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Interventions for the long-term prevention of hereditary angioedema attacks (Protocol)

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[Intervention Protocol]

Interventions for the long-term prevention of hereditary angioedema attacks

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ABSTRACT

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

To assess the efficacy and safety of interventions for the long-term prevention of hereditary angioedema (HAE) attacks in people with HAE types I, II and III.

BACKGROUND

Description of the condition

Hereditary angioedema (HAE) is a rare but serious condition that is characterised by randomly occurring, recurrent attacks of swelling (angioedema). An attack of swelling is often heralded by a transient, non-itchy rash called erythema marginatum (Zeerleder 2016). At first, the swelling is typically painless and not itchy, however it can become extremely painful and disabling. The swelling may affect the face and upper airway, intestinal mucosa, genitals and the extremities. Attacks peak at around 24 hours after onset and can last several days. There may be prodromal symptoms (symptoms indicating onset), such as fatigue and feeling generally unwell. Swelling of the airway is life-threatening, as it can result in death by asphyxiation. Intestinal swelling causes abdominal pain and may be accompanied by nausea, vomiting and diarrhoea; signs and symptoms may present akin to acute bowel obstruction. A swelling attack may cause major fluid shifts, which may result in hypotension and shock. HAE attacks may be triggered by the following: 1) physical triggers such as surgery, injury or infection (Frank 1976); 2) pharmacological triggers such as oestrogens (Frank 1979) and angiotensin converting enzyme (ACE) inhibitors (Agostoni 1999); and 3) psychological factors such as stress or anxiety (Zotter 2014). However, in many cases, no precipitating factor can be identified. It is not known how many HAE attacks do not have any precipitating factor.

Hereditary angioedema affects approximately one in every 50,000 to 150,000 people (Roche 2005; Zuraw 2008), and follows an autosomal dominant pattern of inheritance in the majority of patients (Germenis 2016). Compared with more common causes of angioedema, such as infections and ACE inhibitor medications, HAE is a rare cause of angioedema and so diagnosis is frequently missed or delayed. Misdiagnosis can be fatal, as HAE swelling does not respond to medications routinely used for allergic swelling, such as adrenaline, corticosteroids or antihistamines. HAE should

be considered when a patient presents with recurrent, isolated angioedema without urticaria and with a family history of similar attacks (Henao 2016; Maurer 2018). However, 25% of individuals with HAE will not have a positive family history, as the condition often arises from a somatic mutation in the *SERPING1* gene. Untreated, HAE has a mortality rate of 15% to 33%. It is unclear what the mortality rate is for patients who are treated for HAE.

Most cases of HAE are associated with increased levels of bradykinin, a potent vasodilator. Binding of bradykinin to the bradykinin 2 (B2) receptor on blood vessels results in fluid extravasation and tissue swelling. Bradykinin is a low molecular weight peptide that is formed when kininogen is cleaved by the protease kallikrein. Active kallikrein is generated by cleaving prekallikrein, which involves coagulation factor XII, another serum protease. The proteolytic activity of kallikrein is regulated by the C1 esterase inhibitor (C1-INH), a serine protease inhibitor that is encoded by the *SERPING1* gene. Patients with HAE type I have insufficient amounts of C1-INH; patients with HAE type II may have normal C1-INH concentrations, but mutations in the *SERPING1* gene result in C1-INH variants that can no longer control kallikrein (Germenis 2016). The vast majority of HAE cases can be classified either as type I (80%) or type II (20%). A small number of patients, predominantly females, suffer HAE despite having normal C1-INH levels and C1-INH function (US HAE Association 2018). These rare, type III, cases are often associated with mutations in the *F12* gene. The consequences of these mutations are poorly understood but are believed to affect the factor XII-mediated processing of prekallikrein. At least two other mutations - in the plasminogen and angiopoietin genes - have also been described in patients with HAE with normal C1-INH (Bafunno 2018; Bork 2018).

The clinical diagnosis of angioedema should be followed by laboratory testing for both complement component 4 (C4) concentrations and C1-INH concentration and function. The combination of low C4 and low C1-INH function has a 98% specificity for HAE caused by C1-INH deficiency (Gompels 2002; Tarzi 2007). Routine genetic testing is not usually performed but is indicated in HAE with normal C1-INH, and is occasionally used for prompt diagnosis in the neonate.

Description of the intervention

Treatments for the prevention of HAE attacks aim to prevent HAE attacks from occurring. This is done through the supplementation of insufficient concentrations of C1-INH, or by providing functional inhibitor proteins in the case of subfunctional C1-INH. Functional C1-INH can be provided in the form of a concentrate prepared from plasma or as a recombinant protein (Johnson 2018; Longhurst 2018). This is administered as an intravenous infusion and, more recently, as a subcutaneous injection. Traditionally, tranexamic acid and attenuated androgens have been the most commonly used pharmacological agents for prophylaxis in HAE. Tranexamic acid, an anti-fibrinolytic, interferes with the functions of plasminogen and plasmin, however, the mechanism of action in HAE is not well understood (Winterberger 2014). Tranexamic has been favoured in paediatric patients because of a better side-effect profile than attenuated androgens; however, its efficacy is considered modest (Frank 2016). Attenuated androgens, most commonly danazol, have been used for many years as an oral prophylactic medication in HAE. It is available in capsules of varying doses and is taken by mouth (FDA 2011). Newer preventative approaches target kallikrein. The first of these to reach clinical practice is lanadelumab, a human monoclonal antibody targeting plasma kallikrein, which is given subcutaneously (Banerji 2017; Banerji 2018). A number of other molecules are being tested in clinical trials at present. These include a monoclonal anti-FXII antibody (Cao 2015) and an oral kallikrein inhibitor BCX7353 (Biocryst) (Chen 2017).

Interventions for the treatment of acute HAE attacks - such as C1-INH concentrates that have only been tested for acute use (Berinert, Ruconest), icatibant (Firazyr) and ecallantide (Kalbitor) - are not covered in this review. They will be covered in a separate review (Frese 2019).

How the intervention might work

Treatment with recombinant C1-INH and plasma-derived C1-INH concentrates supplies functional inhibitor proteins in sufficient amounts to improve C1-INH activity levels and ideally restore normal inhibitor activity in patients with a C1-INH deficiency (for example, in cases with insufficient C1-INH plasma levels or with non-functional C1-INH variants). The therapeutic effect of danazol is not fully understood; it may promote C4 and C1-INH synthesis by its anabolic effect, and it may cause a minor increase in C1 concentrations (thus improving the complement system) or prevent C1-INH breakdown (Fabiani 1990). Lanadelumab inhibits the kallikrein protease by blocking its substrate binding site (Kenniston 2014), which prevents the cleavage of high molecular weight kininogen into kininogen and bradykinin. Thus, lanadelumab can be used to control the production of excess bradykinin and therefore the development of acute HAE attacks (Banerji 2017; Banerji 2018). All these drugs prevent attacks by restoring normal C1-INH activity.

Why it is important to do this review

Although HAE is rare, it is highly debilitating, may cause death and is associated with high personal and economic burdens (Lumry 2018; Wilson 2010). The lives of people suffering from this condition are disrupted by the apparently random nature of swelling attacks. HAE attacks can be very painful and are often associated with temporary disfigurement and severe morbidity (Longhurst 2016). Oedema of the upper airway is life-threatening. Thus, se-

vere acute HAE attacks often result in presentations to the emergency department and, occasionally, in admission to hospital. Even with management at home, individuals may need several days away from school or work for recovery. Any effective preventative treatment for HAE should reduce the number of swelling attacks, improve the quality of life for people with HAE and prevent death. There are several options for the prevention of HAE attacks, but there is no systematic review of these treatments, and we currently do not know whether all preventative HAE treatments are equally effective and safe. This review aims to present the available evidence on the safety and efficacy of interventions for the long-term prevention of HAE attacks, allowing evidence-based decision making for health practitioners and patients.

OBJECTIVES

To assess the efficacy and safety of interventions for the long-term prevention of hereditary angioedema (HAE) attacks in people with HAE types I, II and III.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials investigating interventions for the long-term prevention of HAE attacks. We will include blinded and open-label trials. We will exclude studies investigating interventions for the treatment of acute HAE attacks, as these will be covered in another review (Frese 2019).

Types of participants

We will include studies involving children or adults with types I, II and III HAE who were treated for the prevention of HAE attacks. Type I HAE is defined as HAE caused by insufficient amounts of C1-INH. Type II HAE is defined as HAE presenting with sufficient amounts of C1-INH, but subfunctional or non-functional C1-INH. Type III HAE is defined as HAE with normal C1-INH concentrations and function (US HAE Association 2018). If the justification for designating the type of HAE is not specifically given, we will accept the diagnosis stated in the study by the study authors.

Types of interventions

We will include any intervention that has been tested for the prevention of HAE attacks, including concentrated C1 esterase inhibitors (either derived from blood or produced as a recombinant protein), as well as danazol, tranexamic acid, BCX7353 and lanadelumab. There will be no restrictions on dose, frequency or intensity of treatment, but the length of treatment will be restricted to the prevention of HAE attacks. We will compare these interventions with placebo or any active comparator.

Types of outcome measures

For all outcomes, we will include the time points reported by individual studies, as long as they exclude acute attacks. Clinically relevant time points will be six weeks or longer.

Primary outcomes

- HAE attacks (rate of attacks per person, per population).
- Mortality.
- Serious adverse events, such as hepatic dysfunction, hepatic toxicity and deleterious changes in blood tests (for example, glucose tolerance, thyroid hormones, lipids, lipoproteins).

Secondary outcomes

- Quality of life (measured by any validated measure, such as Angioedema Quality of Life questionnaire (AE-QoL), health-related Quality of Life questionnaire for HAE (HAEQoL), 12-item Short Form health survey (SF12)).
- Severity of breakthrough attacks.
- Measures of disability (measured by any validated measure, such as WPAI). This will measure changes in the ability of patients to attend and function well in the workplace and in recreational activities.
- Adverse events, such as weight gain, mild psychological changes (irritability, nervousness, mood changes), body hair, gastrointestinal health, nausea, vomiting, flushing, etc.

Search methods for identification of studies

Electronic searches

The Cochrane Vascular Information Specialist aims to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in-press, or in-progress).

The Information Specialist will search the following databases for relevant trials:

- 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, Ovid MEDLINE® Daily and Ovid MEDLINE®) (1946 onwards);
- Embase Ovid (from 1974 onwards); and
- CINAHL Ebsco (from 1982 onwards).

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

The Information Specialist will search the following trials registries:

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

Searching other resources

We will search grey literature for evidence of studies that have not been published in peer-reviewed journals and, if identified, will contact the authors to obtain the data. We will also contact the manufacturers of the interventions, as well as specialist groups, to help us identify unpublished clinical trials.

Data collection and analysis

Selection of studies

Two review authors (KM, NB) will independently assess each study for inclusion based on the criteria listed above. We will resolve any disagreements by discussion with a third review author (CK). We will illustrate the study selection process in a PRISMA diagram (Liberati 2009). We will list all articles excluded after full-text assessment in a 'Characteristics of excluded studies' table and will provide the reasons for their exclusion.

Data extraction and management

One review author (KM or NB) will collect data into a spreadsheet and this will be checked by another author (MF). We will resolve any disagreements by consensus or by reference to a third review author (PM).

Assessment of risk of bias in included studies

We will assess the risk of bias of included studies using the Cochrane 'Risk of Bias' tool. This tool involves assessing the risk of selection bias, performance bias, detection bias, attrition bias and other bias (Higgins 2011). Two review authors (KM, NB) will assess the risk of bias, and we will resolve disagreements by consensus or by reference to a third review author (MF).

Measures of treatment effect

We will calculate and report dichotomous outcome measures - such as number of attacks, mortality, serious adverse events and adverse events - using risk ratios (RRs) with the associated 95% confidence intervals (CIs). We will calculate and report continuous outcome measures for quality of life and disability scores using the mean difference (MD) and the associated 95% CIs. If the included studies use different scales, we will calculate a standardised mean difference (SMD) instead. Where the included studies report only CIs or standard errors, we will convert these to standard deviations using the Review Manager 5 calculator (Review Manager 2014). We will carry out analyses at different time points, as reported by the trials, and base our calculations on an intention-to-treat approach.

Unit of analysis issues

Our unit of analysis will be the participant. We will report on outcomes at a participant level.

Dealing with missing data

Where measurements of variance (summary data) are missing, we will contact study authors to request the missing information. If the information cannot be obtained, we will impute those values by taking the mean of the variance of other studies reporting on the same outcome using the same methodology. We will do this for all studies with missing standard deviations/errors. We will then undertake a sensitivity analysis excluding those studies. For missing patient data, we will use an intention-to-treat analysis. We will compare the rates of missing data between groups to determine if asymmetry is present.

Assessment of heterogeneity

We will assess heterogeneity using Tau^2, Chi^2 and I^2, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For our assessment of the significance of heterogeneity as measured by I^2, we will take direction and size of effect into consideration and will use the following guidance for interpretation, provided in Higgins 2011:

- 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%: considerable heterogeneity.

Assessment of reporting biases

We will assess reporting bias by creating a funnel plot using Review Manager 5 (Review Manager 2014). If necessary, we may undertake statistical tests such as Egger's test. We will also look at the funding sources of clinical trials and undertake a sensitivity analysis by funding source. Because funnel plots are not informative where there are fewer than 10 studies (Higgins 2011), we will only undertake funnel plot analysis for outcomes containing 10 studies or more.

Data synthesis

We will undertake meta-analysis of data from included studies using a fixed-effect model where possible. If factors in the trials clearly indicate that variance between studies would be likely to be due to factors other than chance, we will use a random-effects model. If we are unable to carry out meta-analysis, we will report the findings of the included studies in the text of the review.

'Summary of findings' table

We will prepare a 'Summary of findings' table, using GRADEpro GDT 2015 software, to list key outcomes of the review and the degree of certainty in these outcomes using GRADE criteria (GRADE 2004). The outcomes we will report on will be the efficacy (rate of attacks, mortality, quality of life, disability) and safety (serious adverse events, adverse events) of interventions for the prevention of HAE attacks, as listed in Types of outcome measures. We will assess and report on the certainty of the evidence for each outcome. We will grade the certainty as high, moderate, low or very low, based on the criteria of risk of bias, inconsistency, indirectness, imprecision, and publication bias, using the GRADE approach (GRADE 2004). We have included a draft 'Summary of findings' table for the primary and secondary outcomes (Table 1). We will report on the outcomes for each type of HAE (I, II and III) in separate 'Summary of findings' tables, where data are available.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses for all outcomes, if data are available, as follows:

- type of HAE (I, II or III);
- baseline number of attacks (per week, per month, per year);
- drug;
- drug dose and frequency;
- age (children versus adolescents versus adults versus older people). Children are defined as aged 0 to 10 years, adolescents as 11 to 17, adults as 18 to 64, and older people as 65 and above;
- sex;
- comorbidities; and
- concomitant medication.

Sensitivity analysis

We plan to undertake sensitivity analysis of studies according to overall risk of bias, with an emphasis on performance and detection bias, and trial funding. We will do this by excluding studies with a high risk of bias in one or more of these domains from the pooled analysis, to assess the impact of these studies on the results. We will also undertake sensitivity analyses in which we remove studies with imputed measures of variance or with significant amounts of missing data (20% or more in a single outcome). We plan to undertake sensitivity analysis for all outcomes, if data are available.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Draft 'Summary of findings' table

Intervention compared with placebo or active control for preventing HAE attacks						
Patient or population: children or adults with type I HAE **Settings:** outpatient setting **Intervention:** intervention **Comparison:** placebo or active control						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No. of Participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

Table 1. Draft 'Summary of findings' table (*Continued*)

	Placebo/active control	**Intervention**				
Number of attacks (per week, per month, per year; follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	[value] per 1000	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])			
Mortality (per week, per month, per year; follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	[value] per 1000	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])			
Incidence of serious adverse events (follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	[value] per 1000	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])			
Quality of life [any validated scale] (follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	The mean change in quality of life ranged	The mean change in quality of life in the intervention groups was **[value] [lower/higher]** [(value to				

Table 1. Draft 'Summary of findings' table (*Continued*)

	across control groups from [value][measure]	value lower/higher)]				
Measures of disability [any validated scale] (follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	The mean change in disability ranged across control groups from [value][measure]	The mean change in disability in the intervention groups was **[value] [lower/higher]** [(value to value lower/higher)]				
Incidence of adverse events (follow-up)	**Study population**			[value] ([value])	[Delete as appropriate] ⊕◯◯◯ **very low** ⊕⊕◯◯ **low** ⊕⊕⊕◯ **moderate** ⊕⊕⊕⊕ **high**	
	[value] per 1000	**[value] per 1000** ([value] to [value])	**RR [value]** ([value] to [value])			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **HAE**: hereditary angioedema; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate.

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Angioedemas, Hereditary/
2 (angioedema adj3 hereditary).ti,ab.
3 HAE.ti,ab.
4 or/1-3
5 exp Antibodies, Monoclonal/
6 exp Bradykinin B2 Receptor Antagonists/
7 exp Complement C1 Inactivator Proteins/
8 exp Complement C1 Inhibitor Protein/
9 exp DANAZOL/
10 exp KALLIKREINS/
11 exp Recombinant Proteins/tu [Therapeutic Use]
12 exp Tranexamic Acid/
13 attenuated androgens.ti,ab.
14 BCX7353.ti,ab.
15 Berinert.ti,ab.
16 bradykinin B2 receptor antagonists.ti,ab.
17 C1 esterase inhibitors.ti,ab.
18 C1INH.ti,ab.
19 C1-INH.ti,ab.
20 Cinryze*.ti,ab.
21 Complement C1*.ti,ab.
22 concentrated C1 esterase inhibitors.ti,ab.
23 Danazol.ti,ab.
24 Ecallantide.ti,ab.
25 FFP.ti,ab.
26 Firazyr.ti,ab.
27 fresh frozen plasma.ti,ab.
28 Icatibant.ti,ab.
29 Kalbitor.ti,ab.
30 kallikrein inhibit*.ti,ab.
31 Lanadelumab.ti,ab.
32 monoclonal antibody.ti,ab.
33 monoclonal anti-f XII antibody.ti,ab.
34 nanofiltered C1 inhibitor.ti,ab.
35 rhC1INH.ti,ab.
36 rhC1-INH.ti,ab.
37 Ruconest.ti,ab.
38 SDP.ti,ab.
39 tranexamic acid.ti,ab.
40 or/5-39
41 4 and 40
42 randomized controlled trial.pt.
43 controlled clinical trial.pt.
44 randomized.ab.
45 placebo.ab.
46 drug therapy.fs.
47 randomly.ab.
48 trial.ab.

49 groups.ab.
50 or/42-49
51 exp animals/ not humans.sh.
52 50 not 51
53 41 and 52

CONTRIBUTIONS OF AUTHORS

NB drafted the protocol. For the full review, she will obtain studies, select studies, assess the risk of bias, extract data, enter data into Review Manager 5, interpret data, draft the final review and update the review.

MF drafted the protocol. For the full review, he will obtain studies, assess the risk of bias, extract data, enter data into Review Manager 5, interpret data, draft the final review and update the review.

PM drafted the protocol. For the full review, he will extract data, enter data into Review Manager 5, analyse data, interpret data and update the review.

CK drafted the protocol. For the full review, she will select studies, interpret data, draft the final review and update the review.

KM drafted the protocol. For the full review, she will obtain studies, select studies, assess the risk of bias, extract data, enter data into Review Manager 5, analyse data, interpret data, draft the final review, update the review and be the guarantor of the review.

DECLARATIONS OF INTEREST

NB: none known.

MF: none known.

PM: none known.

CK: has conducted original investigator-led research in the field of HAE and has participated as a principal investigator in sponsored multinational RCTs of a number of therapies used for HAE management (acute and prophylactic therapies). She has participated actively in a number of Global HAE meetings and has chaired advisory boards discussing HAE management in Australia. CK declared that her institution has received payment for the conduct of multinational clinical trials from Shire Plc, CSL Limited and BioCryst Pharmaceuticals Inc. She received payment from Shire Plc for chairing the advisory board for management of HAE in Australia; and from CSL Limited for chairing an advisory board to discuss use of berinert in Australia. She received payment to support travel to meetings from Shire Plc (active participation in Global Forum: presentation to attendees, submission of a poster); from CSL Limited (for attendance as principal investigator of Vanguard study clinical trial meeting on prophylaxis treatment); and from BioCryst Pharmaceuticals Inc (for attendance as principal investigator in a clinical trial on prophylactic therapy). She has also received payment from Novartis for membership of an advisory board on chronic urticaria and for development of educational presentations and information on urticaria; and from Sanofi for consultancy (ran an educational programme on severe asthma for staff).

KM: has declared that she does comparative effectiveness work for a company (TruDataRx, Inc.), that provides independent advice to employers based on the efficacy of pharmaceutical drugs. This company does not receive funds from the pharmaceutical industry or government.

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NOTES

Parts of the methods section of this protocol are based on a standard template established by Cochrane Vascular.