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Keywords:	Vascular surgery < SURGERY, VASCULAR SURGERY, Substance misuse < PSYCHIATRY, PUBLIC HEALTH

The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

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Key Words: Drug use; Vascular surgery; Infected arterial pseudoaneurysm; Health outcomes

Word count: 2470

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Abstract

Introduction

People who inject drugs (PWID) are at risk of a range of injecting related infections and injuries, which can threaten life and limb. In parallel to escalating rates of drug-related deaths seen in Scotland and the UK, there has also been an increase in hospital admissions for skin and soft tissue infections related to injecting drug use. One such complication is the infected arterial pseudoaneurysm, which risks rupture and life-threatening haemorrhage. Surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use remain contentious, with some advocates for ligation and debridement alone, whilst others promote acute arterial reconstruction (suture or patch repair, bypass or, more recently, endovascular stent-graft placement). Rates of major lower limb amputations related to surgical management for this pathology vary in the literature. This review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including open and endovascular options, for the infected arterial pseudoaneurysm secondary to groin injecting drug use.

Methods and Analysis

The methods will follow the Preferred Reporting Items for Systematic reviews and Meta-Analysis checklist. Three electronic databases will be searched and resultant papers screened according to the study inclusion and exclusion criteria (detailed in the Population, Intervention, Comparison, Outcomes and Study design statement). Grey literature will be excluded. All papers at each stage will be screened by two independent authors, with disagreements arbitrated by a third. Papers will be subject to appropriate standardised quality assessments. Primary outcome: major lower limb amputation. Secondary outcomes: reintervention rate; re-bleeding rate; development of chronic limb-threatening ischaemia and mortality.

Ethics and Dissemination

This is a systematic review based upon previously conducted studies, so there are no ethical approvals required. The results of this work will be published in a peer-reviewed journal and presented at relevant conferences.

PROSPERO Registration Number 42022358209

Strengths and Limitations of This Study

- To our knowledge, this is the first systematic review on this topic to include primary endovascular management through placement of a stent-graft.
- The potential to find some clarity within the evidence base on patient management is of key importance, given the rising burden of disease.
- All relevant English language papers have been accessed and assessed for inclusion.
- A limitation of the study is excluding non-English language papers.

Introduction

In recent years drug-related deaths have been rising across countries such as the United Kingdom, most markedly in Scotland, and the United States, reflecting increases in drug-related harms.[1-3] In parallel to these drug deaths there has also been an observed increase in hospital admissions for skin and soft tissue infections related to injecting drug use.[4,5] People who inject drugs (PWID) are at risk of range of injecting-related infections and injuries, some of which may threaten life and limb.[6,7]

One such injecting injury is the infected arterial pseudoaneurysm. A pseudoaneurysm (or false aneurysm) represents a defect in the arterial wall with haemorrhage contained by the surrounding soft tissues, compressed thrombus and not lined by endothelium.[8] It is distinct from a true aneurysm, which involves dilatation of the arterial wall. Continued extravasation and expansion of a pseudoaneurysm ultimately risks free rupture.[9] The arterial wall in PWID can also be further compromised by the severity of surrounding infection present, as well as the caustic acidifying agents injected.[9-11]

A pseudoaneurysm is the most commonly described arterial complication of injecting drug use. In the context of PWID, they can develop from direct trauma to an artery, usually when attempting to inject intravenously, or during intentional arterial injecting. Given the probable non-sterile injecting technique, this can lead to the formation of an intramural abscess/haematoma complex.[8,12,13] Arterial pseudoaneurysms may also occur as a result of malignant local infective invasion with destruction of arterial integrity from perivascular soft tissue sepsis.[9,12,13] A further aetiology is septic metastases, for example from infective endocarditis.[9,13] Arterial pseudoaneurysms in the groin are the most frequently reported in PWID resultant from injecting into this anatomical region. Although arterial pseudoaneurysms may occur anywhere throughout the arterial vasculature, usually where injecting has been undertaken.[12,13] If untreated they may rupture causing catastrophic, life-threatening haemorrhage.

Management options for arterial pseudoaneurysms secondary to injecting drug use remain contentious.[9,12-14] The options for initial operative management include: arterial ligation and

debridement alone or arterial reconstruction with debridement.[9,12,13,15] Arterial reconstruction comprises primary repair of the defect with a suture or patch repair, or a bypass of the ligated pseudoaneurysm to compensate for the reduced distal blood supply.[9,12,13,16,17] Such bypasses can be routed either extra-anatomically (circumventing the infected field) or anatomically (in-situ). More recently endovascular reconstructions with stent-grafts have also been reported.[18,19]

However, reticence exists regarding arterial reconstruction due to the degree of pathogenic contamination common to these cases, which can risk infection of the reconstruction and predispose to life-threatening haemorrhage.[14] Autologous vein would usually be the preferred conduit for reconstruction, especially in an infected field, although this is often not available in PWID due to venous damage and destruction from injecting.[14,17] Use of the internal iliac artery as an autologous conduit has also been described.[17] Prosthetic grafts are high risk for infection, particularly in this setting. Biosynthetic and biologic (encompassing cadaveric) conduits are alternatives, but also risk infection.[19-21] An additional concern is continued injecting, introduction of further infection and also use of any reconstruction for drug-using vascular access.[14,22] Moreover, arterial reconstruction may not be required due to adequate residual perfusion of the limb post-ligation, and thus may pose more risk to the patient.[14,15] Rates of major lower limb amputation following ligation vary in the literature from 0% to 3.3% to 33%.[15,23-29] The purpose of this systematic review is to analyse published specific outcomes, following the different surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use. The timing of interest for these management options is immediate (at the index procedure) or during the acute admission episode. To our knowledge this is the first systematic review on this topic to incorporate endovascular reconstructions in addition to open management.

Objectives

This systematic review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including endovascular management, for the infected arterial pseudoaneurysm secondary to groin injecting drug use. Arterial reconstructions of interest will be those performed at the index operation and during the acute admission episode for

this pathology. The primary outcome will be major lower limb amputation. Secondary outcomes will be re-intervention rate, re-bleeding rate, development of chronic limb-threatening ischaemia (CLTI) and mortality.

Methods and Analysis

This systematic review will include all studies that meet the eligibility criteria and the Population, Intervention, Comparison, Outcomes and Study design (PICOS) statement (Table 1).

Table 1. PICOS Statement.

Population	Adults (aged ≥18 years) with an infected arterial pseudoaneurysm secondary to groin injecting drug use (this may involve the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries)
Intervention	Arterial reconstruction by way of repair (suture or patch repair), bypass operation (if ligation performed) or endovascular stent-graft placement +/- debridement and undertaken immediately (at the index surgical intervention) or during the acute admission episode
Comparison	Ligation of the infected arterial pseudoaneurysm +/- debridement alone at index surgical intervention
Outcomes	Primary outcome: Major lower limb amputation Secondary outcomes: Re-intervention rate, re-bleeding rate, development of chronic limb-threatening ischaemia (CLTI) and mortality
Study Design	Randomised controlled trials, prospective and retrospective observational cohort studies and case series (four or more patients)

Eligibility criteria

The search will be performed in relevant electronic databases. Only full published papers in English will be included. The grey literature, encompassing conference abstracts, will be excluded.

Population

The population of interest are PWID who have developed infected arterial pseudoaneurysms secondary to groin injecting drug use (*i.e.* infected pseudoaneurysms related to the groin, typically due to injecting drug use in this anatomical region, and can involve the following vasculature: the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries). PWID are defined as individuals who inject drugs, which may be illicit or prescribed, with the latter not being used in conduct with the prescription *e.g.* injection of methadone or crushed tablets in solution originally intended for oral consumption.

Interventions

The intervention consists of any arterial reconstruction undertaken to surgically manage an infected arterial pseudoaneurysm secondary to groin injecting drug use. This may be a suture or patch repair (the patch material may be autologous, prosthetic, biosynthetic or biologic). It also includes a bypass operation to compensate for arterial ligation of an infected arterial pseudoaneurysm (this may be performed prior to the ligation at the index intervention through an extra-anatomical route in an attempt to try and limit contamination of the reconstruction). The bypass operation may be routed extra-anatomically or anatomically and the conduit may be autologous, prosthetic, biosynthetic or biologic. Endovascular management through placement of a stent-graft across anatomically suitable pseudoaneurysms will also be incorporated into the review. The anatomical location of the pseudoaneurysm, the corresponding intervention executed and related outcomes must be reported clearly in the paper or else it will be excluded (*i.e.* if the management and outcomes of pseudoaneurysms in different anatomical locations are described cumulatively along with

each intervention and outcome, rendering those specifically related to the groin indistinguishable).

Comparison

Arterial ligation alone with no arterial reconstruction will be considered to be the comparator.

Outcomes

The studies must report on the primary outcome: major lower limb amputation. Secondary outcomes of interest are: re-intervention rate; re-bleeding rate; development of CLTI and mortality.

Study design

Primary studies, which may be prospective or retrospective, in English will be included. There will be no restrictions to geographical location of the study.

Patient and public involvement

There was no direct patient and public participation in this study as it is a protocol for a systematic review.

Information sources and search strategy

The electronic databases to be systematically searched are: EMBASE; MEDLINE and Scopus. There will be no time restriction to the search (running from 1974 to search date in EMBASE, 1946 in MEDLINE and 1960 in Scopus). The search strategy was devised to fulfil the PICOS statement and employed free search terms (search strategy for each database detailed in the Supplementary Material, Appendix 1). Papers produced from the search will be limited to the English language and any grey literature identified will be excluded. Authors will not be contacted for missing data.

Data

Data selection and coding

All studies resultant from the search will be exported to EndNote 20 (Clarivate) and duplicates removed. These studies will then be transferred to Rayyan, a web-based platform to facilitate collaborative systematic literature review screening. Titles and abstracts will be independently screened by two authors (CSM and DS) in accordance with the selection criteria. Any differences during the screening process will be arbitrated by a third author (SAS) in order to reach a final decision.

The study selection process will be recorded in a Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram.[30] The papers from the title and abstract screening will be then be subject to the PICOS criteria, with those not meeting these elements excluded and the reason recorded.

Data extraction

Data will be extracted from all studies that meet the inclusion criteria and it will be undertaken independently by two authors (CSM and DS). Any disagreements in extraction will be reviewed and decided upon by a third author (SAS). Data to be extracted are: study design; population size and basic demographics (age, gender); anatomical location of the arterial pseudoaneurysm; presentation with rupture; surgical intervention details (ligation and number of arteries ligated and information on reconstruction if performed); major lower limb amputation; need for further intervention; re-bleeding rate; development of CLTI; mortality; wound complications and follow-up duration.

Risk of bias (quality) assessment

The appropriate assessment tool will be used for the design of each study included: the Cochrane Collaboration's risk of bias tool for randomised studies (randomised controlled trials) and the Newcastle-Ottawa Scale for cohort studies and case series.[31,32] Evaluation using

these tools will again be performed independently by two authors (CSM and DS). Divergences in scoring will be settled by a third author (AR).

Synthesis and Analysis

Data to be quantitatively synthesised are: major lower limb amputation rate; re-intervention rate; re-bleeding rate; development of CLTI and mortality. These will be calculated with the denominator as the total number of pseudoaneurysms according to management strategy (arterial ligation alone with debridement versus arterial reconstruction) for all studies with the relevant outcomes for synthesis. The robustness of the resultant evidence will be subject to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework by two authors (CSM and DS), with any differences reviewed by a third author (AR).[33] Heterogeneity will also be assessed using an appropriate statistical tool when the number of identified studies and the amount of variation between trials can be defined. There will also be subgroup analyses of ligation and debridement alone, compared to open and endovascular reconstructions respectively.

This systematic review protocol has also been written in accordance with the PRISMA-P checklist (Supplementary Material, Appendix 2).[34,35]

Potential Implications

There is no current consensus on the surgical management of the infected arterial pseudoaneurysm secondary to groin injecting drug use. This review aims to give a comprehensive and current overview of the literature and relevant outcomes to aid in informing practice.

Ethics and Dissemination

This systematic review will involve studies which have been performed and so ethical approval is not required. The review has been registered on PROSPERO and the final results

will be submitted to a peer-reviewed journal, as well as presented at relevant conferences. Any adjustments to the study protocol will be recorded on PROSPERO.

Review Status

The systematic search of the electronic databases has been undertaken, and the screening of the study titles and abstracts is underway. The review detailed in this protocol is planned to be completed in January 2023, with the report written in March 2023.

Funding

No funding has been received for this study.

Competing Interest

None.

Patient Consent for Publication

Not applicable.

Ethical Approval

This study does not involve human participants.

Provenance and Peer Review

Not commissioned, externally peer-reviewed.

Acknowledgements

We thank Scott McGregor at the University of Dundee library for advice and comments on the search strategy.

Author Contributions

CSM wrote the protocol for the systematic review, has performed the initial searches and will undertake the data collection, quality assessment and will draft the systematic review paper. DS will contribute to independent data collection and quality assessments of the included papers. AR has contributed to the design of the systematic review and will guide study quality assessments and heterogeneity analyses. FK, JN and SAS have also contributed to the design of the systematic review. SAS will also arbitrate in differences between the independently assessing authors, CSM and DS. All authors have contributed to reviewing this protocol and will contribute to the final systematic review manuscript. CSM is the guarantor of the review.

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Supplementary Material

Appendix 1

Search Strategy for EMBASE, MEDLINE and Scopus

("Pseudoan*" OR "Pseudo-an" OR "False an*")

AND

("Femoral*" OR "Groin")

AND

("Intrav* drug use*" OR "Intrav* drug abuse*" OR "Intrav* drug misuse*" OR "Intrav* drug addict*" OR "Drug use*" OR "Drug abuse*" OR "Drug misuse*" OR "Drug addict*" OR "Substance use*" OR "Substance abuse*" OR "Substance misuse*" OR Inject* adj3 drug*)

Appendix 2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No	Checklist item
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	1,2	Identify the report as a protocol of a systematic review
Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	11	Indicate sources of financial or other support for the review
Sponsor	5b	11	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	11	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION			
Rationale	6	4,5	Describe the rationale for the review in the context of what is already known
Objectives	7	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS			
Eligibility criteria	8	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

Information sources	9	8	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	16	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			
Data management	11a	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	9	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	8,10	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale
Risk of bias in individual studies	14	10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	10	Describe criteria under which study data will be quantitatively synthesised
	15b	10	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	10	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	N/A	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	N/A	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	10	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

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Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	11	Indicate sources of financial or other support for the review
Sponsor	5b	11	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	11	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
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METHODS			
Eligibility criteria	8	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	8	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage

Search strategy	10	16	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			
Data management	11a	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	9	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	8,10	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale
Risk of bias in individual studies	14	10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	10	Describe criteria under which study data will be quantitatively synthesised
	15b	10	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	10	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	N/A	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	N/A	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	10	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

Abstract

Introduction

People who inject drugs (PWID) are at risk of a range of injecting-related infections and injuries, which can threaten life and limb. In parallel to escalating rates of drug-related deaths seen in Scotland and the UK, there has also been an increase in hospital admissions for skin and soft tissue infections related to injecting drug use. One such injecting complication is the infected arterial pseudoaneurysm, which risks rupture and life-threatening haemorrhage. Surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use remain contentious, with some advocates for ligation and debridement alone, whilst others promote acute arterial reconstruction (suture or patch repair, bypass or, more recently, endovascular stent-graft placement). Rates of major lower limb amputations related to surgical management for this pathology vary in the literature. This review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including open and endovascular options, for the infected arterial pseudoaneurysm secondary to groin injecting drug use.

Methods and Analysis

The methods will follow the Preferred Reporting Items for Systematic reviews and Meta-Analysis checklist. Three electronic databases will be searched and the resultant papers screened according to the study inclusion and exclusion criteria (detailed in the Population, Intervention, Comparison, Outcomes and Study design statement). Grey literature will be excluded. All papers at each stage will be screened by two independent authors, with disagreements arbitrated by a third. Papers will be subject to appropriate standardised quality assessments. Primary outcome: major lower limb amputation. Secondary outcomes: re-intervention rate; re-bleeding rate; development of chronic limb-threatening ischaemia 30-day mortality and claudication.

Ethics and Dissemination

This is a systematic review based upon previously conducted studies, therefore no ethical approval is required. The results of this work will be published in a peer-reviewed journal and presented at relevant conferences.

PROSPERO Registration Number CRD42022358209

Strengths and Limitations of This Study

- A comprehensive review of operative management methods for this pathology.
- The inclusion of primary endovascular stent-graft placement as a treatment modality.
- All relevant English language papers will be accessed and assessed for inclusion.
- A limitation of the study is excluding non-English language papers and grey literature.

Introduction

In recent years drug-related deaths have been rising across countries such as the United Kingdom, most markedly in Scotland, and the United States, reflecting increases in drug-related harms.[1-3] In parallel to these drug deaths there has also been an observed increase in hospital admissions for skin and soft tissue infections related to injecting drug use.[4,5] People who inject drugs (PWID) are at risk of range of injecting-related infections and injuries, some of which may threaten life and limb.[6,7]

One such injecting injury is the infected arterial pseudoaneurysm. A pseudoaneurysm (or false aneurysm) represents a defect in the arterial wall with haemorrhage contained by the surrounding soft tissues, compressed thrombus and not lined by endothelium.[8] It is distinct from a true aneurysm, which involves dilatation of the arterial wall. Continued extravasation and expansion of a pseudoaneurysm ultimately risks free rupture.[9] The arterial wall in PWID can also be further compromised by the severity of surrounding infection present, as well as the caustic acidifying agents injected.[9-12]

A pseudoaneurysm is the most commonly described arterial complication of injecting drug use. In the context of PWID, they can develop from direct, typically infective, trauma to an artery, usually when attempting to inject intravenously, or during intentional arterial injecting. Given the probable non-sterile injecting technique, this can lead to the formation of an intramural abscess/haematoma complex.[8,9,13,14] Arterial pseudoaneurysms may also occur as a result of malignant local infective invasion with destruction of arterial integrity from perivascular soft tissue sepsis.[9,10,12,13] A further aetiology is septic metastases, for example from infective endocarditis.[10,14] Arterial pseudoaneurysms in the groin are the most frequently reported in PWID resultant from injecting into this anatomical region. However arterial pseudoaneurysms may occur anywhere throughout the arterial vasculature, usually where injecting has been undertaken.[13,14] If untreated they may rupture causing catastrophic, life-threatening haemorrhage.

Management options for arterial pseudoaneurysms secondary to injecting drug use remain contentious.[10,13-15] The options for initial operative management include: arterial ligation and

debridement alone or arterial reconstruction with debridement.[10,13,14,16] Arterial reconstruction comprises primary repair of the defect with a suture or patch repair, or a bypass of the ligated pseudoaneurysm to compensate for the reduced distal blood supply.[10,13,14,17,18] Such bypasses can be routed either extra-anatomically (circumventing the infected field) or anatomically (in-situ). More recently endovascular reconstructions with stent-grafts have also been reported.[19,20]

However, reticence exists regarding arterial reconstruction due to the degree of pathogenic contamination common to these cases, which can risk infection of the reconstruction and predispose to life-threatening haemorrhage.[15] Autologous vein would usually be the preferred conduit for reconstruction, especially in an infected field, although this is often not available in PWID due to venous damage and destruction from injecting.[15,18] Use of the internal iliac artery as an autologous conduit has also been described.[18] Prosthetic grafts are high risk for infection, particularly in this setting. Biosynthetic and biologic (encompassing cadaveric) conduits are alternatives, but also risk infection.[20-22] An additional concern is continued injecting, introduction of further infection and also use of any reconstruction for drug-using vascular access.[15,23] Moreover, arterial reconstruction may not be required due to adequate residual perfusion of the limb post-ligation, and thus may pose more risk to the patient.[15,16] Rates of major lower limb amputation following ligation vary in the literature from 0% to 3.3% to 33%.[16,24-30] The purpose of this systematic review is to analyse published specific outcomes, following the different surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use. The timing of interest for these management options is immediate (at the index procedure) or during the acute admission episode (non-immediate). To our knowledge this is the first systematic review on this topic to incorporate endovascular reconstructions in addition to open management.

Objectives

This systematic review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including endovascular management, for the infected arterial pseudoaneurysm secondary to groin injecting drug use. Arterial reconstructions of interest will be those performed at the index operation and during the acute admission episode for

this pathology. The primary outcome will be major lower limb amputation. Secondary outcomes will be re-intervention rate, re-bleeding rate, development of chronic limb-threatening ischaemia (CLTI), 30-day mortality and claudication.

Methods and Analysis

This systematic review will include all studies that meet the Population, Intervention, Comparison, Outcomes and Study design (PICOS) statement (Table 1) and eligibility criteria.

Table 1. PICOS Statement.

Population	Adults (aged ≥18 years) with an infected arterial pseudoaneurysm secondary to groin injecting drug use (this may involve the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries)
Intervention	Arterial reconstruction by way of repair (suture or patch repair), bypass operation (if ligation performed) or endovascular stent-graft placement +/- debridement and undertaken immediately (at the index surgical intervention) or during the acute admission episode
Comparison	Ligation of the infected arterial pseudoaneurysm +/- debridement alone at index surgical intervention
Outcomes	Primary outcome: Major lower limb amputation Secondary outcomes: Re-intervention rate; re-bleeding rate; development of chronic limb-threatening ischaemia (CLTI); 30-day mortality and claudication
Study Design	Randomised controlled trials, prospective and retrospective observational cohort studies and case series (four or more patients)

Eligibility criteria

The search will be performed in relevant electronic databases. Only full published papers in English will be included. The grey literature, encompassing conference abstracts, will be excluded. The anatomical location of the pseudoaneurysm, the corresponding intervention executed and related outcomes must be reported clearly in the paper or else it will be excluded (*i.e.* if the management and outcomes of pseudoaneurysms in different anatomical locations are described cumulatively along with each intervention and outcome, rendering those specifically related to the groin indistinguishable). Papers that detail only some of the outcomes of interest, however distinctly report the related management method for the correct anatomical area will be included with documentation of the outcomes reported on, and "Not reported" or "Unclear" as applicable.

Population

The population of interest are PWID who have developed infected arterial pseudoaneurysms secondary to groin injecting drug use (*i.e.* infected pseudoaneurysms related to the groin, typically due to injecting drug use in this anatomical region, and can involve the following vasculature: the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries). The case definition will be any arterial pseudoaneurysm secondary to groin injecting drug use. Cases will be ascertained on radiological findings (if imaging performed) and clinically, including at the time of operation. All arterial pseudoaneurysms in this review will be considered infected due to the aetiology. Non-sterile injecting predominantly precipitates the ensuing pathophysiology in these cases, which is typically infective rather than simply traumatic.[9] PWID are defined as individuals who inject drugs, which may be illicit or prescribed, with the latter not being used in conduct with the prescription *e.g.* injection of methadone or crushed tablets in solution originally intended for oral consumption.

Interventions

The intervention consists of any arterial reconstruction undertaken to surgically manage an infected arterial pseudoaneurysm secondary to groin injecting drug use. This may be a suture or patch repair (the patch material may be autologous, prosthetic, biosynthetic or biologic). It also includes a bypass operation to compensate for arterial ligation of an infected arterial pseudoaneurysm (this may be performed prior to the ligation at the index intervention through an extra-anatomical route in an attempt to try and limit contamination of the reconstruction). The bypass operation may be routed extra-anatomically or anatomically and the conduit may be autologous, prosthetic, biosynthetic or biologic. Endovascular management through placement of a stent-graft across anatomically suitable pseudoaneurysms will also be incorporated into the review.

Comparison

Arterial ligation alone with no arterial reconstruction will be considered to be the comparator.

Outcomes

The studies should report on the primary outcome: major lower limb amputation. Secondary outcomes of interest are: re-intervention rate; re-bleeding rate; development of CLTI, 30-day mortality and claudication.

Study design

Primary studies, which may be prospective or retrospective, in English will be included. There will be no restrictions to geographical location of the study.

Patient and public involvement

There was no direct patient and public participation in this study as it is a protocol for a systematic review.

Information sources and search strategy

The electronic databases to be systematically searched are: EMBASE; MEDLINE and Scopus. There will be no time restriction to the search (running from 1974 to search date in EMBASE, 1946 in MEDLINE and 1960 in Scopus). The search strategy was devised to fulfil the PICOS statement and employed free search terms (search strategy for each database detailed in the Supplementary Material, Appendix 1). Papers produced from the search will be limited to the English language and any grey literature identified will be excluded. Authors of recent publications may be contacted for missing data.

Data

Data selection and coding

All studies resultant from the search will be exported to EndNote 20 (Clarivate) and duplicates removed. These studies will then be transferred to Rayyan, a web-based platform to facilitate collaborative systematic literature review screening.[31] Titles and abstracts will be independently screened by two authors (CSM and DS) in accordance with the selection criteria. Any differences during the screening process will be arbitrated by a third author (JN/SAS/AR) in order to reach a final decision.

The study selection process will be recorded in a Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram.[32] The papers from the title and abstract screening will be then be subject to the PICOS criteria, with those not meeting these elements excluded and the reason recorded.

Data extraction

Data will be extracted from all studies that meet the inclusion criteria and it will be undertaken independently by two authors (CSM and DS). Any disagreements in extraction will be reviewed and decided upon by a third author (JN/SAS/AR). Data to be extracted are: study design; population size and basic demographics (age, gender); anatomical location of the

arterial pseudoaneurysm; presentation with rupture; surgical intervention details (ligation and number of arteries ligated and information on reconstruction if performed); major lower limb amputation; need for further intervention; re-bleeding rate; development of CLTI; 30-day mortality; claudication; wound management; wound complications and follow-up duration. For the arterial reconstructions, graft infections and thromboses will also be recorded. If reported, the clinical status of the patient at presentation and influence of this on management will also be documented.

Risk of bias (quality) assessment

The appropriate assessment tool will be used for the design of each study included: the Cochrane Collaboration's risk of bias tool for randomised studies (randomised controlled trials), the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute critical appraisal tool for case series.[33-35] Evaluation using these tools will again be performed independently by two authors (CSM and DS). Divergences in scoring will be settled by a third author (AR/JN/SAS).

Synthesis and Analysis

Data to be quantitatively synthesised are: major lower limb amputation rate; re-intervention rate; re-bleeding rate; development of CLTI, 30-day mortality and claudication. Data for each outcome will be quantitatively pooled and assessed using suitable statistical tools and models (*i.e.* proportional and conventional comparative meta-analyses). The robustness of the resultant evidence will be subject to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework by two authors (CSM and DS), with any differences reviewed by a third author (AR/JN/SAS).[36] Heterogeneity will also be assessed using an appropriate statistical tool when the number of identified studies and the amount of variation between trials can be defined. If the data allows, there will also be subgroup analyses of ligation and debridement alone, compared to open and endovascular reconstructions respectively.

This systematic review protocol has also been written in accordance with the PRISMA-P checklist (Supplementary Material, Appendix 2).[37,38]

Potential Implications

There is no current consensus on the surgical management of the infected arterial pseudoaneurysm secondary to groin injecting drug use. This review aims to give a comprehensive and contemporary overview of the literature and relevant outcomes to aid in informing practice.

Ethics and Dissemination

This systematic review will involve studies which have been performed and so ethical approval is not required. The review has been registered on PROSPERO and the final results will be submitted to a peer-reviewed journal, as well as presented at relevant conferences. Any adjustments to the study protocol will be recorded on PROSPERO.

Review Status

The systematic search of the electronic databases has been undertaken, and the screening of the study titles and abstracts is underway. The review detailed in this protocol is planned to be completed in January 2023, with the report written in April 2023.

Funding

No funding has been received for this study.

Competing Interest

None.

Patient Consent for Publication

Not applicable.

Ethical Approval

This study does not involve human participants.

Provenance and Peer Review

Not commissioned, externally peer-reviewed.

Acknowledgements

We thank Scott McGregor at the University of Dundee library for advice and comments on the search strategy.

Author Contributions

CSM wrote the protocol for the systematic review, has performed the initial searches and will undertake the data collection, quality assessment and will draft the systematic review paper. DS will contribute to independent data collection and quality assessments of the included papers. AR has contributed to the design of the systematic review and will guide study quality assessments and heterogeneity analyses. FK, JN and SAS have also contributed to the design of the systematic review. JN, SAS and AR will also arbitrate in differences between the independently assessing authors, CSM and DS. All authors have contributed to reviewing this protocol and will contribute to the final systematic review manuscript. CSM is the guarantor of the review.

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Supplementary Material

Appendix 1

Search Strategy for EMBASE, MEDLINE and Scopus

("Pseudoan*" OR "Pseudo-an" OR "False an*")

AND

("Femoral*" OR "Groin")

AND

("Intrav* drug use*" OR "Intrav* drug abuse*" OR "Intrav* drug misuse*" OR "Intrav* drug addict*" OR "Drug use*" OR "Drug abuse*" OR "Drug misuse*" OR "Drug addict*" OR "Substance use*" OR "Substance abuse*" OR "Substance misuse*" OR Inject* adj3 drug*)

Appendix 2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No	Checklist item
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	1,2	Identify the report as a protocol of a systematic review
Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	11	Indicate sources of financial or other support for the review
Sponsor	5b	11	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	11	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION			
Rationale	6	4,5	Describe the rationale for the review in the context of what is already known
Objectives	7	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS			
Eligibility criteria	8	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

Information sources	9	8	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	16	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			
Data management	11a	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	9	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	8,10	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale
Risk of bias in individual studies	14	10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	10	Describe criteria under which study data will be quantitatively synthesised
	15b	10	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	10	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	N/A	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	N/A	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	10	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No	Checklist item
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	1,2	Identify the report as a protocol of a systematic review
Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	11	Indicate sources of financial or other support for the review
Sponsor	5b	11	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	11	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION			
Rationale	6	4,5	Describe the rationale for the review in the context of what is already known
Objectives	7	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS			
Eligibility criteria	8	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

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The Management of the Infected Arterial Pseudoaneurysm Secondary to Groin Injecting Drug Use and Outcomes: A Systematic Review Protocol

Abstract

Introduction

People who inject drugs (PWID) are at risk of a range of injecting-related infections and injuries, which can threaten life and limb. In parallel to escalating rates of drug-related deaths seen in Scotland and the UK, there has also been an increase in hospital admissions for skin and soft tissue infections related to injecting drug use. One such injecting complication is the infected arterial pseudoaneurysm, which risks rupture and life-threatening haemorrhage. Surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use remain contentious, with some advocates for ligation and debridement alone, whilst others promote acute arterial reconstruction (suture or patch repair, bypass or, more recently, endovascular stent-graft placement). Rates of major lower limb amputations related to surgical management for this pathology vary in the literature. This review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including open and endovascular options, for the infected arterial pseudoaneurysm secondary to groin injecting drug use.

Methods and Analysis

The methods will follow the Preferred Reporting Items for Systematic reviews and Meta-Analysis checklist. Three electronic databases will be searched and the resultant papers screened according to the study inclusion and exclusion criteria (detailed in the Population, Intervention, Comparison, Outcomes and Study design statement). Grey literature will be excluded. All papers at each stage will be screened by two independent authors, with disagreements arbitrated by a third. Papers will be subject to appropriate standardised quality assessments. Primary outcome: major lower limb amputation. Secondary outcomes: re-intervention rate; re-bleeding rate; development of chronic limb-threatening ischaemia 30-day mortality and claudication.

Ethics and Dissemination

This is a systematic review based upon previously conducted studies, therefore no ethical approval is required. The results of this work will be published in a peer-reviewed journal and presented at relevant conferences.

PROSPERO Registration Number: CRD42022358209

Strengths and Limitations of This Study

- The study design comprises a comprehensive search strategy and selection criteria, with double-screening of all studies to reduce selection bias and data collection errors.
- The inclusion of primary endovascular stent-graft placement as a treatment modality for this pathology.
- The use of proportional meta-analysis to optimise inclusive incorporation of outcomes from non-comparator studies in quantitative analysis.
- Limitations of the study are excluding non-English language papers and grey literature.

Introduction

In recent years drug-related deaths have been rising across countries such as the United Kingdom, most markedly in Scotland, and the United States, reflecting increases in drug-related harms.[1-3] In parallel to these drug deaths there has also been an observed increase in hospital admissions for skin and soft tissue infections related to injecting drug use.[4,5] People who inject drugs (PWID) are at risk of range of injecting-related infections and injuries, some of which may threaten life and limb.[6,7]

One such injecting injury is the infected arterial pseudoaneurysm. A pseudoaneurysm (or false aneurysm) represents a defect in the arterial wall with haemorrhage contained by the surrounding soft tissues, compressed thrombus and not lined by endothelium.[8] It is distinct from a true aneurysm, which involves dilatation of the arterial wall. Continued extravasation and expansion of a pseudoaneurysm ultimately risks free rupture.[9] The arterial wall in PWID can also be further compromised by the severity of surrounding infection present, as well as the caustic acidifying agents injected.[9-12]

A pseudoaneurysm is the most commonly described arterial complication of injecting drug use. In the context of PWID, they can develop from direct, typically infective, trauma to an artery, usually when attempting to inject intravenously, or during intentional arterial injecting. Given the probable non-sterile injecting technique, this can lead to the formation of an intramural abscess/haematoma complex.[8,9,13,14] Arterial pseudoaneurysms may also occur as a result of malignant local infective invasion with destruction of arterial integrity from perivascular soft tissue sepsis.[9,10,12,13] A further aetiology is septic metastases, for example from infective endocarditis.[10,14] Arterial pseudoaneurysms in the groin are the most frequently reported in PWID resultant from injecting into this anatomical region. However arterial pseudoaneurysms may occur anywhere throughout the arterial vasculature, usually where injecting has been undertaken.[13,14] If untreated they may rupture causing catastrophic, life-threatening haemorrhage.

Management options for arterial pseudoaneurysms secondary to injecting drug use remain contentious.[10,13-15] The options for initial operative management include: arterial ligation and

debridement alone or arterial reconstruction with debridement.[10,13,14,16] Arterial reconstruction comprises primary repair of the defect with a suture or patch repair, or a bypass of the ligated pseudoaneurysm to compensate for the reduced distal blood supply.[10,13,14,17,18] Such bypasses can be routed either extra-anatomically (circumventing the infected field) or anatomically (in-situ). More recently endovascular reconstructions with stent-grafts have also been reported.[19,20]

However, reticence exists regarding arterial reconstruction due to the degree of pathogenic contamination common to these cases, which can risk infection of the reconstruction and predispose to life-threatening haemorrhage.[15] Autologous vein would usually be the preferred conduit for reconstruction, especially in an infected field, although this is often not available in PWID due to venous damage and destruction from injecting.[15,18] Use of the internal iliac artery as an autologous conduit has also been described.[18] Prosthetic grafts are high risk for infection, particularly in this setting. Biosynthetic and biologic (encompassing cadaveric) conduits are alternatives, but also risk infection.[20-22] An additional concern is continued injecting, introduction of further infection and also use of any reconstruction for drug-using vascular access.[15,23] Moreover, arterial reconstruction may not be required due to adequate residual perfusion of the limb post-ligation, and thus may pose more risk to the patient.[15,16] Rates of major lower limb amputation following ligation vary in the literature from 0% to 3.3% to 33%.[16,24-30] The purpose of this systematic review is to analyse published specific outcomes, following the different surgical management options for the infected arterial pseudoaneurysm secondary to groin injecting drug use. The timing of interest for these management options is immediate (at the index procedure) or during the acute admission episode (non-immediate). To our knowledge this is the first systematic review on this topic to incorporate endovascular reconstructions in addition to open management.

Objectives

This systematic review aims to evaluate the outcomes of arterial ligation alone compared to arterial reconstruction, including endovascular management, for the infected arterial pseudoaneurysm secondary to groin injecting drug use. Arterial reconstructions of interest will be those performed at the index operation and during the acute admission episode for

this pathology. The primary outcome will be major lower limb amputation. Secondary outcomes will be re-intervention rate, re-bleeding rate, development of chronic limb-threatening ischaemia (CLTI), 30-day mortality and claudication.

Methods and Analysis

This systematic review will include all studies that meet the Population, Intervention, Comparison, Outcomes and Study design (PICOS) statement (Table 1) and eligibility criteria.

Table 1. PICOS Statement.

Population	Adults (aged ≥18 years) with an infected arterial pseudoaneurysm secondary to groin injecting drug use (this may involve the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries)
Intervention	Arterial reconstruction by way of repair (suture or patch repair), bypass operation (if ligation performed) or endovascular stent-graft placement +/- debridement and undertaken immediately (at the index surgical intervention) or during the acute admission episode
Comparison	Ligation of the infected arterial pseudoaneurysm +/- debridement alone at index surgical intervention
Outcomes	Primary outcome: Major lower limb amputation Secondary outcomes: Re-intervention rate; re-bleeding rate; development of chronic limb-threatening ischaemia (CLTI); 30-day mortality and claudication
Study Design	Randomised controlled trials, prospective and retrospective observational cohort studies and case series (four or more patients)

Eligibility criteria

The search will be performed in relevant electronic databases. Only full published papers in English will be included. The grey literature, encompassing conference abstracts, will be excluded. The anatomical location of the pseudoaneurysm, the corresponding intervention executed and related outcomes must be reported clearly in the paper or else it will be excluded (*i.e.* if the management and outcomes of pseudoaneurysms in different anatomical locations are described cumulatively along with each intervention and outcome, rendering those specifically related to the groin indistinguishable). Papers that detail only some of the outcomes of interest, however distinctly report the related management method for the correct anatomical area will be included with documentation of the outcomes reported on, and "Not reported" or "Unclear" as applicable.

Population

The population of interest are PWID who have developed infected arterial pseudoaneurysms secondary to groin injecting drug use (*i.e.* infected arterial pseudoaneurysms related to the groin, typically due to injecting drug use in this anatomical region, and can involve the following vasculature: the common femoral, superficial femoral, profunda femoris, external iliac or common iliac arteries). The case definition will be any arterial pseudoaneurysm secondary to groin injecting drug use. Cases will be ascertained on radiological findings (if imaging performed) and clinically, including at the time of operation. All arterial pseudoaneurysms in this review will be considered infected due to the aetiology. Non-sterile injecting predominantly precipitates the ensuing pathophysiology in these cases, which is typically infective rather than simply traumatic.[9] PWID are defined as individuals who inject drugs, which may be illicit or prescribed, with the latter not being used in conduct with the prescription *e.g.* injection of methadone or crushed tablets in solution originally intended for oral consumption.

Interventions

The intervention consists of any arterial reconstruction undertaken to surgically manage an infected arterial pseudoaneurysm secondary to groin injecting drug use. This may be a suture or patch repair (the patch material may be autologous, prosthetic, biosynthetic or biologic). It also includes a bypass operation to compensate for arterial ligation of an infected arterial pseudoaneurysm (this may be performed prior to the ligation at the index intervention through an extra-anatomical route in an attempt to try and limit contamination of the reconstruction). The bypass operation may be routed extra-anatomically or anatomically and the conduit may be autologous, prosthetic, biosynthetic or biologic. Endovascular management through placement of a stent-graft across anatomically suitable pseudoaneurysms will also be incorporated into the review.

Comparison

Arterial ligation alone with no arterial reconstruction will be considered to be the comparator.

Outcomes

The studies should report on the primary outcome: major lower limb amputation. Secondary outcomes of interest are: re-intervention rate; re-bleeding rate; development of CLTI, 30-day mortality and claudication.

Study design

Primary studies, which may be prospective or retrospective, in English will be included. There will be no restrictions to geographical location of the study.

Patient and public involvement

There was no direct patient and public participation in this study as it is a protocol for a systematic review.

Information sources and search strategy

The electronic databases to be systematically searched are: EMBASE; MEDLINE and Scopus. There will be no time restriction to the search (running from 1974 to search date in EMBASE, 1946 in MEDLINE and 1960 in Scopus). The search strategy was devised to fulfil the PICOS statement and employed free search terms (search strategy for each database detailed in the Supplementary Material, Appendix 1). Papers produced from the search will be limited to the English language and any grey literature identified will be excluded. Authors of recent publications may be contacted for missing data.

Data

Data selection and coding

All studies resultant from the search will be exported to EndNote 20 (Clarivate) and duplicates removed. These studies will then be transferred to Rayyan, a web-based platform to facilitate collaborative systematic literature review screening.[31] Titles and abstracts will be independently screened by two authors (CSM and DS) in accordance with the selection criteria. Any differences during the screening process will be arbitrated by a third author (JN/SAS/AR) in order to reach a final decision.

The study selection process will be recorded in a Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram.[32] The papers from the title and abstract screening will be then be subject to the PICOS criteria, with those not meeting these elements excluded and the reason recorded.

Data extraction

Data will be extracted from all studies that meet the inclusion criteria and it will be undertaken independently by two authors (CSM and DS). Any disagreements in extraction will be reviewed and decided upon by a third author (JN/SAS/AR). Data to be extracted are: study design; population size and basic demographics (age, gender); anatomical location of the

arterial pseudoaneurysm; presentation with rupture; surgical intervention details (ligation and number of arteries ligated and information on reconstruction if performed); major lower limb amputation; need for further intervention; re-bleeding rate; development of CLTI; 30-day mortality; claudication; wound management; wound complications and follow-up duration. For the arterial reconstructions, graft infections and thromboses will also be recorded. If reported, the clinical status of the patient at presentation and influence of this on management will also be documented.

Risk of bias (quality) assessment

The appropriate assessment tool will be used for the design of each study included: the Cochrane Collaboration's risk of bias tool for randomised studies (randomised controlled trials), the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute critical appraisal tool for case series.[33-35] Evaluation using these tools will again be performed independently by two authors (CSM and DS). Divergences in scoring will be settled by a third author (AR/JN/SAS).

Synthesis and Analysis

Data to be quantitatively synthesised are: major lower limb amputation rate; re-intervention rate; re-bleeding rate; development of CLTI, 30-day mortality and claudication. Data for each outcome will be quantitatively pooled and assessed using suitable statistical tools and models (*i.e.* proportional and conventional comparative meta-analyses). The robustness of the resultant evidence will be subject to Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework by two authors (CSM and DS), with any differences reviewed by a third author (AR/JN/SAS).[36] Heterogeneity will also be assessed using an appropriate statistical tool when the number of identified studies and the amount of variation between trials can be defined. If the data allows, there will also be subgroup analyses of ligation and debridement alone, compared to open and endovascular reconstructions respectively.

This systematic review protocol has also been written in accordance with the PRISMA-P checklist (Supplementary Material, Appendix 2).[37,38]

Potential Implications

There is no current consensus on the surgical management of the infected arterial pseudoaneurysm secondary to groin injecting drug use. This review aims to give a comprehensive and contemporary overview of the literature and relevant outcomes to aid in informing practice.

Ethics and Dissemination

This systematic review will involve studies which have been performed and so ethical approval is not required. The review has been registered on PROSPERO and the final results will be submitted to a peer-reviewed journal, as well as presented at relevant conferences. Any adjustments to the study protocol will be recorded on PROSPERO.

Review Status

The systematic search of the electronic databases has been undertaken, and the screening of the study titles and abstracts is underway. The review detailed in this protocol is planned to be completed in January 2023, with the report written in April 2023.

Funding

No funding has been received for this study.

Competing Interest

None.

Patient Consent for Publication

Not applicable.

Ethical Approval

This study does not involve human participants.

Provenance and Peer Review

Not commissioned, externally peer-reviewed.

Data Sharing

Raw data generated from this systematic review will be shared upon request.

Acknowledgements

We thank Scott McGregor at the University of Dundee library for advice and comments on the search strategy.

Author Contributions

CSM has devised the plan for the systematic review, written the protocol, performed the initial searches and will undertake the data collection, quality assessment and will draft the systematic review paper. DS will contribute to independent data collection and quality assessments of the included papers. AR has contributed to the design of the systematic review and will guide study quality assessments and heterogeneity analyses. FK, JN and SAS have also contributed to the design of the systematic review. JN, SAS and AR will also arbitrate in differences between the independently assessing authors, CSM and DS. All authors have contributed to reviewing this protocol and will contribute to the final systematic review manuscript. CSM is the guarantor of the review.

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Supplementary Material

Appendix 1

Search Strategy for EMBASE, MEDLINE and Scopus

("Pseudoan*" OR "Pseudo-an" OR "False an*")

AND

("Femoral*" OR "Groin")

AND

("Intrav* drug use*" OR "Intrav* drug abuse*" OR "Intrav* drug misuse*" OR "Intrav* drug addict*" OR "Drug use*" OR "Drug abuse*" OR "Drug misuse*" OR "Drug addict*" OR "Substance use*" OR "Substance abuse*" OR "Substance misuse*" OR Inject* adj3 drug*)

Appendix 2

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No	Checklist item
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	1,2	Identify the report as a protocol of a systematic review
Update	1b	N/A	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	1	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	11	Indicate sources of financial or other support for the review
Sponsor	5b	11	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	11	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION			
Rationale	6	4,5	Describe the rationale for the review in the context of what is already known
Objectives	7	6	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS			
Eligibility criteria	8	6-8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

Information sources	9	8	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	16	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:			
Data management	11a	8-10	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	8-10	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	8-10	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	9	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	8,10	List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale
Risk of bias in individual studies	14	10	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	10	Describe criteria under which study data will be quantitatively synthesised
	15b	10	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	10	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	N/A	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	N/A	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	10	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Contributions	3b	12	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	N/A	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
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