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[Intervention Protocol]

Pharmacological treatments for vaccine-induced immune thrombocytopenia and thrombosis (VITT) after COVID-19 vaccination

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of pharmacological interventions for vaccine-induced immune thrombocytopenia and thrombosis in people who received COVID-19 vaccination.

BACKGROUND

See Appendix 1 for a glossary of terms.

Description of the condition

Vaccination is a well-known, safe, and effective strategy for eradicating infectious diseases. Currently, more than 13.47 billion doses of the coronavirus disease 2019 (COVID-19) vaccine have been administered worldwide, controlling the SARS-CoV-2 pandemic (Mahase 2020; WHO 2023).

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is a rare and severe adverse effect of vaccination, characterised by thrombocytopenia and major venous or arterial thrombosis. This condition is also known as vaccine-associated thrombosis with thrombocytopenia syndrome or vaccine-induced prothrombotic immune thrombocytopenia (Hafeez 2021; Oldenburg 2021).

VITT occurs after COVID-19 vaccination with two adenovirus viral vector vaccines, the Oxford AstraZeneca (AZD1222 (ChAdOx1) and Johnson & Johnson vaccines (JNJ-78436735 (Ad26.COV2.S (Pavord 2021a; Schultz 2021))). Cases of VITT after other types of vaccines have been described, but it is uncertain whether VITT occurs after vaccines other than the two described above (Lin 2023).

Data are emerging on the mechanisms leading to VITT, including an autoimmune response, IgG antibodies against platelet factor 4 (PF4), platelet activation, and stimulation of the coagulation system. The pathophysiology is very similar to heparin-induced thrombocytopenia (HIT) or autoimmune heparin-induced thrombocytopenia (aHIT (Greinacher 2006; Greinacher 2021)). Heparin-dependent and VITT antibodies can only be differentiated by their binding patterns to distinct PF4 epitopes (Huynh 2021).

By 23 November 2022, the UK government received reports of 445 cases of major thromboembolic events with thrombocytopenia following vaccination with the AstraZeneca COVID-19 vaccine (MHRA 2022).This caused enough concern throughout the population and the medical community that a temporary suspension of the Oxford AstraZeneca vaccine was issued in several European countries(Wise 2021; Petersen 2022). The Oxford-AstraZeneca vaccine is currently authorised and administered in Europe for the active immunisation of individuals aged 18 years and older for the prevention of COVID-19, and the European Medicines Health continues to monitor and uphold the use of the vaccine (EMA 2024).

Data from the USA estimated the overall incidence of VITT at 3.8 cases per million doses of the Johnson & Johnson vaccines, and data from the UK estimated the overall incidence of VITT at 15.9 cases per million of the first doses of the Oxford-AstraZeneca vaccine (See 2022). A recent study from Canada estimated the incidence of VITT at 19.9 cases per million doses of the Oxford-AstraZeneca vaccine, based on data collected between 26 February 2021 and 31 October 2022 (Procter 2023).

A much lower incidence occurred after the second dose, with only 2.1 cases per million doses (MHRA 2022). The mean age of people with VITT is 45.6 years, with a female predominance of 70% (Kim 2022). The risk of hospitalisation, thrombosis, or death-associated complications of SARS-CoV-2 infection is much higher than the incidence of VITT (Correia 2022; COVIDSurg 2022; Flumignan 2022; Santos 2023). Therefore, the benefits of vaccination in preventing COVID-19 still outweigh the risks for most people.

Determining the incidence of VITT in countries with less resources is challenging. For example, in Brazil, international co-operation was necessary to provide broad access to anti-PF4 ELISA and functional platelet tests, and the tests were conducted at a single reference blood centre in Rio de Janeiro. Despite these limitations, a government and vaccine surveillance service study showed similar clinical and laboratory profiles in VITT as demonstrated in Europe and the USA (Oliveira 2022).

The incidence of VITT appears to be lower in South Korea. Only 2 of 8,548,231 people were vaccinated with AstraZeneca ChAdOx1 nCoV-19 with confirmed thrombosis and thrombocytopenia syndrome (Huh 2021). Whether this is a significant data point or not, this trend cannot be confirmed across all of Asia, and the reasons behind the potentially lower incidence of VITT in South Korea are unclear.

VITT appears to have little relevance for children or the elderly. The condition primarily affects adults of working age, with the average age at diagnosis estimated to be 48 years; 85% of cases occurr in people under the age of 60 (Pavord 2021b). VITT is rare in children and adolescents under the age of 18. Two studies, with a total of 277 participants, found no reported cases of VITT in this age group (Pavord 2021b; See 2022). There are limited data comparing the course of VITT in vulnerable and disadvantaged groups with the general population, making it challenging to compare these populations.

A diagnosis of VITT is suspected when people present with new signs and symptoms of thrombocytopenia and thrombosis within 5 to 30 days following a COVID-19 vaccination. The most common symptoms are severe or persistent headaches, blurred vision, shortness of breath, chest pain, leg swelling, or unusual bleeding, which appear after COVID-19 vaccination with viral vector vaccines (Pavord 2021a). Laboratory and imaging procedures, such as PF4 ELISA, d-dimer, fibrinogen, and imaging techniques for thrombosis, can be crucial in diagnosis (Oldenburg 2021).

The diagnostic criteria that confirm VITT are: (1) onset of symptoms 5 to 30 days after COVID-19 vaccine; (2) presence of thrombosis; (3) thrombocytopenia (platelet count fewer than 150,000/mm^3 or over 50% platelet reduction from the previous count); (4) d-dimer higher than 4000 µg/mL; and (5) positive enzyme-linked immunosorbent assay (ELISA) for platelet factor 4 (PF4) antibodies. Diagnosis of VITT is considered definite if all five criteria are present, and probable if one is missing (Pavord 2021b).

Despite thrombocytopenia, bleeding is rare, and the condition is strongly associated with severe and uncommon thromboembolic events. Cerebral venous thrombosis (CVT) is a severe complication occurring in 54% of people with VITT. The pooled incidence rate of CVT after ChAdOx1 nCoV-19 vaccination (23 per 100,000 person-years) is higher than that reported in the general population before the pandemic (0.9 per 100,000 person-years (Kim 2022)). Other major rare thromboembolic events, such as hepatic portal vein thrombosis, are particularly common in people with VITT (Perry 2021).

The baseline platelet count and the presence of intracranial haemorrhage in people with VITT are independent risk factors

for death (Pavord 2021a). VITT mortality rate is high, with an estimated all-cause mortality of 32%, potentially increasing to 54% after decompressive craniectomy for VITT-associated CVT (Kim 2022; Perry 2021). However, the risk of hospitalisation, thrombosis, or death-related complications from SARS-CoV-2 infection is considerably higher (Correia 2022; COVIDSurg 2022; Flumignan 2022; Santos 2023). Therefore, the benefits of vaccination in preventing COVID-19 still outweigh the risks for most people.

Description of the intervention

We will consider any pharmacological interventions currently used by clinicians to treat VITT, such as anticoagulants, intravenous immune globulin (IVIG), corticosteroids, and targeted therapy drugs (Franchini 2021; Makris 2021; Oldenburg 2021).

Anticoagulants

Anticoagulants encompass drugs, such as heparinoids (unfractionated heparin (UFH), low molecular weight heparin (LMWH), and penta saccharides), vitamin K inhibitors, and direct anticoagulants that reduce coat formation (Dias 2021; Flumignan 2021; Flumignan 2022; Flumignan 2023; Santos 2023). Anticoagulants can be the cornerstone for VITT treatment because of the higher risk of thrombotic events. However, as VITT has similarities to HIT, clinicians assume that heparin may exacerbate the condition, so they avoid this class of drugs for treating people with VITT (Greinacher 2021). The main adverse event related to anticoagulants is bleeding, so clinicians also avoid the use of warfarin, since it may trigger microthrombosis, venous limb gangrene, and skin necrosis in people with HIT (Srinivasan 2004).

Direct thrombin inhibitors (e.g. argatroban, bivalirudin, lepirudin), indirect anticoagulants (e.g. fondaparinux, danaparoid), and direct oral anticoagulants (DOACs; e.g. apixaban, rivaroxaban) are the most used anticoagulants for VITT (Clark 2021; Guetl 2021; Makris 2021).

Intravenous immune globulin (IVIG)

IVIG competitively inhibits the interaction of VITT antibodies, reducing platelet activation and increasing platelet count. The presence of a large quantity of non-specific antibodies in IVIG may interfere with the binding of VITT antibodies to PF4, thereby decreasing platelet stimulation and clot formation. IVIG also has immunomodulatory properties, and can regulate the immune response by affecting various immune cells and signalling molecules. The usual IVIG dose to treat VITT is 1 g/kg for two days (Bourguignon 2021; Greinacher 2021). Although considered safe, adverse reactions during this therapy occur in 5% to 15% of infusions. Common reactions include headache, fatigue, abdominal pain, and myalgia. Most reactions are mild, but potentially severe reactions, such as anaphylaxis, thromboembolic, impaired kidney function, aseptic meningitis, or severe haemolysis may occur (Stiehm 2013).

Corticosteroids

Corticosteroids are steroid hormones, known for their inhibitory effects on immune responses. Due to this property, methylprednisolone, dexamethasone, or prednisone have been used to treat VITT. Depending on the person's clinical condition, corticosteroids may be administered orally or intravenously. The effectiveness of this treatment remains a topic of discussion (Clark 2021; Franchini 2021; Makris 2021; WHO 2023a). The adverse effects of corticosteroids depend on the dose and duration, and may have detrimental effects on numerous organ systems. While short courses of corticosteroids are generally safer, there is still a potential for an increased risk of sepsis, venous thromboembolism, and fractures (Waljee 2017).

Targeted therapy drugs

Rituximab, a monoclonal antibody, is used off-label to treat immune thrombocytopenia. This drug acts directed against the CD20 antigen on the surface of B-lymphocytes, and may control the exacerbated immune response of VITT (Gabarin 2022). Infusion-related reactions, bowel obstruction or perforation, cytopenias, and renal toxicity may occur after rituximab infusion. Serious adverse events associated with this drug include the exacerbation of hepatitis B, hypogammaglobulinemia, infection, and progressive multifocal leukoencephalopathy (Salles 2017).

Eculizumab, a monoclonal antibody that targets and inhibits the complement system, is also used off-label to treat VITT. This drug also regulates the immune response to the disease (Tiede 2021). Headache, nasopharyngitis, back pain, and nausea are common adverse events associated with eculizumab (Brodsky 2008). Serious meningococcal infection is a concerning adverse effect of this drug (McNamara 2017).

Ibrutinib, Bruton's tyrosine kinase inhibitor, is an alternative drug to treat VITT. Ibrutinib is approved for B-cell malignancies, may inhibit platelet aggregation, and may be used to treat VITT. There is no defined dose or treatment time for Ibrutinib to treat VITT (von Hundelshausen 2021). Hypertension has commonly been reported in people treated with ibrutinib. Serious adverse events, including cardiac arrhythmias, heart failure, cytopenias, progressive multifocal encephalopathy, and malignancies, have also been documented (Dickerson 2019).

How the intervention might work

The pharmacological interventions for treating VITT may work by addressing thrombosis and its complications, or by regulating the immune-mediated response that leads to thrombocytopenia. (Makris 2021; Oldenburg 2021).

Since there is a close relationship between heparin-induced thrombocytopenia and VITT, non-heparin drugs are the anticoagulants most used to treat venous or arterial thrombosis (Gabarin 2022; Greinacher 2021; Pavord 2021a).

To control the immune response of VITT, a high dose of IVIG may competitively inhibit the platelet-activating antibodies. As there are minimal data for the treatment of VITT, clinicians who use IVIG, base their treatment decisions primarily on treatment guidelines for HIT. In this case, the use of IVIG can rapidly increase the platelet count and reduce thromboembolic events (Oldenburg 2021; Warkentin 2019).

Another way to control the immune-mediated response in VITT is by using corticosteroids or targeted therapy drugs, such as rituximab, eculizumab, or ibrutinib (Pavord 2021a; Tiede 2021; von Hundelshausen 2021). For cerebral thrombosis, corticosteroids may offer extra benefits by reducing brain swelling. Therefore, it might be necessary to analyse and compare the effectiveness of steroids in groups with and without cerebral thrombosis (Di Pietro 2022).

Why it is important to do this review

Even after the control of the COVID-19 pandemic, the vaccination against SARS-CoV-2 remains necessary. Development, testing, and licencing of vaccines against COVID-19 occurred at unprecedented speed to control the disease. Although safe, these vaccines may cause significant adverse effects when administered on a large scale.One of these adverse effects is VITT, a severe and life-threatening condition that develops after a person has received a COVID-19 viral vector vaccine (Nazy 2021).

The current standard treatment for VITT involves anticoagulation; other interventions are under discussion and remain controversial (Franchini 2021; Makris 2021; Oldenburg 2021). This research question, regarding all possible pharmacological interventions for VITT, is highlighted as an area of uncertainty for international guidelines. The German Society of Thrombosis and Haemostasis Research recommends the administration of a high dose of IVIG, and does not provide contraindications to parenteral anticoagulation with heparin (Oldenburg 2021). An Italian group suggests using a high dose of IVIG, non-heparin anticoagulants, and corticosteroids. They also propose the use of Bruton's tyrosine kinase (BTK) inhibitors as an alternative treatment option (Franchini 2021). The National Institute for Health and Care Excellence (NICE) guidelines recommend the use of non-heparin drugs, and are against the use of heparin or warfarin (Makris 2021).

Facing an increasing number of vaccinated people for COVID-19 worldwide, it is reasonable to assume that the population with VITT will increase proportionately. VITT is a severe disease, with high mortality and morbidity rates. It remains pertinent, especially in low- and middle-income countries that can only allocate resources for adenoviral vector-based vaccines.

The evidence for this issue is preliminary; there is no consensus on its treatment. A Cochrane review that considers randomised controlled trials and non-randomised studies of interventions will establish the best available evidence for clinical decision-makers.

OBJECTIVES

To assess the effects of pharmacological interventions for vaccine-induced immune thrombocytopenia and thrombosis in people who received COVID-19 vaccination.

METHODS

Criteria for considering studies for this review

Types of studies

To assess the effects of pharmacological interventions for vaccine-induced immune thrombocytopenia and thrombosis (VITT), we plan to include randomised controlled trials (RCTs). VITT is a rare condition, and we need to capture all the relevant evidence, so we will also consider a broad range of empirical studies of any size that provide a quantitative measure of impact (Reeves 2023). We will not consider studies without a control or comparator group, or those focused on VITT prevention.

If there is insufficient evidence (very low-certainty evidence or no evidence) available from RCTs to answer the objective of this review, we will include quasi-randomised controlled trials (e.g. assignment to treatment by alternation, medical register or by date of birth), and prospective controlled non-randomised studies of interventions (NRSIs).

If there is insufficient evidence (very low-certainty evidence or no evidence) available from RCTs, quasi-RCTs, and prospective cohort studies, we will include retrospective cohort studies with a control group, i.e. a top-down approach, which was used in other COVID-19-related reviews (Flumignan 2022).

Prospective and retrospective cohort studies can be helpful in informing clinical decisions, because vaccines must still be administered, and VITT is a rarely reported life-threatening adverse event. In this case, we consider it a priority to look for the best available evidence and to include prospective and retrospective cohort studies in this review when appropriate. NRSIs may be helpful for rare adverse events and clinical decisions, if there is a lack of randomised controlled studies.

When considering prospective and retrospective cohort studies, we will include studies that did not use statistical adjustment for baseline or confounding factors by using multivariate analyses for confounding factors, such as participants who are already using anticoagulants (e.g. atrial fibrillation) or antiplatelet agents, and those who have a history of venous thromboembolism (VTE). We will assess these factors in the critical appraisal of the included studies.

In future updates of this review, when data from RCTs become available, we will no longer include prospective and retrospective cohort studies, and will exclude all other study designs.

Types of participants

We will include studies with adult participants of both sexes, with a definite or probable diagnosis of VITT, following these criteria:

- onset of symptoms 5 to 30 days after COVID-19 vaccine;
- presence of thrombosis;
- thrombocytopenia (platelet count fewer than 150,000/mm^3 or over 50% platelet reduction from the previous count);
- d-dimer higher than 4000 µg/mL; and
- positive enzyme-linked immunosorbent assay (ELISA) for platelet factor 4 (PF4) antibodies.

Diagnosis of VITT is considered definite if all five criteria are present, and probable if one is missing (Pavord 2021b).

Imaging based on the location of symptoms is necessary to confirm thrombosis. Examples of suitable imaging include:

- deep vein thrombosis: symptomatic or asymptomatic, first episode or recurrent confirmed by ultrasonography or angiography (e.g. by computed tomography angiogram (CTA), magnetic resonance angiogram (MRA), or by digital subtraction (DSA)) at any site (e.g. cerebral vein thrombosis (CVT), lower limbs, upper limbs, abdominal)
- pulmonary embolism (PE): CT pulmonary angiography or ventilation/perfusion scanning

We will include participants with a previous diagnosis of VTE, i.e. any thrombosis, PE, or both, who have finished VTE treatment, regardless of the time of VTE diagnosis relative to the COVID-19 vaccination.

If we find studies with mixed populations (e.g. with and without VITT), and only a subset of the participants meet our inclusion criteria, we will attempt to obtain data for the subgroup of interest from the study authors, so we can include the study. For studies with mixed populations for which we cannot get the subgroup of interest's data, but at least 50% of the study population are of interest, we will include all participants in our analysis. We will explore the effect of this decision in a sensitivity analysis.

We will exclude studies in which less than 50% of the population is of interest, and the subgroup of interest data are unavailable.

We will exclude participants with other causes of thrombocytopenia with thrombosis (e.g. cancer, antiphospholipid syndrome, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and paroxysmal nocturnal haemoglobinuria).

Types of interventions

We will consider the following pharmacological interventions for VITT treatment.

- non-heparin anticoagulants: direct thrombin inhibitors (e.g.argatroban, bivalirudin, lepirudin), indirect anticoagulants (e.g. fondaparinux, danaparoid), and non-vitamin K oral anticoagulants (NOACs)
- heparins, both unfractionated heparin (UFH) and low–molecular weight heparin (LMWH)
- intravenous immune globulin (IVIG)
- corticosteroids
- monoclonal anti-CD20 antibody (rituximab)
- monoclonal anti-C5 antibody (eculizumab)
- Bruton's tyrosine kinase inhibitors (BTKi; ibrutinib)

We will consider studies that compare different formulations, doses, and schedules of the same intervention (e.g. argastroban).

We will include studies that compare one pharmacological intervention versus another active comparator, or placebo, or no treatment with any combination of interventions, provided that co-treatments were balanced between the treatment and control arms. We plan to assess the following comparisons, in order of priority:

- anticoagulant versus placebo or no treatment (we plan to pool all anticoagulants together – direct thrombin inhibitors, indirect anticoagulants, and NOACs and heparins, if possible);
- anticoagulant A versus anticoagulant A plus other pharmacological interventions, such as IVIG;
- anticoagulant A versus anticoagulant B ;
- anticoagulant A versus a different dose, formulation, or schedule of the anticoagulant A;
- pharmacological intervention A versus placebo or no treatment;
- pharmacological intervention A versus pharmacological intervention A plus pharmacological intervention B.

Types of outcome measures

We were unable to identify core outcomes for VITT treatment, even after consulting the Core Outcome Measures in Effectiveness Trials Initiative in response to COVID-19 (COMET 2020). Therefore, we established our own priority outcomes. We will present the outcomes at two different time points following the start of the intervention, if data are available:

- short-term outcomes (at 30 days or less after the start of the intervention); and
- long-term outcomes (more than 30 days after the start of the intervention).

We will also consider the outcomes after hospital discharge. We will include studies in the review regardless of whether they reported outcome data in a usable way. Reporting one or more of the outcomes of interest in the trial is not an inclusion criterion for the review. When a published report does not appear to report one of the outcomes of interest, we will access the trial protocol and contact the trial authors to ascertain whether the outcomes were measured but not reported.

As part of the narrative in the review, we will report relevant trials that measured outcomes of interest, but either did not report the data at all, or did not report data in a usable format.

Primary outcomes

- All-cause mortality
- Necessity for additional respiratory support: oxygen by non-invasive ventilators or high-flow intubation, and mechanical ventilation or extracorporeal membrane oxygenation

Secondary outcomes

- Post-thrombotic syndrome (PTS): diagnosed by objective clinical examination with or without the support of any classification of severity. We will use the following hierarchy of measurement methods if a study measures PTS in more than one way: Villalta score, CEAP (clinical, aetiological, anatomical, and pathological elements), and VCSS (Venous Clinical Severity Score).
- Recurrent DVT: diagnosed by clinical examination and diagnostic assessment, including duplex ultrasound or angiography, i.e. CTA, MRA, or DSA
- Recurrent PE, fatal or non-fatal: diagnosed by clinical examination and diagnostic assessment, including computed tomography, ventilation/perfusion scanning, or angiography
- Major bleeding: defined by a haemoglobin concentration decrease of 2 g/dL or more, a retroperitoneal or intracranial bleed, a transfusion of two or more units of blood, or fatal haemorrhagic events, as defined by the International Society on Thrombosis and Haemostasis (Schulman 2010)
- Adverse events: we will consider all possible adverse events separately, as individual outcomes, in order of priority: minor bleeding, gastrointestinal adverse effects (e.g. nausea, vomiting, diarrhoea, abdominal pain), allergic reactions, renal failure, acute limb ischaemia, lower limb amputation, pulmonary embolism, and necessity for revascularisation. We will only consider the adverse effects described in the included studies.
- Platelet recovery: defined as a platelet count of 100 x 10^9/L or more; doubling of the nadir platelet count, or a 30% increase from the nadir if the nadir was above 100 x 10^9/L (Nilius 2021). If we are unable to extract data dichotomously, we will analyse it as continuous outcomes: platelet count values.

- Quality of Life (QoL) or participant's subjective perception of improvement (yes or no): we will consider any valid score or scale in the following hierarchy of measurement methods, if a study measures QoL in more than one way: chronic venous insufficiency questionnaire score (CIVIQ (Launois 1996)), or Short Form-36 Health Survey (SF-36 (Ware 1992)). If we cannot extract data on QoL, we will consider the participant's subjective perception of improvement (yes or no).

Search methods for identification of studies

Electronic searches

We aim to identify all relevant studies (RCTs, quasi-RCTs, or NRSIs), regardless of language or publication status (published, unpublished, in press, or in progress).

We will search the following databases for relevant trials:

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies-Web (CRS-Web);
- MEDLINE (PubMed MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, PubMed MEDLINE Daily and PubMed MEDLINE; 1946 onwards);
- Embase via Elsevier (1974 onwards);
- Latin American and Caribbean Health Science Information database (LILACS; 1982 onwards) in lilacs.bvsalud.org.

We will adapt the preliminary search strategy for MEDLINE for use in the other databases (Appendix 2). We will not apply any RCT filters for any databases, but will select the study design manually, as we will also consider NRSIs for inclusion in this review.

We will also search ClinicalTrials.gov (www.clinicaltrials.gov/), and the World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch) for ongoing or unpublished trials.

We will search all databases from their inception to the present; we will impose no restriction on language of publication or publication status.

Searching other resources

We will also search the Cochrane COVID-19 Study Register, a specialised register built within the Cochrane Register of Studies, and containing trial registry records, journal articles, and preprints for ongoing or unpublished studies. It is maintained by Cochrane Information Specialists. The register contains study reports from several sources, including:

- monthly searches of CENTRAL;
- weekly searches of PubMed;
- weekly searches of Embase.com;
- daily searches of ClinicalTrials.gov; and
- weekly searches of the ICTRP.

Complete data sources and search methods for the register are available at community.cochrane.org/about-covid-19- study-register.

We will check reference lists of all included studies and any relevant systematic reviews identified for additional references to studies. We will examine any relevant retraction statements and errata for included studies. We will contact the authors of the included studies for any unpublished data. We will contact field specialists to enquire about relevant ongoing or unpublished studies.

Data collection and analysis

Selection of studies

We will consider abstracts and full-text reports in all languages for inclusion. All potentially eligible non-English language abstracts will progress to full-text review, with methods translated for eligibility assessment, and the full text translated for data extraction.

Two review authors (JVM and LCUN) will independently screen titles and abstracts of all articles identified as a result of the search, and we will code them as retrieve (eligible or potentially eligible/unclear), or do not retrieve (non-relevant), using Covidence. We will resolve any disagreement through discussion, or if required, we will consult a third author (RLGF).

We will retrieve the full-text study reports/publications, and two review authors (JVM and LCUN) will independently screen the full text to identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third author (RLGF).

We will identify and exclude duplicates, and collate multiple reports of the same study so that each study, rather than each report, is the unit of interest in the review.

We will list all articles excluded after a full-text assessment in a characteristics of excluded studies table, and will provide the reasons for their exclusion.

We will consider studies reported as full text, those published as abstract or conference proceedings only, and unpublished data.

We will illustrate the study selection process in a PRISMA diagram (Liberati 2009).

Data extraction and management

We will manage and synthesise the available data using Review Manager (RevMan 2024). If there is a conflict between data reported across multiple sources for a single study (e.g. between a published article and a trial registry record), we will use the article published for numerical analysis. We will report the differences and consider any impact on the certainty of evidence (Schünemann 2023).

We will use a data collection form, which we will pilot on at least one study from the review, for study characteristics and outcome data. Two review authors (JVM and LCUN) will independently extract data from the included studies. We will resolve disagreements by discussion. We will extract the following study characteristics.

- **Methods:** study design, prospective or retrospective (which aspects of the study were prospective and which were retrospective), duration of the study, number of study centres and location, study setting, and date of the study
- **Participants:** comorbidities, pregnancy, number randomised, exclusions post-randomisation, number lost to follow-up/withdrawn, number analysed, number of interest, mean age, age range, gender, inclusion criteria, and exclusion criteria

- **Interventions:** intervention and comparison characteristics (e.g.manufacturer, dosage, additional procedures, method of administration), concomitant medications, and excluded medications
- **Outcomes:** primary and secondary outcomes specified and collected (e.g. how outcomes are measured), and time points reported (for NRSIs: confounding factors controlled for each relevant analysis presented and adjusted effect estimates)
- **Notes:** funding for the trial, conflicts of interest of study authors, and registration number. Information needed to assess GRADE (e.g. baseline risk in the control group for key outcomes).

One review author (JVM) will transfer the data into RevMan (RevMan 2024). We will double-check whether data were entered correctly by comparing the data presented in the systematic review with the data extraction form.

Two review authors (JVM and LCUN) will spot-check study characteristics for accuracy against the study report.

We will synthesise the characteristics of all studies that will contribute to each comparison and present them in the characteristics of included studies table in the full review.

Assessment of risk of bias in included studies

We will assess all included studies for risk of bias, using the best tool for each study design. Two review authors (JVM and LCUN) will independently perform this assessment and any disagreements will be resolved by discussion within the review team.

Randomised controlled trials

Two review authors (JVM and LCUN) will assess the risk of bias for each study using the criteria outlined in *the Cochrane Handbook for Systematic Reviews of Interventions* for RCTs – RoB 1 (Higgins 2017). We will assess the risk of bias according to the following domains, judging each of them to be at high risk, low risk, or unsure risk.

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
- selective outcome reporting
- other bias

In cluster-randomised trials, we will consider the following biases, recommended in section 8.15.1.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017):

- recruitment bias;
- baseline imbalance;
- loss of clusters;
- incorrect analysis; and
- comparability with individually randomised trials.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report and a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each domain listed. Where information on the risk of bias relates to unpublished data or correspondence with a study author, we will note this in the risk of bias table.

When considering treatment effects, we will consider the risk of bias for the studies that contributed to that outcome.

Non-randomised studies

Either RoB 1, which assesses the risk of bias per study, or the Risk of bias in non-randomized studies of interventions (ROBINS-I), which assesses the risk of bias per outcome, can be used to assess bias for quasi-RCTs. If we include RCTs and quasi-RCTs, we will use RoB 1 to assess the risk of bias.

However, if we include quasi-RCTs and NRSIs, we will use ROBINS-I to assess the risk of bias.

If we use ROBINS-I tool, two review authors (JVM and LCUN) will independently assess the risk of bias according to the following seven domains (Sterne 2016). We will judge the risk of bias for each domain to be a critical risk, serious risk, moderate risk, low risk, or to have no information.

- bias due to confounding
- bias in the selection of participants into the study
- bias in the classification of interventions
- bias due to deviations from the intended intervention
- bias due to missing data
- bias in measurement of outcomes
- bias in selection of the reported result

We will consider the following confounders to assess the confounding domain.

- participants already using anticoagulants (e.g. atrial fibrillation) or antiplatelet agents
- history of VTE

We will also consider the following co-interventions to assess the confounding domain.

- prescription of antiplatelet therapy isolated or combined with anticoagulants
- prescription of anticoagulants at a therapeutic dose

We will consider the following effect of assignment to assess the deviations from the intended intervention domain.

- use of different doses of anticoagulants than are recommended

We will consider these outcomes to assess the measurement of the outcomes' domain.

- all-cause mortality
- necessity for additional respiratory support
- PTS
- recurrent DVT
- recurrent PE
- major bleeding
- adverse events
- platelet recovery
- QoL

We will use the robvis tool to create the risk of bias graphs for NRSIs (McGuinness 2021).

We will judge the overall risk of bias (across domains) as the worst judgement across all the domains.

The risk of bias assessment will inform the certainty of the evidence for each outcome in the summary of findings table(s).

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the Differences between the protocol and review section of the completed review.

Measures of treatment effect

Dichotomous data

We will calculate the risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous variables.

Continuous data

We will calculate mean differences (MD) and 95% CIs between treatment groups when studies use the same tools to measure an outcome. When outcomes are reported on different scales across studies, we will calculate the standardised mean difference (SMD) and 95% CI. If the standard deviation (SD) or standard error (SE) is not available, we will attempt to extract the P values. We will enter results from scales with a consistent direction of effect. We will estimate the MD using the method reported by Wan 2014 to convert the median and interquartile range into MD and CI. We will narratively describe skewed data reported as medians and interquartile ranges.

To interpret SMD, we will use the following thresholds, recommended in Section 15.5.3.1 of the *Cochrane Handbook of Systematic Reviews of Intervention* (Schünemann 2023):

- SMD less than 0.2 = trivial or no effect;
- SMD equal to or greater than 0.2 and less than 0.5 = small effect;
- SMD equal to or greater than 0.5 and less than 0.8 = medium effect; and
- SMD equal to or greater than 0.8 = large effect.

We will calculate the number needed to treat (NNT) for the primary outcomes (all-cause mortality, necessity for hospitalisation), using NNT = 1/risk difference (RD). We will use the Review Manager calculator to calculate the RD (RevMan 2024). We will express the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH) to indicate the direction of effect, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2023).

We will extract the estimate of the intervention effect together with a measure of precision (e.g. CI) and information about how the estimate was derived for NRSIs, preferably adjusted effect estimates.

If data are not reported in a format that we can enter directly into a meta-analysis, we will convert them to the required format using the information in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023a).

Unit of analysis issues

We will consider each participant as the unit of analysis for all outcomes. If trials include multi-arm interventions, we will consider only the arms relevant to the scope of our review.

Cross-over trials

If we identify any cross-over RCTs, we will only use data from the first phase of the study to avoid the risk of carry-over effects, as described in Section 23.2.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023).

Cluster-randomised trials

We will adjust their sample sizes using the methods described in Section 23.1.5 of the *Cochrane Handbook for Systematic Reviews of Interventions*, using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), from a similar trial, or from a study of a similar population (Higgins 2023). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC.

If we identify both cluster-randomised and individually-randomised trials, we will consider it reasonable to combine the results from both trial designs if there is little heterogeneity between the study designs, and we consider the interaction between the effect of the intervention and the choice of randomisation unit to be unlikely.

Dealing with missing data

We will include all available data from studies. We will describe missing data for each study in the characteristics of included studies table, and consider them in the risk of bias assessment. We will discuss the extent to which the missing data could alter the results of the review.

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data when possible (e.g. when a study is only identified as an abstract).

When possible, we will use the RevMan calculator to calculate missing SDs using other data from the trial, such as CIs (RevMan 2024). We will estimate the MD using the method reported by Wan 2014 to convert the median and interquartile range into MD and CI. When data are reported only as graphs, we will extract data of interest, such as mean, SD, or SE, using software, such as graphreader.com.

For all outcomes, we will follow the ITT principle when possible; that is, we will analyse the participants in their randomised group, regardless of what intervention they actually received. We will use available case data for the denominator if ITT data are not available.

In trials with a large proportion of missing data (more than 20%), or if the missing data are thought to introduce serious bias, we will assess this with a sensitivity analysis, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023a).

Assessment of heterogeneity

We will inspect forest plots visually to consider the direction and magnitude of effects and the degree of overlap between CIs.

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis; we acknowledge that there is substantial uncertainty in the value of I^2 when there are a small number of studies.

If we identify substantial heterogeneity, we will report this and explore possible causes by prespecified subgroup analysis. As strict thresholds for the interpretation of I^2 are not recommended, we will use the rough guide to its interpretation provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2023):

- 0 to 40%, might not be important;
- 30% to 60%, may represent moderate heterogeneity;
- 50% to 90%, may represent substantial heterogeneity; and
- 75% to 100%, represents considerable heterogeneity.

When the I^2 lies in an area of overlap between two categories (e.g. between 50% and 60%), we will consider differences in participants and interventions among the trials contributing data to the analysis (Deeks 2023).

Assessment of reporting biases

We will perform searches using multiple sources to reduce the chance of reporting biases.

We will assess the presence of publication bias and other reporting bias using funnel plots if more than 10 studies are included in a meta-analysis. If asymmetry is present, we will explore possible causes, including publication bias, poor methodological quality, and true heterogeneity.

We may perform additional statistical analysis for continuous outcomes when intervention effects are measured as MD to assess reporting biases, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2017).

Data synthesis

We will synthesise the data using RevMan (RevMan 2024). We will undertake meta-analysis only when this is meaningful; that is, if the treatments, participants, and the underlying clinical question are all similar enough for pooling to be appropriate. If we are confident that trials are estimating the same underlying treatment effect (i.e. that the population, interventions, comparators, and outcome characteristics of the included studies are homogenous), we will use a fixed-effect model. If clinical heterogeneity suggests that underlying treatment effects may differ between trials, or we identify at least 50% heterogeneity, we will use a random-effects model. If there is substantial clinical, methodological, or statistical heterogeneity across trials that precludes the pooling of data, we will use a narrative approach to data synthesis (Deeks 2023).

We will report the results of all outcomes of interest in the order in which they are listed in the outcomes section. We will include the results of individual studies and any statistical summary of these in Data and analyses tables in the review.

For RCTs and quasi-RCTs, we will perform a pooled analysis and sensitivity analysis if sufficient data are available.

When the estimate of effect and variance is available or can be calculated, we will also perform a meta-analysis including NRSIs.

We will not include data from NRSIs with critical risk of bias, in line with the recommendation of section 24.6.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Reeves 2023). However, if we include less than three studies, and there is a balance between loss of information and excluding unreliable information, we will combine data from NRSIs in a meta-analysis and clearly state when studies have a critical risk of bias for such results.

We will undertake a sensitivity analysis for NRSIs with critical, moderate, and serious risk of bias.

If it is possible to undertake meta-analyses from data extracted (i.e. if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense), we will convert data found in studies to a format appropriate for meta-analysis, following methods described in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2023a).

If meta-analysis is not possible, we will synthesise the findings narratively, graphically, or in tabular form, stratified by intervention type. Where possible, we will summarise effect estimates graphically using forest plots (MaKenzie 2023).

We will use the Synthesis without meta-analysis (SWiM) approach, with its nine items to report data (Campbell 2020):

- grouping studies for synthesis; describe the standardised metric and transformation methods used;
- describe the synthesis methods;
- criteria used to prioritise results for summary and synthesis;
- investigation of heterogeneity in reported effects;
- certainty of evidence;
- data presentation methods;
- reporting results, and
- limitations of the synthesis.

Subgroup analysis and investigation of heterogeneity

Following section 10.11.5.1 of the *Cochrane Handbook for Systematic Reviews of Interventions,* we will perform the following subgroup analyses for all outcomes if there are at least 10 studies in the comparison (Deeks 2023).

- different types of drugs (e.g. DOACS versus pentasaccharide);
- different doses of drugs;
- different levels of severity (e.g. CNS complication versus those without CNS complication; or platelet count < 30 $\times 10^9$/L versus platelet count > 30 $\times 10^9$/L);
- different time of treatment (e.g. intervention on admission versus intervention later on during hospitalisation, or after initial treatment failure).

We will use the formal test for the subgroup differences in RevMan, and base our interpretation on this.

Sensitivity analysis

We will carry out the following sensitivity analyses to test whether critical methodological factors or decisions affected the main result.

- We will only include studies with a low risk of bias (see Assessment of risk of bias in included studies).
- We will examine both the fixed-effect model and random-effects model meta-analyses, and explore the differences between the two estimates.
- We will explore the decision to include all participants when at least 50% were of interest in a study with a mixed population.
- We will explore the impact of including studies with missing data (more than 20% missing). If we identify studies with missing data that are unobtainable, we will repeat the analyses excluding these studies, in order to determine their impact on the primary analyses.

We will also carry out sensitivity analyses for cross-over and cluster-RCTs.

- We will investigate the effect of variation in the ICC.
- We will acknowledge heterogeneity in the randomisation unit and investigate the effects of the randomisation unit.

We will present these results and compare them with the overall findings. We will justify any post hoc sensitivity analyses that arose during the review process in the final report.

Summary of findings and assessment of the certainty of the evidence

We will prepare a summary of findings table using GRADEpro GDT, to summarise the main findings of the review (Atkins 2004; GRADEpro GDT).

We will create one table for each of the four main comparisons.

- Anticoagulant versus placebo or no treatment (we plan to pool all anticoagulants together – direct thrombin inhibitors, indirect anticoagulants, and NOACs and heparins, if possible)
- Anticoagulant A versus anticoagulant A plus other pharmacological interventions, such as IVIG
- Anticoagulant A versus a different anticoagulant B
- Pharmacological intervention A versus pharmacological intervention A plus pharmacological intervention B

We will assess all other comparisons, in order of priority, in additional summary of findings tables.

- Anticoagulant A versus a different dose, formulation, or schedule of the same anticoagulant A
- Pharmacological intervention A versus placebo or no treatment

We will include the following outcomes, measured at 30-day follow-up or less, in each table.

- all-cause mortality
- necessity for additional respiratory support
- post-thrombotic syndrome
- recurrent deep vein thrombosis
- recurrent pulmonary embolism
- major bleeding
- adverse events

We will evaluate the certainty of the evidence using the GRADE approach. We will assign one of four levels of certainty: high, moderate, low, or very low, based on overall risk of bias, directness of the evidence, inconsistency of results, precision of the estimates, and risk of publication bias (Atkins 2004; Schünemann 2023).

Two review authors (JVM and LCUN) will independently make judgements, with disagreements resolved by discussion. We will justify, document, and incorporate judgements into the results for each outcome.

We will justify all decisions to downgrade the certainty of the evidence using footnotes, and make comments to aid the reader's understanding of the review where necessary.

We include an example summary of findings table in Table 1.

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Editorial and peer-reviewer contributions

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- Sign-off Editor (final editorial decision): Rui Providencia, Cochrane Heart, Stroke & Circulation Thematic Group
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Anupa Shah, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported the editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Victoria Pennick, Cochrane Central Production Service;
- Peer-reviewers (provided comments and recommended an editorial decision): Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Jo Platt, Central Editorial Information Specialist (search review). Two clinical peer reviewers chose not to be publicly acknowledged.

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ADDITIONAL TABLES

Table 1. Summary of findings table template

Pharmacological interventions for vaccine-induced immune thrombocytopenia and thrombosis (VITT)

Patient or population: people with VITT

Settings: hospital

Intervention: anticoagulants

Comparison: no intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention	**Risk with therapeutic anticoagulants**				
All-cause mortality [follow-up]	Study population **[value] per 1000**	**[value] per 1000** ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ very low ⊕⊕⊝⊝ low ⊕⊕⊕⊝ moderate ⊕⊕⊕⊕ high	
Necessity for additional respiratory support [follow-up]	Study population **[value] per 1000**	**value] per 1000** ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ very low ⊕⊕⊝⊝ low ⊕⊕⊕⊝ moderate ⊕⊕⊕⊕ high	
PTS - Villalta score	The mean PTS was [value] points	MD [value] higher ([value] lower to [value] higher)	-	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝	

Table 1. Summary of findings table template *(Continued)*

[follow-up]					very low ⊕⊕⊙⊙ low ⊕⊕⊕⊙ moderate ⊕⊕⊕⊕ high
Recurrent DVT [follow-up]	Study population **[value] per 1000**	**[value] per 1000** ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊙⊙⊙ very low ⊕⊕⊙⊙ low ⊕⊕⊕⊙ moderate ⊕⊕⊕⊕ high
Recurrent PE [follow-up]	Study population **[value] per 1000**	**[value] per 1000** ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊙⊙⊙ very low ⊕⊕⊙⊙ low ⊕⊕⊕⊙ moderate ⊕⊕⊕⊕ high
Major bleeding [follow-up]	Study population **[value] per 1000**	**[value] per 1000** ([value] to [value])	RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊙⊙⊙ very low ⊕⊕⊙⊙ low ⊕⊕⊕⊙ moderate ⊕⊕⊕⊕

Table 1. Summary of findings table template *(Continued)*

					high
Adverse events [follow-up]	Study population		RR [value] ([value] to [value])	[value] ([value])	[Delete as appropriate] ⊕⊝⊝⊝ very low ⊕⊕⊝⊝ low ⊕⊕⊕⊝ moderate ⊕⊕⊕⊕ high
	[value] per 1000	**[value] per 1000** ([value] to [value])			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **CIVIQ:** Chronic venous insufficiency questionnaire score; **DVT:** deep vein thrombosis; **PE:** pulmonary embolism; **PTS:** post-thrombotic syndrome; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix 1. Glossary of terms

Term	Definition
Anticoagulants	A drug or other substance that prevents or slows down the process of blood forming a clot (a solid mass (Cambridge 2024))
Arterial	Related to or flowing in an artery (Cambridge 2024)
Autoimmune heparin-induced thrombocytopenia (aHIT)	Refers to a condition in which antiplatelet factor-4 (PF4) antibodies activate platelets even in the absence of heparin (heparin-independent platelet activation (Greinacher 2017))
COVID-19	An infectious disease caused by a coronavirus (Cambridge 2024)
Deep vein thrombosis (DVT)	Occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis. DVTs can also occur in the arms, especially if there is a large intravenous central line in the vein (NIH 2024).

(Continued)

Heparin (also known as unfractionated heparin (UFH))	A fast-acting blood thinner that works together with antithrombin, a natural protein in the body, to block clot formation. Specifically, UFH binds to antithrombin and enhances its ability to inhibit two of the body's most potent clotting factors – factor Xa and factor IIa – usually within minutes. As with all forms of heparin, UFH does not break down clots, but keeps them from growing and stops new ones from forming. This allows the body the time necessary to dissolve existing blood clots gradually. UFH is administered in the hospital via an intravenous (IV) catheter inserted into an arm vein or as a subcutaneous injection under the skin. The initial dosage is determined by body weight. If you are administered IV UFH, you can expect frequent blood monitoring – even several blood tests daily – to ensure proper dosing, as blood levels of the medication can change periodically (NBCA 2024a).
Heparin-induced thrombocytopenia (HIT)	A life and limb-threatening prothrombotic, immune-mediated complication that occurs with an incidence of up to 5% following administration of UFH for a variety of prophylactic or therapeutic applications (Greinacher 2006)
Low molecular weight heparin (LMWH)	Derived from UFH by digestion or depolymerisation of longer chains of heparin into shorter chains by chemical or enzymatic means. These short strands make LMWH last longer and act more predictably in the body than UFH. Although LMWH and UFH work similarly to inhibit clotting factors, LMWH can be self-administered at home via subcutaneous injection and does not require regular blood monitoring, which is necessary for UFH treatment. As with all heparins, LMWH dosing is based on a person's weight (NBCA 2024)
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment that is given to participants in the experimental group. The aim is to determine what effect the experimental treatment had - over and above any placebo effect caused because someone had (or thinks they had) care or attention (NICE 2024).
Platelet	A very small cell in the blood that makes it thicker and more solid in order to stop bleeding caused by an injury (Cambridge 2024)
Pulmonary embolism (PE)	Occurs when a clot breaks loose and travels through the bloodstream to the lungs (NIH 2024)
Quasi-randomised controlled trial (quasi-RCT)	A study in which participants are divided by date of birth or by hospital register number, i.e. not truly randomly divided into separate groups, to compare different treatments
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug, treatment, or other intervention. One group (the experimental group) receives the intervention being tested, the other (the comparison or control group) receives an alternative intervention, a dummy intervention (placebo), or no intervention at all. The groups are followed to see how effective the experimental intervention was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias (NICE 2024)
SARS-CoV-2	A form of coronavirus that causes a serious infectious illness with difficulty in breathing and sometimes death, and has been responsible for many cases of illness since 2019. SARS-CoV-2 is an abbreviation for Severe Acute Respiratory Syndrome Coronavirus 2 (Cambridge 2024)
Thrombosis	A medical condition in which the flow of blood in the body is blocked by a clot of blood (Cambridge 2024)
Vaccine-induced thrombocytopenia and thrombosis (VITT)	A vaccine adverse event; an immune-mediated disease that can lead to thromboembolic complications, platelet activation, and thrombocytopenia (Oldenburg 2021)

(Continued)

Vascular	Relating to the vessels (Cambridge 2024)
Venous	Of or relating to the veins (Cambridge 2024; OED 2024)
Venous thromboembolism (VTE)	Venous thromboembolism (VTE) is a condition that occurs when a blood clot forms in a vein. VTE includes deep vein thrombosis (DVT) and pulmonary embolism (PE (NIH 2024))

Appendix 2. Preliminary MEDLINE (PubMed) search strategy

1 Vaccines[mh] OR Vaccine*[tw]

2 Vaccination[mh] OR Vaccination*[tw] OR (Immunization*[tw] Active[tw]) OR vaccin*[tw]

3 Immunization[mh] OR Immunization*[tw] OR (Sensitization*[tw] Immunologic[tw]) OR (Sensitization*[tw] OR Immunological[tw]) OR (Immunologic[tw] Stimulation*[tw]) OR Immunostimulation[tw] OR (Immunological[tw] Stimulation*[tw]) OR Variolation*[tw] OR immuni*[tw]

4 COVID-19 Vaccines[mh] OR (COVID 19 Vaccine*[tw]) OR (Vaccine*[tw] COVID-19[tw]) OR (COVID-19 Virus[tw] Vaccine*[tw]) OR (COVID 19 Virus Vaccine*[tw]) OR (COVID19[tw] Virus[tw] Vaccine*[tw]) OR (COVID19[tw] Vaccine*[tw]) OR (SARS-CoV-2 Vaccine*[tw) OR (SARS CoV 2 Vaccine*[tw]) OR (Vaccine*[tw] SARS-CoV-2) OR (SARS2 Vaccine*[tw]) OR (Coronavirus[tw] Disease[tw] 2019[tw] Vaccine*[tw]) OR (Coronavirus[tw] Disease[tw] 2019[tw] Virus[tw] Vaccine*[tw]) OR (Coronavirus[tw] Disease-19[tw] Vaccine*[tw]) OR (Coronavirus[tw] Disease[tw] 19 Vaccine*[tw]) OR (2019-nCoV[tw] Vaccine*[tw]) OR (2019 nCoV[tw] Vaccine[tw]) OR (2019 Novel Coronavirus[tw] Vaccine*[tw]) OR (SARS[tw] Coronavirus[tw] 2 Vaccine*[tw]) OR "COVID Vaccine"[tiab:~3] OR "COVID-19 Vaccine"[tiab:~3] OR "SARS-CoV-2 Vaccine"[tiab:~3]

5 Ad26COVS1[mh] OR Ad26.COV2.S[tw] OR (Johnson[tw] Covid-19[tw] Vaccine*[tw]) OR (Johnson[tw] Covid[tw] 19 Vaccine*[tw]) OR (COVID-19[tw] Vaccine*[tw] Johnson[tw]) OR (COVID[tw] 19 Vaccine*[tw] Johnson[tw]) OR JNJ-78436735[tw] OR JNJ78436735[tw] OR JNJ 78436735[tw] OR "Johnson Vaccine"[tiab:~3]

6 ChAdOx1 nCoV-19[mh] OR (ChAdOx1 nCoV 19[tw]) OR (nCoV-19[tw] ChAdOx1[tw]) OR (COVID-19[tw] Vaccine*[tw] AstraZeneca[tw]) OR (COVID[tw] 19 Vaccine*[tw] AstraZeneca[tw]) OR (ChAdOx1[tw] COVID-19[tw] Vaccine*[tw]) OR (COVID-19[tw] Vaccine*[tw] ChAdOx1[tw]) OR (ChAdOx1[tw] COVID[tw] 19 Vaccine*[tw]) O (Oxford-AstraZeneca[tw] COVID[tw] Vaccine*[tw]) OR (Oxford[tw] AstraZeneca[tw] COVID[tw] Vaccine*[tw]) OR (Oxford-AstraZeneca[tw] COVID-19[tw] Vaccine*[tw]) OR (Oxford[tw] AstraZeneca[tw] COVID[tw] 19 Vaccine[tw]) OR AZD1222[tw] OR AZD-1222[tw] OR AZD 1222[tw] OR Vaxzevria[tw] OR Covishield[tw]

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6

8 Thrombocytopenia[mh] OR Thrombocytopenia*[tw] OR Thrombopenia*[tw]

9 Thrombosis[mh] OR Thrombose*[tw] OR Thrombus[tw] OR (Blood[tw] Clot*[tw])

10 Thrombocytopeni*[tw] OR Thrombopeni*[tw] OR Thrombosis[tw] OR Thromboses[tw] OR Thrombotic*[tw] OR Thrombus[tw] OR Blood Clot*[tw] OR Paris Trousseau Syndrome*[tw] OR Kasabach Merritt[tw] OR Hemolytic Uremic Syndrome*[tw] OR Non Stx Hus[tw] OR Nonenteropathic HUS[tw] OR Non Shiga Like Toxin Associated HUS[tw] OR Thrombotic Microangiopath*[tw] OR Werlhof*[tw] OR Moschcowitz[tw] OR Moschkowitz[tw] OR Schulman Upshaw[tw] OR Upshaw Schulman[tw] OR Upshaw Factor[tw] OR Livedoid Vasculopath*[tw] OR "Livedo Reticularis with Summer Ulceration"[tw] OR Livedoid Vasculitis[tw] OR Thromboinflammat*[tw] OR Immunothrombo*[tw] OR Phlebothrombosis[tw] OR Phlebothromboses[tw] OR Venous Outflow Obstruction*[tw] OR Chiari*[tw] OR Postthrombotic[tw] OR Postthrombosis[tw] OR Venous Stasis Syndrome*[tw] OR Vein Occlusion*[tw] OR Thrombophlebiti*[tw] OR Phlegmasia Alba Dolens[tw] OR Lemierre*[tw] OR Postanginal Sepsis[tw] OR Postanginal Sepses[tw] OR Paget Schroetter[tw] OR CVT[tw] OR central vein thrombos*[tw] OR central venous thrombos*[tw]

11 #8 OR #9 OR #10

12 #11 AND #7

13 (Animals[mh]) NOT (humans[mh])

14 #12 NOT #13 (9,026 results on 23 October 2023)

CONTRIBUTIONS OF AUTHORS

JVM: drafted the protocol, and clinical content

RLGF: drafted the protocol, clinical and methods content, and the search strategy

VTC: drafted the protocol, and methods content

CDQF: drafted the protocol, clinical and methods content

MABC: drafted the protocol, clinical and methods content

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DECLARATIONS OF INTEREST

JVM declares working as a physician specialising in allergy and immunology in Hospital Mater Dei, Belo Horizonte, Brazil, and being a postgraduate student at the Universidade Federal de Sao Paulo, Brazil. This does not present a conflict of interest.

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