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Percutaneous thrombectomy for initial management of acute limb ischaemia (Protocol)

Araujo ST, Moreno DH, Cacione DG

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[Intervention Protocol]

Percutaneous thrombectomy for initial management of acute limb ischaemia

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ABSTRACT

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

To assess the safety and effectiveness of percutaneous thrombectomy for the initial management of acute limb ischaemia in adults.

BACKGROUND

Description of the condition

Acute limb ischaemia (ALI) is defined as the sudden and significant reduction of blood flow to the limb, with the onset of symptoms usually occurring less than two weeks from presentation. This loss of blood flow leads to limb ischaemia of differing severity, which may promote various complications, including the risk of major amputation and death (Norgren 2007). ALI manifests with various symptoms such as pain, paralysis, paraesthesia, pulselessness, pallor, and poikilothermy. Due to the severity of complications and the rapid progression to possible irreversible damage, ALI is considered a vascular emergency. The estimated incidence in the general population is 14 per 100,000 (Dormandy 1999). There is no difference in the incidence between men and women (Purushottam 2014).

The most frequent cause of ALI is an embolism (a blocked vessel caused by a foreign body such as a blood clot (thrombus), which has travelled to, and reduced the blood flow in the blood vessel), native artery thrombosis (reduced blood flow due to a blood clot formed in one's own artery), thrombosis of a stented artery (reduced blood flow due to a blood clot formed in an artery that has been stented), trauma, and graft or reconstruction occlusions (Katsanos 2017; Norgren 2007).

The most common sources of emboli are the heart: blood clots formed as a results of atrial fibrillation, and mural thrombi formed after a myocardial infarction (Rutherford 2014). Other risk factors associated with an embolism are myxoma of the left ventricle, prosthetic valves, or rheumatic valves. Thrombosis in patients with peripheral arterial disease, is usually caused by atherosclerosis (a complicated rupture of the atherosclerotic plaque is suggested), or occlusion of a prosthetic graft in patients who have undergone previous surgical procedures (Falluji 2014).

The clinical presentation of ALI varies according to the presence or absence of collateral circulation in the affected limb (Falluji 2014). People with atherosclerotic disease may have a more developed collateral circulation, due to a pre-existing ischaemic condition, which can lead to a more variable presentation of the symptoms and subsequent neuromuscular impairment (Rutherford 2014).

Limb ischaemia is defined as subacute when presentation is more than 14 days after the onset of symptoms (Schernthaner 2014). The most common aetiologies in patients with later presentation of symptoms are thromboses of native arteries and graft occlusions (Norgren 2007).

The severity of ALI is graded according to Rutherford's classification for ALI: the limb can be classified as viable (I), marginally threatened (IIa), immediately threatened (IIb), and irreversible (III) (Rutherford 1997). Rutherford's classification uses the evaluation of sensory loss, muscle weakness, and Doppler signals (arterial and venous) to guide treatment and suggest prognosis.

Complementary investigations may help plan therapy and suggest aetiology, but should not delay treatment in cases of severe ischaemia. The prognosis depends on the time it takes to diagnose and begin appropriate treatment (six to eight hours from the onset of the symptoms is considered the ideal time to achieve revascularisation). Delays should be avoided, as they may result in irreversible damage, more severe ischaemia and reperfusion injury (Fukuda 2015). Duplex ultrasonography and computed tomography angiography may help to define the location of the occlusion and the patency of other vascular territories. Computed tomography angiography has better results in the aortoiliac territory, but requires the use of contrast material. Arteriography is an important component in the assessment of patients with ALI. It may be both diagnostic and therapeutic, allowing endovascular treatment (thrombolysis, percutaneous thrombectomy, angioplasty, or stenting (Rutherford 2014)).

At initial presentation of ALI, 45% of the limbs are classified as viable, and 45% of the limbs are classified as threatened (Norgren 2007). ALI classified as class I (viable) may require elective revascularisation or may be treated with medical therapy; ALI classified as class II (threatened) generally requires revascularisation (Rutherford 2014).

Description of the intervention

The standard interventional treatment modalities for ALI are endovascular interventions and open surgery (Rutherford 2014). According to the American College of Cardiology/American Heart Association (AHA/ACC) guideline, the choice of intervention depends on local resources and patient factors, in particular, the aetiology and severity of the ischaemia (class I recommendation; level of evidence C – limited data (Gerhard-Herman 2017)). The European Society of Vascular Surgery (ESVS) guideline recommends urgent revascularisation in patients with ALI classified as Rutherford II (class I recommendation; level of evidence C – limited data); revascularisation is also indicated for patients with ALI classified as Rutherford I, but after image evaluation and discussion of the case (class I recommendation; level of evidence C – limited data (Aboyans 2018)).

Conventional open surgery is used more often than endovascular interventions in the USA (Eliason 2003). Open surgery is preferred in cases of proximal embolism of the lower limbs (e.g. above the inguinal ligament), and when there is no associated atherosclerosis. Surgery consists of clot removal, and may be combined with control arteriography and catheter-directed thrombolysis (Norgren 2007). According to the AHA/ACC guideline, surgical embolectomy may be useful for patients with embolic ALI and a viable limb (class IIa recommendation; level of evidence C – limited data (Gerhard-Herman 2017)).

Endovascular interventions are less invasive, and have a lower morbidity associated with the procedure compared with open surgery (Norgren 2007). In catheter-directed thrombolysis, thrombolytic enzymes are injected into the vessel to dissolve the thrombus, which may potentially reveal the aetiological factor (e.g. stenosis or occlusions) and guide further treatment. Increased risk of bleeding and stroke are associated with catheter-directed thrombolysis (Darwood 2018). There is no evidence of a difference in limb salvage, amputation, or death at 30 days, 6 months, or 1 year between initial thrombolysis or initial open surgery (Darwood 2018). According to the AHA/ACC guideline, catheter-directed thrombolysis may be used for patients with ALI and a viable limb (class I recommendation; level of evidence A (Gerhard-Herman 2017)).

Percutaneous thrombectomy has also been performed as an alternative endovascular technique. Percutaneous thrombectomy encompasses different techniques, or modalities, which aim to remove the embolus or the thrombus (or both) from circulation, and

restore blood flow. These modalities can be mechanical (including aspiration or suction, rheolysis, rotation, or ultrasound), or mechanical combined with pharmacological thrombolysis (pharmomechanical thrombectomy (Kasirajan 2001)). According to the AHA/ACC guideline, percutaneous thrombectomy may be used in association with catheter-directed thrombolysis for patients with ALI and a viable limb (class IIa recommendation; level of evidence B – non-randomised (Gerhard-Herman 2017)).

The benefits of percutaneous thrombectomy versus open surgery or thrombolysis are uncertain (Veenstra 2019). Limb salvage after percutaneous thrombectomy in different aetiologies has not yet been fully verified (Liang 2019).

How the intervention might work

Like surgery and thrombolysis, the aim of percutaneous thrombectomy is to restore limb perfusion. Percutaneous thrombectomy includes percutaneous mechanical thrombectomy and pharmomechanical thrombectomy (Purushottam 2014). The proposed advantages of percutaneous thrombectomy include reducing the time to revascularisation, and when combined with catheter-directed thrombolysis, reducing the dose and the time of infusion of thrombolytic agents, and the risk of associated complications, such as major bleeding (Purushottam 2014). To perform all forms of percutaneous thrombectomy, the team needs to have the necessary equipment and supplies available in a timely manner (Hynes 2012).

Percutaneous mechanical thrombectomy

In **aspiration thrombectomy**, the surgeon inserts a large-lumen catheter with a thin wall, and with a large volume syringe, withdraws part or all of the embolus or thrombus from arterial circulation (Norgren 2007). The possible complications of aspiration thrombectomy are dissection of the intimal layer of the vessel in areas with atherosclerotic plaque, distal embolisation, and proximal clot movement (Hynes 2012).

In **rheolytic thrombectomy**, the surgeon uses pressurised and pulsatile saline to fragment and macerate the thrombus. This generates a low pressure zone (Venturi – Bernnoulli effect), which facilitates aspiration and withdrawal of the thrombus from circulation (Leung 2015). Potential complications of this technique are embolisation and haemolysis (which may lead to bradyarrhythmia and renal failure (Rutherford 2014)). Intrathrombus thrombolytic agents may be administered during the procedure (Hynes 2012).

In **fragmentation or rotational thrombectomy**, a catheter is inserted and spun at a high frequency, which fragments the thromboembolic material. Some devices will also aspirate the fragments into a collection bag (Lichtenberg 2013). Possible complications of this technique include distal embolisation of thrombus particles (Rutherford 2014).

In the last decade, **ultrasound-enhanced thrombolysis** has been used. Low-intensity and high-frequency waves are used to break down fibrin fibres, increasing the permeability of the clot, and exposing fibrinogen receptors to thrombolytic medication (Schrijver 2015). The aim of this modality is to accelerate the process of thrombolysis. A possible adverse event of this therapy is the overheating of the device system, causing vessel injury (Rutherford 2014).

Pharmomechanical thrombectomy

Some devices have been developed to link mechanical thrombectomy with the delivery of thrombolytic agents. This is referred to as **pharmomechanical thrombectomy**. The aim of this technique is to reduce the dose of the medication and the time required to dissolve the clot (Rutherford 2014). Potential complications of pharmomechanical thrombectomy are bleeding, distal embolisation, rethrombosis and arterial injury (Gandhi 2018).

Why it is important to do this review

Although percutaneous thrombectomy has been used over the last two decades, no systematic review currently describes this treatment in patients with ALI. This review aims to present all the available evidence for percutaneous thrombectomy in the initial management of ALI, to aid decision making for patients and healthcare professionals, including vascular surgeons and interventional radiologists.

OBJECTIVES

To assess the safety and effectiveness of percutaneous thrombectomy for the initial management of acute limb ischaemia in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will search for randomised controlled trials (RCTs) or quasi-RCTs that assess percutaneous thrombectomy (mechanical thrombectomy such as aspiration or suction, rheolysis, rotational, ultrasound-enhanced thrombolysis and pharmomechanical thrombectomy) for the management of acute limb ischaemia. We will exclude studies which compare thrombolysis alone with open surgery as this topic is covered by another Cochrane review (Darwood 2018).

Types of participants

We will include studies with adult participants (at least 18 years old), who were clinically diagnosed with acute limb ischaemia, classified as I or II in the Rutherford's classification (Rutherford 1997). We will also consider participants with subacute limb ischaemia, i.e. limb ischaemia that has lasted longer than 14 days, but shorter than 21 days since the onset of symptoms.

Types of interventions

We will evaluate the effects of percutaneous thrombectomy in the treatment of patients with ALI. Percutaneous thrombectomy includes mechanical thrombectomy (aspiration, rheolysis, rotation, and ultrasound (US)-enhanced thrombolysis), and pharmomechanical thrombectomy resulting in the following possible comparisons:

- Percutaneous thrombectomy (any modality) versus open surgery;
- Percutaneous thrombectomy (any modality) versus each other, thrombolysis alone, or no treatment.

Types of outcome measures

Primary outcomes

- Primary patency: vessel patency at 6 months and 12 months after the intervention, as measured by image evaluation (Doppler ultrasound, tomography, or angiography)
- Amputation rate: number of patients undergoing major amputations (defined as amputation above the ankle in the lower limb, or above the wrist in the upper limb), at 12 and 24 months after procedure
- Major bleeding: defined as bleeding that causes a haemoglobin level drop of 3 g/dL or more, requires transfusion, requires surgical intervention for control, or requires vasoactive intravenous drugs; cardiac tamponade; intracranial haemorrhage; intraocular bleed compromising vision, type 3; or fatal bleeding, type 5 (Mehran 2011)

Secondary outcomes

- Clinical success: defined as improvement by at least one category in the Rutherford's classification for ALI, or elevation of the ankle-brachial index by at least 0.2, at 6 and 12 months after procedure
- Secondary patency: patency of the vessel after secondary interventions at 6 and 12 months after the primary intervention, as measured by image evaluation (Doppler ultrasound, tomography, or angiography)
- Adverse effects: embolism to new vascular territories, vessel dissection

Search methods for identification of studies

We will have no restrictions based on language or publication status.

Electronic searches

The Cochrane Vascular Information Specialist will search the following databases, in an effort to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

- The Cochrane Vascular Specialised Register via the Cochrane Register of Studies (CRS-Web).
- The Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO).
- MEDLINE Ovid (MEDLINE® Epub Ahead of Print, In-Process & Other Non-indexed Citations, MEDLINE® Daily, and MEDLINE®; 1946 onwards)).
- Embase Ovid (1974 onwards).
- CINAHL EBSCO (1982 onwards).

The Information Specialist has devised a draft search strategy for RCTs for MEDLINE, which is displayed in Appendix 1, and will be used as the basis for search strategies for the other databases.

The Information Specialist will search the following trials registries.

- The World Health Organization International Clinical Trials Registry Platform (who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We will review the bibliographies of the studies identified by the search for further relevant references. We will contact specialists in the field, and the study authors to request information on any possible unpublished data. We will search the grey literature by consulting the OpenGrey Database (opengrey.eu).

Data collection and analysis

Selection of studies

We will evaluate all titles and abstracts of the articles identified by the literature searches. After screening the titles and abstracts, two review authors (STA, DHM) will independently assess the full text of studies that appear to meet the inclusion criteria. We will consult a third review author (DGC) in case of discrepancies.

Data extraction and management

Two review authors (STA, DHM) will extract data from the included trials, using the Cochrane Vascular data extraction form. We will consult a third review author (DGC) in case of any discrepancies. We will enter the data into Review Manager 5 software (Review Manager 2014).

Assessment of risk of bias in included studies

Two review authors (STA, DHM) will assess the risk of bias of included studies using Cochrane's 'Risk of Bias' tool, and according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will classify he following domains as low risk of bias, high risk of bias or unclear risk of bias: selection bias, performance bias, detection bias, attrition bias, outcome reporting bias, and other biases. This information will be presented in risk of bias tables and risk of bias summary figures.

Measures of treatment effect

We will estimate the effect of treatment in dichotomous variables using risk ratios (RR) with 95% confidence interval (CI), using Review Manager 5 (Review Manager 2014).

Unit of analysis issues

We will consider the individual participant as the unit of analysis.

Dealing with missing data

We will contact the authors of the studies to request missing data or additional information if necessary. We will use intention-to-treat analysis to analyse the available data and not the analysis per protocol.

Assessment of heterogeneity

We intend to use the Chi^2 test with significant level set at $P < 0.1$, included in the forest plot, to assess the statistical heterogeneity. We also intend to use the I^2 statistic to assess the inconsistency across the studies. We will interpret the I^2 statistic according to *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- 0% to 25%: low heterogeneity;
- 25% to 75%: moderate heterogeneity;
- More than 75%: substantial heterogeneity.

Assessment of reporting biases

We will explore any publication bias by creating a funnel plot if there are enough included trials in the review (more than 10), as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We will perform data synthesis with Review Manager 5 (Review Manager 2014). If we do not find substantial heterogeneity among the included studies, we intend to use a fixed-effect model to perform the meta-analysis. If the statistical heterogeneity among the included studies is substantial (I^2 > 75%), we intend to use a random-effects model. If it is not possible to pool data, we will provide clear reasons for this and report results narratively.

Subgroup analysis and investigation of heterogeneity

In the face of substantial statistical heterogeneity (I^2 > 75%), and if sufficient data are available, we will perform the following subgroup analyses for all planned outcomes, to investigate the effects of clinical heterogeneity (according to the criteria listed in Assessment of heterogeneity).

- Variants of percutaneous thrombectomy (mechanical thrombectomy such as aspiration, rheolysis, rotation, US-enhanced thrombolysis, and pharmomechanical thrombectomy)
- Severity of ischaemia: acute versus subacute limb ischaemia
- Severity of ischaemia: immediately threatened limbs (Rutherford IIb) versus Rutherford I or IIa (Rutherford 1997)
- Previous interventions (endovascular or open surgery) versus no previous interventions
- Number of patent leg arteries measured by image evaluation (Doppler ultrasound, tomography, or angiography) at baseline (0 patent artery versus 1 patent artery versus > 1 patent arteries)
- Aetiology of ischaemia (embolism versus thrombosis)

Sensitivity analysis

We will perform sensitivity analysis to investigate the impact of study characteristics including sponsorship, existence of publication bias, and high risk of bias. We will consider a study as being at high risk of bias if we assessed two or more bias domains at high risk.

Summary of findings and assessment of certainty of the evidence

We will present the findings of this review in a 'Summary of findings' table, based on the methods described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will present separate tables for each comparison addressed in this review (see Types of interventions) with the outcomes listed in Types of outcome measures (primary patency, amputation rate, major bleeding, clinical success, secondary patency, and adverse effects) at the clinically most relevant timepoint.

We will prepare the tables with GRADEpro GDT software (GRADEpro GDT 2015). We will follow the GRADE approach to evaluate the certainty of the evidence in the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Atkins 2004; Higgins 2011). Based on this, we will classify the certainty of the body of evidence from included studies as high, moderate, low or very low. An example of a 'Summary of the findings' table is provided in Table 1.

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ADDITIONAL TABLES

Table 1. Example Summary of findings table: percutaneous thrombectomy for initial management of acute limb ischaemia

Percutaneous thrombectomy versus open surgery						
Patient or population: adults with acute limb ischaemia (ALI), classified as Rutherford classification I and II **Settings:** hospital **Intervention:** percutaneous thrombectomy[1] **Comparison:** open surgery						
Outcomes	**Anticipated absolute effects * (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with open surgery	**Risk with percutaneous thrombectomy**				
Primary patency (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**	
Amputation rate (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low**	

Table 1. Example Summary of findings table: percutaneous thrombectomy for initial management of acute limb ischaemia *(Continued)*

					⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Major bleeding (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Clinical success (improvement by at least one category in the Rutherford's classification for ALI) (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Secondary patency (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**
Adverse effects (follow-up)	**[value] per 1000**	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])	[value] ([value])	⊕⊖⊖⊖ **very low** ⊕⊕⊖⊖ **low** ⊕⊕⊕⊖ **moderate** ⊕⊕⊕⊕ **high**

* **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)
ALI: acute limb ischaemia; **CI:** confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

Table 1. Example Summary of findings table: percutaneous thrombectomy for initial management of acute limb ischaemia *(Continued)*

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

[1]Percutaneous thrombectomy may involve any of the following techniques: mechanical thrombectomy (aspiration, rheolysis, rotation, and ultrasound-enhanced thrombolysis) and pharmomechanical thrombectomy

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1 Arterial Occlusive Diseases/

2 Ischemia/

3 exp Peripheral Vascular Diseases/

4 acute limb ischaemia.ti,ab.

5 acute limb ischemia.ti,ab.

6 ((arter* or vascular or vein* or veno* or peripher*) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

7 (peripheral adj3 dis*).ti,ab.

8 (leg adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

9 (limb adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

10 (lower adj3 extrem* adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

11 ((iliac or femoral or popliteal or femoro* or fempop* or crural) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

12 ((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) adj3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)).ti,ab.

13 or/1-12

14 exp Thrombectomy/

15 exp Thrombolytic Therapy/

16 ((Percutaneous or mechanical or Aspiration or Rheolytic or Fragmentation or rotational or ultrasound enhanced or Pharmomechanical) adj3 thrombectomy).ti,ab.

17 or/14-16

18 13 and 17

19 randomized controlled trial.pt.

20 controlled clinical trial.pt.

21 randomized.ab.

22 placebo.ab.

23 drug therapy.fs.

24 randomly.ab.

25 trial.ab.

26 groups.ab.

27 or/19-26

28 exp animals/ not humans.sh.

29 27 not 28

30 18 and 29

WHAT'S NEW

Date	Event	Description
21 November 2019	Amended	Affiliation of external reviewer amended

CONTRIBUTIONS OF AUTHORS

STA: contact person, guarantor of the review, protocol drafting, addressing clinical comments from the referees, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, and future review updates
DHM: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, and review drafting
DGC: protocol drafting, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, and review drafting

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