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CADTH Health Technology Review

Thrombopoietin Receptor Agonists as Second-Line Treatment in Children with Ongoing Immune Thrombocytopenia

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Abbreviations

AE	Adverse events
DB	Double blind
HRQoL	Health-related quality of life
HTA	Health technology assessment
ITP	Immune thrombocytopenia
ITT	Intent to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
KIT	Kid's ITP Tools questionnaire
PICOS	Population(s), Intervention(s), Comparator(s), Outcome(s), Study Design(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SAE	Serious adverse event
SC	Subcutaneous
TPO-RA	Thrombopoietin receptor agonist
WHO	World Health Organization

Key Messages

What is the problem?

- Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelets and an increase in bleeding risk; in the pediatric population, the reported incidence rate varies between 2 and 5 per 100,000 children per year. Spontaneous remission may be observed in up to 70% of patients, while 20% of patients may experience severe bleeding symptoms.
- In children who do not respond to first-line corticosteroids, intravenous immunoglobulin (IVIG) or anti-D immunoglobulin, guidelines[1,2] recommend the use of thrombopoietin receptor agonists (TPO-RAs), i.e., eltrombopag or romiplostim (avatrombopag was not included as it did not hold a Health Canada indication at the time this review was performed). Rituximab is considered a subsequent-line therapy, with high value placed on avoiding immunosuppression. Splenectomy is not usually considered an appropriate treatment option in children.
- The ultimate goal of therapy in pediatric patients with ITP is to reduce bleeding and improve quality of life. Platelet response is considered a valid and appropriate surrogate[3] to these treatment goals, both for study conduct and routine assessment in clinical practice.
- There is an unmet need in children who did not respond to first-line therapy; without access to TPO-RAs, patients are being exposed to subsequent-line off-label therapies, with uncertainty surrounding their effectiveness and numerous potential harms such as immunosuppression.

What did we do?

- A systematic review of the literature identified 5 studies (4 randomized controlled trials [RCTs] and 1 observational study), which were synthesized narratively.
- The review addressed the following policy questions:
  - In children with ongoing active ITP, what is the overall body of evidence supporting the use of TPO-RAs 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, instead of being required to try a course of rituximab prior to accessing eltrombopag or romiplostim?

What did we find?

- Evidence from two RCTs (n = 159) suggests that eltrombopag likely increases and maintains platelet response over time, in addition to decreasing the use of rescue medication and clinically significant bleeding compared to placebo, which were considered clinically meaningful to pediatric patients with ITP. There was a low risk of bias in the studies, but uncertainty was introduced due to the small sample sizes.
- Evidence from one RCT (n = 62) suggests that romiplostim may also increase and maintain platelet response, as well as reduce clinically significant bleeding compared to placebo; however, there was some concern to a high risk of bias in the studies, and uncertainty was introduced due to the small sample size, which suggests some caution in the interpretation of the findings. One additional pilot RCT (n = 18) comparing romiplostim to placebo was included in the systematic review, but contributed only minimally to the available evidence.
- Due to the scarcity of evidence in the patient population, conclusions could not be drawn for the impact of TPO-RAs on HRQoL and function in children.
- Assessment of the effectiveness of rituximab was inconclusive due to the lack of evidence, as no comparative RCTs could be identified, while the observational study included only presented descriptive comparisons. In addition, no evidence was identified in support of trying rituximab prior to accessing TPO-RAs. Considering the balance of benefits, harms, patient preference and feasibility, relevant guidelines[1,2] recommend the use of rituximab as a subsequent-line therapy (after TPO-RAs). This guideline recommendation is conditional, based on very low certainty evidence (no available direct comparisons).

What does this mean?

- Decision-makers may consider tolerating a greater level of uncertainty when interpreting the findings and drawing conclusions regarding the use of eltrombopag and romiplostim. ITP is a rare disease in children and large RCTs in this patient population are unlikely to be conducted.
- Jurisdictions may consider requesting an implementation advice panel or expert committee reimbursement recommendation for eltrombopag and romiplostim, for use after failure of first-line therapies in children with ongoing active ITP.

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Executive Summary

Background and Policy Context

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelets and an increase in bleeding risk.[3-6] In the pediatric population, the reported incidence rate varies between 2 and 5 per 100,000 children per year.[7] ITP differs between the adult and pediatric populations; both spontaneous remission and severe bleeding are substantially more frequent in children than in adults.[8-10]

First-line therapy may include observation, but in the presence of non–life threatening mucosal bleeding or bleeding that impacts quality of life, first-line therapy is a short course of corticosteroids.[1,2] Alternatively, intravenous immunoglobulin (IVIG) and anti-D immunoglobulin may be used in patients who are unresponsive or have a contraindication to taking corticosteroids.[1,2] Considering the balance of benefits and harms, costs, patient preference and feasibility, guidelines suggest that thrombopoietin receptor agonists (TPO-Ras; eltrombopag or romiplostim) are the preferred second-line therapy in pediatric patients who do not respond to first-line treatment; rituximab would be considered a subsequent-line therapy, with a high value being placed on avoiding immunosuppression in this population.[1,2] Splenectomy is usually not an appropriate treatment option in children.[1,2]

A systematic review was undertaken at the request of public drug plans to determine what treatment(s) should be used in pediatric patients with ITP who have failed first-line treatments. For jurisdictions, knowing the level of evidence for, and efficacy of, TPO-RAs will add to what is currently known and may help inform decision-making regarding the reimbursement of these agents.

Clinical Evidence

The research protocol was developed a priori, by engaging with patient groups and clinical experts, and the systematic review used robust methodology. Eight publications were identified, reporting findings from 5 unique studies. The populations in the studies contributing to the evidence were considered generalizable to most children with ITP in the clinical setting. A narrative synthesis was conducted due to clinical and methodological heterogeneity between studies that precluded an indirect treatment comparison. Avatrombopag was not included as it did not hold a Health Canada indication at the time this review was performed.

Evidence from two double blind (DB) RCTs (n= 159) suggests that eltrombopag likely results in a clinically important, long-lasting platelet response when compared to placebo (at least 6 weeks and up to 12 months) in pediatric patients with ITP who have failed first-line treatments. Eltrombopag also likely results in a reduction in the use of rescue medication and clinically significant bleeding compared to placebo, which were considered clinically meaningful to patients. There is a low risk of bias in the studies, but uncertainty is introduced due to the small sample size. Evidence from one DB RCT (n=62) suggests that romiplostim may result in a clinically important, long-lasting platelet response and reduction in clinically significant bleeding, when compared to placebo (at least 24 weeks and up to 12 months); however, there is some concern to a high risk of bias and uncertainty was introduced due to the small sample size, which suggests a need for caution in the interpretation of the findings.

Due to the scarcity of evidence in the patient population, conclusions could not be drawn for the impact of TPO-RAs on HRQoL and function in children. Assessment of the effectiveness of rituximab was inconclusive due to the lack of evidence, as no comparative RCTs could be identified, while the 1 observational study included only presented descriptive within-arm data (i.e., no direct comparisons). In addition, no evidence was identified in support of trying rituximab prior to accessing TPO-RAs.

Limitations

The review was based on limited availability of evidence. No head-to-head RCT in the target patient population was identified in the literature and methodological consideration prevented a meaningful indirect treatment comparison from being conducted. As such, direct comparisons of effectiveness between treatments cannot be made. Most included studies were of relatively small sample size, which limited the level of precision and affected the certainty in the findings. Decision-makers may consider tolerating a greater level of uncertainty when interpreting the findings and drawing conclusions regarding the use of eltrombopag and romiplostim, given that ITP is a rare disease in children, and large RTCs are unlikely. One observational study was included in the review, however the authors did not present comparative effect estimates. Results of this study should be interpretated with caution and findings should be viewed as complementary to those from RCTs.

Conclusions and Implications for Decision- or Policy-Making

Jurisdictions may consider revisiting reimbursement criteria for eltrombopag and romiplostim, for use after failure of first-line therapies in children with ongoing active ITP. No evidence was identified in support of trying rituximab prior to accessing TPO-RAs. Interested jurisdictions may implement strategies to manage the clinical uncertainty identified in the report.

Introduction

Background 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.[3-6] It was previously called idiopathic thrombocytopenic purpura, but is no longer considered to be an idiopathic disease.[3,6] The specific cause of ITP is unknown but may be a mix of genetic and environmental factors.[11] In addition, not all patients will experience bleeding symptoms such as purpura.[11]

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

- 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; and
- 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,[8,9] which is substantially 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).[8,9]

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.[7] Bleeding symptoms are often present, including severe bleeding (such as in the gastrointestinal tract or in the brain) in approximately 20% of children.[9,10]

Newly diagnosed pediatric patients with no or minor bleeding may undergo observation according to the American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia[1] and the 2019 International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia.[2] In the presence of non–life threatening mucosal bleeding or bleeding that impacts 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 intravenous immunoglobulin and anti-D immunoglobulin.[1] According to the international standardized definition, a platelet count response may be defined as a platelet count ≥ 30 x 10^9/L, with at least a two-fold increase in platelet count from baseline, combined with the absence of bleeding; a complete platelet response would typically be defined as a platelet count ≥ 100 x 10^9/L, as long as there is an absence of bleeding.[3]

In pediatric patients who do not respond to first-line treatment, which is often simplified in the literature as a platelet count below 50 x 10^9/L,[2] guidelines recommend the use of thrombopoietin receptor agonists (TPO-RAs), i.e., eltrombopag or romiplostim (avatrombopag was not included in this review as at the time it was performed, it did not hold a Health Canada indication).[1,2] Considering the balance of benefits and harms, patient preference and feasibility, the American Society of Hematology suggests the use of TPO-RAs rather than rituximab, which would instead be considered a subsequent-line therapy.[1,2] Issues such as the scarcity of evidence however led to this recommendation being conditional, based on very low certainty in the evidence of effects.[1] 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.[1] These were also favoured over immunosuppressants, as a high value is being placed on avoiding immunosuppression in children.[1] The importance of avoiding immunosuppression in the pediatric population was emphasized by the clinical experts consulted for this review. For example, the clinical experts mentioned the issue of delay in standard immunization schedule with the

use of immunosuppressive therapies, which has been described in the literature[12-14] and became even more serious in clinical practice during the recent COVID-19 pandemic.

Other subsequent-line therapies include azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone, mycophenolate mofetil, and vinca alkaloids used off-label; 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, lack of direct comparisons, and large variability in outcome measures.[1] The clinical experts also confirmed that there is now only a very limited role for immunosuppressants in children with ITP in clinical practice, that is, in patients who do not respond to TPO-RAs.

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.[1] We 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 the adult population after failure of first-line therapies.[15] A similar need for a HTA in children with ITP was identified.

Before being authorized to access a TPO-RA, children who require second-line pharmacotherapy may be required, in some jurisdictions, to trial of another drug such as rituximab and not a TPO-RA. In the few patients who did not respond to first-line therapy, TPO-RAs for children are not publicly reimbursed.

Therefore, we performed a systematic review assessing the efficacy and safety of TPO-RAs (i.e., eltrombopag and romiplostim) and other relevant agents identified by the jurisdictions (i.e. rituximab for children with ITP who have failed first-line therapies) to help inform decision-making regarding public reimbursement.

Of note, only eltrombopag has a Health Canada indication in children with ITP;[16] romiplostim holds an indication in adults patients but Health Canada has not authorized an indication for pediatric use.[17] Avatrombopag did not hold a notice of compliance (NOC) from Health Canada at the time this review was performed. A NOC was granted on January 22, 2024, for the use of avatrombopag in adult patients; however, a placebo-controlled, phase III RCT evaluating the use of avatrombopag in children with ITP is currently ongoing,[18] and may provide further insights on the use of TPO-RAs in this patient population once results become available.

The final scope of this HTA project was informed by feedback received from stakeholders and patient group(s) following publication of the HTA on the comparative effectiveness and cost-effectiveness of treatments for ITP in the adult population after failure of first-line therapies.[15]

Splenectomy

Based on major guidelines[1,2] and clinical expert opinion, splenectomy is usually not considered an appropriate treatment option in children with ITP. Guidelines placed high value on avoiding splenectomy in children.[1,2] The clinician feedback received emphasized that splenectomy should not be a criterion to access TPO-RAs, as it would not be considered appropriate for reimbursement purposes to request a child to undergo a major surgery, especially when other therapies are recommended by relevant guidelines as prior lines of treatment. The feedback highlighted that only physicians and surgeons would be legitimated to make this clinical decision. As such, splenectomy was not part of the interventions assessed in this systematic review. Splenectomy comes with negative effects for children, including lifetime immune suppression.

The clinical experts consulted for this review emphasized that lifetime immune suppression caused by splenectomy leads to loss of protection against encapsulated bacterial species such as *Streptococcus pneumoniae, Neisseria meningiditis, and Haemophilus spp*, all of which posing the risk to cause life-threatening infections, as is being described extensively in the literature.[19-21] Children who undergo splenectomy therefore require prolonged antibiotic prophylaxis for years, and have a life-long need to present to the emergency room when they develop a fever to receive broad spectrum antibiotics until blood cultures rule out an encapsulated bacterial infection that could result in life-threatening sepsis. There are additional challenges related to the use of antibiotics, including the well-documented development of antibiotic resistance, as well as poorly tolerated options in the numerous patients who are allergic to first-line penicillin. Immunizations against the pathogens listed above may provide some protection for patients; however, not all relevant vaccines are part of the routinely reimbursed immunization calendar. In addition, splenectomy cannot be

considered a guaranteed cure to ITP. As there is no predictive factor to determine who is more likely to respond to splenectomy, making the decision to have a child undergo this major surgery remains challenging.

Clinical Review Objectives

The objective of this HTA was 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 agents.

Policy Questions

To assist jurisdictions in making local decisions, the systematic review aimed to address 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, instead of being required to try a course of rituximab prior to accessing eltrombopag or romiplostim?

Research Questions

The project aimed to 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?

Opportunities for Stakeholder Feedback

Patient Engagement

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. We have 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 guided our patient engagement activities.

Engagement Activities

Patient Group Input
We received a patient group input submission for an earlier report on adult ITP, outlining patient priorities and concerns.

Patient Advocacy Group Dialogue
A patient advocacy group focused on platelet disorders was approached about participating in this report. A Patient Engagement Officer gave an overview of the purpose and scope of the project and the purpose of the engagement.

The Platelet Disorder Support Association outlined several areas of particular interest to the pediatric population, as distinct from the adult population with ITP. With consent, the dialogue was recorded for notetaking purposes and for sharing with members of the project team.

Team Presentation

A presentation, developed by the Patient Engagement Officer and reviewed by Platelet Disorder Support Association, was shared at a project team meeting to enhance the team's understanding of the issues surrounding pediatric ITP from patients and caregivers perspectives. This presentation occurred during the protocol drafting phase, so that patients' perspectives could be considered during the drafting of the protocol and the development of the report from the start.

Stakeholder Feedback

The draft report is released to the public for a 10-day Stakeholder Feedback period. Members of the public, including patients, patient groups, and clinicians, may review and submit their written feedback on the findings of the report.

Stakeholder Input and Feedback

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

Several key themes were identified as specific to the pediatric population with ITP.

As there are different disease courses between pediatric and adult ITP, the Platelet Disorder Support Association felt that it is important to focus research on the smaller percentage of children who have more frequent, severe bleeding than those who spontaneously recover within a short period of time. Children are typically treated very conservatively with limited focus on the prevention of bleeding, and Platelet Disorder Support Association was concerned about this tendency continuing into children who develop chronic ITP, and for those children who experience serious bleeding beyond mild skin bleeding. They report that children are usually not treated for a low platelet count, whereas adults would be treated at those same levels regardless of their bleeding symptoms. They feel the guidelines for treating children are less clear than those for treating adults.

Due to the heterogeneity of pediatric ITP, the Platelet Disorder Support Association felt strongly about the need for multiple forms of treatment and for patients to have the ability to try different therapies according to their symptoms, rather than be forced to follow a stepwise order of treatment since everyone (adults and children) all respond differently to ITP treatments. The heterogeneity is not only seen in the clinical symptoms, but also in treatment response, duration of response, and other aspects of the natural history of the disorder. There are also concerns about requiring splenectomies prior to accessing second-line treatments, with all the inherent risks. The adult HTA identified that there wasn't strong evidence to suggest a splenectomy must be performed before other access to treatment, which the patient group felt may also hold true for children. Not to mention that children with ITP have fewer treatment options than adults.

There are barriers to treatment, including the requirement for parental insurance that ends when children are no longer in school, patient-borne costs, invasiveness of treatment, time-consuming nature of some treatments, and method of delivery. For example, infusions performed in hospitals or clinics necessitate taking time away from work and school, affecting job performance and academic achievement. Most patients would choose to take medication orally over an infusion for many hours.

Quality of life was an important concern for Platelet Disorder Support Association. Having frequent bleeds in public, including visible bleeds such as dense petechiae, large ugly bruises, oral blood blisters in mouth and lips can be humiliating and can contribute to poor self-esteem and mental health. Spending significant amounts of time in clinics or hospitals can impact school and social participation.

Ultimately, Platelet Disorder Support Association reported that patients want treatments that won't cause them to go into financial debt, that have minimal side effects, that work long-term, reduce their fatigue, and are convenient.

Clinical Review Methods

To inform the conduct of this systematic review, a preliminary informal scoping of the existing literature was conducted. Stakeholder feedback was solicited at key steps. The systematic review protocol was developed a priori[22] and was registered in the PROSPERO international prospective registry of systematic review (https://www.crd.york.ac.uk/PROSPERO/) as project number CRD42023429164.[23] The protocol was followed throughout the study process, without deviations. The project is a HTA that includes

a clinical evaluation only; although jurisdictions mentioned potential interest in an economic evaluation, this was not deemed feasible due to the limited evidence available.

Eligibility Criteria

Pre-specified selection criteria for inclusion of studies in this systematic review are presented in Table 1. To be included, studies had to meet all the eligibility criteria.

Table 1: Selection Criteria

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/safety) and Question 2 (comparative clinical efficacy/safety): ▪ Eltrombopag (Revolade) ○ 25 orally once daily (starting dose) in patients < 6 years of age ○ 50 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 μg/kg SC injection once weekly (starting dose) ○ Dose adjustments of 1 μg/kg/week to achieve and maintain a platelet count ≥ 50 x 10^9/L (maximum dose of 10 μg/kg) ▪ Rituximab (including biosimilars) ○ 375 mg/m^2 IV infusion once weekly for 4 weeks
Comparators[b]	Question 1 (clinical efficacy/safety): ○ Placebo Question 2 (comparative clinical efficacy/safety): ○ Eltrombopag ○ Romiplostim ○ Rituximab (including biosimilars)
Outcomes	**Efficacy outcomes** ▪ 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 relevant in pediatric ITP) ▪ Function (i.e., measured with an assessment tool relevant 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
Study Design	Published phase II, phase III, and phase IV RCTs If no RCTs are available to adequately inform a particular comparison: Published non-randomized controlled trials and comparative prospective cohort studies

HRQoL = health related quality of life; ITP = immune thrombocytopenia; IV = intravenous; IVIG = intravenous immunoglobulin; RCT = randomized controlled trial; SC = subcutaneous.

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

[a] Only eltrombopag has a Health Canada indication in children with ITP.[16] Romiplostim holds an indication in adults with ITP; Health Canada has not authorized an indication for pediatric use.[17] Rituximab does not have a Health Canada indication for ITP.[24]
[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, i.e., total numbers and proportions of patients with adverse events or serious adverse events.

The following was considered when selecting studies for inclusion:

- For research question 1 (clinical efficacy), evidence was sought from placebo-controlled RCTs. We discourage the use of informal naïve 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 was sought first, since well-designed and conducted RCTs typically offer the highest internal validity to inform causal inferences. When no such head-to-head RCTs could be identified for any given outcome-comparison, then eligible evidence included the following:
    - Non-randomized controlled trials and comparative prospective cohort studies. To be considered prospective, comparative cohort studies must have clearly defined a hypothesis prior to the enrollment of patients and collection of outcomes data.
- Full texts of titles or abstracts describing potentially relevant studies in a wider patient population were retrieved for assessment and included in the systematic review if appropriate subgroup results were reported.
- Drug regimens eligible for inclusion in the systematic review for interventions and comparators were those that have been approved by Health Canada for ITP or were considered clinically relevant based on expert advice or on the major ITP Guidelines.[1,2]
- This review was limited to studies reported in English or French, given the capacity for reviewing in both languages. No eligible studies were excluded for being published in a language other than English or French.
- In the event that multiple reports were identified for the same study, they were all included and cited; however, only unique data was extracted without duplication and the reports were considered as one single study in the analysis. The first complete report of a study was identified as the primary report, others were referred to as associated reports.
- Abstracts, conference proceedings, or results posted on clinicaltrials.gov were not 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 were not included in the systematic review. However, we reported on ongoing trials registered in clinicaltrials.gov at the time the final report for this project was published.

Literature Search Methods

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[25] The complete search strategy is presented in Appendix 1.

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were pediatrics, immune thrombocytopenia, and eltrombopag, romiplostim, or rituximab. The following clinical trials registries were 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 were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Appendix 1 contains the detailed search strategies.

The initial search was completed May 2, 2023. Regular alerts to update the search were run until project completion.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from 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 was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers (i.e., the included studies and relevant systematic reviews) and through contacts with appropriate experts. In addition, a list of included studies was posted on the website for feedback, where stakeholders were welcome to highlight any potentially relevant studies that could have been missed.

Study Selection Process

Prior to beginning screening, two reviewers conducted a pilot round by independently screening 50 randomly selected articles in duplicate, after which they met to resolve disagreements. No additional pilot round was needed. Then, the two reviewers independently (in duplicate) screened 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 were judged to be potentially relevant by at least one reviewer were retrieved and independently assessed by two reviewers for possible inclusion based on the pre-determined selection criteria outlined in Table 1. The two reviewers then compared their chosen included and excluded studies; disagreements at the full-text level were discussed until consensus was reached. If consensus could not be reached, a third reviewer was consulted. The study selection process is presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) flowchart.[26] Studies excluded at the full-text screening stage, along with reasons for exclusion, were recorded and reported. Reference lists of included studies and relevant systematic reviews identified during screening were screened following the same selection process. Reviewers did not attempt to retrieve further information from study investigators as it was not deemed necessary.

Studies identified via stakeholder feedback and reference list scanning were reviewed following the previously outlined process.

Data Extraction

All relevant data was extracted directly into a standardized data abstraction form, which was part of a review-specific Microsoft Excel workbook. It was planned that the form would be piloted before beginning full data extraction to ensure that it was usable and that it completely and reliably captured the items of interest, while avoiding redundancies; however, this was not deemed necessary due to the small number of included studies.

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

Relevant information to be extracted included 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 (e.g., 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 intent-to-treat (ITT) effect was preferentially extracted. All numerical data, including data presented in text or in figures, was extracted.

Where multiple variations of the same outcome were reported in the included studies, we collected the most clinically-relevant definitions and timepoints for each outcome (based on clinical expert input, where needed), which facilitated later synthesis of the findings. Wherever possible we prioritized data reported according to established definitions as suggested by Rodheghiero and colleagues (2009).[3]

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

Risk of Bias Assessment

The reviewers used 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), was assessed using the Cochrane Risk of Bias tool, version 2 (RoB 2).[27] 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 was assigned for each domain.

- Outcome-level risk of bias in non-randomized studies were assessed using the Risk Of Bias In Non-randomized Studies – Interventions tool (ROBINS-I).[28] 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 was assigned for each domain.

For each tool, the overall risk of bias of each study was rated and designated based on the domain-level assessments. Where possible, attempts were made to predict the direction of the potential bias. A rationale is provided for decisions about the risk of bias for both the domain-level and overall assessments.

It was planned that all reviewers involved in the risk of bias assessment would independently pilot the selected tools across a few studies and meet to resolve disagreements, to ensure a mutual understanding of the tool and methodological intricacies across studies; however, this was not deemed necessary due to the small number of included studies. The risk of bias was evaluated in duplicate by two independent reviewers. Any disagreements were resolved through discussion, with involvement of a third reviewer if consensus could not be reached.

In addition to the risk of bias, a generalizability assessment of the findings was also performed (i.e., patient population, choice of outcomes, treatment regimen and length of follow-up). Throughout the critical appraisal process, reviewers included clinical input from experts consulted for this review.

Studies were not 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 were used to inform conclusions about the body of evidence for each outcome-comparison.

Data Analysis and Synthesis

Prior to embarking on synthesis, the team considered the clinical and methodological heterogeneity of the relevant studies (i.e., with respect to methodology, outcomes definition and measurement, timing of assessment, and populations). We tabulated the characteristics of the included studies, and presented these in a table with accompanying textual summary. We then charted the available studies and considered whether they were similar enough in their PICO elements (including timepoint of outcome measurement) to be grouped in the synthesis.

The included studies were deemed too heterogenous to combine statistically, mainly due to heterogeneity in the outcome measures that were reported. Findings were therefore synthesized narratively considering the guidance by Popay et al.[29] There were only 2

studies for eltrombopag vs. placebo and 2 for romiplostim vs. placebo. For these comparisons, we developed preliminary conclusions by organizing the studies by direction and size of effect. We intended to explore within- and between-study relationships and factors (including the a priori subgroups) that might have influenced the direction and magnitude of observed effects, however this was infeasible due to the small number of studies. We considered the robustness of the findings (e.g., impact of risk of bias) and drew a single final conclusion about our best estimate of the size and direction of the anticipated effect across studies.

Interpretation and drawing conclusions

Conclusions were drawn for each outcome-comparison. The following items were 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), and the generalizability (or applicability) of the findings. The risk of publication bias could not be formally appraised due to the small number of studies in each synthesis.

Results of Clinical Evaluation

Selection of Primary Studies

A total of 733 records were identified in the literature searches. Following screening of titles and abstracts, 43 reports were identified as potentially relevant and retrieved for full-text review. No report retrieved from other sources was included as potentially relevant (i.e., grey literature, hand search, and search alerts). Of these 43 potentially eligible reports, a total of 8 reports of 5 studies met the inclusion criteria and were included for review: 6 reports[30-35] presenting data from 4 unique RCTs; and 2 reports[36,37] presenting data from 1 unique observational study. No relevant ongoing studies were identified.

The study selection process is illustrated in Appendix 2. A list of included and excluded studies with details describing the rationale for those excluded, are presented in Appendix 3 and 4 respectively.

Study and Patient Characteristics

Study and patient characteristics are shown in Appendix 5 and outlined in Table 2. Two of the included RCTs compared eltrombopag to placebo and 2 RCTs compared romiplostim to placebo. No RCTs evaluating rituximab were identified. A prospective cohort study with eltrombopag, rituximab, and romiplostim arms was included in attempt to fill the gap in comparative evidence. However, the study provided only within-arm data without formal direct comparisons.

Table 2: High-Level Study Characteristics

Criteria	Bussel 2015[30] PETIT	Grainger 2015[32] PETIT2	Tarantino 2016[34]	Elalfy 2011[33]	Grace 2019[36] ICON1
Design	RCT				Cohort study
Population	Patients < 18 years with diagnosis of ITP who have active disease, i.e., who relapsed or are refractory, after having tried ≥ 1 prior treatment option.			Patients with ITP who failed to maintain response to ≥ 2 prior treatment options.	Patients < 18 years with diagnosis of ITP starting second-line treatments as monotherapy.
N	67	92	62	18	120
Key baseline characteristics	• Mean age 9-10 yrs • Disease duration ≥ 12 months • Mean platelet counts 12-16x10^9/L	• Mean age 9 yrs • Disease duration ≥ 12 months • 60-66% with platelet count ≤15x10^9/L	• Median age 8-10 yrs • Median disease duration 2 yrs • Median platelet count 18x10^9/L	• Median age 7-10 yrs • Median disease duration 2-3 yrs • Median platelet count 11x10^9/L	• Mean age 10-12 yrs • Disease duration: ≥ 50% had ≥ 12 months • 40-55% with platelet count <10x10^9/L
Interventions	Eltrombopag (dose to be adjusted according to platelet response)		Romiplostim (dose to be adjusted according to platelet response)		Rituximab Romiplostim Eltrombopag
Comparators	Matching placebo	Matching placebo	Matching placebo	Placebo	Interventions compared to one another (descriptive comparisons only)
Primary outcome	Platelet count response – various definitions were used across the studies				
Timepoint for key measures	6 weeks	12 weeks	24 weeks	NR	1, 6 and 12 months
Other key outcomes	• Additional measures of platelet response • Concomitant ITP medication and/or rescue therapy • Bleeding (WHO bleeding scale) • HRQoL (KIT questionnaire) • Harms	• Additional measures of platelet response • ITP rescue therapy • Bleeding (WHO bleeding scale) • Harms	• Additional measures of platelet response • ITP rescue therapy • Bleeding composite: (Grade ≥ 2 AEs / use of rescue therapy related to bleeding) • HRQoL (KIT questionnaire)[35] • Harms	• Use of IVIG • Harms	• Bleeding (IBLS) • ITP rescue treatment (identified as IVIG and corticosteroids) • Change in HRQoL based on KIT questionnaire

HRQoL = health-related quality of life; IBLS = ITP Bleeding Scale; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; KIT = Kid's ITP Tools; NA = non-applicable; NR = not reported; RCT = randomized controlled trial; WHO = World Health Organization; yrs = years.

Eltrombopag versus Placebo - RCTs

In the two RCTs comparing eltrombopag to placebo,[30,32] eltrombopag was administered orally once daily at a prespecified starting dosage, then adjusted based on platelet response; the target platelet count was 50 – 200x10^9/L. The mean age of patients was between 9 to 10 years across treatment groups at baseline; patients were well distributed among age cohorts. Between 82 to 91% of patients in one RCT,[30] and all patients in the other RCT,[32] had ITP that lasted for at least 12 months (i.e., chronic ITP). Between 50% and 66% of patients across treatment groups had a baseline platelet count of 15x10^9/L or lower. The proportions of patients using concomitant ITP medication ranged from 3% to 21%; some imbalance between arms could be observed in one of the studies.[32] Almost all patients had received previous ITP medication, but details of the specific therapies received were not consistently reported.

Both RCTs reported platelet count response as the primary outcome and used a minimal platelet count threshold of 50×10^9/L as part of the platelet response definition, in addition to the absence of rescue therapy; however, there were differences as to the conditions to be observed for patients to be considered responders, such as the time needed to be spent above the threshold value (ranging from at least once during the study to throughout the last 6 weeks of study follow-up). Both RCTs also reported on the use of concomitant ITP medications and/or rescue therapies, as well as bleeding as an outcome for efficacy assessment using the World Health Organization (WHO) bleeding scale, which has been validated in adults with ITP.[38] One RCT[30] reported findings on health-related quality of life (HRQoL) using the Kid's ITP Tool (KIT) questionnaire, which is a validated measure used in pediatric patients with ITP.[31] The score ranges from 0 to 100, with higher scores being associated with a better state. Using data from the PETIT study, the within-group minimally clinically important difference (MCID) was estimated as ranging from 5.9 to 8.4 points by parent report and 6.9 to 9.2 points by child report, using a distribution-based approach.[31] No data were reported for the outcomes of function.

Romiplostim versus Placebo - RCTs

In the two RCTs comparing romiplostim to placebo,[33,34] romiplostim was administered by subcutaneous (SC) injection once weekly at a starting dosage of 1 µg/kg. However, there were substantial differences between the two studies in their respective designs, patient populations (age, disease duration, and prior treatments), timepoints for outcome assessment, and outcome definitions; as such, we opted to describe them separately.

In the double-blind RCT,[34] the dose was to be titrated weekly in 1 µg/kg increments based on platelet response; the target platelet count was 50 – 200x10^9/L. The median age of patients was 7.5 to 10 years across treatment groups at baseline; patients were well distributed among age cohorts. The median time since diagnosis averaged 2 years (interquartile range [IQR] 1.0 – 4.2), which was consistent with chronic ITP. The median baseline platelet count was 17.8x10^9/L. Twelve to 20% of patients received concomitant ITP medication, suggesting some imbalance; as for previous first-line ITP medication, 76% of patients had received corticosteroids, 82% had received IVIG and 31% had received anti-D immunoglobulin. The primary outcome was platelet count response, using a minimal platelet count threshold of 50×10^9/L that needed to be maintained for at least 6 of the final 8 weeks, in addition to the absence of rescue therapy. The RCT also reported on the use of concomitant ITP medications and/or rescue therapies, as well as bleeding using Grade ≥ 2 bleeding-related AEs. Findings on HRQoL were reported using the KIT questionnaire in a separate publication;[35] no data were reported for the outcomes of function.

In the small, single-blinded pilot RCT,[33] the dose was to be escalated to 5 µg/kg, then tapered; no detail was provided in the publication as to the target platelet count, or regarding the escalation and tapering regimen. The median age of patients was 7 to 9.5 years across treatment groups at baseline (range not reported). The median disease duration was 2 to 3 years across treatment groups at baseline, with substantial variability as shown by the IQR between 1 to 7 years. The median baseline platelet count was 10.5x10^9/L; no patient had a platelet count above 20x10^9/L. Details were not reported regarding the use of concomitant or previous ITP medication received, apart from the fact that all patients received prior corticosteroids. The study provided no detail as to how response to treatment was assessed. No data were reported for the use of concomitant ITP medications and/or rescue therapies, or for the outcomes of bleeding, HRQoL and function.

Rituximab versus Placebo RCTs

Assessment of the effectiveness of rituximab compared to placebo was inconclusive due to the lack of evidence, as no comparative RCTs could be identified, while the observational study included only presented descriptive comparisons with TPO-RAs.

Rituximab, Romiplostim and Eltrombopag – Observational Evidence

In the prospective cohort study evaluating the comparative effectiveness of rituximab, romiplostim and eltrombopag given as monotherapy,[36] medications were administered according to physicians' best judgment. No details were reported on whether there were any pre-specified target platelet counts to achieve, or to inform on the doses of medication patients actually received. The mean age of patients ranged from 9.8 to 12.2 years across treatment groups at baseline. Approximately 50% of patients had chronic ITP in every study group, with approximately 30% having persistent ITP and between 15% to 20% having newly diagnosed ITP. The vast majority of patients had primary ITP. Between 40% to 58% of patients had a baseline platelet count that was below $10x10^9$/L; the proportions of patients with a platelet count of no less than $30x10^9$/L ranged from 7% to 20% of patients across treatment groups. The baseline Grade 2 bleeding scores reported were consistent with the conclusion that substantial proportions of patients were experiencing clinically significant skin and non-skin bleeding at baseline; however, these proportions varied across treatment groups and bleeding category. Information about the use of concomitant treatments was not reported.

The primary outcome was platelet count response, using a minimal platelet count threshold of $30\text{-}100\times10^9$/L depending on the outcome definition, which needed to be attained at least half the time; there was no criterion related to the use of rescue medication. The cohort study did not report on the use of concomitant ITP medications and/or rescue therapies; however, bleeding was assessed as an efficacy outcome using the ITP Bleeding Scale (IBLS) and findings on HRQoL were reported using the KIT questionnaire. No data were reported for the outcomes of function.

Summary of Risk of Bias and External Validity Assessment

The risk of bias appraisal of all the included trials is presented for each domain in Table 3 and Table 4, and described in detail in Appendix 6. The key limitations, i.e., those having an impact on the interpretation of the findings, are summarized in this section for each treatment comparison.

Eltrombopag Compared to Placebo

Eltrombopag was compared to placebo in two DB RCTs of 7 weeks[30] and 12 weeks duration.[32] Of these, both were rated as having a low risk of bias for all outcomes, with the exception of HRQoL, which was rated as having a high risk of bias. More specifically, there were large amounts of missing data for HRQoL in PETIT,[30] large enough to have the potential to bias the outcome. In terms of generalizability, both study populations appear to be representative of Canadian clinical practice.

Romiplostim Compared to Placebo

Romiplostim was compared to placebo in two RCTs with substantial heterogeneity in methodology. Of these, Tarantino et al.[34] was a DB RCT of 24 weeks duration rated as having some concern for the risk of bias for all efficacy outcomes, and at low risk of bias for the harms outcomes. No information was reported regarding missing efficacy outcome data and how they were handled; based on patient withdrawals, it is possible that missing data amount to proportions sufficiently high to introduce a risk of bias. In terms of generalizability, the study population appears to be representative of Canadian clinical practice.

Elalfy et al.[33] was a single-blinded pilot RCTs of 15 weeks duration rated as having a high risk of bias for all outcomes assessed in the study. In addition, the trial publication suffers from poor reporting. Platelet response was not defined and therefore, it is not possible to assess whether the threshold used and conditions required to be considered as having a platelet response were valid and relevant according to the definitions described in the guidelines and used in clinical practice; in addition, there is the possibility that multiple and inconsistent definitions could have been used by assessors, again affecting precision and confidence in the findings. No information was reported regarding missing outcome data and how they were handled; no pre-specified analysis plan was reported, and considering the overall setting and trial conduct, it was impossible to determine whether investigators were blinded to outcome data. The trial was performed exclusively in Egypt; it is possible that standard of care is different in other countries, which would affect generalizability of the results to the Canadian population. As such, the fact that the study included some patients who had

ongoing disease for up to 7 years, and who had a platelet count that still did not exceed $20x10^9$/L, raises questions on generalizability of the population, i.e., whether these patients have been appropriately treated prior to entering the study according to current Canadian practice standards.

Rituximab, Romiplostim and Eltrombopag – Observational Evidence

The use of rituximab, romiplostim and eltrombopag was evaluated in a prospective, longitudinal cohort study of 12 months duration. ICON1[36] was rated using the ROBINS-I tool[28] as having a serious risk of bias for all outcomes assessed in the study.

More specifically, the study was considered at increased risk of bias due to confounding, especially considering the fact that the authors did not attempt to control for post-intervention variables that could have affected the interventions; the direction of potential bias cannot be predicted. Interventions were well defined and based on information obtained before the start of follow-up; however, there is the possibility that the choice of treatment may have been influenced by disease characteristics. There was an increased risk of bias due to significant patient attrition, with proportions differing between treatment groups and missingness reasons not detailed in the publications. This suggest that patients contributing to the analyses at further timepoints are likely to be more representative of responders. The outcome of HRQoL was subject to additional bias, considering the subjectivity of the outcome, making it vulnerable to influence by knowledge of the intervention received as assessors were aware of the intervention received. These issues introduce uncertainty around the true treatment effect; as such, result from the study should be interpretated with caution and findings should be viewed as complementary to those from RCTs. In terms of generalizability, the study population appears to be representative of Canadian clinical practice.

Table 3: Risk of Bias Assessment Per Outcome Within Each RCT Using RoB2[27]

Study	Randomization process	Deviations from intended interventions (assignment)	Deviations from intended interventions (adherence)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Platelet Response							
Bussel 2015[30] (PETIT)	Low	Low	Low	Low	Low	Low	Low
Grainger 2015[32] (PETIT2)	Low	Low	Low	Low	Low	Low	Low
Tarantino 2016[34]	Low	Some concern	Low	Some concern	Low	Low	Some concern
Elalfy 2011[33]	Some concern	High	High	High	Low	Some concern	High
Use of Concomitant or Rescue Medication							
Bussel 2015[30] (PETIT)	Low	Low	Low	Low	Low	Low	Low
Grainger 2015[32] (PETIT2)	Low	Low	Low	Low	Low	Low	Low
Tarantino 2016[34]	Low	Some concern	Low	Some concern	Low	Low	Some concern
Elalfy 2011[33]	Some concern	High	High	High	Low	Some concern	High
Bleeding							
Bussel 2015[30] (PETIT)	Low	Low	Low	Low	Low	Low	Low
Grainger 2015[32] (PETIT2)	Low	Low	Low	Low	Low	Low	Low
Tarantino 2016[34]	Low	Some concern	Low	Some concern	Low	Low	Some concern
HRQoL							
Bussel 2015[30] (PETIT)	Low	High	Low	High	Low	Low	High
Tarantino 2016[34] (Mathias 2016[35] reporting on HRQoL)	Low	Some concern	Low	Some concern	Low	Low	Some concern
Harms							
Bussel 2015[30] (PETIT)	Low	Low	Low	Low	Low	Low	Low
Grainger 2015[32] (PETIT2)	Low	Low	Low	Low	Low	Low	Low
Tarantino 2016[34]	Low	Low	Low	Low	Low	Low	Low
Elalfy 2011[33]	Some concern	High	High	High	High	Some concern	High

HRQoL = health-related quality of life; RoB2 = Cochrane Risk of Bias tool, version 2.

Table 4: Risk of Bias Assessment Per Outcome for the ICON1 Observational Study Using ROBINS-I[28]

Grace 2019[36] (ICON1)	Confounding	Patient selection	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of reported results	Overall
Platelet Response	Serious	Low	Moderate	Low	Serious	Low	Moderate	Serious
Use of Rescue Medication						Low	Low	
Bleeding						Serious	Low	
HRQoL						Serious	Low	

HRQoL = health-related quality of life; ROBINS-I = Risk Of Bias In Non-randomized Studies – Interventions tool.

Data Analysis and Synthesis

Results

Detailed outcome results for studies included in the narrative synthesis are outlined in Table 5 and Table 6, and presented in Appendix 7. All the studies included in the systematic review reported platelet count response as the primary outcome; however, the definitions used to assess platelet response varied substantially across the studies. According to the international standardized definition, a platelet count response may be defined as a platelet count ≥ 30 x 10^9/L, with at least a two-fold increase in platelet count from baseline, combined with the absence of bleeding; a complete platelet response would typically be defined as a platelet count ≥ 100 x 10^9/L, as long as there is an absence of bleeding.[3] In addition to the platelet count thresholds, there were differences among all the studies as to the conditions to be observed for patients to be considered responders, such as the time needed to be spent above the threshold value (ranging from at least once during the study to throughout the last 6 weeks of study follow-up), as well as criteria related to the use of rescue medication.

Eltrombopag Compared to Placebo

Platelet Response:

In PETIT (n = 67),[30] the proportions of patients achieving a platelet count of 50×10^9/L or more at least once over 6 weeks, in the absence of rescue therapy, were 62% in the eltrombopag arm and 32% in the placebo arm (OR = 4.31, 95% CI = 1.39 to 13.34; p = 0.011). The outcome definition was consistent with a basic measure by only requiring patients to achieve an adequate platelet count threshold once throughout 6 weeks. A more stringent outcome definition was used as a secondary outcome; the proportions of patients achieving a platelet count of 50×10^9/L or more in at least 60% of assessments were 36% in the eltrombopag arm and 0% in the placebo arm (OR = 5.84, 95% CI = 1.18 to 28.90; p = 0.0017) versus placebo. The magnitude of the point estimate for the between-group difference may be considered clinically meaningful according to the clinical experts consulted.

In PETIT2 (n = 92),[32] the proportions of patients achieving a platelet count of 50×10^9/L or more in the absence of rescue therapy for at least 6 weeks from Week 5 to 12, were 40% in the eltrombopag arm and 3% in the placebo arm (OR = 18.0, 95% CI = 2.3 to 140.9; p = 0.0004) versus placebo. The magnitude of the point estimate for the between-group difference may be considered clinically meaningful according to the clinical experts. The outcome definition was considered stringent, meaning that patients who were counted as responders had to achieve an adequate platelet count threshold and maintain response for at least 6 of the last 8 weeks of study duration, which was 12 weeks. Results for the secondary outcome of likelihood of maintaining a response during 12 weeks (repeated-measures analysis of platelet response) were consistent with these findings, as the use of eltrombopag was associated with an OR of 25.3 (95% CI 8.2 to 78.7); p < 0.0001) versus placebo; no absolute effect estimates were reported.

Need for Rescue Medication:

In PETIT (n = 67)[30] the proportions of patients initiating rescue medication was 13% in the eltrombopag arm and 50% in the placebo arm over 6 weeks (OR = 0.1, 95% CI = 0.04 to 0.49; p = 0.0020). The between-group difference was of much smaller magnitude in PETIT2 (n = 92),[32] where the corresponding proportions were 19% in the eltrombopag arm and 24% in the placebo arm over 12 weeks (OR = 0.44, 95% CI = 0.2 to 0.9; p = 0.032). This is consistent with the findings from platelet response, suggesting that more patients in the placebo group failed to achieve platelet response and therefore required the use of rescue therapy.

Bleeding:

Clinically significant bleeding was assessed in the studies using the WHO bleeding scale. In PETIT (n = 67),[30] the proportions of patients with WHO Grade 2 – 4 bleeding, with the use of a logical regression model, were 27% in the eltrombopag arm and 59% in the placebo arm over 6 weeks, yielding an OR of 0.21 (95% CI 0.06 to 0.72; p = 0.013). In PETIT2 (n = 92),[32] 5 % of patients in the eltrombopag group and 7% of patients in placebo had WHO Grade 2 – 4 bleeding at week 12; no comparison between groups was reported. The magnitude of the point estimate for the between-group difference may be considered clinically meaningful according to the clinical experts.

Health-Related Quality of Life:

HRQoL was assessed in PETIT (n = 62)[30] using the KIT questionnaire (range 0 to 100, higher scores indicate a better state), but was not assessed in PETIT2.[32] The mean difference between treatment groups for change from baseline to Week 6 was -1.5 points (95% CI -8.1, 5.1 points; p = 0.64) in favour of eltrombopag. The magnitude of the between-group difference was not considered clinically meaningful according to the MCID identified in the literature.[31]

Function:

No data were reported for the outcome of function.

Harms Outcomes:

High proportions of patients experienced AEs throughout the studies and proportions were relatively similar between treatment groups. The proportions of patients who experienced SAEs ranged between 8% to 14% across treatment groups, and were overall not higher with eltrombopag than with placebo. No deaths were reported in the studies.

Romiplostim Compared to Placebo

Platelet Response:

In Tarantino et al. (n = 62)[34] the proportions of patients achieving a platelet count of 50×10^9/L or more at least 6 of the final 8 weeks (out of a total of 24 weeks), without rescue medication within the prior 4 weeks, were 52% in the romiplostim arm and 10% in the placebo arm (OR = 9.1, 95% CI = 1.9 to 43.2; p = 0.002). The magnitude of the point estimate for the between-group difference may be considered clinically meaningful according to current clinical practice standards. The outcome definition was considered stringent, meaning that patients who were counted as responders had to achieve an adequate platelet count threshold and maintain response for at least 6 of the last 8 weeks of study duration, which was 24 weeks. Results for a less stringent secondary outcome measure were consistent with those findings. The proportions of patients achieving at least 4 weekly platelet counts of 50×10^9/L or more without rescue medication during the 24-week follow-up were 71% in the romiplostim arm and 20% in the placebo arm (OR = 9.0, 95% CI = 2.5 to 32.3; p = 0.0002).

In Elalfy et al. (n = 18)[33] the proportions of patients achieving a platelet response was 83% in the romiplostim arm and 0% in the placebo arm. No statistical comparison between groups was reported. Platelet response was not defined and therefore, it is not possible to assess whether the threshold used and conditions required to be considered as having a platelet response were valid and relevant according to the definitions described in the guidelines and used in clinical practice.

Need for Rescue Medication:

The proportions of patients initiating rescue medication were similar between treatment groups in Tarantino et al (41% vs. 45%, p = 0.7103; n = 62).[34] In Elalfy et al. (n = 18)[33] the corresponding proportions were 8% in the romiplostim arm and 33% in the placebo arm; however, no statistical comparison between groups was reported.

Bleeding:

Clinically significant bleeding was assessed and reported in Tarantino et al. (n = 62)[34] using the grade ≥ 2 AEs of bleeding; the rate of events (i.e., the total number of events/100 patient-weeks) was 8% in the romiplostim arm and 18% in the placebo arm over 24 weeks (p = 0.0006). The magnitude of the point estimate for the between-group difference may be considered clinically meaningful according to current clinical practice standards. This outcome was not collected in Elalfy et al.[33]

Health-Related Quality of Life:

HRQoL was assessed in Tarantino et al. (n = 62)[34] and reported in Mathias et al.[35] using the KIT questionnaire, which would be completed by both children and parents. For Child Self-Report, the mean (SD) difference within treatment groups for change from baseline to Week 25 was 13.7 (16.7) in the romiplostim arm and 9.8 (15.7) in the placebo arm. The between-group difference in change from baseline was not reported, and the p-value was reported as non-significant. For Parent Impact, the mean (SD) change from baseline was 17.5 (16.7) in the romiplostim arm and 12.8 (16.3) in the placebo arm (between-group difference not reported, p =

0.015). Considering the MCID estimates identified in the literature,[31] the point estimates for the between-group differences would not be considered clinically meaningful.

Function:

No data were reported for the outcome of function.

Harms Outcomes:

High proportions of patients experienced SAEs in Tarantino et al. (n = 62)[34] and proportions were higher with romiplostim than with placebo (24% versus 5%, respectively). In Elalfy et al. (n = 18)[33] AEs were experienced by 50% of patients in both groups, and the proportion of patients experiencing SAEs was not reported. No deaths were reported in the studies.

Rituximab versus Placebo RCTs

Assessment of the effectiveness of rituximab compared to placebo was inconclusive due to the lack of evidence, as no comparative RCTs could be identified, while the observational study included only presented descriptive comparisons with TPO-RAs.

Rituximab, Romiplostim and Eltrombopag – Observational Evidence

Platelet Response:

ICON1 (n = 120)[36] assessed platelet response as the within-group change from Month 1 to Month 6; findings for these comparisons are reported as descriptive information as a result of the lack of statistical between-group comparisons. The proportions of patients with either a complete or a partial response to treatment were 79% at 6 months vs 55% at 1 month with rituximab (p = 0.0003), 83% at 6 months vs 52% at 1 month with romiplostim (p = 0.0001), and 67% at 6 months vs 55% at 1 month with eltrombopag (p reported as not meeting the a priori defined threshold for statistical significance). The thresholds set in the study for achieving a complete or partial platelet response were consistent with the international standardized definition,[3] but had to be met for at least 50% of the platelet counts over the time period. One limitation to the interpretation of this outcome assessment is that the effect of the medications will be already observed by Month 1. Therefore, the within-group change from Month 1 to Month 6 should not be viewed as the true treatment effect; findings will speak to the capacity of the drug to maintain efficacy over time rather than informing on the proportions of patients who responded to the drugs compared to before it was initiated.

Need for Rescue Medication:

The reduction in use of rescue therapy from 1 to 6 months was 6.1% with rituximab, 12.5% with romiplostim, and 40% with eltrombopag. No confidence intervals were reported. This suggests that response to treatment in patients who received eltrombopag was achieved while requiring less rescue medication over time. Further interpretation of the results is limited by the fact that the use of concomitant ITP drugs at baseline and throughout the study was not reported. Differential use of rescue medications has the potential to impact other outcome results, the direction of which would be against eltrombopag.

Bleeding:

The proportions of patients with grade 1 – 2 bleeding decreased from baseline to 6 months within each individual treatment. In patients who received rituximab, the proportions of patients experiencing skin bleeding were 81.4% at baseline versus 36.4% at 6 months (p < 0.0001), and the proportions of patients experiencing non-skin bleeding were 53.5% at baseline versus 15.2% at 6 months (p = 0.003). In patients who received romiplostim, the corresponding proportions for skin bleeding were 83.9% at baseline versus 50.0% at 6 months (p = 0.024), and, for non-skin bleeding, were 58.1% at baseline versus 33.3% at 6 months (p = 0.264). Finally, in patients who received eltrombopag, the corresponding proportions for skin bleeding were 85.0% at baseline versus 26.7% at 6 months (p = 0.005), and, for non-skin bleeding, were 50.0% at baseline versus 20.0% at 6 months (p = 0.276).

Health-Related Quality of Life:

HRQoL was assessed using the KIT questionnaire. Median and range were reported both at baseline and at 12 months; difference within treatment groups were calculated, while the publication reported p-values. The median within-group change from baseline to 12 months was 18.5 with rituximab (p < 0.0001), 11.9 with romiplostim (p = 0.0001), and 15.1 with eltrombopag (p = 0.0003). It

should be noted that there was significant patient attrition at 12 months, and that these results are based on a limited sample of the initial study population. The magnitude of the within-group differences appears consistent with that reported in one RCT,[34] suggesting that there might be clinically meaningful improvement in HRQoL after 12 months of treatment with all three agents.

Function:

No data were reported for the outcome of function.

Harms Outcomes:

No harms data were reported.

Table 5: Outcomes Assessing Platelet Count Response

Interventions	Eltrombopag vs placebo		Romiplostim vs placebo		Rituximab vs Romiplostim vs Eltrombopag
Study	**Bussel 2015[30] (PETIT)**	**Grainger 2015[32] (PETIT2)**	**Tarantino 2016[34]**	**Elalfy 2011[33]**	**Grace 2019[36] (ICON1)**
Platelet Count Response					
Primary outcome	**Proportion of patients achieving a platelet count of ≥ 50×10^9/L at least once from weeks 1 to 6, in the absence of rescue therapy**	**Proportion of patients achieving a platelet count of ≥ 50×10^9/L, in the absence of rescue therapy for ≥ 6 weeks from Week 5 to 12**	**Proportions of patients achieving weekly platelet counts of ≥ 50×10^9/L in at least 6 of the final 8 weeks (no rescue medication within 4 weeks)**	**Not defined in the publication**	**Proportions of patients with platelet response (complete + partial)[a] – Within-group change from 1 to 6 months**
	Eltrombopag (N = 45): 62% Placebo (N = 22): 32% at week 6 OR 4.31 (95% CI 1.39 - 13.34); p = 0.011	Eltrombopag (N = 63): 40% Placebo (N = 29): 3% at week 12 OR 18.0 (95% CI 2.3 - 140.9); p = 0.0004	Romiplostim (N=42): 52% Placebo (N = 20): 10% at 24 weeks OR 9.1 (95% CI 1.9 - 43.2); p = 0.002	Romiplostim (N=12): 83% Placebo (N = 6): 0% no statistical comparison reported	Rituximab: 79% at 6 months (N=33) vs 55% at 1 month (N=42); Romiplostim: 83% at 6 months (N=24) vs 52% at 1 month (N=29); Eltrombopag: 67% at 6 months (N=15) vs 55% at 1 month (N=20).
Relevant secondary outcome	**Proportion of patients achieving a platelet count of ≥ 50×10^9/L in at least 60% of assessments from weeks 2 to 6**	**Likelihood of maintaining a response (repeated-measures analysis of platelet response during 12 weeks)**	**Proportions of patients achieving at least 4 weekly platelet counts ≥ 50×10^9/L (no rescue medication) during study**	**None reported**	**Proportions of patients with complete response / Proportions of patients with partial response**
	Eltrombopag (N = 45): 36% Placebo (N = 22): 0% at week 6 OR 5.84 (95% CI 1.18 - 28.90); p = 0.0017	Eltrombopag (N = 63) vs Placebo (N = 29) Over 12 weeks: OR 25.3 (95% CI 8.2 - 78.7); p < 0.0001	Romiplostim (N=42): 71% Placebo (N = 20): 20% at 24 weeks OR 9.0 (95% CI 2.5 - 32.3); p = 0.0002	—	Rituximab: 19% / 36% at 1 month (N=42) 52% / 27% at 6 months (N=33) 55% / 26% at 12 months (N=31) Romiplostim: 21% / 31% at 1 month (N=29) 71% / 15% at 6 months (N=24) 56% / 25% at 12 months (N=16) Eltrombopag: 30% / 25% at 1 month (N=20) 27% / 40% at 6 months (N=15) 42% / 33% at 12 months (N=12)

CI = confidence interval; nr=not reported; OR = odds ratio; ns = did not meet the a priori defined threshold for statistical significance.

[a] Complete platelet response: ≥ 50% of platelet counts >100 × 10^9/L. Partial platelet response: ≥ 50% of platelet counts >30 × 10^9/L and twice the baseline value

Table 6: Additional Outcomes

Interventions	Eltrombopag vs placebo		Romiplostim vs placebo		Rituximab vs Romiplostim vs Eltrombopag
Study	**Bussel 2015[30] (PETIT)**	**Grainger 2015[32] (PETIT2)**	**Tarantino 2016[34]**	**Elalfy 2011[33]**	**Grace 2019[36] (ICON1)**
Initiation of rescue therapy	Eltrombopag (N = 45): 13% Placebo (N = 22): 50% over 6 weeks OR 0.1 (95% CI 0.04 - 0.49); p = 0.0020	Eltrombopag (N = 63): 19% Placebo (N = 29): 24% over 12 weeks OR 0.44 (95% CI 0.2 - 0.9); p = 0.032	Romiplostim (N=42): 41% Placebo (N = 20): 45% over 24 weeks p = 0.7103	Romiplostim (N=12): 8% Placebo (N = 6): 33%	**Reduction from 1 to 6 months in the use of rescue medication** Rituximab (N=33): 6.1% Romiplostim (N=24): 12.5% Eltrombopag (N=15): 40%
Clinically significant bleeding	**WHO Grade 2 – 4 Logistical regression model**	**WHO Grade 2 – 4 Proportions**	**Grade ≥ 2 AEs of bleeding**	**None reported**	**None reported**
	Eltrombopag (N = 45): 27% Placebo (N = 22): 59% over 6 weeks OR 0.21 (95% CI 0.06 - 0.72); p = 0.013	Baseline Eltrombopag (N = 63): 25% Placebo (N = 29): 21% End of study (week 12) Eltrombopag (N = 63): 5% Placebo (N = 29): 7%	Rate (events/100 patient-weeks) Romiplostim (N=42): 8 Placebo (N = 20): 18 over 24 weeks p = 0.0006	—	—
HRQoL **Change from baseline in KIT scores**	**Change from baseline to week 6, Mean (SD)**	**None reported**	**Change from baseline to week 25, Mean (SD)**	**None reported**	**Within-group change from baseline to 12 months, Median (range)**
	Eltrombopag (N = 20): 3 (10) Placebo (N = 22): 2 (8) Mean difference –1.5 (95% CI –8.1 to 5.1); p=0.64	—	**Child self-report** Within-group change: Romiplostim (N=28): 13.7 (16.7) Placebo (N = 11): 9.8 (15.7) Between-group: ns **Parent impact** Within-group change: Romiplostim (N=37): 17.5 (16.7) Placebo (N = 16): 12.8 (16.3) Between-group: p = 0.015	—	Rituximab Baseline (N=43): 66.7 (32.7 - 96.2) 12 months (N=31): 85.2 (47.1 - 100.0) Romiplostim Baseline (N=31): 75.6 (51.0 - 98.1) 12 months (N=16): 87.5 (70.2 - 99.0) Eltrombopag: Baseline (N=20): 69.9 (43.3 - 94.2) 12 months (N=12): 85.0 (61.5 - 97.1)
Harms outcomes	AEs Eltrombopag (N = 45): 82% Placebo (N = 22): 95% SAEs Eltrombopag (N = 45): 9% Placebo (N = 22): 10% Deaths nr	AEs Eltrombopag (N = 63): 81% Placebo (N = 29): 72% SAEs Eltrombopag (N = 63): 8% Placebo (N = 29): 14% Deaths nr	AEs nr SAEs Romiplostim (N=42): 24% Placebo (N = 20): 5% Deaths nr	AEs Romiplostim (N=12): 50% Placebo (N = 6): 50% SAEs nr Deaths nr	nr

AEs = adverse events; CI = confidence interval; nr=not reported; HRQoL = health-related quality of life; KIT = Kid's ITP Tools; OR = odds ratio; nr = not reported; ns = did not meet the a priori defined threshold for statistical significance; SAEs = serious adverse events.

Discussion

Summary of Evidence

The aim of this HTA was to review the clinical effectiveness and safety of TPO-RAs (i.e., eltrombopag and romiplostim) and rituximab in children with ongoing active ITP after failure of first-line therapies. The project scope and research protocol were informed by engaging with patient groups to better understand the challenges associated with pediatric ITP and current treatments. A total of 8 publications met the final inclusion criteria, reporting findings from 5 unique studies on the use of eltrombopag, romiplostim and rituximab as second-line treatments in pediatric patients with ITP.

Overall, the studies included in the systematic review were performed in pediatric patients (< 18 years of age) with a confirmed diagnosis of ITP of various duration, who still had active disease after having tried at least one prior treatment option. Most studies required patients to have chronic ITP (ongoing, active disease lasting longer than 12 months), with a platelet count < 30×10^9/L prior to study entry. Two DB RCTs compared eltrombopag to placebo over 6 or 12 weeks; both were rated as having a low risk of bias for most outcomes. Two studies evaluated the use of romiplostim; one had some concern for the risk of bias, and the other had a high risk of bias. Of these, one DB RCT compared romiplostim to placebo over 24 weeks, while one small single-blinded pilot RCT compared romiplostim to placebo over 15 weeks. Finally, one prospective, longitudinal cohort study assessed the efficacy of rituximab, romiplostim and eltrombopag given as monotherapy over a maximum of 12 months; the study was rated as having a serious risk of bias. The populations in the studies contributing to the evidence were considered generalizable to most children with ITP in the clinical setting. The primary efficacy outcome was platelet response. Considering the clinical and methodological heterogeneity of the included studies with respect to methodology, outcomes definition and measurement, timing of assessment, and populations, the studies were deemed too heterogenous to combine statistically and findings were synthesized narratively.

Interpretation of Clinical Results

Eltrombopag versus Placebo - RCTs

Evidence from two DB RCTs (n = 159) with a low risk of bias suggests that eltrombopag likely results in a clinically important increase in the proportions of patients achieving a platelet response at 6 weeks and at 12 weeks compared to placebo. At least one outcome definition for platelet response in each study was considered stringent, meaning that patients who were counted as responders had to achieve an adequate platelet count threshold and maintain the response over time. Eltrombopag likely results in a clinically important reduction in the use of rescue therapy throughout the study durations compared to placebo, therefore preventing exposition of patients to the numerous harmful AEs associated with the use of IVIG or prednisone. In addition, eltrombopag likely results in a clinically important reduction in clinically significant bleeding compared with placebo. There is however uncertainty being introduced by the small sample sizes of the studies, resulting in wide confidence intervals for between-group comparisons, suggesting a large range of possible effects for eltrombopag versus placebo. One DB RCT assessed the impact of eltrombopag on HRQoL; findings suggest that the drug may not result in a clinically important improvement compared to placebo after 6 weeks, but the evidence is very uncertain due to several limitations. It should be noted that large amounts of missing data for HRQoL had the potential to bias the outcome, and that differential use of rescue therapy may overestimate measures of efficacy in the placebo group. The magnitude and direction of the sum of all sources of bias are uncertain and significantly affect our confidence in the findings. The harms profile of eltrombopag was similar to that of placebo in the studies and did not raise new safety concerns.

Romiplostim versus Placebo - RCTs

Evidence from one DB RCT (n = 62) with some concern for the risk of bias suggests that romiplostim may result in a clinically important increase in the proportions of patients achieving a platelet response at 24 weeks compared to placebo. The key outcome definition for platelet response was considered stringent, as once again, patients who were counted as responders had to achieve an adequate platelet count threshold and maintain the response over time. However, the lack of information reported regarding missing outcome data and how they were handled introduced uncertainty across all outcomes, as it is possible that missing data amount to proportions sufficiently high to impact the results. The magnitude and direction of potential bias is uncertain. Findings suggest that romiplostim may also result in a clinically important reduction in clinically significant bleeding compared with placebo. Once again,

uncertainty is being introduced by the small sample sizes of the study, resulting in wide confidence intervals for between-group comparisons, suggesting a large range of possible effects for romiplostim versus placebo. Romiplostim may not result in a clinically important reduction in the use of rescue therapy in the study compared to placebo, or in between-group improvement in HRQoL compared to placebo at 25 weeks. In the study though, within-group improvements in HRQoL were observed with both romiplostim and placebo, the magnitude of which was not considered clinically significant; this may be indicative of a confoundant overestimating treatment effect in the placebo group. Finally, romiplostim was associated with additional toxicity in the study compared with placebo. Overall, uncertainty suggests some caution in the interpretation of efficacy and safety findings.

One small single-blinded pilot RCT comparing romiplostim to placebo was included in the systematic review, but contributed only minimally to the available evidence. The high risk of bias, combined with the small sample size of 18 patients and concerns regarding generalizability of the population to the Canadian setting, introduced substantial uncertainty and considerably diminished our confidence in the findings. Poor reporting regarding key outcome definitions and lack of statistical comparison between groups also limited the conclusions that could be drawn from this study.

Romiplostim and Eltrombopag – Observational Evidence

As part of the overall body of evidence, findings from one observational study that included eltrombopag, romiplostim, and rituximab arms may help to inform decision-making regarding the optimal use of ITP medications in children who failed to respond to first-line therapy in the context of limited evidence. Findings were however reported only as descriptive information as a result of the lack of statistical between-group comparisons, which constitutes a major limitation to the evidence. Additionally, the lack of randomization and other methodological limitations place the study at serious risk of bias. The observational cohort study supports the conclusions drawn from the RCTs, suggesting that romiplostim and eltrombopag may result in a clinically important, long-lasting platelet response, as assessed within each treatment group, as well as in a clinically important improvement in HRQoL over up to 12 months, providing that the uncertainty surrounding the results is taken into account when interpreting the findings. As missingness reasons were not detailed in the publications, it is not possible to assess whether patients discontinued due to non-response, or whether some patients may have experienced spontaneous remission; therefore, the magnitude and direction of potential bias cannot be ascertained. Romiplostim and eltrombopag may also be effective at reducing bleeding; however, interpretation of the results is made difficult by the absence of details on the evaluation tool used to assess bleeding, as Grade 1 – 2 AEs of bleeding, or WHO Grade 1 – 2 bleeding, would not be considered clinically meaningful bleeding events. Therefore, although the findings suggest a substantial reduction in some types of bleedings, there is uncertainty as to whether this corresponds to clinically relevant events that have a negative impact on patients.

As part of the overall body of evidence, findings from this observational study may help inform decision-making regarding the optimal use of second-line ITP medications in children in the context of limited RCT evidence in this patient population, as long as the uncertainty surrounding the results is taken into account when interpreting the results.

Rituximab – RCTs and Observational Evidence

As no RCT was identified in the literature comparing rituximab to placebo, the within-arm evidence from the observational study alone is too uncertain to adequately inform on the use of rituximab in the patient population. The study was at serious risk of bias and there were no formal between-group comparisons. In addition, the study did not assess harms outcomes, which constitutes the main drawback of using rituximab in children. Therefore, assessment of the effectiveness and safety of rituximab was inconclusive due to the lack of evidence.

Strengths and Limitations of the Systematic Review

Strengths

The systematic review was developed using robust methodology. The research protocol was developed a priori, registered with the PROPSERO database, and a detailed scoping plan was posted publicly for stakeholder input. Input from those with lived experience was used to inform the research protocol. The literature search was comprehensive and the included studies list was also publicly posted for stakeholder feedback. Evidence collection and evaluation of the quality of the studies was completed using methods that reduced the risk of bias and error.

Limitations

The systematic review was based on limited availability of evidence. No head-to-head RCT in the target patient population was identified in the literature; therefore, the evidence relies on placebo-controlled trials. We discourages the use of informal naïve 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. Most included studies were of relatively small sample size, introducing some uncertainty in the findings, which were affected by wide variability. The organization acknowledges that ITP is a rare disease in children, and that large RCTs in this patient population are impractical; in this particular context, decision-makers may consider tolerating a greater level of uncertainty when interpreting the findings and drawing conclusions regarding the use of eltrombopag and romiplostim. One comparative observational study was included in the review, but only descriptive comparisons across drugs could be made, as the study authors performed no formal comparisons; due to serious risk of bias, results from the study should be interpretated with caution and findings should be viewed as complementary to those from RCTs.

Conclusions and Implications for Decision or Policy-Making

There is an unmet need in children with ITP who did not respond to first-line therapy; input from clinical experts suggests that without access to TPO-RAs, patients are being exposed to subsequent-line off-label therapies, with uncertainty surrounding their effectiveness and numerous potential harms such as immunosuppression. Considering the balance of benefits and harms, patient preference and feasibility, guidelines[1,2] recommend the use of TPO-RAs in this patient population rather than rituximab or other subsequent-line treatments. A high value is being placed on avoiding immunosuppression in the pediatric population,[1] which was also emphasized in the literature[12-14] and by the clinical experts consulted for this review. The clinical experts noted that splenectomy is not an appropriate treatment option in children with ITP, considering the unclear efficacy, the risks associated with such major surgical procedure, equity concerns, and long-term harms such as permanent immunosuppression posing the risk of life-threatening infections and leading to prolonged antibiotic prophylaxis.[19-21]

To determine what treatment(s) should be used in pediatric patients with ITP who have failed first-line treatments, a systematic review of the efficacy of treatments was undertaken at the request of public drug plans. A narrative review of 8 publications , reporting findings from 4 RCTs and one observational cohort study, informed the conclusions. Evidence from two DB RCTs with a low risk of bias and one comparative cohort study suggests that eltrombopag likely increases and maintains platelet response over time compared to placebo. Eltrombopag also likely reduces the use of rescue medication and clinically significant bleeding compared to placebo, which were considered clinically meaningful to patients. Evidence from one DB RCT and one comparative cohort study suggests that romiplostim may also increase and maintain platelet response, as well as reduce clinically significant bleeding compared to placebo; as the evidence was scarce and potentially subject to bias, uncertainty suggests a need for caution in the interpretation of the findings. Due to the scarcity of evidence in the patient population conclusions could not be drawn for the impact of TPO-RAs on HRQoL and function in children. Assessment of the effectiveness of rituximab was inconclusive due to the lack of evidence. It is worth noting that ITP is a rare disease in children and larger RCTs may not be feasible.

Jurisdictions may consider revisiting reimbursement criteria for eltrombopag and romiplostim, for use after failure of first-line therapies in children with ongoing active ITP. In addition, no evidence was identified in support of trying rituximab prior to accessing TPO-RAs.

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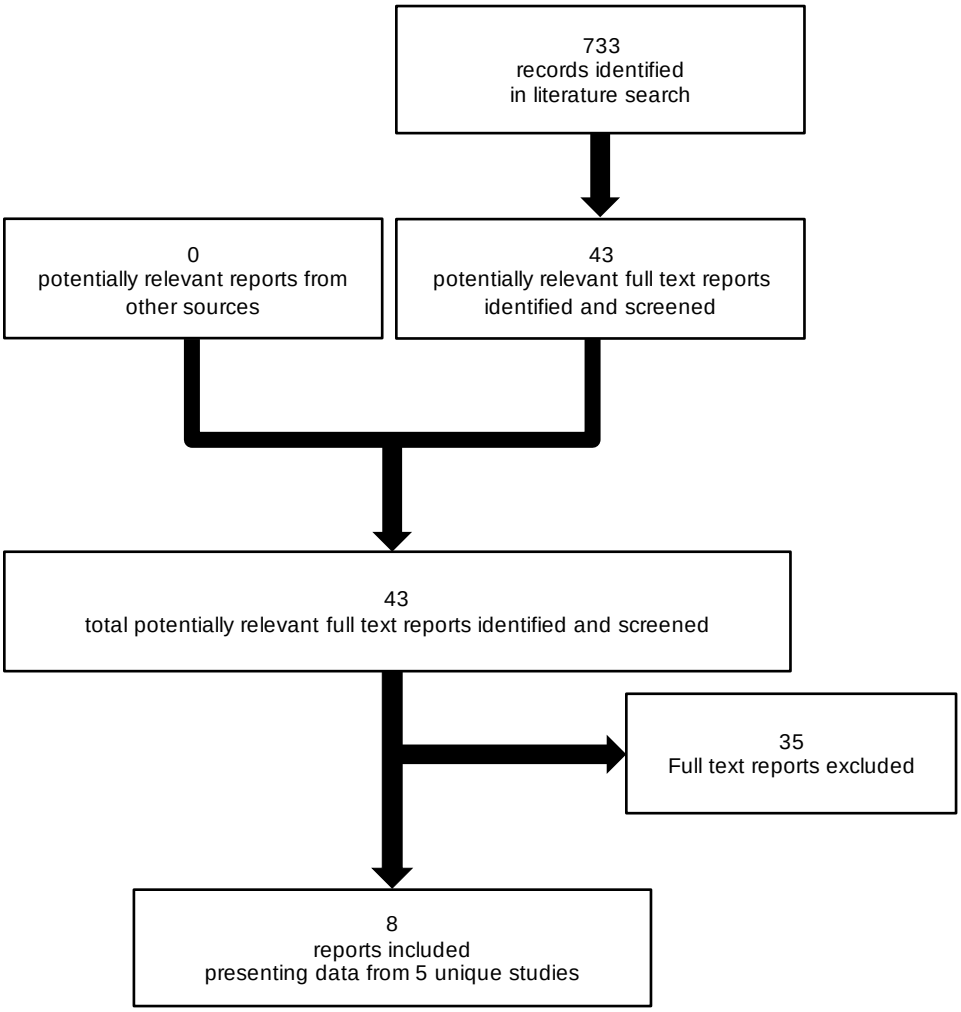
39. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *Res Involv Engagem.* 2017;3:13.

Appendix 1: Flow Diagram of Selection Process

Figure 1 : Flow Diagram of the Selection Process



Alt Text: The flow diagram indicates that 733 records were identified in the initial literature search. Subsequently, 43 potentially relevant reports were identified and screened by full text. A total of 8 reports were included in the final analyses which presented data from 5 unique studies.

Appendix 2: 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 7: 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
.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

Multi-Database 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 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

Appendix 3: List of Included Studies

Randomized Controlled Trials

1. PETIT Main publication:

   Bussel JB, de Miguel PG, Despotovic JM, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. *Lancet Haematol.* 2015;2(8):e315-325.

   Related publication:

   Grainger JD, Blanchette VS, Grotzinger KM, Roy A, Bussel JB. Health-related quality of life in children with chronic immune thrombocytopenia treated with eltrombopag in the PETIT study. *Br J Haematol.* 2019;185(1):102-106.

2. PETIT2 Main publication:

   Grainger JD, Locatelli F, Chotsampancharoen T, et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet.* 2015;386(10004):1649-1658.

3. Main publication:

   Tarantino MD, Bussel JB, Blanchette VS, et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet.* 2016;388(10039):45-54.

   Related publication:

   Mathias SD, Li X, Eisen M, Carpenter N, Crosby RD, Blanchette VS. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Determine the Effect of Romiplostim on Health-Related Quality of Life in Children with Primary Immune Thrombocytopenia and Associated Burden in Their Parents. *Pediatr Blood Cancer.* 2016;63(7):1232-1237.

4. Main publication:

   Elalfy MS, Abdelmaksoud AA, Eltonbary KY. Romiplostim in children with chronic refractory ITP: randomized placebo controlled study. *Ann Hematol.* 2011;90(11):1341-1344.

Observational Studies

1. Main publication:

   Grace RF, Shimano KA, Bhat R, et al. Second-line treatments in children with immune thrombocytopenia: Effect on platelet count and patient-centered outcomes. *Am J Hematol.* 2019;94(7):741-750.

   Related publication:

   Grace RF, Klaassen RJ, Shimano KA, et al. Fatigue in children and adolescents with immune thrombocytopenia. *Br J Haematol.* 2020;191(1):98-106.

Appendix 4: List of Excluded Studies

Author (year)	Reason for Exclusion	Reference
RCT		
Grainger 2023	Design	Blood Advances 2023 7(3):396-405
Shimano 2021	Population	BMJ Open 2021 11(8):e044885
White 2020	Design	British Journal of Haematology 2020 191(1)(15-16
Gurlek Gokcebay 2018	Design	Transfusion & Apheresis Science 2018 57(3):416-417
Anonymous 2017	Unavailable	Blood. Conference: 59th Annual Meeting of the American Society of Hematology, ASH 2017 130(Supplement 1):
Uhl 2017	Population	Transfusion 2017 57(10):2532-2538
Chaturvedi 2016	Design	Lancet 2016 388(10039):4-6
Anonymous 2015	Design	The Lancet Haematology 2015 2(10):
Grainger 2015	Design	The Lancet 2015 386(10004)(1630
Neunert 2015	Design	Lancet 2015 386(10004):1606-9
Bussel 2015	Design	Pediatric Blood & Cancer 2015 62(2):208-213
Seidel 2014	Design	British Journal of Haematology 2014 165(3):419-21
Kluter 2012	Population	American Journal of Hematology 2012 87(5):558-61
Citak 2011	Design	Journal of Tropical Pediatrics 2011 57(1):71-2
Anonymous 2010	Unavailable	Annals of Hematology. Conference: 3rd Intercontinental Cooperative ITP Study Group 2010 89(SUPPL. 1):
Bay 2006 (J Peds)	Design	Journal of Pediatrics 2006 148(3):423-4; author reply 424
Bay 2006 (Peds Int)	Design	Pediatrics International 2006 48(5):514-6
Bennett 2006	Design	Blood 2006 107(7):2639-42
Taube 2006	Design	Journal of Pediatrics 2006 148(3):423
Roganovic 2005	Design	European Journal of Pediatrics 2005 164(5):334
Observational studies		
Fang 2023	Design	Expert Opinion on Drug Safety 2023 1-8
Chaudhury 2021	Intervention	Archives of Disease in Childhood 2021 106(9):929-931
Yasser 2020	Design	Pediatric Hematology/Oncology and Immunopathology 2020 19(3)(26-30
Depre 2018	Design	PLoS ONE [Electronic Resource] 2018 13(6):e0198184
Neunert 2016	Design	Pediatric Blood & Cancer 2016 63(8):1407-13
Weide 2016	Design	Oncology Research and Treatment 2016 39(1-2):41-4
Ghanima 2014	Design	Haematologica 2014 99(5):937-44
Ramaswamy 2014	Design	Journal of Pediatrics 2014 165(3):600-5.e4
Saleh 2013	Population	Blood 2013 121(3):537-45
Grace 2012	Outcome	Pediatric Blood & Cancer 2012 58(2):221-5
Perel 2012	Design	Archives de Pediatrie 2012 19(6 SUPPL. 1)(H168-H169
Wang 2005	Design	Journal of Pediatrics 2005 146(2):217-21

Appendix 5: Summary of Study Characteristics

Table 8: Details of Included RCTs

	Bussel 2015[30] (PETIT)	Grainger 2015[32] (PETIT2)	Tarantino 2016[34]	Elalfy 2011[33]
Designs & Populations				
Study Design	DB phase 2 RCT	DB phase 3 RCT	DB phase 3 RCT	Single-blind pilot RCT
Enrolment dates	March 17, 2010 to January 15, 2013	March 15, 2012 to January 2, 2014	January 24, 2012 to February 19, 2015	March 2010 to July 2010
Locations	Multicenter: 22 centers in US, Canada, UK and Europe	Multicenter: 38 centers US, UK, Europe and Asia	Multicenter: 27 centers in US, Canada and Australia	Single center: Egypt
Randomized	N = 67 Randomized in a 2:1 ratio. Stratified by age cohort.	N = 92 Randomized in a 2:1 ratio. Stratified by age cohort.	N = 62 Randomized in a 2:1 ratio. Stratified by age cohort.	N = 18 Randomization was not described
Place in Therapy	Patients < 18 years with diagnosis of ITP who have active disease, i.e., who relapsed or are refractory, after having tried ≥ 1 prior treatment option.			Patients with ITP who failed to maintain response to ≥ 2 prior treatment options.
Inclusion Criteria	• Patients 1 to 17 years. • Confirmed ITP lasting for at least 6 months. • Relapsed or refractory to at least 1 treatment or not eligible to other treatments. • Platelet count < $30x10^9$/L.	• Patients 1 to 17 years. • Confirmed ITP lasting for more than 12 months. • Relapsed or refractory to at least 1 treatment. • Platelet count < $30x10^9$/L.	• Patients 1 to <18 years. • Confirmed ITP lasting for at least 6 months. • Disease continuing after at least 1 prior treatment. • Mean of two platelet counts ≤ $30x10^9$/L, with no single count > $35x10^9$/L.	• No age criterion reported. • Confirmed ITP lasting for more than 12 months. • Non-responder (or failed to maintain response) to at least 2 prior treatments. • No platelet count criterion reported.
Exclusion Criteria	• Presence of other hematological disorders.	• None reported.	• History of bone marrow stem cell disorder, malignancy, congenital thrombocytopenia, VTE or thrombotic events. • Recent rituximab or splenectomy.	• History of bone marrow disorder or serious bleeding. • Splenectomy.
Drugs				
Intervention	**Eltrombopag** orally once daily		**Romiplostim** SC injection once weekly	
Starting Dose	Starting dose according to age.		Starting dose of 1 µg/kg.	
Dose Adjustments	Based on target platelet count 50 – $200x10^9$/L.			Dose escalated to 5 µg/kg/week, then tapered.
Maximal Dose	Maximum dose of 75 mg per day.		Maximum dose of 10 µg/kg.	
Comparator(s)	Matching placebo			Placebo
Concomitant Medications	Stable dose of maintenance ITP medication.		Standard-of-care therapy at stable dose.	NR
Duration				
Length of follow-up	7 weeks	12 weeks	24 weeks	15 weeks

Outcomes				
Primary Outcome	Platelet count response *Outcome measure:* Proportion of patients achieving a platelet count of ≥ 50×10^9/L in the absence of rescue therapy[a] at least once from weeks 1 to 6.	Platelet count response *Outcome measure:* Proportion of patients achieving a platelet count of ≥ 50×10^9/L in the absence of rescue therapy[a] for ≥ 6 weeks throughout weeks 5 – 12.	Platelet count response *Outcome measure:* Incidence of durable platelet response, i.e., achieving weekly platelet responses (≥ 50 × 10^9/L with no rescue therapy[b] in prior 4 weeks) in ≥ 6 of the final 8 weeks.	Platelet count response *Outcome measure:* NR
Secondary / Exploratory Outcomes	• Platelet count response (additional measures) • Use of concomitant ITP medication and/or rescue treatment[a] • Bleeding: reduction in symptoms based on WHO bleeding scale • Change in HRQoL based on KIT questionnaire • Harms	• Platelet count response (additional measures) • Use of ITP rescue treatment[a] • Bleeding: incidence based on WHO bleeding scale • Harms	• Platelet count response (additional measures) • Use of ITP rescue treatment[b] • Bleeding: composite of clinically significant bleeding (Grade ≥ 2 AEs) and/or use of rescue medication for prevention • Change in HRQoL based on KIT questionnaire • Harms	• Use of IVIG • Bleeding (assessed but not reported) • Harms
Notes				
Funding Source	GlaxoSmithKline		Amgen	NR
Publications	Bussel 2015[30] Related publication: Grainger 2019[31]	Grainger 2015[32]	Tarantino 2016[34] Related publication: Mathias 2016[35]	Elalfy 2011[33]

AEs = adverse events; DB = double-blind; HRQoL = health related quality of life; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; KIT = Kid's ITP Tools; NR = not reported; RCT = randomized controlled trials; SC = subcutaneous; UK = United Kingdom; US = United States; VTE = venous thromboembolism; WHO = World Health Organization.

[a] Rescue therapy was defined in the studies as any new ITP drug, dose increase in a concomitant ITP drug, platelet transfusion, or splenectomy.[30,32]

[b] Rescue therapy was defined in the study as either: any medication intended to increase platelet count or to treat or prevent bleeding; or any increase in dose or frequency of concomitant ITP therapy; or addition of a new ITP therapy.[34]

Table 9: Details of Included Cohort Study

	Grace 2019[36] (ICON1)
Designs & Populations	
Study Design	Prospective, longitudinal cohort study
Enrolment dates	September 2013 to December 2015
Locations	Multicenter: 21 centers in US and Canada
N	120
Place in Therapy	Patients < 18 years with diagnosis of ITP starting second-line treatments as monotherapy.
Inclusion Criteria	• Patients 1 to 17 years with ITP of any duration. • Starting second-line treatments as monotherapy (any treatment allowed except observation, IVIG, corticosteroids, or anti-D immunoglobulin).
Exclusion Criteria	• Patients with Evans syndrome with prior or ongoing autoimmune hemolytic anemia (other patients with secondary ITP could be included).
Drugs	
Interventions	Any ITP treatment based on physician and patient preference. A minimum of 15 evaluable patients was required for a treatment to be included in the study cohort
Concomitant Medications	NR
Duration	
Length of follow-up	12 months (primary analyses were performed at 1 month and at 6 months)
Outcomes	
Primary Outcome	Platelet count response *Outcome measure:* Change in response category from baseline visit (within-group and between-group): Complete platelet response (CR): ≥ 50% of platelet counts >100 × 10^9/L Partial platelet response (PR): ≥ 50% of platelet counts >30 × 10^9/L and twice the baseline value No response (NR): any platelet count change not meeting the criteria for CR or PR
Secondary / Exploratory Outcomes	• Bleeding: change in bleeding score on IBLS (dichotomized into grade 0 / grade 1-2 bleeding, and into skin / non-skin bleeding) • Use of ITP rescue treatment (i.e., corticosteroids and IVIG) • Change in HRQoL based on KIT questionnaire
Notes	
Funding Source	Pediatric ITP Consortium of North America (ICON)
Publications	Grace 2019[36] Related publication: Grace 2020[37]

IBLS = ITP Bleeding Scale; ITP = immune thrombocytopenia; IVIG = intravenous immunoglobulin; KIT = Kid's ITP Tools; NR = not reported; US = United States.

Table 10: Summary of Baseline Patient Characteristics – RCTs

Baseline Characteristics	Bussel 2015[30] (PETIT)		Grainger 2015[32] (PETIT2)		Tarantino 2016[34]		Elalfy 2011[33]	
	Eltrombopag N = 45	Placebo N = 22	Eltrombopag N = 63	Placebo N = 29	Romiplostim N = 42	Placebo N = 20	Romiplostim N = 12	Placebo N = 6
Age in years	Mean (95% CI)		Mean (95% CI)		Median (IQR)		Median (range)	
	9 (8 - 10)	10 (8 - 12)	9.4 (8.2 - 10.5)	9.8 (8.3 - 11.3)	10 (6 - 14)	7.5 (6.5 - 13.5)	9.5 (2.5 - 16)	7 (4 - 15)
Age cohorts, n (%)								
12-17 years	16	8	23	10	16 (38)	7 (35)	nr	
6-11 years	19	9	26	13	18 (43)	9 (45)		
1-5 years	10	5	14	6	8 (19)	4 (20)		
Sex, n (%)								
Boys	18 (40)	9 (41)	33 (52)	15 (52)	18 (43)	9 (45)	10 (83)	3 (50)
Girls	27 (60)	13 (59)	30 (48)	14 (48)	24 (57)	11 (55)	2 (17)	3 (50)
Ethnic origin, n (%)								
White	40 (89)	20 (91)	nr		nr		nr	
Caucasian	nr				26 (62)	15 (75)		
African-American					6 (14)	2 (10)		
Asian					3 (7)	2 (10)		
East Asian			20 (32)	10 (34)	nr			
Other	5 (11)	2 (9)	43 (68)	19 (66)	7 (17)	1 (5)		
Weight in kg	Mean (95% CI)		Mean (range)		nr		nr	
	39 (34 - 45)	43 (33 - 53)	41.0 (35.5 - 46.4)	42.7 (33.2 - 52.3)				
Average duration of ITP	nr		Time in months since diagnosis, mean (SD)		Time in years since diagnosis, median (IQR)		Disease duration in years, Median (range)	
			41 (34.1)	53 (40.3)	1.9 (1.0 - 4.2)	2.2 (1.5 - 3.7)	2.3 (1.2 - 7.0)	3.0 (1.5 - 6.5)
Disease duration – category, n (%)								
6-12 months	8 (18)	2 (9)	nr		nr		nr	
≥ 12 months	37 (82)	20 (91)						
Baseline platelet count (x10^9/L)	Mean (SD)		nr		Median (IQR)		Median (range)	
	15.5 (8.0)	12.4 (8.8)			17.8 (7.5 - 24.5)	17.7 (9.8 - 24.1)	10.5 (2 - 20)	10.5 (6 - 20)
≤15x10^9/L, n (%)	23 (51)	11 (50)	38 (60)	19 (66)	nr		nr	
Baseline concomitant ITP drug use								
Any, n (%)	5 (11)	2 (9)	13 (21)	1 (3.4)	5 (12)	4 (20)	nr	
Previous ITP medication, n (%)								
Any	43 (96)	22 (100)	60 (95)	28 (97)	nr		nr	
> 2 previous treatments	38 (84)	19 (86)	46 (73)	26 (90)				
Type, n (%)								
Corticosteroids	nr		nr		32 (76)	15 (75)	12 (100)	6 (100)
Anti-D immunoglobulin			13 (21)	3 (10)	12 (29)	7 (35)	nr	
IV immunoglobulin			nr		35 (83)	16 (80)		
Rituximab			9 (14)	6 (21)	11 (26)	7 (35)		
Other			nr		10 (23)	6 (30)		

CI = confidence interval; IQR = interquartile range; ITP = immune thrombocytopenia; nr = not reported; RCT = randomized controlled trial; SD = standard deviation.

Appendix 6: Risk of Bias Assessment

Table 11: Risk of Bias Assessment Per Outcome Within Each RCT Using RoB2[27]

Study	Randomization process	Deviations from intended interventions (assignment)	Deviations from intended interventions (adherence)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Bussel 2015[30] (PETIT)							
Platelet Response	**Low** Central, random component in the sequence generation process (telephone-based interactive voice). No apparent baseline imbalances.	**Low** Patients and study personnel blinded (matching placebo / no apparent differential toxicity). ITT analysis, patients with missing data included as non-responders (small amount that is unlikely to cause bias).	**Low** Patients and study personnel blinded to study treatment.	**Low** Small amount of missing data unlikely to cause bias.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Low** Data appeared to have been analyzed according to a pre-specified plan. Outcomes were assessed using one measurement tool.	**Low risk of bias**
Use of Concomitant / Rescue Medication							
Bleeding							
Harms							
HRQoL		**High** Large amount of missing data having the potential to bias the outcome.		**High** Large amount of missing data with potential of bias.			**High risk of bias**
Grainger 2015[32] (PETIT2)							
Platelet Response	**Low** Central, random component in the sequence generation process (telephone-based interactive voice). Baseline imbalances not incompatible with chance.	**Low** Patients and study personnel blinded to study treatment (matching placebo / no apparent differential toxicity). ITT analysis, patients with missing data included as having a negative response (small amount of missing data that is unlikely to cause bias).	**Low** Patients and study personnel blinded to study treatment.	**Low** Small amount of missing data unlikely to cause bias.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Low** Data appeared to have been analyzed according to a pre-specified plan. Outcomes were assessed using one measurement tool.	**Low risk of bias**
Use of Rescue Medication							
Bleeding							
Harms							
HRQoL	NR						

Study	Randomization process	Deviations from intended interventions (assignment)	Deviations from intended interventions (adherence)	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Tarantino 2016[34] (related publication: Mathias 2016[35] reporting on HRQoL)							
Platelet Response **Use of Rescue Medication** **Bleeding** **Harms** **HRQoL**	**Low** Central, random component in the sequence generation process (interactive voice response system). No apparent baseline imbalances.	**Some concern** Patients and study personnel blinded (matching placebo / no apparent differential toxicity). Type of analysis not reported. No information on the number of patients with missing data and how they were handled.	**Low** Patients and study personnel blinded to study treatment.	**Some concern** No information reported on missing outcome data and how they were handled.	**Low** Outcomes measured appropriately and similarly between groups. Outcome assessors unaware of treatment received.	**Low** Data appeared to have been analyzed according to a pre-specified plan. Outcomes were assessed using one measurement tool.	**Some concern** for the risk of bias
Elalfy 2011[33]							
Platelet Response	**Some concern** No details reported on randomization process / placebo.	**High** Single-blinded, no further detail on who was blinded, or on the appearance of placebo. No information on how missing data were handled.	**High** Single-blinded, no further detail. No analysis estimating the effect on bias.	**High** No information reported on missing outcome data and how they were handled.	**Low** Objective outcome; appropriate and similar measure between groups.	**High** No pre-specified analysis plan reported. Investigators may not have been blinded to outcome data.	**High risk of bias**
Harms					**High** Vulnerable to influence by knowledge of the intervention.		
Use of Concomitant / Rescue Medication **Bleeding** **HRQoL**	NR						

HRQoL = health-related quality of life; RoB2 = Cochrane Risk of Bias tool, version 2; NR = not reported.

Table 12: Risk of Bias Assessment Per Outcome for the ICON1 Observational Study Using ROBINS-I[28]

Grace 2019[36] (ICON1)	Confounding	Patient selection	Classification of interventions	Deviations from intended interventions	Missing data	Outcome measurement	Selection of reported results	Overall
Platelet Response	**Serious** Potential for confounding of the effect of interventions; no evidence from the publications that authors controlled for post-intervention variables that could have affected the intervention.	**Low** Treatment was initiated based on physician / patient preference after enrollment. All eligible patients expected to be included in the study; start of follow-up and start of intervention coincided.	**Moderate** Interventions well defined and based solely on information collected at time of intervention. Choice of treatment may however be influenced by disease characteristics.	**Low** Deviations from intended interventions reflected usual practice (no information suggested otherwise).	**Serious** Significant patient attrition reported. Proportions differed across interventions. Missingness reasons not detailed. No analyses intended to mitigate the risk of bias.	**Low** Comparable methods of assessment. Objective outcomes. No evidence of systematic error relative to intervention status.	**Moderate** No indication of selection of reported analysis; though possible, as multiple measurements likely for platelet counts.	**Serious** Uncontrolled for confounding. Missing data due to attrition.
Use of Rescue Medication							**Low** Reported results correspond to all intended outcomes, analyses and sub cohorts.	
Bleeding						**Serious** Outcomes vulnerable to influence by knowledge of the intervention received; assessors aware of intervention received.		**Serious** Uncontrolled for confounding. Missing data due to attrition. Subjective outcome assessed while aware of intervention received.
HRQoL								

HRQoL = health-related quality of life; ROBINS-I = Risk Of Bias In Non-randomized Studies – Interventions tool.

Appendix 7: Detailed Outcome Data

Table 13: Detailed Outcome Data – RCTs

Outcomes	Bussel 2015[30] (PETIT)		Grainger 2015[32] (PETIT2)		Tarantino 2016[34]		Elalfy 2011[33]	
	Eltrombopag N = 45	Placebo N = 22	Eltrombopag N = 63	Placebo N = 29	Romiplostim N = 42	Placebo N = 20	Romiplostim N = 12	Placebo N = 6
Platelet Response								
Primary outcome in the study	**Proportion of patients achieving a platelet count of ≥ 50×10⁹/L at least once from weeks 1 to 6, in the absence of rescue therapy**		**Proportion of patients achieving a platelet count of ≥ 50×10⁹/L, in the absence of rescue therapy for ≥ 6 weeks from Week 5 to 12**		**Proportions of patients achieving weekly platelet counts of ≥ 50×10⁹/L in ≥ 6 of the final 8 weeks (no rescue medication within 4 weeks)**		**Platelet response not defined in the publication**	
n (%)	28 (62)	7 (32)	25 (40)	1 (3)	22 (52)	2 (10)	10 (83)	0
OR (95% CI); p-value	4.31 (1.39 - 13.34); p=0.011		18.0 (2.3 - 140.9); p=0.0004		9.1 (1.9 - 43.2); p=0.002		nr	
Relevant secondary outcomes in the study	**Proportion of patients achieving a platelet count of ≥ 50×10⁹/L in ≥ 60% of assessments from weeks 2 to 6**		**Likelihood of maintaining a response (repeated-measures analysis of platelet response during 12 weeks)**		**Proportions of patients achieving at least 4 weekly platelet counts ≥ 50×10⁹/L (no rescue medication) during weeks 2 to 25**		nr	
n (%)	16 (36)	0	nr		30 (71)	4 (20)		
OR (95% CI); p-value	5.84 (1.18 - 28.90); p=0.0017		25.3 (8.2 - 78.7); p<0.0001		9.0 (2.5 - 32.3); p=0.0002			
Relevant additional measures of platelet response in the study	nr		**Weighted mean platelet change up to week 12**		**Median number of weeks with platelet response (primary outcome)**		nr	
Mean area under the curve			63.9	23.7	nr			
Median (IQR) in weeks			nr		12 (3 - 20)	1 (0 - 2.5)		
p-value			p<0.0001		p=0.0004			
Use of Concomitant and/or Rescue Medication								
Initiation of rescue therapy, n (%)	6 (13)	11 (50)	12 (19)	7 (24)	17 (41)	9 (45)	1 (8)	2 (33)
OR (95% CI); p-value	0.1 (0.04 - 0.49); p=0.0020		0.44 (0.2 - 0.9); p=0.032		p=0.7103		nr	
Concomitant and/or rescue ITP medications received throughout study duration, n (%)								
IV immunoglobulin	6 (13)	8 (36)	nr		9 (21)	4 (20)	nr	
Corticosteroids	4 (9)	7 (32)			5 (12)	6 (30)		
Anti-D	3 (7)	2 (9)			3 (7)	2 (10)		
Vincristine or vinblastine	0	1 (5)			nr			
Antifibrinolytic	nr				6 (14)	2 (10)		
Platelets	nr				1 (2)	1 (5)		
Bleeding								
Clinically significant bleeding	**WHO Grade 2 – 4 Logistical regression model**		**WHO Grade 2 – 4 Proportions**		**Grade ≥ 2 AEs of bleeding**		nr	
Baseline, n (%)	9 (20)	6 (27)	16 (25)	6 (21)	nr			
End of study, n (%)	4 (9)	7 (32)	3 (5)	2 (7)				
n (rate)[a]	nr		nr		80 (8)	79 (18)		
Logical regression model, n (%)	12 (27)	13 (59)			nr			

Outcomes	Bussel 2015[30] (PETIT)		Grainger 2015[32] (PETIT2)		Tarantino 2016[34]		Elalfy 2011[33]	
	Eltrombopag N = 45	Placebo N = 22	Eltrombopag N = 63	Placebo N = 29	Romiplostim N = 42	Placebo N = 20	Romiplostim N = 12	Placebo N = 6
OR (95% CI); p-value	0.21 (0.06 - 0.72); p=0.013				p=0.0006			
Other bleeding measures	nr		nr		**Composite bleeding and/or rescue therapy**		nr	
Duration-adjusted rates per 100 patient-weeks					5.9	17.9		
p-value					p<0.0001			
Health-Related Quality of Life								
Change from Baseline in KIT Total Score								
Patients contributing to the analysis	n = 20	n = 15	nr		nr		nr	
Baseline, mean (SD)	74 (14)	76 (17)						
Change from baseline to Week 6 in KIT total score, mean (SD)	3 (10)	2 (8)						
Model-adjusted change from baseline to Week 6 in KIT total score,[b] mean (SE)	3 (2)	2 (2)						
Difference from placebo, mean (95% CI); p-value	–1.5 (–8.1 to 5.1); p=0.64							
Change from Baseline in KIT Total Score by Child Self-Report and Parent Impact								
Child self-report								
N	nr		nr		N = 28	N = 12	nr	
Baseline					66.8 (16.0)	68.9 (16.8)		
N					N = 30	N = 13		
Week 8					76.3 (14.8)	77.2 (17.4)		
N					N = 28	N = 11		
Change from baseline to week 8					9.4 (13.9)	9.1 (12.8)		
N					N = 29	N = 12		
Week 16					78.1 (14.4)	76.9 (17.3)		
N					N = 27	N = 10		
Change from baseline to week 16					10.7 (14.3)	8.4 (15.6)		
N					N = 30	N = 13		
Week 25					80.2 (14.8)	78.0 (18.9)		
N					N = 28	N = 11		
Change from baseline to week 25					**13.7 (16.7)**	**9.8 (15.7)**		
Between-group difference in mean change from baseline,[c] p-value					Reported as non significant			
Parent impact								
N	nr		nr		N = 40	N = 18	nr	
Baseline					34.4 (19.0)	35.5 (17.0)		
N					N = 42	N = 17		
Week 8					48.3 (22.5)	39.2 (20.7)		
N					N = 40	N = 16		
Change from baseline to week 8					13.3 (11.7)	3.6 (17.3)		
N					N = 41	N = 18		
Week 16					50.1 (22.9)	48.3 (18.9)		
N					N = 39	N = 17		

Outcomes	Bussel 2015[30] (PETIT)		Grainger 2015[32] (PETIT2)		Tarantino 2016[34]		Elalfy 2011[33]	
	Eltrombopag N = 45	Placebo N = 22	Eltrombopag N = 63	Placebo N = 29	Romiplostim N = 42	Placebo N = 20	Romiplostim N = 12	Placebo N = 6
Change from baseline to week 16					15.4 (16.4)	12.3 (15.4)		
N					N = 39	N = 17		
Week 25					53.7 (25.4)	49.4 (18.2)		
N					N = 37	N = 16		
Change from baseline to week 25					**17.5 (16.7)**	**12.8 (16.3)**		
Between-group difference in mean change from baseline,[c] p-value					p=0.015			
Harms								
AEs	36 (82)	20 (95)	51 (81)	21 (72)	nr		6 (50)	3 (50)
SAEs	4 (9)	2 (10)	5 (8)	4 (14)	10 (24)	1 (5)	nr	
Deaths	0[d]	0[d]	0	0	nr		0	0

AEs = adverse events; CI = confidence interval; IQR = interquartile range; ITP = immune thrombocytopenia; KIT = Kid's ITP Tools; nr = not reported; RCT = randomized controlled trial; SAEs = serious adverse events; SD = standard deviation; SE = standard error; World Health Organization.

[a] Rate = total number of events/100 patient-weeks.
[b] ANCOVA.
[c] Mixed-effects repeated measures analysis.
[d] Fatal AEs.

Table 14: Detailed Outcome Data – Cohort Study

Outcomes	Grace 2019[36] (ICON1)		
	Rituximab N = 43	Romiplostim N = 31	Eltrombopag N = 20
Patients Contributing to the Analyses			
At 1 month	N = 42	N = 29	N = 20
At 6 months	N = 33	N = 24	N = 15
At 12 months	N = 31	N = 16	N = 12
Platelet Response			
Patients with Complete Platelet Response, n (%)			
At 1 month	8 (19)	6 (21)	6 (30)
At 6 months	17 (52)	17 (71)	4 (27)
At 12 months	17 (55)	9 (56)	5 (42)
Patients with Partial Platelet Response, n (%)			
At 1 month	15 (36)	9 (31)	5 (25)
At 6 months	9 (27)	3 (15)	6 (40)
At 12 months	8 (26)	4 (25)	4 (33)
Proportions of Patients with Platelet Response (Complete + Partial) – Change from 1 to 6 Months			
At 1 month	55%	52%	55%
At 6 months	79%	83%	67%
p-value for within-group change	p=0.0003	p=0.0001	reported as non significant
Average Platelet Count x10^9/L, Median (range)			
At 1 month	65 (4 to 230)	67 (1 to 357)	89 (10 to 402)
At 6 months	151 (3 to 412)	160 (6 to 598)	97 (6 to 301)
At 12 months	156 (4 to 408)	147 (29 to 408)	106 (15 to 300)
Reduction in the Use of Rescue Medication			
Change from 1 to 6 months, %	6.1%	12.5%	40%
Bleeding			
Proportions of Patients with Grade 1 – 2 Skin Bleeding, %			
Baseline	81.4%	83.9%	85.0%
At 1 month	42.9%	48.3%	65.0%
At 6 months	36.4%	50.0%	26.7%
At 12 months	34.5%	18.8%	33.3%
Within-Group Change from Baseline			
p-value at 1 month	p=0.0004	p=0.011	p=0.33
p-value at 6 months	p<0.0001	p=0.024	p=0.005
Proportions of Patients with Grade 1 – 2 Non-Skin Bleeding, %			
Baseline	53.5%	58.1%	50.0%
At 1 month	16.7%	13.8%	20.0%
At 6 months	15.2%	33.3%	20.0%
At 12 months	24.1%	6.3%	16.7%
Within-Group Change from Baseline			
p-value at 1 month	p=0.0006	p=0.0001	p=0.067
p-value at 6 months	p=0.003	0=0.264	p=0.276
Health-Related Quality of Life – Change from Baseline in KIT Scores, median (range)			
Baseline	66.7 (32.7 - 96.2)	75.6 (51.0 - 98.1)	69.9 (43.3 - 94.2)
At 1 month	75.2 (35.6 - 97.1)	83.7 (57.0 - 98.1)	80.8 (32.7 - 97.1)
At 12 months	85.2 (47.1 - 100.0)	87.5 (70.2 - 99.0)	85.0 (61.5 - 97.1)
Within-Group Change from Baseline			
p-value at 1 month	p=0.0001	p=0.0003	p=0.0008
p-value at 12 months	p<0.0001	p=0.0001	p=0.0003

Note: No data was reported in the publication for harms outcomes.

Appendix 8: Patient Engagement

Table 7: Patient Engagement in Drugs to Treat Children with Immune Thrombocytopenia report

Section & Topic	Item	Section
Aim	The Platelet Disorder Support Association contributed to this HTA. This engagement offered insights to the project team, highlighting key issues and priorities of the patient population and contextualizing the information gleaned from the literature.	
Methods	A previous patient group submission on adult ITP was reviewed, and a patient group participated in a dialogue with staff. A Patient Engagement Officer presented the key themes to the project team during the protocol development phase.	
Results of Engagement	The Platelet Disorder Support Association contributed thoughts and perspectives on the nuances of pediatric ITP compared to adult ITP, highlighting some important distinctions and priorities for the treatment of pediatric ITP. See Patient Engagement section.	Patient Engagement
Discussion and Conclusions	There were many distinctions between pediatric and adult ITP that the patient group highlighted as their priorities. They wanted to ensure that we considered these nuances when reviewing the literature. The project team benefited from these insights and appreciated understanding patient priorities when developing the protocol, reviewing the literature, and drafting the report.	
Critical Reflections	The success of this engagement was related to several factors. Firstly, there was an existing relationship with an active and involved patient group who was familiar with our mandate and earlier work with adult ITP. Secondly, the patient group representative was supported in the engagement by a Patient Engagement Officer who acted as a liaison between the project team and the patient group. Thirdly, the project team was receptive to patient group involvement. We informed the Platelet Disorder Support Association about the Stakeholder Feedback period, advising them that the draft report would be going out for public review and that they would have an opportunity to provide feedback. That way, they could both submit feedback as a patient group, and could disseminate the link to their members for individual patients to provide feedback.	N/A

Based on GRIPP2 Reporting Checklist[39]