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### The Incidence of Admission Ionised Hypocalcaemia in Paediatric Major Trauma: Protocol for a Systematic Review and Meta-Analysis

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### The Incidence of Admission Ionised Hypocalcaemia in Paediatric Major Trauma: Protocol for a **Systematic Review and Meta-Analysis**

### Registration

PROSPERO registration number: CRD42023425172

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### Abstract

### Introduction

Hypocalcaemia forms part of the 'diamond of death' in major trauma, alongside hypothermia, acidosis, and coagulopathy. In adults, admission hypocalcaemia prior to transfusion is associated with increased mortality, increased blood transfusion requirements, and coagulopathy. Data in paediatric major trauma patients are limited. This systematic review and meta-analysis aims to describe and synthesise the available evidence relevant to paediatric trauma, admission hypocalcaemia, and outcome.

### Methods and analysis

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline will be used to construct this review. A planned literature search for articles in the English language will be conducted from inception to the date of searches using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The grey literature will also be searched. Both title and abstract screening, and full-text screening will be done by two reviewers, with an adjudicating third reviewer. Heterogeneity will be assessed using I<sup>2</sup> test, and risk of bias will be assessed using the ROBINS-I tool. A meta-analysis will be undertaken using ratio measures (odds ratio) and mean differences for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Prospero registration number

CRD42023425172

### Strengths and limitations of this study

- ⇒ The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- $\Rightarrow$  This is a novel review that addresses an area of uncertainity in the current evidence base surrounding paediatric major trauma through systematic review and meta-analysis of published data and the grey-literature.
- $\Rightarrow$  The review methodology is at risk of limitation by publication bias.

# Background

Major trauma is one of the leading causes of death in children in the United Kingdom (UK).<sup>[1][2]</sup> A key cause of potentially-survivable death from trauma is haemorrhage.<sup>[3]</sup> Uncontrollable haemorrhage may be related to the injury mechanism itself, or as a result of Trauma Induced Coagulopathy (TIC).<sup>[4]</sup> TIC is common, occurring in at least a quarter of haemorrhagic deaths, and has a number of proposed pathophysiological mechanisms, which generally involve injury and shock provoking a immunological, endothelial, and platelet response.<sup>[4]</sup> All forms of haemorrhage are further exacerbated by the 'lethal triad' of coagulopathy, hypothermia and acidosis.<sup>[5][6][7]</sup> More recently biochemical abnormalities such as hyperkalaemia and hypocalcaemia have been recognised to contribute to deaths from haemorrhage.<sup>[6][8]</sup> In particular, calcium's role is important for clot formation, vascular tone, and cardiac contractility, with hypocalcaemia contributing to coagulopathy and cardiovascular decompensation.<sup>[5][6]]</sup> As such the 'lethal triad' is now considered a 'diamond of death' with hypocalcaemia forming a key component of this deleterious combination.<sup>[5][6]]</sup> The early recognition and treatment of these components in the 'diamond of death' are essential for trauma resuscitation.<sup>[5][7][9]</sup>

# Rationale

The free form of calcium (ionised calcium (iCa)) is the physiologically relevant component of calcium in the blood.<sup>[10]</sup> iCa is measured on blood gases, which are often taken on arrival for major trauma patients, and there is good agreement between arterial and venous measurements.<sup>[11]</sup> Blood gas measurement will also record the pH and lactate, and can affect the availability of iCa.<sup>[12][13]</sup> Ionised hypocalcaemia (iHypoCa) in major trauma patients is multifactorial.<sup>[5][6][7][14]</sup> The infusion of citrated blood products is a recognised cause of hypocalcaemia in trauma due to calcium chelation with citrate.<sup>[6][15]</sup> There is also emerging evidence in adults that early hypocalcaemia may occur in trauma patients prior to the receipt of blood products containing citrate.<sup>[16][17][18][19]</sup> Potential pathophysiological mechanisms underpinning this include calcium binding by lactate, intracellular influx of calcium due to ischaemia and reperfusion, impaired calcium homeostasis secondary to trauma, and secondary to dilution by crystalloid fluid resuscitation.<sup>[5][6][7]]</sup> A systematic review and meta-analysis, which included a total of 1213 major trauma patients, 18 years or older, with a

document iCa level on admission explored the incidence and outcomes associated with admission iHypoCa.<sup>[20]</sup> Studies that involved patients in whom calcium concentration may have been confounded by prior blood transfusion were excluded.<sup>[20]</sup> Overall, the incidence of admission ionised hypocalcaemia (iHypoCa) was 56.2%, and iHypoCa was associated with: increased mortality, increased blood transfusion requirements, and coagulopathy.<sup>[16][17][18][19][20]]</sup> Evidence of admission iHypoCa and the association with adverse outcomes in adult trauma patients has led to the early measurement and replacement of calcium being recommended in adult trauma guidelines.<sup>[21][22]</sup> In paediatric major trauma data are limited. A search of PROSPERO did not find any similar planned systematic reviews or meta-analyses. Moreover, a preliminary search of the literature has found a few heterogenous studies, which indicate that admission iHypoCa may be less prevalent in children compared to adults.<sup>[23][24][25][26]</sup>

### Aims

The primary aim of this systematic review and meta-analysis is to explore the limited evidence related to the incidence of admission iHypoCa in paediatric major trauma patients. The review also aims to explore whether admission iHypoCa, compared to normocalcaemia, is associated with adverse clinical outcomes.

### Methods

### Eligibility criteria

This proposed systematic review and meta-analysis will explore the incidence of iHypoCa in paediatric (<16 years old) major trauma patients (Injury Severity Score (ISS) >15) and explore whether admission iHypoCa (iCa <1.16 mmol/L), compared to normocalcaemia (iCa  $\geq$  1.16 mmol/L) is associated with a greater incidence of adverse outcomes.<sup>[12]</sup> The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1.

### Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The reference lists of all included studies, and the grey literature will also be searched.

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### Search strategy

The search strategy can be found in online supplementary tables 2,3 and 4.

The search will also involve checking reference lists of retrieved articles, conference abstracts, and online study results. If data is incomplete, then corresponding authors will be contacted for additional information.

### Study records

The search strategy will be undertaken by a trained librarian. The combined abstracts from the search strategy will be independently screened by two reviewers to identify studies meeting inclusion criteria, any duplications will be removed manually. For abstracts meeting inclusion criteria, full texts will be retrieved and again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer.

A standardised data sheet (Microsoft ® Excel for Mac, Version 16.72, 2023) will be used to extract data from included studies to facilitate data synthesis and assessment of quality and risk of bias.

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Extracted data will be independently verified by the second reviewer, and any discrepancies again adjudicated by the third reviewer.

The following data items will be extracted:

- 1. Hospital setting
- 2. Study type
- 3. Country of treatment
- 4. Cohort size
- 5. Median [interquartile range (IQR)] severity of injury (ISS)
- 6. Abbreviated Injury Scale (AIS) score for injury regions
- 7. Ionised hypocalcaemia definitions
- 8. Incidence of admission iHypoCa (iCa <1.16 mmol/L) (yes/no)<sup>[12]</sup>
- 9. Definitions, and presence of, coagulopathy
- 10. The presence of hyperkalaemia (>5.5 mmol/L)(yes/no/not reported)<sup>[27]</sup>
- 11. The presence of hyperlactataemia (>2.0mmol/L) (yes/no/not reported)<sup>28]</sup>
- 12. Haemodynamic instability (hypotension (based upon age specific Advanced Paediatric Life Support (APLS) values) or elevated Shock Index Paediatric Age-Adjusted (SIPA))(yes/no/not reported)<sup>[29][30][31]</sup>
- 13. Administration of calcium (yes/no/not reported)
- 14. Vasopressor requirements within the first 24 hours (yes/no/not reported)
- 15. Total blood product transfusion requirement during the first 24 hours (yes/no/not reported)
- 16. Activation of the major haemorrhage protocol within the first 24 hours (yes/no/not reported)
- 17. Requirement for invasive (operative or interventional radiology) intervention within 24 hours (yes/no/not reported)
- 18. Hospital length of stay (LOS) (days)
- 19. Paediatric Intensive Care Unit (PICU) LOS (days)
- 20. Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days (yes/no/not reported)

### Outcomes and prioritisation

The primary outcome of this systematic review and meta-analysis is the overall incidence of admission iHypoCa. Secondary outcomes are the associations with physiological abnormalities, and adverse outcomes. Physiological abnormalities are classified dichotomously as the presence of hypotension (based upon age specific APLS values)<sup>[29]</sup> or elevated SIPA(0-6yrs >1.22, 7-12yrs > 1.00, 13-16yrs > 0.90)<sup>30][31]</sup>, hyperkalaemia (>5.5 mmol/L)<sup>[27]</sup>, and hyperlactataemia (>2.0mmol/L)<sup>[28]</sup>. Adverse outcomes are classified dichotomously as the requirement for vasopressors, transfusion, activation of the major haemorrhage protocol, or invasive (operative or interventional radiology) intervention in the first 24 hours and mortality within 30 days. Hospital LOS, and PICU LOS in days are classified continuously.

Ratio measures (odds ratio) and mean differences will be used for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

### Risk of bias

Risk of bias will be assessed for all included studies. For any randomised controlled trials GRADE methodology will be used, and for observational studies, the ROBINS-I tool will be used.<sup>[32][33]</sup>

The risk of publication bias will be assessed with funnel plots as appropriate.<sup>36</sup>

### Data synthesis

Data will be synthesised following PRISMA guidelines. Studies will be assessed clinically (PICO) and methodologically (study design, comparability, outcome ascertainment, and risk of bias). Given that current evidence is likely to be limited, the minimum number of studies is two. A preliminary search has identified four studies.<sup>[23][24][25][26]]</sup> The I<sup>2</sup> test will be conducted to determine if data are suitable for quantitative synthesis.<sup>[34]</sup>

Meta-analysis of effect estimates is intended and will be displayed using a forest plot. If there is limited evidence for pre-specified comparison, then the haemodynamic instability and vasopressor PICO groups may be combined. Definitions of hypocalcaemia will also be combined if required, providing values are iCa <1.16. Other elements are unlikely to be suitable as contingencies for combination. If different effect measures are used attempts will be made to transform the effect measures for meta-analysis.

A narrative synthesis and summary of effect measures (with the use of box-and-whisker plots) will be conducted if heterogeneity is deemed too substantial across studies to allow for meaningful metaanalysis or if there are major concerns about bias from the three reviewers.

Meta-analysis or narrative synthesis of elements will focus on the incidence of hypocalcaemia in paediatric trauma patients and trend towards adverse outcomes. Subgroup analysis may be undertaken for severe iHypoCa (iCa <1mmol/L).

### Patient and public involvement

No patients will be directly involved in the design of this study and dissemination of findings to participants is not applicable.

### **Ethics and Dissemination**

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

### Discussion

The study has the advantage of using rigorous methodology in accordance with the Cochrane handbook and will be reported as per PRISMA guidelines. The methodology is at risk of publication bias.

As paediatric trauma remains a leading cause of death in the UK this study will add to the knowledge base on the management of paediatric major trauma. Given the different physiology of children compared to adults, children may be more vulnerable to the effects of iHypoCa and the results of studies involving adult major trauma patients may not be able to be extrapolated to a paediatric cohort.<sup>[35]</sup> This study aims to provide further knowledge on the incidence and association of admission hypocalcaemia in paediatric major trauma. Findings of a high incidence of hypocalcaemia, and adverse outcomes, may prompt the consideration of early calcium testing and early replacement for injured children.

### Acknowledgements

The authors would like to acknowledge and thank Catherine Hancox and the Defence Medical Academic Library Team for their assistance with the search strategy.

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# Tables

# Table 1. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Strategy for Inclusion and Exclusion

PICOS Strategy	Inclusion Criteria	Exclusion Criteria
P – Population	Paediatric (<16yrs) major trauma patients (Injury Severity Score> 15) with a documented ionised calcium (iCa) level on admission.	iCa level taken after the administration of blood products.
I – Intervention	Hypocalcaemia on admission (iCa <1.16 mmol/L)	N/A
C – Comparator	Normocalcaemia on admission (iCa $\geq$ 1.16 mmol/L)	N/A
O – Outcome	Primary outcome, the incidence of admission ionised hypocalcaemia. Secondary outcomes include the association with physiological abnormalities: • Haemodynamic instability • Hyperkalaemia • Hyperkalaemia and adverse outcomes: • Vasopressor requirement within 24 hours • Transfusion requirement within 24 hours • Activation of the major haemorrhage protocol within 24 hours • Activation of the major haemorrhage protocol within 24 hours • Requiring invasive (operative or interventional radiology) intervention within 24 hours • Hospital length of stay • PICU length of stay • Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days	N/A
S – Study design	Clinical trials (randomised and non-randomised), observational studies (cohort and case-controlled) case	Systematic reviews. Opinion articles.

	reports, case series and literature reviews.	
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	06/Why%20children%20die%20-
	%20Death%20in%20infants%2C%20children%20and%20young%20people%20in%20the%20
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### **Online Supplementary Tables**

# Table 2. CINAHL search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

Search ID#	Search Terms	Last Run Via	Results from 3 <sup>rd</sup> July 2023
S29	S25 AND S28	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2
S28	S26 OR S27	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	95,090
S27	AB trauma	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	77,482
S26	TI trauma	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	39,417
S25	S23 OR S24	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	11
S24	AB paediatric hypocalcaemia or pediatric hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2
S23	TI paediatric hypocalcaemia or pediatric hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	9
S22	S3 AND S17	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	351
S21	S3 AND S12	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0

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<b>S19</b>	AB admission	Interface - EBSCOhost Research	18
	hypocalcaemia	Databases	
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	hypocalcemia	Search	
		Database - CINAHL	
<b>S18</b>	TI admission	Interface - EBSCOhost Research	1
	hypocalcaemia	Databases	
	or admission	Search Screen - Advanced	
	hypocalcemia	Search	
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<b>S17</b>	S15 OR S16	Interface - EBSCOhost Research	835,597
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<b>S16</b>	AB outcomes	Interface - EBSCOhost Research	732,991
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<b>S15</b>	TI outcomes	Interface - EBSCOhost Research	213,098
		Databases	
		Search Screen - Advanced	
		Search	
		Database - CINAHL	
S14	S3 AND S9	Interface - EBSCOhost Research	0
	AND S12	Databases	
		Search Screen - Advanced	
		Search	
<b>210</b>		Database - CINAHL	
813	S3 AND S6	Interface - EBSCOhost Research	2
		Databases	
		Search Screen - Advanced	
		Search Database CDIAIII	
S12	S10 OP S11	Interface EDSCOhost Descerab	82
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		Databases Search Sereen Advanced	
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<b>S</b> 11	AD	Interface EBSCOhost Pasarch	79
511	normocalesomia	Databases	/0
	or	Search Screen - Advanced	
	normocalcamia	Search	
	normocalcenna	Database - CINAHL	
<b>S10</b>	TI	Interface - EBSCOhost Research	8
510	normocalcaemia	Databases	
	or	Search Screen - Advanced	
	normocalcemia		

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		Search	
<b>S9</b>	S7 OR S8	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,406
S8	AB hospital arrival	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,349
S7	TI hospital arrival	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	107
<b>S</b> 6	S4 OR S5	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,745
S5	AB hypocalcaemia or hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,451
S4	TI hypocalcaemia or hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	584
S3	S1 OR S2	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,003
S2	AB paediatric trauma patients or pediatric trauma patients	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	805
S1	TI paediatric trauma patients or pediatric trauma patients	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	364

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Table 3. MEDLINE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

SearcSearch TermsLast Run ViaResults from 3 <sup>rd</sup> July 2023h ID#
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	S30	S26 AND S29	Interface - EBSCOhost Research	5
			Search Screen - Advanced Search	
			Database - MEDLINE	
	S29	S27 OR S28	Interface - EBSCOhost Research	276,599
			Databases	
			Search Screen - Advanced Search	
		· -	Database - MEDLINE	
	S28	AB trauma	Interface - EBSCOhost Research	245,191
			Databases	
			Search Screen - Advanced Search	
	\$27	TI trauma	Interface - FBSCOhost Research	87 100
	527	11 traunna	Databases	07,100
			Search Screen - Advanced Search	
			Database - MEDLINE	
	S26	S24 OR S25	Interface - EBSCOhost Research	38
			Databases	
			Search Screen - Advanced Search	
	825	A D ma a diatmia	Database - MEDLINE	22
	525	AB paediatric	Interface - EBSCOnost Research	22
		or pediatric	Search Screen - Advanced Search	
		hypocalcemia	Database - MEDLINE	
	S24	TI paediatric	Interface - EBSCOhost Research	18
		hypocalcaemia	Databases	
		or pediatric	Search Screen - Advanced Search	
		hypocalcemia	Database - MEDLINE	
	S23	S6 AND S22	Interface - EBSCOhost Research	4
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			Database MEDI INE	
	S22	S3 AND S17	Interface - EBSCOhost Research	746
	522	55 11(2 51)	Databases	7.0
			Search Screen - Advanced Search	
			Database - MEDLINE	
	S21	S3 AND S12	Interface - EBSCOhost Research	0
			Databases	
			Search Screen - Advanced Search	
	\$20	S18 OR S10	Database - MEDLINE	72
	520	510 OK 519	Databases	12
			Search Screen - Advanced Search	
			Database - MEDLINE	
	S19	AB admission	Interface - EBSCOhost Research	71
ļ		hypocalcaemia	Databases	
		or admission	Search Screen - Advanced Search	
ļ	010	hypocalcemia	Database - MEDLINE	
	818	11 admission	Interface - EBSCOhost Research	4
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		hypocalcemia	Database - MEDLINE	
	S17	S15 OR S16	Interface - EBSCOhost Research	2,179,197
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		Search Screen - Advanced Search Database - MEDLINE	
S16	AB outcomes	Interface - EBSCOhost Research Databases	2,053,450
		Search Screen - Advanced Search Database - MEDLINE	
S15	TI outcomes	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	450,999
S14	S3 AND S9 AND S12	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	0
S13	S3 AND S6	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	5
S12	S10 OR S11	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	870
S11	AB normocalcaemi a or normocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	837
S10	TI normocalcaemi a or normocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	52
S9	S7 OR S8	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	80,231
S8	AB hospital arrival or hospital admission	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	76,431
S7	TI hospital arrival or hospital admission	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	8,797
S6	S4 OR S5	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	11,987
S5	AB hypocalcaemia or hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	10,707
S4	TI hypocalcaemia or hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - MEDLINE	3,153

S3	S1 OR S2	Interface - EBSCOhost Research	2,051
		Databases Search Sereen Advanced Search	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S2	AB paediatric	Interface - EBSCOhost Research	1,764
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - MEDLINE	
S1	TI paediatric	Interface - EBSCOhost Research	649
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - MEDLINE	

Table 4. EMBASE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

#	Query	Results from 3rd July 2023
1	(paediatric trauma patients or pediatric trauma patients).m_titl.	384
2	(paediatric trauma patients or pediatric trauma patients).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,172
3	limit 2 to abstracts	1,155
4	1 or 3	1,172
5	(hypocalcaemia or hypocalcemia).m_titl.	3,811
6	(hypocalcaemia or hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	31,406
7	limit 6 to abstracts	26,928
8	5 or 7	27,890
9	(hospital arrival or hospital admission).m_titl.	4,381
10	(hospital arrival or hospital admission).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	292,976
11	limit 10 to abstracts	245,800
12	9 or 11	246,388
13	(normocalcaemia or normocalcemia).m_titl.	63
14	(normocalcaemia or normocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,223

16       [1,3 or 15]       1,223         17       4 and 8 and 12       1         18       4 and 8       6         19       (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       4         21       limit 20 to abstracts       2         22       19 or 2.1       4         23       (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         24       drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	1.6	12 15	1.000
17       4 and 8 and 12       1         18       4 and 8       6         19       hypocalcemia).m_titl.       2         (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       4         21       limit 20 to abstracts       2         22       19 or 21       4         23       (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         24       floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	16	13 or 15	1,223
18       4 and 8       6         19       (paediatric hypocalcaemia or pediatric hypocalcemia).m titl.       2         (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       4         21       limit 20 to abstracts       2         22       19 or 21       4         23       (admission hypocalcaemia or admission hypocalcemia).m titl.       2         (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	17	4 and 8 and 12	1
19       (paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.       2         20       (paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       4         21       limit 20 to abstracts       2         22       19 or 21       4         23       (admission hypocalcaemia or admission hypocalcemia).m_titl.       2         24       (admission hypocalcaemia or admission hypocalcemia).m_titl.       11         24       drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       111         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	18	4 and 8	6
(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       4         21       limit 20 to abstracts       2         22       19 or 21       4         23       (admission hypocalcaemia or admission hypocalcemia).m_ titl.       2         24       (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	19	(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.	2
21       limit 20 to abstracts       2         22       19 or 21       4         23       (admission hypocalcaemia or admission hypocalcemia).m_titl.       2         24       (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	20	(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	4
22     19 or 21     4       23     (admission hypocalcaemia or admission hypocalcemia).m_titl.     2       24     (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]     11       25     limit 24 to abstracts     11       26     23 or 25     11       27     4 and 16     0	21	limit 20 to abstracts	2
23       (admission hypocalcaemia or admission hypocalcemia).m_titl.       2         24       (admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	22	19 or 21	4
(admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       11         25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	23	(admission hypocalcaemia or admission hypocalcemia).m_titl.	2
25       limit 24 to abstracts       11         26       23 or 25       11         27       4 and 16       0	24	(admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	11
26       23 or 25       11         27       4 and 16       0	25	limit 24 to abstracts	11
27 4 and 16 0	26	23 or 25	11
	27	4 and 16	0

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 Page 16 of 17

PRISMA-P (Preferred Rep address in a systematic rev	oorting Iten iew protoco	ns for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to	
Section and topic	Item No	Checklist item of z	
ADMINISTRATIVE INFORMA	ATION		
Title:		reice	
Identification	1a	Identify the report as a protocol of a systematic review <b>Page 1</b>	
Update	1b	If the protocol is for an update of a previous systematic review, identify as stated as she is the protocol is for an update of a previous systematic review, identify as she is the protocol is for an update of a previous systematic review, identify as she is the protocol is for an update of a previous systematic review, identify as she is the protocol is for an update of a previous systematic review, identify as she is the protocol is for an update of a previous systematic review, identify as the protocol is for an update of a previous systematic review, identify as she is the protocol is for an update of a previous systematic review, identify as the protocol is for an update of a previous systematic review, identify as the protocol is for a previous systematic review.	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Page 1	
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors and the solution of corresponding author Bage 1	
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the the second	
Amendments	4	If the protocol represents an amendment of a previously completed or public protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	- 1
Sponsor	5b	Provide name for the review funder and/or sponsor	3 1
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION		nd "pic	
Rationale	6	Describe the rationale for the review in the context of what is already known	Page
Objectives	7	Provide an explicit statement of the question(s) the review will address with $\frac{1}{8}$ efergence to participants, interventions, comparators, and outcomes (PICO)	Page
METHODS		hnot 8	
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time and and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page
Information sources	9	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	Page
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, in duding planned limits, such that it could be repeated	Page
Study records:			Pane
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	i age

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-	Selection process	11b	State the process that will be used for selecting studies (such as two independent eviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
	Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms clone independently, in duplicate), any processes for obtaining and confirming data from investigators	g
	Data items	12	List and define all variables for which data will be sought (such as PICO ite standing sources), any pre-planned data assumptions and simplifications	
1	Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including priorite for of main and additional outcomes, with rationale	°
	Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies and the fourth outcome or study level, or both; state how this information will be used in details of the state of the sta	0
	Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
		15b	If data are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ and $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, describe planned summary $\vec{h}$ are appropriate for quantitative synthesis, including any planned exploration $\vec{h}$ are appropriate for quantitative synthesis, including any planned exploration $\vec{h}$ are appropriate for quantitative synthesis, including any planned exploration $\vec{h}$ are appropriate for quantitative synthesis, including any planned exploration $\vec{h}$ and $\vec{h}$ and $\vec{h}$ and $\vec{h}$ are appropriate for quantitative synthesis, including any planned exploration $\vec{h}$ are appropriate for quantitative synthesis. The synthesis are appropriate for quantitative synthesis and the synthesis are appropriate for quantitative synthesis and the synthesis are appropriate for quantitative synthesis and the synthesis are appropriate for quantitative synthesis are appropriate for quantitativ	a
		15c	Describe any proposed additional analyses (such as sensitivity or subgroup and zes, meta-regression)	
		15d	If quantitative synthesis is not appropriate, describe the type of summary plate	
	Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias aprosestudies, selective reporting within studies)	
	Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as $R$ DE)	
	PRISMA-P Group and is distribute	d under a	a Creative Commons Attribution Licence 4.0.	
·	From: Shamseer L, Moher D, Clarke meta-analysis protocols (PRISMA-P)	M, Ghers 2015: ela	i D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferrad reporting items for systematic review and boration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.	
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**BMJ** Open

# **BMJ Open**

### The Incidence of Admission Ionised Hypocalcaemia in Paediatric Major Trauma: Protocol for a Systematic Review and Meta-Analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-077429.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Oct-2023
Complete List of Authors:	Hibberd, Owen; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK Price, James ; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK; East Anglian Air Ambulance, Department of Research, Audit, Innovation, & Development (RAID) Harris, T; Queen Mary University of London Blizard Institute Barnard, Ed; Cambridge University, Emergency and Urgent Care Research in Cambridge (EUReCa), PACE Section, Department of Medicine, Cambridge University, UK; Royal Centre for Defence Medicine, Academic Department of Military Emergency Medicine
<b>Primary Subject Heading</b> :	Paediatrics
Secondary Subject Heading:	Emergency medicine, Intensive care, Surgery
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE, Paediatric A&E and ambulatory care < PAEDIATRICS, Paediatric orthopaedic & trauma surgery < PAEDIATRIC SURGERY, Calcium & bone < DIABETES & ENDOCRINOLOGY
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### Introduction

Hypocalcaemia forms part of the 'diamond of death' in major trauma, alongside hypothermia, acidosis, and coagulopathy. In adults, admission hypocalcaemia prior to transfusion is associated with increased mortality, increased blood transfusion requirements, and coagulopathy. Data in paediatric major trauma patients are limited. This systematic review and meta-analysis aims to describe and synthesise the available evidence relevant to paediatric trauma, admission hypocalcaemia, and outcome.

### Methods and analysis

The Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guideline will be used to construct this review. A planned literature search for articles in the English language will be conducted from inception to the date of searches using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The grey literature will also be searched. Both title and abstract screening, and full-text screening will be done by two reviewers, with an adjudicating third reviewer. Heterogeneity will be assessed using I<sup>2</sup> test, and risk of bias will be assessed using the ROBINS-I tool. A meta-analysis will be undertaken using ratio measures (odds ratio) and mean differences for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a p-value.

### Ethical review and dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

Prospero registration number

CRD42023425172

# Strengths and limitations of this study

- ⇒ The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines.
- ⇒ This is a novel review that addresses an area of uncertainity in the current evidence base surrounding paediatric major trauma through systematic review and meta-analysis of published data and the grey-literature.
- $\Rightarrow$  The review methodology is at risk of limitation by publication bias. Where appropriate this will be assessed using funnel plots.

# Background

Major trauma is one of the leading causes of death in children in the United Kingdom (UK).[1][2] A key cause of potentially-survivable death from trauma is haemorrhage.[3] Uncontrollable haemorrhage may be related to the injury mechanism itself, or as a result of Trauma Induced Coagulopathy (TIC).[4] TIC is common, occurring in at least a quarter of haemorrhagic deaths, and has a number of proposed pathophysiological mechanisms, which generally involve injury and shock provoking a immunological, endothelial, and platelet response.[4] All forms of haemorrhage are further exacerbated by the 'lethal triad' of coagulopathy, hypothermia and acidosis.[5][6][7] More recently biochemical abnormalities such as hyperkalaemia and hypocalcaemia have been recognised

to contribute to deaths from haemorrhage.[6][8] In particular, calcium's role is important for clot formation, vascular tone, and cardiac contractility, with hypocalcaemia contributing to coagulopathy and cardiovascular decompensation.[5][6]] As such the 'lethal triad' is now considered a 'diamond of death' with hypocalcaemia forming a key component of this deleterious combination.[5][6]] The early recognition and treatment of these components in the 'diamond of death' are essential for trauma resuscitation.[5][7][9]

### Rationale

The free form of calcium (ionised calcium (iCa)) is the physiologically relevant component of calcium in the blood.[10] iCa is measured on blood gases, which are often taken on arrival for major trauma patients, and there is good agreement between arterial and venous measurements.[11] Blood gas measurement will also record the pH and lactate, and can affect the availability of iCa.[12][13] Ionised hypocalcaemia (iHypoCa) in major trauma patients is multifactorial.[5][6][7][14] The infusion of citrated blood products is a recognised cause of hypocalcaemia in trauma due to calcium chelation with citrate.[6][15] There is also emerging evidence in adults that early hypocalcaemia may occur in trauma patients prior to the receipt of blood products containing citrate.[16][17][18][19] Potential pathophysiological mechanisms underpinning this include calcium binding by lactate, intracellular influx of calcium due to ischaemia and reperfusion, impaired calcium homeostasis secondary to trauma, and secondary to dilution by crystalloid fluid resuscitation.[5][6][7] A systematic review and meta-analysis, which included a total of 1213 major trauma patients, 18 years or older, with a document iCa level on admission explored the incidence and outcomes associated with admission iHypoCa.[20] Studies that involved patients in whom calcium concentration may have been confounded by prior blood transfusion were excluded.[20] Overall, the incidence of admission ionised hypocalcaemia (iHypoCa) was 56.2%, and iHypoCa was associated with: increased mortality, increased blood transfusion requirements, and coagulopathy.[16][17][18][19][20] Evidence of admission iHypoCa and the association with adverse outcomes in adult trauma patients has led to the early measurement and replacement of calcium being recommended in adult trauma guidelines.[21][22] In paediatric major trauma data are limited. Given the different physiology of children compared to adults, children may be more vulnerable to the effects of iHypoCa and the results of studies involving adult major trauma patients may not be able to be extrapolated to a paediatric cohort.[23] A search of PROSPERO did not find any similar planned systematic reviews or meta-analyses. Moreover, a preliminary search of the literature has found a few heterogenous studies, which indicate that admission iHypoCa may be less prevalent in children compared to adults.[24][25][26][27]

### Aims

The primary aim of this systematic review and meta-analysis is to explore the limited evidence related to the incidence of admission iHypoCa in paediatric major trauma patients. The review also aims to explore whether admission iHypoCa, compared to normocalcaemia, is associated with adverse clinical outcomes.

### Methods

### Eligibility criteria

This proposed systematic review and meta-analysis will explore the incidence of iHypoCa in paediatric (<18 years old) major trauma patients (Injury Severity Score (ISS) >15) and explore whether admission iHypoCa (iCa <1.16 mmol/L), compared to normocalcaemia (iCa  $\geq$  1.16 mmol/L) is associated with a greater incidence of adverse outcomes.[12] An iCa of <1.16 mmol/L was chosen to reflect different levels of hypocalcacemia thresholds across the literature and facilitate inclusion of all relevant studies.[24][25][26] The Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) eligibility criteria are detailed in Table 1.

# Information sources

A planned literature search for articles in the English language will be conducted from inception to the search date using MEDLINE on EBSCO platform, CINAHL on EBSCO platform, and Embase on Ovid platform. The reference lists of all included studies, and the grey literature will also be searched.

# Search strategy

The search strategy can be found in online supplementary tables 1,2 and 3.

The search will also involve checking reference lists of retrieved articles, conference abstracts, and online study results. If data is incomplete, then corresponding authors will be contacted for additional information.

# Study records

The search strategy will be undertaken by a trained librarian and information specialist. The combined abstracts from the search strategy will be independently screened by two reviewers to identify studies meeting inclusion criteria, any duplications will be removed manually. For abstracts meeting inclusion criteria, full texts will be retrieved and again be independently reviewed against the inclusion and exclusion criteria by two reviewers and an adjudicating third reviewer.

A standardised data sheet (Microsoft ® Excel for Mac, Version 16.72, 2023) will be used to extract data from included studies to facilitate data synthesis and assessment of quality and risk of bias. Extracted data will be independently verified by the second reviewer, and any discrepancies again adjudicated by the third reviewer.

The following data items will be extracted:

- 1. Hospital setting
- 2. Study type
- 3. Country of treatment
- 4. Cohort size
- 5. Injury severity score (ISS)
- 6. Abbreviated Injury Scale (AIS) score for injury regions
- 7. Ionised hypocalcaemia definitions
- 8. Incidence of admission iHypoCa (iCa <1.16 mmol/L)[12]
- 9. Definitions, and presence of, coagulopathy
- 10. The presence of hyperkalaemia (>5.5 mmol/L)[28]
- 11. The presence of hyperlactataemia (>2.0mmol/L)[29]
- Haemodynamic instability (hypotension (based upon age specific Advanced Paediatric Life Support (APLS) values) or elevated Shock Index Paediatric Age-Adjusted (SIPA))[30][31][32]
- 13. Administration of exogenous calcium
- 14. Vasoactive medication requirements within the first 24 hours
- 15. Total blood product transfusion requirement during the first 24 hours
- 16. Activation of the major haemorrhage protocol within the first 24 hours
- 17. Requirement for invasive (operative or interventional radiology) intervention within 24 hours
- 18. Hospital length of stay (LOS) (days)
- 19. Paediatric Intensive Care Unit (PICU) LOS (days)
- 20. Early mortality within 24 hours and medium mortality during episode of hospital admission (>24 hours) or within 30 days



# Outcomes and prioritisation

The primary outcome of this systematic review and meta-analysis is the overall incidence of admission iHypoCa. Secondary outcomes are the associations with physiological abnormalities, and adverse outcomes. Physiological abnormalities are classified dichotomously as the presence of hypotension (based upon age specific APLS values)[30] or elevated SIPA(0-6yrs >1.22, 7-12yrs > 1.00, 13-16yrs > 0.90),[31][32] hyperkalaemia (>5.5 mmol/L),[28] and hyperlactataemia (>2.0mmol/L).[29] Adverse outcomes are classified dichotomously as the requirement for vasopressors, transfusion, activation of the major haemorrhage protocol, or invasive (operative or interventional radiology) intervention in the first 24 hours and mortality within 30 days. Hospital LOS, and PICU LOS in days are classified continuously.

Ratio measures (odds ratio) and mean differences will be used for measures of effect. When possible, the estimate of effect will be presented along with a confidence interval and a *p*-value.

# Risk of bias

Risk of bias will be assessed for all included studies. For any randomised controlled trials GRADE methodology will be used, and for observational studies, the ROBINS-I tool will be used.[33][34]

The risk of publication bias will be assessed with funnel plots as appropriate.[35]

# Data synthesis

Data will be synthesised following PRISMA guidelines. Studies will be assessed clinically (PICO) and methodologically (study design, comparability, outcome ascertainment, and risk of bias). Given that current evidence is likely to be limited, the minimum number of studies is two. A preliminary search has identified four studies.[24][25][26][27] The I2 test will be conducted to determine if data are suitable for quantitative synthesis.[36]

Meta-analysis of effect estimates is intended and will be displayed using a forest plot. If there is limited evidence for pre-specified comparison, then the haemodynamic instability and vasopressor PICO groups may be combined. Definitions of hypocalcaemia will also be combined if required, providing values are iCa <1.16 mmol/L. Other elements are unlikely to be suitable as contingencies for combination. If different effect measures are used attempts will be made to transform the effect measures for meta-analysis.

A narrative synthesis and summary of effect measures (with the use of box-and-whisker plots) will be conducted if heterogeneity is deemed too substantial across studies to allow for meaningful metaanalysis or if there are major concerns about bias from the three reviewers.

Meta-analysis or narrative synthesis of elements will focus on the incidence of hypocalcaemia in paediatric trauma patients and trend towards adverse outcomes. Subgroup analysis may be undertaken for severe iHypoCa (iCa <1.0 mmol/L).

Patient and public involvement

None

# Ethics and Dissemination

Ethical review is not required as no original data will be collected. Results will be disseminated through peer-reviewed publication and at academic conferences.

### **Contributorship statement**

OH conceptualised the protocol. OH, JP, TH, and EB all contributed to the design, data interpretation, critical revision and final approval of the protocol.

### **Competing interests**

None

### Funding

None

### Acknowledgements

The authors would like to acknowledge and thank Catherine Hancox and the Defence Medical Academic Library Team for their assistance with the search strategy.

### <u>Tables</u>

 Table 1. Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) Strategy for Inclusion and Exclusion

PICOS Strategy	Inclusion Criteria	Exclusion Criteria
P – Population	Paediatric (<18yrs) major	iCa level taken after the
	trauma patients (Injury	administration of blood
	Severity Score> 15) with a	products in the Emergency
	documented ionised calcium	Department.
	(iCa) level on admission.	_
I – Intervention	Hypocalcaemia on admission	N/A
	(iCa <1.16 mmol/L)	
C – Comparator	Normocalcaemia on admission	N/A
*	$(iCa \ge 1.16 \text{ mmol/L})$	
O – Outcome	Primary outcome, the	N/A
	incidence of admission ionised	
	hypocalcaemia.	
	Secondary outcomes include	
	the association with	
	physiological abnormalities.	
	<ul> <li>Haemodynamic</li> </ul>	
	instability	
	<ul> <li>Hyperkalaemia</li> </ul>	
	<ul> <li>Hyperlactataemia</li> </ul>	
	<ul> <li>nH abnormalities</li> </ul>	
	<ul> <li>Coagulopathy</li> </ul>	
	Couguropuury	
	and adverse outcomes:	
	<ul> <li>Vasopressor</li> </ul>	
	requirement within 24	
	hours	
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	<ul> <li>Transfusion requirement within 24 hours</li> <li>Activation of the major haemorrhage protocol within 24 hours</li> <li>Requiring invasive (operative or interventional radiology) intervention within 24 hours</li> <li>Hospital length of stay</li> <li>PICU length of stay</li> <li>Early mortality within 24 hours and medium mortality during episode of hospital admission (&gt;24 hours) or within 30 days</li> </ul>	
S – Study design	Clinical trials (randomised and non-randomised), observational studies (cohort and case-controlled) case reports, case series and literature reviews.	Systematic reviews. Opinion articles.

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### **Online Supplementary Tables**

# Supplementary Table 1. CINAHL search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

Search ID#	Search Terms	Last Run Via	Results from 3 <sup>rd</sup> July 2023
S29	S25 AND S28	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2
S28	S26 OR S27	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	95,090
S27	AB trauma	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	77,482
S26	TI trauma	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	39,417
S25	S23 OR S24	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	11
S24	AB paediatric hypocalcaemia or pediatric hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	2
S23	TI paediatric hypocalcaemia or pediatric hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	9
S22	S3 AND S17	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	351
S21	S3 AND S12	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	0
S20	S18 OR S19	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	19
S19	AB admission hypocalcaemia or admission hypocalcemia	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	18

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S11         S10         S9         S8         S7	AB normocalcaemia or normocalcemia TI normocalcaemia or normocalcemia S7 OR S8 AB hospital arrival	Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search	78 8 1,406 1,349 107
S11         S10         S9         S8         S7	AB normocalcaemia or normocalcemia TI normocalcaemia or normocalcemia S7 OR S8 AB hospital arrival TI hospital arrival	Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search	78 8 1,406 1,349 107
S11         S10         S9         S8         S7         S6	AB normocalcaemia or normocalcemia TI normocalcaemia or normocalcaemia S7 OR S8 AB hospital arrival TI hospital arrival S4 OR S5	Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search Database - CINAHL Interface - EBSCOhost Research Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search Databases Search Screen - Advanced Search Databases	78 8 1,406 1,349 107 1,745
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S11         S10         S9         S8         S7         S6         S5	AB normocalcaemia or normocalcemia TI normocalcaemia or normocalcemia S7 OR S8 AB hospital arrival TI hospital arrival S4 OR S5	Database - CINAHLInterface - EBSCOhost ResearchDatabasesSearch Screen - Advanced SearchDatabase - CINAHLInterface - EBSCOhost ResearchDatabasesSearch Screen - Advanced SearchDatabase - CINAHLInterface - EBSCOhost ResearchDatabasesSearch Screen - Advanced SearchDatabasesSearch Screen - Advanced SearchDatabase - CINAHLInterface - EBSCOhost ResearchDatabasesSearch Screen - Advanced SearchDatabasesSearch Screen - Advanced SearchDatabase - CINAHLInterface - EBSCOhost ResearchDatabase - CINAHLInterface - EBSCOhost Research <th>78 8 1,406 1,349 107 1,745 1,451</th>	78 8 1,406 1,349 107 1,745 1,451

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	hypocalcemia	Database - CINAHL	
<b>S4</b>	TI	Interface - EBSCOhost Research	584
	hypocalcaemia	Databases	
	or	Search Screen - Advanced Search	
	hypocalcemia	Database - CINAHL	
<b>S3</b>	S1 OR S2	Interface - EBSCOhost Research	1,003
		Databases	
		Search Screen - Advanced Search	
		Database - CINAHL	
S2	AB paediatric	Interface - EBSCOhost Research	805
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - CINAHL	
<b>S1</b>	TI paediatric	Interface - EBSCOhost Research	364
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - CINAHL	

Supplementary Table 2. MEDLINE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

Sector	Secure Terrer		Describe from 2rd Int. 2022
Searc	Search Terms	Last Kun Via	Results from 3 <sup>rd</sup> July 2023
II ID#	SOC AND SOO	Interface EDSCObest Dessemb	E
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		Databases Secret Server Advanced Secret	
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S20	S27 OD S29	Interface EDSCOheat Descenth	276 500
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		Databases Search Sereen Advanced Search	
		Detebase MEDI INE	
579	AD trauma	Interface EPSCOheat Passarch	245 101
520	AD trauina	Detebases	243,191
		Search Screen Advanced Search	
		Database MEDLINE	
\$27	TI trauma	Interface EBSCOheat Bassarch	87 100
527	11 traullia	Databases	87,100
		Search Screen - Advanced Search	
		Database - MEDI INE	
\$26	\$24 OR \$25	Interface - FBSCOhost Research	38
520	524 OK 525	Databases	50
		Search Screen - Advanced Search	
		Database - MEDLINE	
S25	AB paediatric	Interface - EBSCOhost Research	22
520	hypocalcaemia	Databases	
	or pediatric	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	
S24	TI paediatric	Interface - EBSCOhost Research	18
	hypocalcaemia	Databases	
	or pediatric	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	

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S23	S6 AND S22	Interface - EBSCOhost Research	4
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S22	S3 AND S17	Interface - EBSCOhost Research	746
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S21	S3 AND S12	Interface - EBSCOhost Research	0
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S20	S18 OR S19	Interface - EBSCOhost Research	72
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S19	AB admission	Interface - EBSCOhost Research	71
	hypocalcaemia	Databases	
	or admission	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	
S18	TI admission	Interface - EBSCOhost Research	4
	hypocalcaemia	Databases	
	or admission	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	
S17	S15 OR S16	Interface - EBSCOhost Research	2,179,197
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S16	AB outcomes	Interface - EBSCOhost Research	2,053,450
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S15	TI outcomes	Interface - EBSCOhost Research	450,999
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S14	S3 AND S9	Interface - EBSCOhost Research	0
	AND S12	Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S13	S3 AND S6	Interface - EBSCOhost Research	5
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S12	S10 OR S11	Interface - EBSCOhost Research	870
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S11	AB	Interface - EBSCOhost Research	837
	normocalcaemi	Databases	
	a or	Search Screen - Advanced Search	
1	normocalcemia	Database - MEDLINE	
S10	TI	Interface - EBSCOhost Research	52

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	a or	Search Screen - Advanced Search	
	normocalcemia	Database - MEDLINE	
S9	S7 OR S8	Interface - EBSCOhost Research	80,231
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S8	AB hospital	Interface - EBSCOhost Research	76,431
	arrival or	Databases	
	hospital	Search Screen - Advanced Search	
	admission	Database - MEDLINE	
S7	TI hospital	Interface - EBSCOhost Research	8,797
	arrival or	Databases	
	hospital	Search Screen - Advanced Search	
	admission	Database - MEDLINE	
S6	S4 OR S5	Interface - EBSCOhost Research	11,987
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S5	AB	Interface - EBSCOhost Research	10,707
	hypocalcaemia	Databases	
	or	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	
S4	TI	Interface - EBSCOhost Research	3,153
	hypocalcaemia	Databases	
	or	Search Screen - Advanced Search	
	hypocalcemia	Database - MEDLINE	
S3	S1 OR S2	Interface - EBSCOhost Research	2,051
		Databases	
		Search Screen - Advanced Search	
		Database - MEDLINE	
S2	AB paediatric	Interface - EBSCOhost Research	1,764
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - MEDLINE	
S1	TI paediatric	Interface - EBSCOhost Research	649
	trauma patients	Databases	
	or pediatric	Search Screen - Advanced Search	
	trauma patients	Database - MEDLINE	

# Supplementary Table 3. EMBASE search strategy for a systematic review and meta-analysis exploring the incidence and associated outcomes with admission hypocalcaemia in paediatric major trauma

#	Query	Results from 3rd July 2023
1	(paediatric trauma patients or pediatric trauma patients).m_titl.	384
2	(paediatric trauma patients or pediatric trauma patients).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,172

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	limit 2 to abstracts	1 155				
4		1,155				
4		1,1/2				
5 6	(hypocalcaemia or hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]       31,406					
7	limit 6 to abstracts	26,928				
8	5 or 7	27,890				
9	(hospital arrival or hospital admission).m titl.	4.381				
10	(hospital arrival or hospital admission).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	292,976				
11	limit 10 to abstracts	245,800				
12	9 or 11	246,388				
13	(normocalcaemia or normocalcemia).m_titl.	63				
14	(normocalcaemia or normocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	1,223				
15	limit 14 to abstracts	1,213				
16	13 or 15	1,223				
1 5						
17	4 and 8 and 12	1				
17 18	4 and 8 and 12 4 and 8	1 6				
17 18 19	4 and 8 and 12 4 and 8 (paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.	1 6 2				
17 18 19 20	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> </ul>	1 6 2 4				
17 18 19 20 21	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> </ul>	1 6 2 4 4 2				
17 18 19 20 21 22	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> <li>19 or 21</li> </ul>	1 6 2 4 4 2 4				
17 18 19 20 21 22 23	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> <li>19 or 21</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl.</li> </ul>	1 6 2 4 4 2 4 2 4 2				
17         18         19         20         21         22         23         24	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> <li>19 or 21</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl.</li> <li>(admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> </ul>	1         6         2         4         2         4         2         4         11				
17         18         19         20         21         22         23         24         25	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> <li>19 or 21</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl.</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl, device manufacturer, drug trade name, original title, device manufacturer, drug trade name, original title, device manufacturer, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 24 to abstracts</li> </ul>	1         6         2         4         2         4         2         4         11         11				
17         18         19         20         21         22         23         24         25         26	<ul> <li>4 and 8 and 12</li> <li>4 and 8</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).m_titl.</li> <li>(paediatric hypocalcaemia or pediatric hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 20 to abstracts</li> <li>19 or 21</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl.</li> <li>(admission hypocalcaemia or admission hypocalcemia).m_titl.</li> <li>(admission hypocalcaemia or admission hypocalcemia).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]</li> <li>limit 24 to abstracts</li> <li>23 or 25</li> </ul>	$ \begin{array}{c} 1 \\ 6 \\ 2 \\ 4 \\ 2 \\ 4 \\ 2 \\ 11 \\ 11 \\ 11 \\ 11 \\ 11 \\ 11 \\ 11 $				

PRISMA-P (Preferred Rep address in a systematic rev	orting Item iew protoco	s for Systematic review and Meta-Analysis Protocols) 2015 c l*	office filding	Bilist: recommended items to	
Section and topic	Item No	Checklist item	for	0 Z	
ADMINISTRATIVE INFORMA	ATION		Ens	ven	
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Registration	2	If registered, provide the name of the registry (such as PROSPERO) and reg	<u>.</u>	Son number Page 1	
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INTRODUCTION			nd s	<u>n</u>	
Rationale	6	Describe the rationale for the review in the context of what is already known	ឆ្ល		Pag
Objectives	7	Provide an explicit statement of the question(s) the review will address with comparators, and outcomes (PICO)	arefe tec	nce to participants, interventions,	Pa
METHODS			hnol	ne 8	
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time considered, language, publication status) to be used as criteria for eligibility	ame For t	and report characteristics (such as years e review	Ра
Information sources	9	Describe all intended information sources (such as electronic databases, con grey literature sources) with planned dates of coverage	itact	with study authors, trial registers or other	Ра
Search strategy	10	Present draft of search strategy to be used for at least one electronic databas repeated	e, ind	Ruding planned limits, such that it could be	Ра
Study records:					Pa
Data management	11a	Describe the mechanism(s) that will be used to manage records and data thr	ough	Out the review	īα

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Selection process	11b	State the process that will be used for selecting studies (such as two independent deviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms clone independently, in duplicate), any processes for obtaining and confirming data from investigators	je 3
Data items	12	List and define all variables for which data will be sought (such as PICO ite standing sources), any pre-planned data assumptions and simplifications	
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including priorite for of main and additional outcomes, with rationale	age 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies in the full be done at the control outcome or study level, or both; state how this information will be used in diagonates is	Page 3
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	15b	If data are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, describe planned summary $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, including any planned exploration $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, including any planned exploration $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, including any planned exploration $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis, including any planned exploration $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ and $\mathbf{F}_{\mathbf{r}}$ are appropriate for quantitative synthesis.	ige 4
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup and subgr	
	15d	If quantitative synthesis is not appropriate, describe the type of summary plate	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias aprosestudies, selective reporting within studies)	Page
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as RDE)	Page
<b>PRISMA-P Group and is distribute</b> From: Shamseer L, Moher D, Clarke meta-analysis protocols (PRISMA-P)	ed under a M, Ghersa 2015: ela	a Creative Commons Attribution Licence 4.0. i D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and boration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.	
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