
• hospitalization  
• health-related quality of life  
• symptoms (e.g., fatigue)  
• treatment-free remission  
• need for rescue medication (e.g., IVIG, corticosteroids, platelet transfusions)  
• reduction or discontinuation of corticosteroids  
• mortality  
Safety:  
• adverse events, serious adverse events, withdrawal due to adverse events, death  
• notable harm: infection |
| **Study design** | Phase III and phase IV randomized controlled trials |

**ITP** = immune thrombocytopenia; **IVIG** = intravenous immunoglobulin.

<sup>a</sup> Rituximab dose for ITP: 375 mg/m<sup>2</sup> IV infusion once a week for 4 weeks (4 total doses; days 1, 8, 15, and 22). There is also a lower dose that can be used for ITP: 100 mg IV infusion once a week for 4 weeks (4 total doses; days 1, 8, 15, and 22).

<sup>b</sup> Includes biosimilars.

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**Data Extraction and Critical Appraisal**

Study and participant characteristic data will be extracted by 1 reviewer and verified by a second reviewer using a standardized data extraction form developed a priori, which will be piloted and modified as necessary:

- study characteristics, inclusion and exclusion criteria, and definitions if required
- baseline patient characteristics
- interventions evaluated, including dose, duration, route of administration, and concurrent and previous relevant therapies
• type of analysis (e.g., intention-to-treat, safety population, per protocol)
• clinical safety and efficacy and effectiveness outcomes

Study-specific outcomes data will be extracted independently by 2 reviewers. Any disagreements will be resolved through discussion and consensus with a third reviewer, if necessary.

The primary publication for each unique study included will be used for data extraction, except when multiple publications for a single primary study are found. Multiple publications for a unique study (e.g., substudies, reports of additional outcomes or longer follow-up) will be used if they include data relevant to our research question. The data will adjudicated under the main study publication, but the related articles will be referenced as needed.

Quality Assessment

Risk of bias in the individual trials will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool or other appropriate tool. Risk of bias assessments will be completed in duplicate for each trial. The risk of bias assessments will include assessing the randomization process, deviations from intended interventions, missing outcome data, and measurement of the outcome as well as bias in selection of the reported results. We do not anticipate including any crossover or cluster randomized controlled trials. For each of these domains, a judgment of high risk of bias (the study is judged to be at high risk of bias in at least 1 domain or some concerns for multiple domains), some concerns (the study is judged to raise some concerns in at least 1 domain, but not at high risk of bias for any domain) or low risk of bias (the study is judged to be at low risk of bias from all domains) can be made. If we find any crossover or cluster trials, we will only use estimates that account for the correlation between participants in cluster trials and within participants in crossover trials. For each trial, the estimate of the effect of randomization, such as intention-to-treat versus the effect of adhering to the intervention (per protocol), will be considered. The robvis tool for visualizing risk of bias will be used to display the results of these assessments. Overall risk of bias will be used as the basis for sensitivity analyses; we will drop the studies at high risk of bias and examine how this affects the results.

In addition to searching for unpublished and ongoing studies, we will investigate small-study effects using Harbord test for binary outcomes and Egger test for continuous outcomes. We will also inspect the network funnel plot for asymmetry.

Data Analysis and Synthesis

A qualitative feasibility assessment will be performed before the network meta-analysis (NMA) to assess clinical and methodological heterogeneity in the available data. Trials included in the same evidence network will be compared to identify any potential heterogeneity based on differences in participants, interventions, comparisons, outcomes, or study design. If substantial heterogeneity exists in certain comparisons or subsets of studies, and the data are not meaningful to pool, narrative summaries of findings will be reported, including the report on the types of trials required to fill the knowledge gap. Quantitative analyses will not be conducted if there is insufficient data. The qualitative assessment of feasibility will be determined through close collaboration between the reviewers, methodologists, and clinical experts working on the HTA.

If feasible, we will evaluate the efficacy and safety of the interventions and comparators outlined in Table 1 through an indirect treatment comparison using NMA. However, if data
on any outcomes listed in Table 1 are limited, meta-analysis of direct comparisons will be provided. If NMA or direct comparisons are not feasible, narrative syntheses will be performed, including the presentation of study characteristics and findings within summary tables and in the main text. Findings will be summarized within and across studies (by comparator), including the direction and magnitude of any observed effects, trends, and deviations, and an assessment of the likelihood of clinical benefit. Data from different populations or different time points will not be combined but rather described separately.

The NMAs will be conducted under a frequentist framework using the multivariate meta-analysis approach. Random-effects models will be used as the primary approach if feasible because of the anticipated clinical and methodological heterogeneity across studies. For sparse networks, fixed-effects models will be considered if the available network for a given outcome is insufficient for estimating a random-effects model (i.e., the confidence intervals are inaccurate). For each NMA, we will use the design-by-treatment model (global test) to assess network coherence and the side-splitting method to assess loop-specific coherence, computed as the difference between direct and indirect evidence. If there is large incoherence, we will use an inconsistency model to conduct the NMA.

The multivariate random-effects meta-analysis will be estimated using restricted maximum likelihood applied to arm-based or contrast-based data. The results will be presented as network plots, contribution plots, and league tables.

If an NMA is not feasible, we will conduct a pairwise random-effects meta-analysis, comparing all available treatments to placebo or to the most common (i.e., reported in most studies) available comparison or the most relevant standard of care.

For binary outcomes, odds ratios and 95% confidence intervals will be reported. In cases when events are rare, the Peto odds ratio will be used. For continuous outcomes measured on the same scale, mean differences and 95% confidence intervals will be reported. For continuous outcomes measured on different scales, standardized mean differences and 95% confidence intervals will be reported. If insufficient data are found for conducting meta-analyses, narrative descriptions will be provided.

For the network or pairwise meta-analysis, we will conduct subgroup analyses comparing outcomes in trials belonging to the following subgroups:

- adult patients with chronic ITP (> 12 months)
- adult patients with persistent ITP (between 3 and 12 months)
- patients who have previously failed at least 1 second-line therapy.

We will also conduct a sensitivity analysis by excluding studies with high risk of bias or studies with missing data to a relevant outcome. We will also explore the effect of outliers and influential trials by running models with and without them. All analyses will be conducted using Stata 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). All comparisons will be 2-tailed using a threshold of $P < 0.05$. 

...
Economic Analysis

Economic Evaluation
An economic evaluation will be conducted to evaluate the cost-utility of various treatments for adult patients with ITP.

Primary Economic Analysis
A de novo decision analytic model will be developed to assess the costs and health outcomes associated with the various treatment options for patients with ITP in Canada. Treatment options for the economic model will be determined based on data availability, relevance for Canadian clinical practice, and feedback from the clinical experts and members of the Formulary Working Group for HTA. The interventions considered will align with those in the clinical review, should data be available, and will include rituximab, eltrombopag, romiplostim, fostamatinib, avatrombopag, and splenectomy.

The patient cohort will be described by clinical characteristics identified in the clinical review and Canadian real-world data. Separate patient subgroups may be assessed based on feedback from clinical experts consulted for this project and the availability of subgroup data.

If there is insufficient clinical data to inform a cost-utility analysis, a budget impact analysis will be performed.

Model Design
An economic model will be developed to describe the movement of patients between health states reflective of the typical clinical pathway of ITP. During a patient’s lifetime, their ITP may fall into remission, recur, or deteriorate to refractory ITP (defined as non-response to splenectomy or relapse after surgery with a high risk of bleeding). The model(s) used will evaluate the most cost-effective treatment in 3 distinct populations: those who have had first-line treatment failure, those with persistent ITP, and those with chronic ITP.

A Markov cohort or microsimulation model will be developed that depicts health states relevant to the natural history of ITP and the long-term effects of treatment. Health states may include, but are not limited to, controlled ITP (platelet count of ≥ 50 × 10^9/L), remission, uncontrolled ITP (platelet count remains < 50 × 10^9/L), and death. If a Markov cohort model is used, a cycle length of 2 months may be selected because it reflects the earliest time point that clinical experts can discontinue treatment due to unresponsive platelet counts.

Depending on availability, real-world data may be used in the base case. Specifically, time on treatment and overall survival data from patients treated in Canadian clinical practice are parameters of interest to ensure generalizability. Furthermore, real-world data may be used to inform baseline parameters describing patient characteristics.

Further details of the model will be developed based on feedback from the CADTH clinical review team and consultation with clinical experts to ensure that it reflects current clinical literature and clinical practice. Checks on the internal and external validity of the model will be performed to assess for any logical discrepancies.
**Perspective**

The primary perspective in the model will be that of a publicly funded health care system (i.e., a provincial ministry of health).

**Resource Use and Cost Data**

The costs captured in the model will reflect the scope of the project and the perspective of the economic analysis. Costs will include those related to the treatment regimens (e.g., drug costs, administration costs, inpatient and day surgery costs, and professional fees), disease management (e.g., hospitalizations, outpatient visits, laboratory and diagnostic testing), and event-related costs (e.g., adverse events of treatment), as well as any other relevant costs identified in consultation with clinical experts and the literature.

Canadian-specific costs will be used, if available. If unavailable, costs will be estimated from the medical literature, with preference for settings with comparable health systems to Canada. If necessary, costs will be adjusted to 2021 Canadian dollars, using the general Consumer Price Index in Canada.

**Utilities**

Utilities associated with each health state and the disutility of complications will be obtained from a focused literature search, and expert opinion may be used if the data are not available. Canadian sources are preferred, if available.

**Clinical Parameters**

Parameters describing the natural history of patients with ITC will be identified from peer-reviewed medical literature. Estimates of the comparative clinical efficacy of individual treatment may be informed by an NMA from the clinical review, and its 95% credible interval may be used to incorporate uncertainty of the effectiveness of the treatments. In cases in which no data are available to describe the impact of treatments to certain clinical outcomes, a clinical expert will be consulted.

**Outcomes**

The expected costs and quality-adjusted life-years (QALYs) associated with different treatment strategies over the model’s time horizon will be estimated. QALYs will represent the main clinical outcome modelled because this single measure is multi-dimensional and can capture the effect of the disease and its treatment on patient morbidity and mortality. The primary economic outcome calculated will be the incremental cost-effectiveness ratios, measured in terms of the incremental cost per QALY gained.

In addition, costs and QALYs will be reported in a disaggregate manner. Additional outcomes, such as life-years and time on each line of treatment, will also be reported.
**Time Horizon and Discounting**

ITP can last several years to a lifetime and treatment duration varies; rituximab treatment primarily consists of 4-week infusions, while treatment with fostamatinib, romiplostim, and eltrombopag targets a minimum of 1 year. The time horizon selected will ensure all relevant costs and health outcomes are captured in the model.

Per existing guidelines, discounting will be set at 1.5% per year for both costs and QALYs, with sensitivity analysis conducted on this value (e.g., 0% and 5%).

**Sensitivity Analysis**

The base-case analysis will represent the probabilistic findings, capturing the extent to which parameter uncertainty may impact the incremental cost-effectiveness findings. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability curve, whereby treatments on the efficiency frontier will be highlighted across different willingness-to-pay thresholds. Uncertainty in the model will be further evaluated in several ways.

Scenario and subgroup analyses will be performed to evaluate key model assumptions while retaining the model’s probabilistic element. Potential scenarios of interest may include different scenarios from the NMA that inform the treatment effectiveness parameters (e.g., random-effect versus fixed-effect NMA), alternate time horizons, different treatment duration times, and testing of structural assumptions. Further scenarios will be discussed with clinical experts.

**Assumptions**

During the development of the economic model, assumptions and limitations will be identified and acknowledged in the report. If possible, assumptions will be tested by conducting the appropriate sensitivity analyses.

**Opportunities for Stakeholder Feedback**

Stakeholders were given the opportunity to comment on the proposed project scope that informed this protocol. Stakeholders will be given the opportunity to provide feedback on the list of included studies and a draft report.

**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, the previous literature search will be re-screened or an updated literature search will be performed to capture additional data according to the amendments.
References


Appendix 1: Literature Search Strategy

Draft 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: Summer 2021

Alerts: Monthly search updates until project completion

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

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

Table 2: Syntax Guide

<table>
<thead>
<tr>
<th>Syntax</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>/</td>
<td>At the end of a phrase, searches the phrase as a subject heading</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Heading</td>
</tr>
<tr>
<td>exp</td>
<td>Explode a subject heading</td>
</tr>
<tr>
<td>*</td>
<td>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</td>
</tr>
<tr>
<td>adj#</td>
<td>Requires terms to be adjacent to each other within # number of words (in any order)</td>
</tr>
<tr>
<td>.ti</td>
<td>Title</td>
</tr>
<tr>
<td>.ot</td>
<td>Original title</td>
</tr>
<tr>
<td>.ab</td>
<td>Abstract</td>
</tr>
<tr>
<td>.hw</td>
<td>Heading word; usually includes subject headings and controlled vocabulary</td>
</tr>
<tr>
<td>.kf</td>
<td>Author keyword heading word (MEDLINE)</td>
</tr>
<tr>
<td>.kw</td>
<td>Author keyword (Embase); keyword (CDSR)</td>
</tr>
<tr>
<td>.dq</td>
<td>Candidate term word (Embase)</td>
</tr>
<tr>
<td>.pt</td>
<td>Publication type</td>
</tr>
<tr>
<td>.rn</td>
<td>Registry number</td>
</tr>
<tr>
<td>.nm</td>
<td>Name of substance word (MEDLINE)</td>
</tr>
<tr>
<td>.yr</td>
<td>Publication year</td>
</tr>
<tr>
<td>medall</td>
<td>Ovid database code: MEDLINE All, 1946 to present, updated daily</td>
</tr>
<tr>
<td>oemezd</td>
<td>Ovid database code: Embase, 1974 to present, updated daily</td>
</tr>
</tbody>
</table>
Multi-Database Strategy

**Search strategy**

1. (romiplostim* or Nplate* or Romiplate* or amg531 or amg 531 or amgen megakaryopoiesis protein 531 or GN5XU2DXKV).ti,ab,kw,ot,hw,nm,rm.
2. (eltrombopag* or Revolade* or Promacta* or Elbonix* or SB-497115 or SB497115 or SB-497-115 or SSS-20 or SSS20 or HSDB-8212 or HSDB8212 or S56D65XJ9G).ti,ab,kf,kw,ot,hw,nm,rm.
3. (avatrombopag* or Doptelet* or AKR 501 or AKR501 or E 5501 or E5501 or AS 1670542 or AS1670542 or YM 477 or YM477 or 3H8GSZ4SQL or GDW7M2P1IS).ti,ab,kf,kw,ot,hw,nm,rm.
4. (((thrombopoietin or TPO) adj2 (receptor agonist* or RA or RAs)) or TPORA or TPORAS).ti,ab,kf,kw.
5. Rituximab/ or (rituximab* or Rituxan* or Truxima* or MabThera* or MabThera* or Truxima* or blizima* or reditux* or ritemvia* or rituxin* or rituzena* or rixathon* or riximyo* or truxella* or riabni* or rituenza* or ritumax* or ruxience* or hycela* or acellbia* or abp798 or abp798 or "hlx 01" or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDECC2B8 or IDECC2B8 or PF-05280586 or PF05280586 or PF-5280586 or PF5280586 or RO-452294 or RO452294 or RG105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kf,kw,ot,hw,nm,rm.
6. (fostamatinib* or Tavilisste* or Tavlesse* or R935788 or R788 or R-788 or SQ8A3S5101 or 86EEZ49YVB or X9417132K8 or R406 or R406 or R950091 or R 950091 or tamatlinib fosdium).ti,ab,kf,ot,hw,nm,rm.
7. Splenectomy/ or (splenectom* or (spleen* adj2 (removal or resection))).ti,ab,kf,kw.
8. ((secondary or tertiary or failure or failed) adj3 (therap* or treatment*)).ti,ab,kf,kw.
9. (second-line or secondline or third-line or thirdline).ti,ab,kf,kw.
10. or/1-9
11. Purpura, thrombocytopenic/ or idiopathic thrombocytopenic purpura/ 
12. ((autoimmune* or immum* or idiopathic* or purpur*) adj2 thrombocytop*).ti,ab,kf,kw.
13. (Werlhof disease* or morbus werlhof*).ti,ab,kf,kw.
14. ITP.ti,ab,kf,kw.
15. or/11-14
16. 10 and 15
17. 16 use cctr
18. 16 use medall
19. *(romiplostim/ or (romiplostim* or Nplate* or Romiplate* or amg531 or amg 531 or amgen megakaryopoiesis protein 531 or GN5XU2DXKV).ti,ab,kw,dq.
20. *(eltrombopag/ or (eltrombopag* or Revolade* or Promacta* or Elbonix* or SB-497115 or SB497115 or SB-497-115 or SSS-20 or SSS20 or HSDB-8212 or HSDB8212).ti,ab,kw,dq.
21. *(avatrombopag/ or (avatrombopag* or Doptelet* or AKR 501 or AKR501 or E 5501 or E5501 or AS 1670542 or AS1670542 or YM 477 or YM477 or 3H8GSZ4SQL or GDW7M2P1IS).ti,ab,kw,dq.
22. (((thrombopoietin or TPO) adj2 (receptor agonist* or RA or RAs)) or TPORA or TPORAS).ti,ab,kw,dq.
23. *rituximab* or (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 riximyo* or truxella* or riabni* or rituenza* or ritumax* or tuxella* or ruxience* or hycela* or acellbia* or abp 798 or abp798 or "hix 01" or hlx01 or SAIT101 or SAIT 101 or GP2013 or GP 2013 or mk 8808 or mk8808 or HSDB 7455 or HSDB7455 or IDEC-102 or IDEC102 or IDECC2B8 or IDEC-C2B8 or PF-05280586 or PF05280586 or RO-452294 or RO452294 or RG-105 or RG105 or CT-P10 or CTP10 or 4F4X42SYQ6).ti,ab,kw,dq.
24. *fostamatinib* or (fostamatinib* or Tavalisse* or Tavlesse* or R935788 or R788 or R-788 or SQ8A3S5101 or 86EEZ49YVB or X9417132K8 or R 406 or R406 or R950091 or R 950091 or tamatinib fosdium).ti,ab,kw,dq.
25. Splenectomy/ or (splenectom* or (spleen* adj2 (removal or resection))).ti,ab,kw,dq.
26. (secondary or tertiary or failure or failed) adj3 (therap* or treatment*).ti,ab,kw,dq.
27. (second-line or secondline or third-line or thirdline).ti,ab,kw,dq.
28. or/19-27
29. thrombocytopenic purpura/ or idiopathic thrombocytopenic purpura/
30. (autoimmune* or immun* or idiopathic* or purpur*) adj2 thrombocytop*.ti,ab,kw,dq.
31. (Werlhof disease* or morbus werlhof*).ti,ab,kw,dq.
32. ITP.ti,ab,kw,dq.
33. or/29-32
34. 28 and 33
35. 34 use oemezd
36. (conference abstract or conference review).pt.
37. 35 not 36
38. (systematic review or meta-analysis).pt.
39. 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/
40. (systematic* adj3 (review* or overview*))) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
41. ((quantitative adj3 (review* or overview* or syntheses*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
42. (integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*).ti,ab,kf,kw.
43. (data syntheses* or data extraction* or data abstraction*).ti,ab,kf,kw.
44. (handsearch* or hand search*).ti,ab,kf,kw.
45. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
46. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
47. (meta regression* or metaregression*).ti,ab,kf,kw.
48. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
49. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
50. (cochrane or (health adj2 technology assessment) or evidence report).jw.
51. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
52. (outcomes research or relative effectiveness).ti,ab,kf,kw.
53. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
54. (multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
55. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
56. umbrella review*.ti,ab,kf,kw.
57. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
58. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
60. or/38-59
61. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
62. Randomized Controlled Trial/
63. exp Randomized Controlled Trials as Topic/
64. "Randomized Controlled Trial (topic)"
65. Controlled Clinical Trial/
66. exp Controlled Clinical Trials as Topic/
67. "Controlled Clinical Trial (topic)"
68. Randomization/
69. Random Allocation/
70. Double-Blind Method/
71. Double Blind Procedure/
72. Double-Blind Studies/
73. Single-Blind Method/
74. Single Blind Procedure/
75. Single-Blind Studies/
76. Placebos/
77. Placebo/
78. Control Groups/
79. Control Group/
80. (random* or sham or placebo*).ti,ab,hw,kf,kw.
81. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
82. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
83. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
84. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
85. allocated.ti,ab,hw.
86. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
87. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
88. (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
89. (pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
90. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
91. (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
92. or/61-91
93. 60 or 92
94. 18 and 93
95. 37 and 93
96. 94 or 95
97. limit 96 to (english or french)
98. 17 or 97
99. remove duplicates from 98

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 | ITP or immune thrombocytopenia]

Health Canada’s Clinical Trials Database
Produced by Health Canada. Targeted search used to capture registered clinical trials.
[Search – Studies with results | ITP or immune thrombocytopenia]

EU Clinical Trials Register
European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search – Studies with results | ITP or immune thrombocytopenia]

Grey Literature

Search dates: Summer 2021

Keywords: ITP or immune thrombocytopenia

Limits: Publication years: 1996-present

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 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

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