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Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

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4 1 **Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a**
5
6 2 **Systematic Review**

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30 24
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26 **ABSTRACT**

27 **Introduction**

28 Thrombocytopenia is one of the most common haemostatic abnormalities among
29 neonates. It affects approximately one-quarter of neonates admitted into neonatal
30 intensive care units (NICUs) and may lead to high risks of bleeding and mortality,
31 which are great concerns of neonatologists. Platelet transfusion (PT) is a specific
32 treatment for thrombocytopenia. To date, PT thresholds are diverse, since the
33 associations between low platelet count and negative outcomes are not clear. We
34 propose this protocol for a systematic review to collect and assess evidence concerning
35 the best PT threshold to reduce mortality, bleeding and major morbidity among
36 neonates with thrombocytopenia.

37 **Methods and analysis**

38 The systematic review will be performed according to the Cochrane Handbook for
39 Systematic Review of Interventions, the PRISMA statement, and the GRADE system.
40 Two independent researchers will perform the study selection, data extraction/coding,
41 quality assessment and further analyses of the included studies, with disagreements
42 being resolved by a third researcher. We will search for neonatal PT in the following
43 electronic databases: MEDLINE, The Cochrane Library, and EMBASE. All
44 randomized controlled trials (RCTs) and cohort studies will be included without any
45 restrictions regarding publication date or language. The primary outcome will comprise
46 in-hospital mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3
47 software will be used to manage the selection process and statistical analysis,
48 respectively. If the included studies are sufficient and homogeneous for any of the
49 outcomes, a quantitative synthesis (meta-analysis) may be performed. Otherwise, we
50 will conduct a narrative systematic review of the results.

51 **Ethics and dissemination**

52 Ethical approval is not required for this study because the data are from published
53 studies and will not include individual patient data. The results of this study are
54 anticipated to be published in a peer-reviewed journal.

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4 55 **Strengths and limitations of this study**

- 56 ▶ This study will be the first systematic review to evaluate the evidence regarding PT
57 therapy for neonates with thrombocytopenia.
- 58 ▶ Comprehensive outcomes including in-hospital mortality, bleeding episodes,
59 morbidity, the adverse effects of transfusion, and length of stay will be evaluated.
- 60 ▶ The approach of the review will be performed according to the Cochrane Handbook
61 and the PRISMA statement.
- 62 ▶ The quality of evidence will be affected by the bias in original studies.
- 63 ▶ The results of this systematic review may be helpful for both clinical decisions and
64 further study.
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65 BACKGROUND

66 Thrombocytopenia, defined as a platelet count less than 150 000/ μ L, is a common
67 haemostatic abnormality among neonates, especially premature infants.^{1 2} The
68 aetiology of thrombocytopenia is complicated and involves multiple factors, including
69 abnormal immunity, infection, and asphyxia.³⁻⁷ Thrombocytopenia may be a sole
70 clinical manifestation or complication of other diseases, such as sepsis or necrotizing
71 enterocolitis.^{3-5 8} Approximately 9.4% to 35% of neonates admitted to neonatal
72 intensive care units (NICUs) develop thrombocytopenia.^{5 9-12} Theoretically, neonates
73 with thrombocytopenia may develop a high risk of bleeding and mortality. Thus, this
74 condition is a significant and unresolved problem for neonatologists.

75 Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic
76 treatment for bleeding episodes in neonates with thrombocytopenia. To date, the
77 relationship between low platelet count and major bleeding or mortality is not clear,
78 and the efficacy of PT remains controversial.^{5 13-15} Current guidelines generally
79 recommend prophylactical PT for thrombocytopenic neonates.¹⁶⁻¹⁹ The recommended
80 thresholds vary from 20 000/ μ L to 30 000/ μ L^{15-17 20-25} for non-bleeding stable neonates,
81 while the thresholds range from 30 000/ μ L to 50 000/ μ L^{15 21 24-26} for non-bleeding
82 unstable neonates. These guidelines are consensus guidelines rather than evidence-
83 based guidelines.^{19 27} Thus, there is great diversity in PT thresholds among different
84 NICUs.^{28 29}

85 Theoretically, compared with that at a low threshold, PT at a high threshold may
86 reduce the risks of severe thrombocytopenia, subsequent mortality and bleeding
87 episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that PT at
88 a high threshold increased mortality and bleeding episodes in preterm infants with
89 severe thrombocytopenia compared with PT at a low threshold.¹⁴ On the other hand, as
90 an invasive therapy, PT has some acknowledged adverse events, including transfusion-
91 transmitted infections, bacterial sepsis, febrile nonhemolytic transfusion reaction,
92 transfusion-associated circulatory overload, transfusion-related acute lung injury, and
93 immune-mediated platelet destruction.^{3 30-32} Furthermore, PT has a higher risk of these

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4 94 adverse events than transfusions of other blood products due to its pro-inflammatory
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6 95 function.

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8 96 Recently, more clinical trials regarding PT in neonates with thrombocytopenia
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10 97 have been completed. To assess the best threshold and safety of PT, we will perform
11
12 98 this systematic review and meta-analysis to summarize current evidence for PT in
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14 99 neonates.

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101 **Objectives**

102 Several reports have argued that a lower transfusion threshold may reduce the incidence
103 of unnecessary transfusion and financial costs without the extra risks of bleeding and
104 mortality.^{13 15} We propose this protocol for a systematic review to collect and assess the
105 evidence concerning the best threshold for PT to reduce mortality, bleeding and major
106 morbidity among neonates with thrombocytopenia. We will further explore the best
107 thresholds for PT for neonates with thrombocytopenia due to various causes and more
108 specific clinical characteristics. Furthermore, the safety of PT will be assessed by
109 comparing its side effects at different thresholds.

110

111 **METHODS AND ANALYSIS**

112 This protocol will be conducted on the basis of the Preferred Reporting Items for
113 Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,³³ and
114 further systematic review will be performed according to the Cochrane Handbook for
115 Systematic Review of Interventions,³⁴ the PRISMA statement,³⁵ and the Grading of
116 Recommendations Assessment, Development and Evaluation (GRADE) approach.³⁶

117

118 **Data sources and search strategy**

119 Comprehensive searches will be performed by two researchers independently in the
120 following databases: MEDLINE, the Cochrane Library, and EMBASE. No restriction
121 for language or publication year will be applied to the search. We will use the following
122 keywords to search for and select relevant studies.

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4 123 1. For neonates, the following combination of search terms will be used: “infant” or
5 124 “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.
6
7 125 2. For thrombocytopenia, the following search terms will be used: “thrombocytopenia”
8 126 or “thrombocytopenic” or “NT”.
9
10
11 127 3. For PT, the following search terms will be used: “platelet transfusion” or “platelet
12 128 infusion therapy” or “platelet administration” or “PT”
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14
15 129 4. Steps 1, 2 and 3 will be combined with “and”.

16
17 130 The detailed search strategy is shown in supplemental table 1.

18
19 131 Furthermore, we will hand-check the references of all identified trials, relevant
20 132 systematic reviews, and current treatment guidelines to avoid missing important studies.
21
22 133 Missing data will be handled by contacting relevant investigators for unreported
23 134 materials or additional details.
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28 136 **Study eligibility**

29 137 Types of studies

30
31 138 We will include RCTs and cohort studies and exclude animal researches, in vitro studies,
32 139 cross-sectional studies, case-control studies, case reports, case series, and secondary or
33 140 tertiary articles (systematic reviews and meta-analyses).
34
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37 141 If there are enough data to answer this review's questions using only data from
38 142 RCTs, we will report only data from RCTs.

39 143 Types of participants

40
41 144 New-born infants (less than 28 postnatal days) with thrombocytopenia (platelet
42 145 counts < 150 000/ μ L) admitted to NICUs will be included. We will exclude studies for
43 146 infants with congenital malformations.¹⁴
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47 147 Types of interventions and comparators

48 148 The intervention of the included study is PT for thrombocytopenia. We will compare
49 149 the effects of different transfusion platelet count thresholds. We will also record the
50 150 type and dose of the platelet component received.
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53 151 Types of outcomes

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4 152 The primary outcome will be in-hospital mortality or bleeding episodes [including
5 153 intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary
6 154 haemorrhage (PH), frank rectal bleeding, and other bleeding].

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9 155 The secondary outcomes will be morbidity [including patent ductus arteriosus
10 156 (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD),
11 157 retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and length of
12 158 stay (LOS).^{5 14 29 37-39}

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18 19 160 **Study selection**

20
21 161 Two researchers will independently screen the titles and abstracts of the references
22 162 retrieved by the searches. If eligible, the full texts of potential references will be
23 163 obtained and assessed by two researchers. Studies approved by both investigators will
24 164 be included in this meta-analysis. Discrepancies in inclusion and exclusion decisions
25 165 will be solved with a third senior researcher. Endnote X9 software will be used to tract
26 166 and manage the selection process, and there will be a PRISMA flow diagram to help
27 167 demonstrate this process (see supplemental figure 1).

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34 169 **Data extraction**

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37 170 A structured extraction sheet (see supplemental table 2) as well as Review Manager
38 171 V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extractions
39 172 by two investigators independently, and disagreement will be resolved by a third senior
40 173 researcher. The included data items are as follows:

41
42
43 174 1. Publication and study details: authors, year of publication, country, study design, and
44 175 number of participants.

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46
47 176 2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count
48 177 before transfusion or severity of thrombocytopenia, platelet count thresholds, type and
49 178 dose of platelet component, and the number of PTs.

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52 179 3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and
53 180 LOS.

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4 181 4. Other information: any sponsorship or funding.

5 182 Missing information will be handled by contacting relevant investigators for
6
7 183 unreported data or additional details.

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11 185 **Risk of bias in individual studies**

12
13 186 Risk of bias will be assessed by two independent reviewers, and disagreement will be
14
15 187 resolved by a third reviewer.

16
17 188 For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3 software
18
19 189 (Cochrane Collaboration, UK) will be used. This tool includes random sequence
20
21 190 generation (selection bias), allocation concealment (selection bias), blinding of
22
23 191 participants and personnel (performance bias), blinding of outcome assessment
24
25 192 (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting
26
27 193 bias), and other bias. The bias of the included studies will be divided into high risk of
28
29 194 bias, low risk of bias, or unclear in each domain (see supplemental table 3).⁴⁰

30
31 195 The Newcastle-Ottawa scale (NOS) will be used for observational studies in terms
32
33 196 of selection, comparability, and outcome, with a minimum score of 0 and a maximum
34
35 197 score of 9. We will grade trials with scores of 9 as high quality and those with scores
36
37 198 from 1-8 as low quality (see supplemental table 4).

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41 200 **Data synthesis**

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43 201 When the studies are sufficiently homogeneous for any of the described outcome
44
45 202 measures, a quantitative synthesis (meta-analysis) may be performed according to the
46
47 203 recommendations of the Cochrane handbook. If quantitative analysis cannot be
48
49 204 performed, we will conduct a narrative systematic review of the results from the studies
50
51 205 included, and we will not pool the data from the individual studies.

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53 206 For dichotomous data (occurrence of mortality, bleeding episode, morbidity,
54
55 207 adverse events, etc.), the risk ratio (RR) and odds ratio (OR) will be used for analysis.
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57 208 For continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean
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59 209 difference (SMD) with 95% confidence intervals (CIs) will be used to represent the

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4 210 summary statistics of the outcome with the same units and different scales, respectively.

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8 212 **Assessment of heterogeneity**

9 213 The χ^2 test ($P \leq 0.1$ indicates substantial or considerable heterogeneity) will be used to
10
11 214 determine whether heterogeneity is statistically significant. We will also assess the
12
13 215 degree of statistical heterogeneity by examining I^2 . The data will be pooled by applying
14
15 216 a random-effects model following $I^2 \geq 50\%$ or $P \leq 0.1$. Otherwise, the fixed-effects model
16
17 217 will be used.

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19 218

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21 219 **Sensitivity analysis**

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23 220 We will assess the robustness of the results by excluding low-quality studies.

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27 222 **Subgroup analysis**

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29 223 If sufficient data are identified, subgroup analyses will be performed to detect possible
30
31 224 heterogeneity based on the following participant characteristics:

32
33 225 1) GA (<28 w, 28 – 32 w, 32 – 37 w, >37 w)

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35 226 2) BW (<1000 g, 1000 – 1500 g, 1500 – 2500 g, >2500 g)

36
37 227 3) The severity of thrombocytopenia [mild (100 000 – 150 000/ μ L), moderate (50 000
38
39 228 – 100 000/ μ L), severe (<50 000/ μ L)]

40
41 229 4) The platelet count thresholds for PT

42
43 230 5) The cause for thrombocytopenia

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45 231 6) The design of the study (RCTs, cohort studies)

46
47 232 We will explore the possible heterogeneity among subgroups with I^2 and P values.

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51 234 **Quality of the evidence**

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53 235 We will use the GRADE approach^{36 40} to assess the quality of evidence and propose to
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55 236 present “Summary of findings” tables (see supplemental table 5).

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59 238 **DISCUSSION**

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4 239 We will include RCTs and observational cohort studies in this review to strengthen the
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6 240 statistical power because of the limited number of relevant studies. To the best of our
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8 241 knowledge, this review will be the first to aim to determine the best transfusion platelet
9
10 242 threshold for thrombocytopenic neonates admitted to NICUs. We expect to provide the
11
12 243 best available evidence for neonatologists and guideline developers on PT, which will
13
14 244 help both clinical practice and further study design.

15 245

17 246 **ETHICS AND DISSEMINATION**

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19 247 Ethical approval is not required for this study because the data are from published
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21 248 studies and will not include individual patient data. The results of this study are
22
23 249 anticipated to be published in a peer-reviewed journal.

24 250

27 251 **Contributors**

28
29 252 TX contributed to the conception of the study. The framework of the systematic review
30
31 253 was developed by all authors. The search strategy was designed by TX and will be run
32
33 254 by YY and DJL, who will further independently screen the relevant records, extract
34
35 255 data from included studies and assess the risk of bias. JLW will perform the data
36
37 256 synthesis. TX and JT will arbitrate in cases of any disagreement and ensure no errors
38
39 257 occur during the study. The manuscript for this protocol was drafted by DJL and revised
40
41 258 by TX. All authors have approved the publication of this protocol.

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48 262 Xiong).

50 263 **Competing interests**

51
52 264 None declared.

54 265 **Patient consent**

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56 266 Not required.

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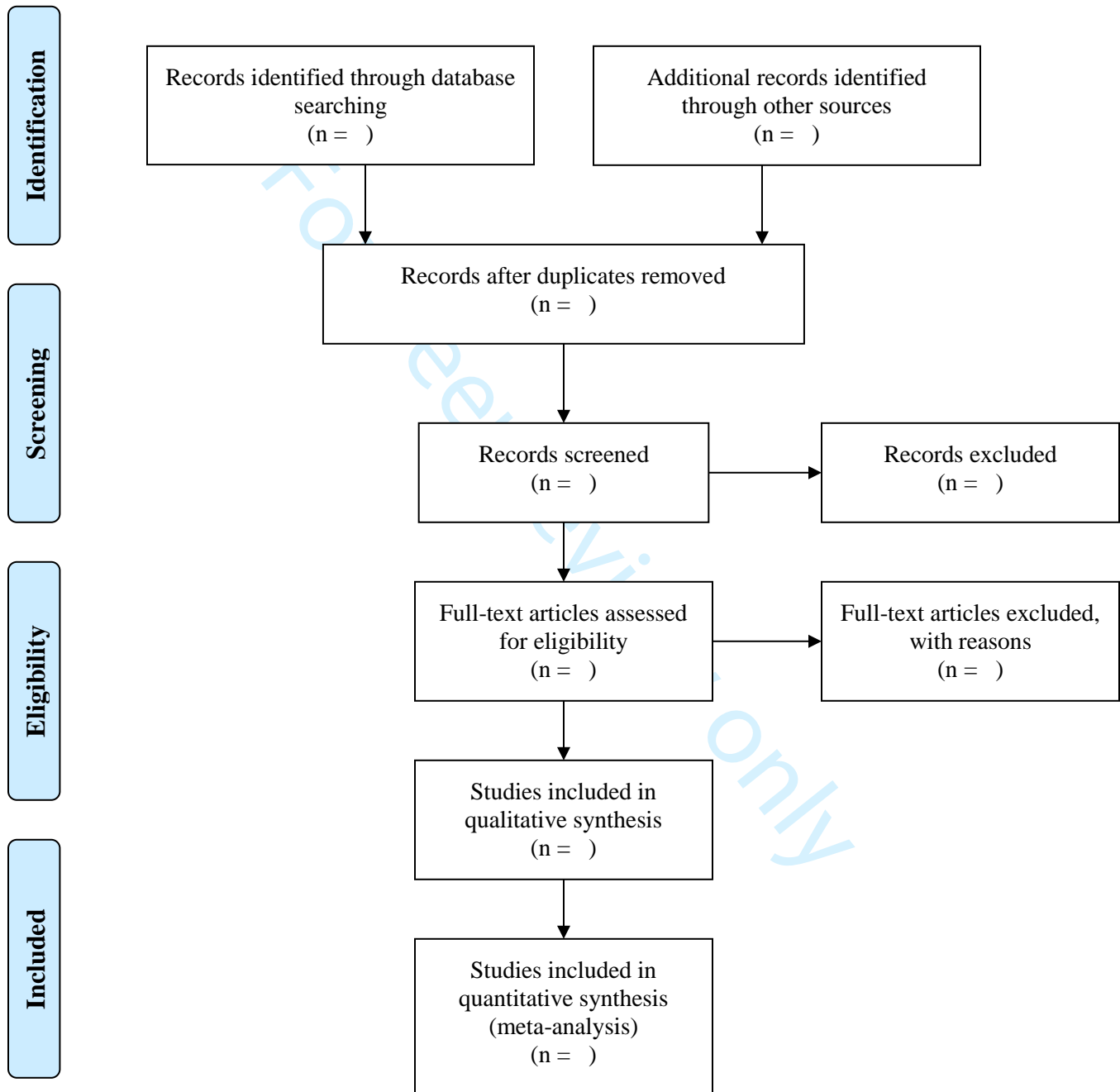
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Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



Supplemental Table 1. Search Strategy
(for Each Electronic Database to Be Searched)

#	Search terms	No of records returned
1	infant	
2	newborn	
3	neonatal	
4	neonate	
5	preterm	
6	premature	
7	neonatology	
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	
9	thrombocytopenia	
10	thrombocytopenic	
11	NT	
12	#9 OR #10 OR #11	
13	platelet transfusion	
14	platelet infusion therapy	
15	platelet administration	
16	PT	
17	#13 OR #14 OR #15 OR #16	
18	#8 AND #12 AND #17	
19	limit #18 to humans	

Supplemental Table 2. Data Extraction Sheet

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Group 1 platelet count threshold (*10 ³ per cubic millimeter)			Group 2 platelet count threshold (*10 ³ per cubic millimeter)		
Clinical characteristics						
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total
GA (w)						
BW (g)						
Platelet count (*10 ³ per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Group 1 event	Group 1 total	Group 2 event	Group 2 total		
In-hospital mortality or major bleeding						
Bleeding episodes						
IVH						
ICH						
PH						

Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						
	Group 1 event	Group 1 total	Group 2 event	Group 2 total		
PDA						
BPD						
Sepsis						
NEC						
ROP						
Other outcome measures						
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total
Adverse effects of transfusion	Group 1 event	Group 1 total	Group 2 event	Group 2 total		
Other information						
Type and dose of platelet component						
Any sponsorship or funding						

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

**Supplemental Table 3. The Risk of Bias Assessment Tool for Randomized
Controlled Studies**

Supplemental Table 3.1 The Risk of Bias Table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 3.2 The Recommended List of Items in the Risk of Bias Tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
	Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describe all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provide any information relating to whether the intended	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		blinding was effective	
Detection bias	Blinding of outcome assessment*	Describe all measures used, if any, to blind outcome assessment from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomised participants),	Attrition bias due to amount, nature, or handling of incomplete outcome data

		reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review	
Reporting bias	Selective reporting	State how selective outcome reporting was examined and what was found	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	State any important concerns about bias not covered in the other domains in the tool	Bias due to problems not covered elsewhere

*Assessments should be made for each main outcome or class of outcomes.

Supplemental Table 3.3 Approach to Formulating Summary Assessments of Risk of Bias for Each Important Outcome (Across Domains) within and Across Trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains	Most information is from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains	Most information is from trials at low or unclear risk of bias
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental Table 4. The Newcastle-Ottawa Scale (NOS)

Supplemental Table 4.1 The Newcastle-Ottawa Scale (NOS) – for Cohort Studies

Study	Item & score							
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that outcome of interest was not present at start of study (1)	Compare ability of cohorts on the basis of the design or analysis (2)	Assessment of outcome (1)	Was follow up long enough for outcomes to occur (1)	Adequacy of follow up of cohorts (1)

Supplemental 4.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average _____ (describe) in the community *
- b) somewhat representative of the average _____ in the community *
- c) selected group of users eg nurses, volunteers
- d) no description of the derivation of the cohort

2) Selection of the non exposed cohort

- a) drawn from the same community as the exposed cohort *
- b) drawn from a different source
- c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure

- a) secure record (eg surgical records) *
- b) structured interview *
- c) written self report
- d) no description

4) Demonstration that outcome of interest was not present at start of study

- a) yes *
- b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

- a) study controls for _____ (select the most important factor) *
- b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blind assessment *
- b) record linkage *
- c) self report
- d) no description

2) Was follow-up long enough for outcomes to occur

- a) yes (select an adequate follow up period for outcome of interest) *
- b) no

3) Adequacy of follow up of cohorts

- a) complete follow up - all subjects accounted for *
- b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) *
- c) follow up rate < ____ % (select an adequate %) and no description of those lost
- d) no statement

**Supplemental Table 5. The Grading of Recommendations Assessment,
Development and Evaluation (GRADE) Approach**

Supplemental Table 5.1 The Summary of Findings Table

Outcomes	Illustrate comparative risks (95% CI)		Relative effect (95% CI)	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

Supplemental Table 5.2 GRADE Evidence Profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 1	Group 2	Relative (95% CI)	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

Supplemental Table 5.3 Quality of Evidence Grades

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Supplemental Table 5.4 Factors that can reduce the quality of the evidence

Factor	Consequence
Limitations in study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of results	↓ 1 or 2 levels
Indirectness of evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 5.5 Factors that can increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding would reduce the demonstrated effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	n/a under review
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

1	Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	10
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5	Amendments			
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7		#4	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	2
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14	Support			
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16	Sources	#5a	Indicate sources of financial or other support for the review	1
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18	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
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21	Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
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25	Introduction			
26				
27	Rationale	#6	Describe the rationale for the review in the context of what is already known	4-5
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31	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
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36	Methods			
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38	Eligibility criteria	#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	6-7
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45	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	5-6
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52	Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-6
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1	Study records -	#11a	Describe the mechanism(s) that will be used to manage	7
2	data management		records and data throughout the review	
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4	Study records -	#11b	State the process that will be used for selecting studies	7
5	selection process		(such as two independent reviewers) through each phase	
6			of the review (that is, screening, eligibility and inclusion in	
7			meta-analysis)	
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11	Study records -	#11c	Describe planned method of extracting data from reports	7-8
12	data collection		(such as piloting forms, done independently, in duplicate),	
13	process		any processes for obtaining and confirming data from	
14			investigators	
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18	Data items	#12	List and define all variables for which data will be sought	7-8
19			(such as PICO items, funding sources), any pre-planned	
20			data assumptions and simplifications	
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23	Outcomes and	#13	List and define all outcomes for which data will be sought,	6-7
24	prioritization		including prioritization of main and additional outcomes,	
25			with rationale	
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29	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	8
30	individual studies		individual studies, including whether this will be done at the	
31			outcome or study level, or both; state how this information	
32			will be used in data synthesis	
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36	Data synthesis	#15a	Describe criteria under which study data will be	8-9
37			quantitatively synthesised	
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39				
40	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	8-9
41			planned summary measures, methods of handling data and	
42			methods of combining data from studies, including any	
43			planned exploration of consistency (such as I ² , Kendall's τ)	
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46	Data synthesis	#15c	Describe any proposed additional analyses (such as	9
47			sensitivity or subgroup analyses, meta-regression)	
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50	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	8
51			type of summary planned	
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54	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	9
55			publication bias across studies, selective reporting within	
56			studies)	
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1 Confidence in [#17](#) Describe how the strength of the body of evidence will be 9
2 cumulative assessed (such as GRADE)
3 evidence
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BMJ Open

Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039132.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Aug-2020
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Secondary Subject Heading:	Haematology (incl blood transfusion), Intensive care
Keywords:	Blood bank & transfusion medicine < HAEMATOLOGY, Bleeding disorders & coagulopathies < HAEMATOLOGY, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

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4 1 **Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a**
5
6 2 **Systematic Review**

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28 ABSTRACT**29 Introduction**

30 Thrombocytopenia is one of the most common haemostatic abnormalities among
31 neonates. It affects approximately one-quarter of neonates admitted into neonatal
32 intensive care units (NICUs) and may lead to high risks of bleeding and mortality,
33 which are substantial causes for concern in neonatologists. Platelet transfusion (PT) is
34 a specific treatment for thrombocytopenia. To date, PT thresholds are diverse, since
35 the associations between low platelet count and negative outcomes are not clear. We
36 propose this protocol for a systematic review to collect and assess evidence
37 concerning the best PT threshold to reduce mortality, bleeding and major morbidity
38 among neonates with thrombocytopenia.

39 Methods and analysis

40 The systematic review will be performed according to the Cochrane Handbook for
41 Systematic Review of Interventions, the Preferred Reporting Items for Systematic
42 Review and Meta-Analysis (PRISMA) statement, and the Grading of
43 Recommendations Assessment, Development and Evaluation (GRADE) system. Two
44 independent researchers will perform the study selection, data extraction/coding,
45 quality assessment and further analyses of the included studies, with disagreements
46 being resolved by a third researcher. A systematic search of the literature will be
47 conducted in the PubMed, Cochrane Library, and Embase databases from database
48 inception through October 13, 2020. All randomized controlled trials (RCTs), cohort
49 studies and case control studies will be included without any restrictions regarding
50 publication date or language. The primary outcome will comprise in-hospital
51 mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3 software
52 will be used to manage the selection process and statistical analysis, respectively. If
53 the included studies are sufficient and homogeneous for any of the outcomes, a
54 quantitative synthesis (meta-analysis) may be performed. Otherwise, we will conduct
55 a narrative systematic review of the results.

56 Ethics and dissemination

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4 57 Ethical approval is not required for this study because the data will be obtained from
5
6 58 published studies and will not include individual patient data. The results of this study
7
8 59 are anticipated to be published in a peer-reviewed journal.
9
10 60 **PROSPERO registration number:** CRD42020169262.
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For peer review only

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4 61 **Strengths and limitations of this study**

- 5 62 ▶ This study will be the most recent systematic review to evaluate the PT threshold
6
7 63 for neonates with thrombocytopenia based on recent evidence. We will include
8
9 64 RCTs and observational studies and separately combine the results of each study
10
11 65 design.
12
13 66 ▶ Comprehensive and extensive analyses of the outcomes, including in-hospital
14
15 67 mortality, bleeding events, morbidity, the adverse effects of transfusion, and
16
17 68 length of stay, will be performed.
18
19 69 ▶ The approach of the review will be performed according to the Cochrane
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21 70 Handbook and the PRISMA statement.
22
23 71 ▶ Formal risk of bias analyses will be performed. The quality of evidence will be
24
25 72 affected by the bias in original studies.
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27 73 ▶ The results of this systematic review may be helpful for both clinical decisions
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29 74 and further study.
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76 BACKGROUND

77 Thrombocytopenia, defined as a platelet count less than 150 000/ μ L, is a common
78 haemostatic abnormality among neonates, particularly premature infants.^{1 2} The
79 aetiology of thrombocytopenia is complicated and involves multiple factors, including
80 abnormal immunity, infection, and asphyxia.³⁻⁷ Thrombocytopenia may be a sole
81 clinical manifestation of alloimmune thrombocytopenia or a complication of other
82 diseases, such as intrauterine growth restriction, polycythaemia, sepsis or necrotizing
83 enterocolitis.^{3-5 8} Approximately 9.4% to 35% of neonates admitted to neonatal
84 intensive care units (NICUs) develop thrombocytopenia.^{5 9-12} Theoretically, neonates
85 with thrombocytopenia may develop a high risk of bleeding and mortality. This
86 increased risk is attributed to the important role of platelets in the whole process of
87 haemostasis, and thrombocytopenia may lead to dysfunctional haemostasis. Thus, this
88 condition is a significant and unresolved problem for neonatologists.

89 Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic
90 treatment for bleeding episodes in neonates with thrombocytopenia. To date, the
91 relationship between a low platelet count and major bleeding or mortality is not clear,
92 and the efficacy of PT remains controversial, as supported by the evidence from
93 recent trials.^{5 13-15} Current guidelines generally recommend prophylactic PT for
94 neonates with thrombocytopenia.¹⁶⁻¹⁹ The recommended thresholds vary from 20
95 000/ μ L to 30 000/ μ L^{15-17 20-25} for non-bleeding stable neonates, while the thresholds
96 range from 30 000/ μ L to 50 000/ μ L^{15 21 24-26} for non-bleeding unstable neonates.
97 These guidelines are consensus guidelines rather than evidence-based guidelines.^{19 27}
98 Thus, a wide range of PT thresholds has been reported among different NICUs.^{28 29}

99 Theoretically, compared with that at a low threshold, PT at a high threshold may
100 reduce the risks of severe thrombocytopenia, subsequent mortality and bleeding
101 episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that PT at
102 a high threshold increased the mortality rate and bleeding events in preterm infants
103 with severe thrombocytopenia compared with PT at a low threshold.¹⁴ On the other
104 hand, as an invasive therapy, PT results in some acknowledged adverse events,

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4 105 including transfusion-transmitted infections, bacterial sepsis, febrile nonhemolytic
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6 106 transfusion reaction, transfusion-associated circulatory overload, transfusion-related
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8 107 acute lung injury, and immune-mediated platelet destruction.^{3 30-32} Furthermore, PT
9
10 108 has a higher risk of these adverse events than transfusions of other blood products due
11
12 109 to its pro-inflammatory function.

13
14 110 Recently, more clinical trials regarding PT in neonates with thrombocytopenia
15
16 111 have been completed. Several reports have argued that a lower transfusion threshold
17
18 112 may reduce the incidence of unnecessary transfusions and financial costs without the
19
20 113 extra risks of bleeding and mortality.^{13 15} We will perform this systematic review and
21
22 114 meta-analysis to summarize current evidence for PT in neonates and to assess the best
23
24 115 threshold and safety of PT.

25 116

27 117 **Objectives**

28
29 118 We propose this protocol for a systematic review to collect and assess the evidence
30
31 119 concerning the best threshold for PT to reduce mortality, bleeding and major
32
33 120 morbidity among neonates with thrombocytopenia. We will further explore the best
34
35 121 thresholds for PT for neonates with thrombocytopenia due to various causes and more
36
37 122 specific clinical characteristics. Furthermore, the safety of PT will be assessed by
38
39 123 comparing its side effects at different thresholds.

40
41 124

42 125 **METHODS AND ANALYSIS**

43
44 126 This protocol will be conducted based on the Preferred Reporting Items for
45
46 127 Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,³³ and a
47
48 128 subsequent systematic review will be performed according to the Cochrane Handbook
49
50 129 for Systematic Review of Interventions,³⁴ the PRISMA statement,³⁵ and the Grading
51
52 130 of Recommendations Assessment, Development and Evaluation (GRADE)
53
54 131 approach.³⁶

55
56 132

58 133 **Data sources and search strategy**

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2
3
4 134 Comprehensive searches will be separately performed by two independent researchers
5
6 135 in the PubMed, Cochrane Library, and Embase databases from database inception
7
8 136 through October 13, 2020. No restrictions on the language will be applied to the
9
10 137 search. We will use the following keywords to search for and select relevant studies.

11 138 1. For neonates, the following combination of search terms will be used: “infant” or
12
13 139 “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.

14
15 140 2. For thrombocytopenia, the following search terms will be used:
16
17 141 “thrombocytopenia” or “thrombocytopenic” or “NT”.

18
19 142 3. For PT, the following search terms will be used: “platelet transfusion” or “platelet
20
21 143 infusion therapy” or “platelet administration” or “PT”

22
23 144 4. Steps 1, 2 and 3 will be combined with “and”.

24
25 145 The detailed search strategy is shown in supplemental table 1.

26
27 146 Furthermore, we will hand-check the references of all identified trials, relevant
28
29 147 systematic reviews, and current treatment guidelines to avoid missing important
30
31 148 studies. Missing data will be handled by contacting relevant investigators for
32
33 149 unreported materials or additional details.

34
35 150

36 37 151 **Study eligibility**

38 39 152 Types of studies

40
41 153 We will include RCTs, cohort studies, and case control studies, and exclude animal
42
43 154 studies, in vitro studies, cross-sectional studies, case reports, case series, and
44
45 155 secondary or tertiary articles (systematic reviews and meta-analyses).

46
47 156 If there are enough data to answer this review's questions using only data from
48
49 157 RCTs, we will report only data from RCTs.

50 51 158 Types of participants

52
53 159 New-born infants with thrombocytopenia (platelet counts < 150 000/μL, the diagnosis
54
55 160 was established at less than 28 postnatal days and the follow-up time may extend to a
56
57 161 postnatal age > 28 days) admitted to NICUs will be included. We will exclude studies
58
59 162 of infants with congenital malformations.¹⁴

1
2
3
4 163 Types of interventions and comparators

5 164 The intervention of the included study is PT for thrombocytopenia. We will compare
6
7 165 the effects of different transfusion platelet count thresholds. We will also record the
8
9 166 type and dose of the platelet component received.

10
11 167 Types of outcomes

12
13 168 The primary outcome will be in-hospital mortality or bleeding episodes [including
14
15 169 intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary
16
17 170 haemorrhage (PH), frank rectal bleeding, and other bleeding].

18
19 171 The secondary outcomes will be morbidity [including patent ductus arteriosus
20
21 172 (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD),
22
23 173 retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and the length
24
25 174 of stay (LOS).^{5 14 29 37-39} The minimum length of follow-up for assessing these
26
27 175 outcomes will be 7 days. Detailed descriptions of the definitions of the outcomes are
28
29 176 provided in supplemental table 2.

30
31 177 If the studies provided both adjusted and unadjusted results, we will only present
32
33 178 the adjusted results in the review.

34
35 179

36 37 180 **Study selection**

38
39 181 Two researchers will independently screen the titles and abstracts of the references
40
41 182 retrieved by the searches. If eligible, the full texts of potential references will be
42
43 183 obtained and assessed by two researchers. Studies approved by both investigators will
44
45 184 be included in this meta-analysis. Discrepancies in inclusion and exclusion decisions
46
47 185 will be solved with a third senior researcher. Endnote X9 software will be used to
48
49 186 tract and manage the selection process, and a PRISMA flow diagram will be
50
51 187 constructed to depict this process (see supplemental figure 1).

52
53 188

54 55 189 **Data extraction**

56
57 190 Structured extraction sheets (see supplemental tables 3.1-3.3) and Review Manager
58
59 191 V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extraction

1
2
3
4 192 by two independent investigators, and disagreements will be resolved by a third senior
5
6 193 researcher. The included data items are as follows:

7
8 194 1. Publication and study details: authors, year of publication, country, study design,
9
10 195 and number of participants.

11
12 196 2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count
13
14 197 before transfusion or severity of thrombocytopenia, platelet count thresholds, type and
15
16 198 dose of platelet component, and the number of PTs.

17
18 199 3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and
19
20 200 LOS.

21
22 201 4. Other information: any sponsorship or funding.

23
24 202 Missing information will be handled by contacting relevant investigators for
25
26 203 unreported data or additional details.

27
28 204

29 205 **Risk of bias in individual studies**

30
31 206 Risk of bias will be assessed by two independent reviewers, and disagreement will be
32
33 207 resolved by a third reviewer.

34
35 208 For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3
36
37 209 software (Cochrane Collaboration, UK) will be used. This tool includes random
38
39 210 sequence generation (selection bias), allocation concealment (selection bias), blinding
40
41 211 of participants and personnel (performance bias), blinding of outcome assessment
42
43 212 (detection bias), incomplete outcome data (attrition bias), selective reporting
44
45 213 (reporting bias), and other bias. The bias of the included studies will be divided into a
46
47 214 high risk of bias, low risk of bias, or unclear risk of bias in each domain (see
48
49 215 supplemental table 4).⁴⁰

50
51 216 The Newcastle-Ottawa scale (NOS) will be used for observational studies in
52
53 217 terms of selection, comparability, and outcome, with a minimum score of 0 and a
54
55 218 maximum score of 9. We will grade trials with scores of 9 points as high quality and
56
57 219 trials with scores of 1-8 points as low quality (see supplemental table 5).

58
59 220
60

221 **Data synthesis**

222 When the studies are sufficiently homogeneous for any of the described outcome
223 measures, a quantitative synthesis (meta-analysis) may be performed according to the
224 recommendations of the Cochrane handbook. If quantitative analysis cannot be
225 performed, we will conduct a narrative systematic review of the results from the
226 studies included, and we will not pool the data from the individual studies.

227 For dichotomous data (occurrence of mortality, bleeding events, morbidity,
228 adverse events, etc.), the risk ratio (RR) will be used in the analysis of RCTs and
229 cohort studies and the odds ratio (OR) will be used for case control studies. For
230 continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean
231 difference (SMD) with 95% confidence intervals (CIs) will be used to represent the
232 summary statistics of the outcome with the same units and different scales,
233 respectively.

234

235 **Assessment of heterogeneity**

236 The χ^2 test ($P \leq 0.1$ indicates substantial or considerable heterogeneity) will be used
237 to determine whether heterogeneity is statistically significant. We will also assess the
238 degree of statistical heterogeneity by examining I^2 . The data will be pooled by
239 applying a random-effects model following $I^2 \geq 50\%$ or $P \leq 0.1$. Otherwise, the
240 fixed-effects model will be used.

241

242 **Sensitivity analysis**

243 We will assess the robustness of the results by including or excluding the
244 controversial studies, such as low-quality studies or studies with temporal ambiguity
245 (whether the bleeding event occurred after PT is unknown).

246

247 **Subgroup analysis**

248 If sufficient data are identified, subgroup analyses will be performed to detect
249 possible heterogeneity based on the following participant characteristics:

- 250 1) GA (<28 w, 28 – 32 w, 32 – 37 w, and >37 w)
- 251 2) BW (<1 000 g, 1 000 – 1 500 g, 1 500 – 2 500 g, and >2 500 g)
- 252 3) The severity of thrombocytopenia [mild (100 000 – 150 000/ μ L), moderate (50 000
- 253 – 100 000/ μ L), and severe (<50 000/ μ L)]
- 254 4) The platelet count thresholds for PT
- 255 5) The cause of thrombocytopenia and
- 256 6) The design of the study (RCTs and cohort studies)

257 We will explore the possible heterogeneity among subgroups with I^2 and P
258 values.

259

260 **Quality of the evidence**

261 We will use the GRADE approach^{36 40} to assess the quality of evidence and propose to
262 present “Summary of findings” tables (see supplemental table 6). We will construct
263 funnel plots and perform Egger’s test to assess publication bias for each of the pooled
264 outcomes when more than 10 included studies are available. Asymmetry may arise as
265 a result of publication bias or of a relationship between the trial size and effect size.
266 Egger’s linear regression analysis will be performed to test for funnel plot asymmetry.

267

268 **Patient and public involvement**

269 No patients are involved.

270

271 **DISCUSSION**

272 Due to the limited number of RCTs, observational studies are a great source of
273 potentially high-quality data. Furthermore, observational studies have additional
274 benefits that may justify the evidence obtained from RCTs as well. We will include
275 RCTs and observational studies in this review because of the limited number of
276 relevant RCTs examining neonates with thrombocytopenia. We will separately
277 combine the results of RCTs and observational studies. To the best of our knowledge,
278 this review will be the most recent systematic review to aim to determine the best PT

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4 279 threshold for neonates with thrombocytopenia who are admitted to NICUs. We expect
5
6 280 to provide the best available evidence for neonatologists and guideline developers on
7
8 281 PT, which will help both clinical practice and further study design.
9

10 282

11 283 **Contributors**

12
13 284 TX contributed to the conception of the study. The framework of the systematic
14
15 285 review was developed by all authors. The search strategy was designed by TX and
16
17 286 will be completed by YY and DJL, who will further independently screen the relevant
18
19 287 records, extract data from included studies and assess the risk of bias. JLW will
20
21 288 perform the data synthesis. TX and JT will arbitrate in cases of any disagreement and
22
23 289 ensure that no errors occur during the study. The manuscript describing this protocol
24
25 290 was drafted by DJL and revised by TX. All authors have approved the publication of
26
27 291 this protocol.

28
29 292 **Competing interests**

30
31 293 None declared.

32
33 294 **Patient consent**

34
35 295 Not required.

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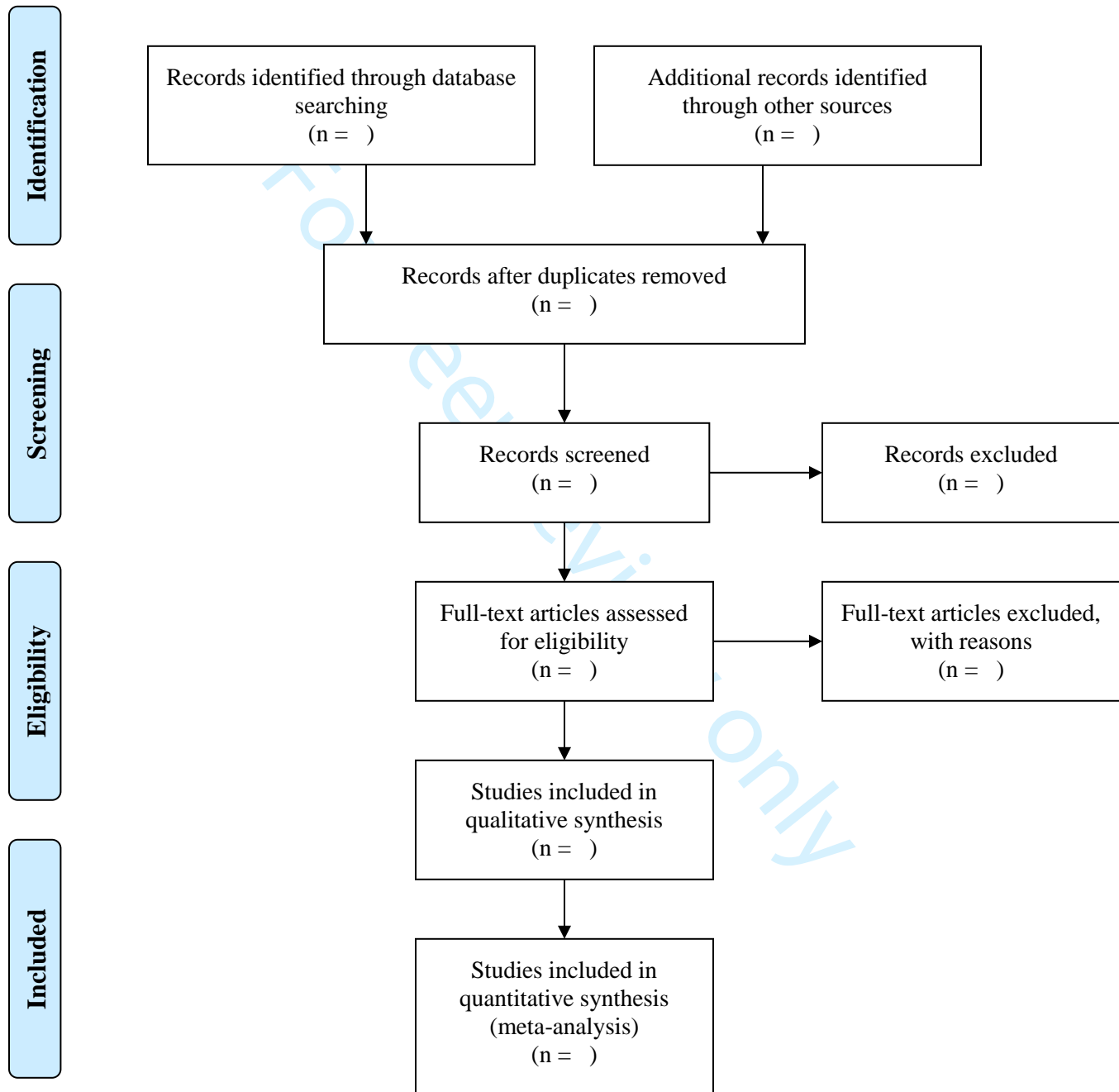
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Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



**Supplemental Table 1. Search strategy used for the following databases:
PubMed, The Cochrane Central Register of Controlled Trials and Embase.**

Table 1.1 PubMed

Query	
#1	“Platelet Transfusion” [MeSH]
#2	platelet transfusion
#3	platelet transfus*
#4	platelet infusion therapy
#5	platelet infus*
#6	platelet administration
#7	platelet administrat*
#8	PT
#9	thrombocyte transfusion
#10	thrombocyte transfus*
#11	thrombocyte infusion therapy
#12	thrombocyte infus*
#13	thrombocyte administration
#14	thrombocyte administrat*
#15	“Thrombocytopenia” [MeSH]
#16	thrombocytopenia
#17	thrombocytopenic
#18	thrombocytopen*
#19	NT
#20	“Infant, Newborn” [MeSH]

#21	infant
#22	newborn
#23	neonatal
#24	neonate
#25	neonatology
#26	neonat*
#27	preterm
#28	premature
#29	prematu*
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#30 and #31 and #32 Filters: Humans

Table 1.2 The Cochrane Central Register of Controlled Trials

Query	
#1	MeSH descriptor: [Platelet Transfusion] explode all trees
#2	(platelet transfusion): ti, ab, kw (word variations have been searched)
#3	(platelet transfus*): ti, ab, kw (word variations have been searched)
#4	(platelet infusion): ti, ab, kw (word variations have been searched)
#5	(platelet infus*): ti, ab, kw (word variations have been searched)
#6	(platelet administration): ti, ab, kw (word variations have been searched)
#7	(platelet administrat*): ti, ab, kw (word variations have been searched)
#8	(PT): ti, ab, kw (word variations have been searched)
#9	(thrombocyte transfusion): ti, ab, kw
#10	(thrombocyte transfus*): ti, ab, kw
#11	(thrombocyte infusion therapy): ti, ab, kw
#12	(thrombocyte infus*): ti, ab, kw
#13	(thrombocyte administration): ti, ab, kw
#14	(thrombocyte administrat*): ti, ab, kw
#15	MeSH descriptor: [Thrombocytopenia] explode all trees
#16	(thrombocytopenia): ti, ab, kw (word variations have been searched)
#17	(thrombocytopenic): ti, ab, kw (word variations have been searched)
#18	(thrombocytopeni*): ti, ab, kw (word variations have been searched)
#19	(NT): ti, ab, kw (word variations have been searched)
#20	MeSH descriptor: [Infant, Newborn] explode all trees
#21	(infant): ti, ab, kw
#22	(newborn): ti, ab, kw

#23	(neonatal): ti, ab, kw
#24	(neonate): ti, ab, kw
#25	(neonatology): ti, ab, kw
#26	(neonat*): ti, ab, kw
#27	(preterm): ti, ab, kw
#28	(premature): ti, ab, kw
#29	(prematu*): ti, ab, kw
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#30 and #31 and #32 in Trials

Table 1.3 Embase

Query	
#1	'thrombocyte transfusion'/exp
#2	'thrombocyte transfusion'
#3	thrombocyte transfus*
#4	'thrombocyte infusion therapy'
#5	thrombocyte infus*
#6	'thrombocyte administration'
#7	thrombocyte administrat*
#8	'platelet transfusion'/exp OR 'platelet transfusion'
#9	platelet transfus*
#10	'platelet infusion therapy'
#11	platelet infus*
#12	'platelet administration'
#13	platelet administrat*
#14	pt
#15	'thrombocytopenia'/exp
#16	'thrombocytopenia'
#17	thrombocytopenic
#18	thrombocytopen*
#19	nt
#20	'newborn'/exp
#21	infant
#22	newborn

#23	neonatal
#24	neonate
#25	neonatology
#26	neonat*
#27	preterm
#28	premature
#29	prematu*
#30	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#31	#15 or #16 or #17 or #18 or #19
#32	#20 or #21 or #22 or #22 or #23 or #24 or #25 or #26 or #26 or #27 or #28 or #29
#33	#32 AND ('clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'feasibility study'/de OR 'human'/de OR 'human experiment'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'open study'/de OR 'outcomes research'/de OR 'phase 2 clinical trial'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de)

Supplemental Table 2. Definitions of outcome measures

Outcome measures	Definitions
IVH	<p>The presence of blood inside the ventricles on CT or cranial ultrasonography.</p> <p>Grading of IVH (as described by J. Volpe):</p> <ul style="list-style-type: none"> -Grade I: Bleeding confined to the periventricular area (germinal matrix) -Grade II: Intraventricular bleeding (10-50% of the ventricular area on a sagittal view) -Grade III: Intraventricular bleeding (>50% of the ventricular area or distends the ventricle) -Intra-parenchymal echodensity (IPE) represents periventricular haemorrhagic infarction and is often referred to as Grade IV IVH.
ICH	The presence of blood within the skull on CT or cranial ultrasonography.
PH	The presence of frank tracheal blood and multi-lobular opacity on chest X-rays.
Frank rectal bleeding	Macroscopic faecal bleed.
PDA	The ductus arteriosus remains open on the echocardiography or associated Doppler studies.
BPD	Treated with more than 21% oxygen for at least 28 days.
Sepsis	A bacterial bloodstream infection (blood culture-proven infection).
NEC	At least one clinical finding (bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum).
ROP	Diagnosed by the ophthalmologist according to the International Classification of Retinopathy of Prematurity, first published in 1985 and revised in 2005.

IVH: intraventricular haemorrhage; CT: computed tomography; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity.

Supplemental Table 3.1 Data extraction sheet for RCTs

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Experimental platelet count threshold (*10 ⁻³ per cubic millimeter)			Control platelet count threshold (*10 ⁻³ per cubic millimeter)		
Clinical characteristics						
	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
GA (w)						
BW (g)						
Platelet count (*10 ⁻³ per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Experimental event	Experimental total	Control event	Control total		
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						
PH						
Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						

	Experimental event	Experimental total	Control event		Control total	
PDA						
BPD						
Sepsis						
NEC						
ROP						
Other outcome measures						
LOS (days)	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
Adverse effects of transfusion	Experimental event	Experimental total	Control event		Control total	
Other information						
Type and dose of platelet component						
Any sponsorship or funding						

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.2 Data extraction sheet for cohort studies

Publication and study details									
Authors									
Year of publication									
Country									
Study design									
Number of participants									
Groups	Group 1 platelet count threshold (*10 ⁻³ per cubic millimetre)			Group 2 platelet count threshold (*10 ⁻³ per cubic millimetre)			Group N platelet count threshold (*10 ⁻³ per cubic millimetre)		
Clinical characteristics									
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
GA (w)									
BW (g)									
Platelet count (*10 ⁻³ per cubic millimetre)									
Number of platelet transfusions									
Primary outcomes									
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
In-hospital mortality or major bleeding events									
Bleeding episodes									
IVH									
ICH									
PH									
Frank rectal bleeding									
Other bleeding									

Secondary outcomes									
Major morbidity									
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
PDA									
BPD									
Sepsis									
NEC									
ROP									
Other outcome measures									
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
Adverse effects of transfusion	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
Other information									
Type and dose of platelet component									
Any sponsorship or funding									

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.3 Data extraction sheet for case control studies

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Exposed group platelet count threshold (*10 ⁻³ per cubic millimetre)			Unexposed group platelet count threshold (*10 ⁻³ per cubic millimetre)		
Clinical characteristics						
	Exposed group median (or mean)	Exposed group IQR (or SD)	Exposed group total	Unexposed group median (or mean)	Unexposed group IQR (or SD)	Unexposed group total
GA (w)						
BW (g)						
Platelet count (*10 ⁻³ per cubic millimetre)						
Number of platelet transfusions						
Primary outcomes						
	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total		
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						

PH						
Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						
	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total		
PDA						
BPD						
Sepsis						
NEC						
ROP						
Other outcome measures						
LOS (days)	Exposed group median (or mean)	Exposed group IQR (or SD)	Exposed group total	Unexposed group median (or mean)	Unexposed group IQR (or SD)	Unexposed group total
Adverse effects of transfusion	Exposed group event	Exposed group total	Unexposed group event	Unexposed group total		
Other information						
Type and dose of platelet component						
Any sponsorship or funding						

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 4. The risk of bias assessment tool for randomized controlled studies

Supplemental Table 4.1 The risk of bias table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 4.2 The recommended list of items in the risk of bias tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describes the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to the inadequate generation of a randomised sequence
	Allocation concealment	Describes the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describes all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provides any information related to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		whether the intended blinding was effective.	
Detection bias	Blinding of outcome assessment*	Describes all measures used, if any, to blind outcome assessments from knowledge of which intervention a participant received. Provides any information related to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. States whether attrition and exclusions were reported, the numbers in each intervention group (compared with the total number of randomised	Attrition bias due to the amount, nature, or handling of incomplete outcome data

		participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review.	
Reporting bias	Selective reporting	States how selective outcome reporting was examined and what was found.	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	States any important concerns about bias not covered in the other domains of the tool.	Bias due to problems not covered elsewhere

*Assessments of each main outcome or class of outcomes should be performed.

Supplemental Table 4.3 Approach to formulating summary assessments of the risk of bias for each important outcome (across domains) within and across trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	A low risk of bias for all key domains	Most information is obtained from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	A low or unclear risk of bias for all key domains	Most information is obtained from trials at low or unclear risk of bias
High risk of bias	Bias may substantially alter the results	A high risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental 5.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars are possible for Comparability.

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average _____ (describe) in the community *
- b) somewhat representative of the average _____ (describe) in the community *
- c) selected group of users, e.g., nurses and volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort *
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (e.g., surgical records) *
- b) structured interview *
- c) written self-report
- d) no description

4) Demonstration that the outcome of interest was not present at the start of the study

- a) yes *
- b) no

Comparability

1) Comparability of cohorts based on the design or analysis

- a) study controls for _____ (select the most important factor) *
- b) study controls for any additional factor * (This criteria could be modified to indicate a specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blinded assessment *
- b) record linkage *
- c) self-report
- d) no description

2) Was the follow-up period long enough for outcomes to occur

- a) yes (selected an adequate follow-up period for the outcome of interest) *
- b) no

3) Adequacy of the follow-up of cohorts

- a) complete follow up - all subjects accounted for *
- b) subjects lost to follow-up, unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those individuals lost to follow-up) *
- c) follow-up rate < ____ % (select an adequate %) and no description of those individuals lost to follow-up
- d) no statement

Supplemental 5.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars is possible for Comparability.

Selection

1) Is the case definition adequate?

- a) yes, with independent validation *
- b) yes, e.g., record linkage or based on self-reports
- c) no description

2) Representativeness of the cases

- a) consecutive or obviously representative series of cases *
- b) potential for selection bias or not stated

3) Selection of Controls

- a) community controls *
- b) hospital controls
- c) no description

4) Definition of Controls

- a) no history of disease (endpoint)
- b) no description of the source

Comparability

1) Comparability of cases and controls based on the design or analysis

- a) study controls for _____ (Select the most important factor.) *
- b) study controls for any additional factor * (This criteria could be modified to indicate a specific control for a second important factor.)

Exposure

1) Ascertainment of exposure

- a) secure record (e.g., surgical records) *
- b) structured interview where the interviewer was blinded to the case/control status *
- c) interviewer was not blinded to the case/control status
- d) written self-report or medical record only
- e) no description

2) Same method of ascertainment for cases and controls

- a) yes *
- b) no

3) Non-response rate

- a) same rate for both groups *
- b) non-respondents described
- c) rates differed and no designation was provided

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Supplemental Table 6. The GRADE approach

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Supplemental Table 6.1 The summary of findings table

Outcomes	Illustrates comparative risks (95% CI)		Relative effect (95% CI)	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

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Supplemental Table 6.2 GRADE evidence profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 1	Group 2	Relative (95% CI)	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

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Supplemental Table 6.3 Quality of evidence grades

Grade	Definition
High	We are very confident that the true effect lies is similar to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but it may be substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Supplemental Table 6.4 Factors that may reduce the quality of the evidence

Factor	Consequence
Limitations in the study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of the results	↓ 1 or 2 levels
Indirectness of the evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 6.5 Factors that may increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding factors would reduce the described effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

1	Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
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5	Amendments			
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7		#4	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	2
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14	Support			
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16	Sources	#5a	Indicate sources of financial or other support for the review	1
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18	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
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21	Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
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24				
25	Introduction			
26				
27	Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
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31	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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36	Methods			
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38	Eligibility criteria	#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	7-8
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45	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	6-7
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51	Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
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56	Study records - data management	#11 a	Describe the mechanism(s) that will be used to manage records and data throughout the review	2, 8
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1	Study records -	#11	State the process that will be used for selecting studies (such	8
2	selection process	b	as two independent reviewers) through each phase of the	
3			review (that is, screening, eligibility and inclusion in meta-	
4			analysis)	
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8	Study records -	#11	Describe planned method of extracting data from reports	8-9
9	data collection	c	(such as piloting forms, done independently, in duplicate),	
10	process		any processes for obtaining and confirming data from	
11			investigators	
12				
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14	Data items	#12	List and define all variables for which data will be sought	8-9
15			(such as PICO items, funding sources), any pre-planned data	
16			assumptions and simplifications	
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20	Outcomes and	#13	List and define all outcomes for which data will be sought,	8-9
21	prioritization		including prioritization of main and additional outcomes, with	
22			rationale	
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25	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	9
26	individual studies		individual studies, including whether this will be done at the	
27			outcome or study level, or both; state how this information	
28			will be used in data synthesis	
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32	Data synthesis	#15	Describe criteria under which study data will be quantitatively	10
33		a	synthesised	
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36	Data synthesis	#15	If data are appropriate for quantitative synthesis, describe	10
37		b	planned summary measures, methods of handling data and	
38			methods of combining data from studies, including any	
39			planned exploration of consistency (such as I ² , Kendall's τ)	
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43	Data synthesis	#15	Describe any proposed additional analyses (such as	10-11
44		c	sensitivity or subgroup analyses, meta-regression)	
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47	Data synthesis	#15	If quantitative synthesis is not appropriate, describe the type	10
48		d	of summary planned	
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51	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	10
52			publication bias across studies, selective reporting within	
53			studies)	
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56	Confidence in	#17	Describe how the strength of the body of evidence will be	11
57	cumulative		assessed (such as GRADE)	
58	evidence			
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Platelet Transfusion for Neonates with Thrombocytopenia: Protocol for a Systematic Review

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Date Submitted by the Author:	20-Sep-2020
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Keywords:	Blood bank & transfusion medicine < HAEMATOLOGY, Bleeding disorders & coagulopathies < HAEMATOLOGY, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE

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4 1 **Platelet Transfusion for Neonates with Thrombocytopaenia: Protocol for a**
5
6 2 **Systematic Review**

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28 **ABSTRACT**

29 **Introduction**

30 Thrombocytopenia is one of the most common haemostatic abnormalities among
31 neonates. It affects approximately one-quarter of neonates admitted into neonatal
32 intensive care units (NICUs) and may lead to a high risk of bleeding and mortality,
33 which are substantial causes for concern by neonatologists. Platelet transfusion (PT) is
34 a specific treatment for thrombocytopenia. To date, PT thresholds are diverse since
35 the associations between low platelet count and negative outcomes are not clear. We
36 propose this protocol for a systematic review to collect and assess evidence
37 concerning the best PT threshold to reduce mortality, bleeding and major morbidity
38 among neonates with thrombocytopenia.

39 **Methods and analysis**

40 The systematic review will be performed according to the Cochrane Handbook for
41 Systematic Review of Interventions, the Preferred Reporting Items for Systematic
42 Review and Meta-Analysis (PRISMA) statement, and the Grading of
43 Recommendations Assessment, Development and Evaluation (GRADE) system. Two
44 independent researchers will perform the study selection, data extraction/coding,
45 quality assessment and further analyses of the included studies, with disagreements
46 being resolved by a third researcher. A systematic search of the literature will be
47 conducted in the PubMed, Cochrane Library, and Embase databases from database
48 inception through October 13, 2020. All randomized controlled trials (RCTs), cohort
49 studies and case-control studies will be included without any restrictions regarding
50 publication date or language. The primary outcomes will comprise in-hospital
51 mortality and bleeding episodes. Endnote X9 and Review Manager V.5.3 software
52 will be used to manage the selection process and statistical analysis, respectively. If
53 the included studies are sufficient and homogeneous for any of the outcomes, a
54 quantitative synthesis (meta-analysis) may be performed. Otherwise, we will conduct
55 a narrative systematic review of the results.

56 **Ethics and dissemination**

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4 57 Ethical approval is not required for this study because the data will be obtained from
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6 58 published studies and will not include individual patient data. The results of this study
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8 59 are anticipated to be published in a peer-reviewed journal.
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10 60 **PROSPERO registration number:** CRD42020169262.
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61 **Strengths and limitations of this study**

- 62 ▶ This study will be the most recent systematic review to evaluate the PT threshold
- 63 for neonates with thrombocytopenia based on recent evidence. We will include
- 64 RCTs and observational studies and separately combine the results of each study
- 65 design.
- 66 ▶ Comprehensive and extensive analyses of the outcomes, including in-hospital
- 67 mortality, bleeding events, morbidity, adverse effects of transfusion, and length of
- 68 stay, will be performed.
- 69 ▶ The review will be performed according to the Cochrane Handbook and the
- 70 PRISMA statement.
- 71 ▶ Formal risk of bias analyses will be performed. The quality of evidence will be
- 72 affected by the bias in original studies.
- 73 ▶ The results of this systematic review may be helpful for both clinical decisions
- 74 and further study.

76 **BACKGROUND**

77 Thrombocytopenia, defined as a platelet count less than 150 000/ μ L, is a common
78 haemostatic abnormality among neonates, particularly premature infants.^{1 2} The
79 aetiology of thrombocytopenia is complicated and involves multiple factors,
80 including abnormal immunity, infection, and asphyxia.³⁻⁷ Thrombocytopenia may be
81 a sole clinical manifestation of alloimmune thrombocytopenia or a complication of
82 other diseases, such as intrauterine growth restriction, polycythaemia, sepsis or
83 necrotizing enterocolitis.^{3-5 8} Approximately 9.4% to 35% of neonates admitted to
84 neonatal intensive care units (NICUs) develop thrombocytopenia.^{5 9-12} Theoretically,
85 neonates with thrombocytopenia may develop a high risk of bleeding and mortality.
86 This increased risk is attributed to the important role of platelets in the whole process
87 of haemostasis, and thrombocytopenia may lead to dysfunctional haemostasis. Thus,
88 this condition is a significant and unresolved problem for neonatologists.

89 Platelet transfusion (PT) is commonly used as a prophylactic and therapeutic
90 treatment for bleeding episodes in neonates with thrombocytopenia. To date, the
91 relationship between a low platelet count and major bleeding or mortality is not clear,
92 and the efficacy of PT remains controversial, as supported by the evidence from
93 recent trials.^{5 13-15} Current guidelines generally recommend prophylactic PT for
94 neonates with thrombocytopenia.¹⁶⁻¹⁹ The recommended thresholds vary from 20
95 000/ μ L to 30 000/ μ L^{15-17 20-25} for non-bleeding stable neonates, while the thresholds
96 range from 30 000/ μ L to 50 000/ μ L^{15 21 24-26} for non-bleeding unstable neonates.
97 These guidelines are consensus guidelines rather than evidence-based guidelines.^{19 27}
98 Thus, a wide range of PT thresholds has been reported among different NICUs.^{28 29}

99 Theoretically, compared with that at a low threshold, PT at a high threshold may
100 reduce the risks of severe thrombocytopenia, subsequent mortality and bleeding
101 episodes. Surprisingly, a recent randomized controlled trial (RCT) reported that
102 compared with PT at a low threshold, PT at a high threshold increased the mortality
103 rate and bleeding events in preterm infants with severe thrombocytopenia.¹⁴ On the
104 other hand, as an invasive therapy, PT is associated with some acknowledged adverse

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4 105 events, including transfusion-transmitted infections, bacterial sepsis, febrile
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6 106 nonhaemolytic transfusion reaction, transfusion-associated circulatory overload,
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8 107 transfusion-related acute lung injury, and immune-mediated platelet destruction.^{3 30-32}
9
10 108 Furthermore, PT has a higher risk of these adverse events than transfusions of other
11
12 109 blood products due to its pro-inflammatory function.

13
14 110 Recently, additional clinical trials regarding PT in neonates with
15
16 111 thrombocytopaenia have been completed. Several reports have argued that a lower
17
18 112 transfusion threshold may reduce the incidence of unnecessary transfusions and
19
20 113 financial costs without the extra risks of bleeding and mortality.^{13 15} We will perform
21
22 114 this systematic review and meta-analysis to summarize current evidence for PT in
23
24 115 neonates and assess the safety and best threshold for PT.

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27 117 **Objectives**

28
29 118 We propose this protocol for a systematic review to collect and assess the evidence
30
31 119 concerning the best threshold for PT to reduce mortality, bleeding and major
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33 120 morbidity among neonates with thrombocytopaenia. We will further explore the best
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35 121 thresholds for PT in neonates with thrombocytopaenia due to various causes and
36
37 122 specific clinical characteristics. Furthermore, the safety of PT will be assessed by
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39 123 comparing its side effects at different thresholds.

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42 125 **METHODS AND ANALYSIS**

43
44 126 This protocol will be conducted based on the Preferred Reporting Items for
45
46 127 Systematic Review and Meta-Analysis Protocol (PRISMA-P) 2015 guidelines,³³ and a
47
48 128 subsequent systematic review will be performed according to the Cochrane Handbook
49
50 129 for Systematic Review of Interventions,³⁴ the PRISMA statement,³⁵ and the Grading
51
52 130 of Recommendations Assessment, Development and Evaluation (GRADE)
53
54 131 approach.³⁶

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57 133 **Data sources and search strategy**

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4 134 Comprehensive searches will be separately performed by two independent researchers
5
6 135 in the PubMed, Cochrane Library, and Embase databases from database inception
7
8 136 through October 13, 2020. No restrictions on language will be applied to the search.

9
10 137 We will use the following keywords for the search and selection of relevant studies.

11
12 138 1. For neonates, the following combination of search terms will be used: “infant” or
13
14 139 “newborn” or “neonatal” or “neonate” or “preterm” or “premature” or “neonatology”.

15
16 140 2. For thrombocytopaenia, the following search terms will be used:

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18 141 “thrombocytopaenia” or “thrombocytopaenic” or “NT”.

19
20 142 3. For PT, the following search terms will be used: “platelet transfusion” or “platelet
21
22 143 infusion therapy” or “platelet administration” or “PT”.

23
24 144 4. Steps 1, 2 and 3 will be combined with “and”.

25
26 145 The detailed search strategy is shown in supplemental table 1.

27
28 146 Furthermore, we will manually check the references of all identified trials,
29
30 147 relevant systematic reviews, and current treatment guidelines to avoid missing
31
32 148 important studies. Missing data will be handled by contacting relevant investigators
33
34 149 for unreported materials or additional details.

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37 151 **Study eligibility**

38 39 152 Types of studies

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41 153 We will include RCTs, cohort studies, and case-control studies and exclude animal
42
43 154 studies, in vitro studies, cross-sectional studies, case reports, case series, and
44
45 155 secondary or tertiary articles (systematic reviews and meta-analyses).

46
47 156 If enough data are available from only RCTs that will answer the questions posed
48
49 157 by this review, we will report only data from RCTs.

50 51 158 Types of participants

52
53 159 Newborn infants with thrombocytopaenia (platelet counts < 150 000/μL, the diagnosis
54
55 160 was established at less than 28 postnatal days, and the follow-up time could extend to
56
57 161 a postnatal age > 28 days) who were admitted to the NICU will be included. We will
58
59 162 exclude studies of infants with congenital malformations.¹⁴

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4 163 Types of interventions and comparators

5 164 The intervention of the included studies is PT for thrombocytopenia. We will
6
7 165 compare the effects of different transfusion platelet count thresholds and record the
8
9 166 type and dose of the platelet component received.

10
11 167 Types of outcomes

12
13 168 The primary outcome will be in-hospital mortality or bleeding episodes [including
14
15 169 intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary
16
17 170 haemorrhage (PH), frank rectal bleeding, and other bleeding].

18
19 171 The secondary outcomes will be morbidity [including patent ductus arteriosus
20
21 172 (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD),
22
23 173 retinopathy of prematurity (ROP), etc.], adverse effects of transfusion, and the length
24
25 174 of stay (LOS).^{5 14 29 37-39} Detailed descriptions of the outcome measures are provided
26
27 175 in supplemental table 2. If the data are sufficient, we will conduct additional analyses
28
29 176 according to the severity of the outcomes (for example, severe PV–IVH (grade III or
30
31 177 IV). The minimum length of follow-up for assessing these outcomes should include
32
33 178 the time point for their diagnosis (for example, the follow-up for BPD should extend
34
35 179 to 28 postnatal days). If a similar outcome measure had different follow-up times in
36
37 180 different original studies, we will try to manage the data according to the timeline.

38
39 181 If the studies provide both adjusted and unadjusted results, only the adjusted
40
41 182 results will be presented in the review.

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43 183

44 184 **Study selection**

45
46 185 Two researchers will independently screen the titles and abstracts of the references
47
48 186 retrieved by the searches. If eligible, the full texts of potential references will be
49
50 187 obtained and assessed by the two researchers. Studies approved by both investigators
51
52 188 will be included in this meta-analysis. Discrepancies in inclusion and exclusion
53
54 189 decisions will be solved by a third senior researcher. Endnote X9 software will be
55
56 190 used to track and manage the selection process, and a PRISMA flow diagram will be
57
58 191 constructed to depict this process (see supplemental figure 1).

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5 193 **Data extraction**

6
7 194 Structured extraction sheets (see supplemental tables 3.1-3.3) and Review Manager
8
9 195 V.5.3 (Cochrane Collaboration, Oxford, UK) software will be used for data extraction
10
11 196 by two independent investigators, and disagreements will be resolved by a third senior
12
13 197 researcher. The included data items are as follows:

- 14
15 198 1. Publication and study details: authors, year of publication, country, study design,
16
17 199 and number of participants.
18
19 200 2. Clinical characteristics: gestational age (GA), birth weight (BW), platelet count
20
21 201 before transfusion or severity of thrombocytopaenia, platelet count thresholds, type
22
23 202 and dose of platelet component, and the number of PTs.
24
25 203 3. Outcomes: mortality, bleeding episodes, IVH grade, NEC, BPD, ROP, sepsis, and
26
27 204 LOS.
28
29 205 4. Other information: any sponsorship or funding.

30
31 206 Attempts will be made to retrieve missing information by contacting relevant
32
33 207 investigators for unreported data or additional details.
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35 208

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37 209 **Risk of bias in individual studies**

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39 210 Risk of bias will be assessed by two independent reviewers, and disagreement will be
40
41 211 resolved by a third reviewer.

42
43 212 For RCTs, the 'Risk of Bias Assessment Tool' in Review Manager V.5.3
44
45 213 software (Cochrane Collaboration, UK) will be used. This tool includes random
46
47 214 sequence generation (selection bias), allocation concealment (selection bias), blinding
48
49 215 of participants and personnel (performance bias), blinding of outcome assessment
50
51 216 (detection bias), incomplete outcome data (attrition bias), selective reporting
52
53 217 (reporting bias), and other bias. The bias of the included studies will be divided into a
54
55 218 high risk of bias, low risk of bias, or unclear risk of bias in each domain (see
56
57 219 supplemental table 4).⁴⁰

58
59 220 The Newcastle-Ottawa scale (NOS) will be used for observational studies in
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4 221 terms of selection, comparability, and outcome, with a minimum score of 0 and a
5
6 222 maximum score of 9. Trials with scores of 9 points will be graded as high quality, and
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8 223 trials with scores of 1-8 points will be graded as low quality (see supplemental table
9
10 224 5).

11 225 12 13 226 **Data synthesis**

14
15 227 When the studies are sufficiently homogeneous for any of the described outcome
16
17 228 measures, a quantitative synthesis (meta-analysis) may be performed according to the
18
19 229 recommendations of the Cochrane Handbook. If quantitative analysis cannot be
20
21 230 performed, a narrative systematic review of the results from the studies included will
22
23 231 be conducted, and we will not pool the data from the individual studies.

24
25 232 For dichotomous data (occurrence of mortality, bleeding events, morbidity,
26
27 233 adverse events, etc.), the risk ratio (RR) will be used in the analysis of RCTs and
28
29 234 cohort studies, and the odds ratio (OR) will be used for case-control studies. For
30
31 235 continuous data (GA, BW, etc.), the mean difference (MD) or standardized mean
32
33 236 difference (SMD) with 95% confidence intervals (CIs) will be used to represent the
34
35 237 summary statistics of the outcome with the same units or different scales,
36
37 238 respectively.

38 39 239 40 41 240 **Assessment of heterogeneity**

42
43 241 The χ^2 test ($P \leq 0.1$ indicates substantial or considerable heterogeneity) will be used
44
45 242 to determine whether heterogeneity is statistically significant. Additionally, we will
46
47 243 assess the degree of statistical heterogeneity by examining I^2 . The data will be pooled
48
49 244 by applying a random-effects model following $I^2 \geq 50\%$ or $P \leq 0.1$. Otherwise, the
50
51 245 fixed-effects model will be used.

52 246 53 54 247 **Sensitivity analysis**

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56 248 We will assess the robustness of the results by including or excluding controversial
57
58 249 studies, such as low-quality studies or studies with temporal ambiguity (e.g., whether
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4 250 the bleeding event occurred after PT is unknown).

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6 251

7 252 **Subgroup analysis**

9 253 If sufficient data are identified, subgroup analyses will be performed to detect
11 254 possible heterogeneity based on the following participant characteristics:

13 255 1) GA (<28 w, 28 – 32 w, 32 – 37 w, and >37 w);

15 256 2) BW (<1 000 g, 1 000 – 1 500 g, 1 500 – 2 500 g, and >2 500 g);

17 257 3) the severity of thrombocytopenia [mild (100 000 – 150 000/ μ L), moderate (50 000
19 258 – 100 000/ μ L), and severe (<50 000/ μ L)];

21 259 4) the platelet count thresholds for PT;

23 260 5) the cause of thrombocytopenia; and

25 261 6) the design of the study (RCTs and cohort studies).

27 262 We will explore the possible heterogeneity among subgroups using I^2 and P
29 263 values.

31 264

33 265 **Quality of the evidence**

35 266 We will use the GRADE approach^{36 40} to assess the quality of evidence and propose to
37 267 present “Summary of findings” tables (see supplemental table 6). We will construct
39 268 funnel plots and perform the Egger’s test to assess publication bias for each of the
41 269 pooled outcomes when more than 10 included studies are available. Asymmetry may
43 270 arise as a result of publication bias or a relationship between the trial size and effect
45 271 size. Egger’s linear regression analysis will be performed to test for funnel plot
47 272 asymmetry.

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51 274 **Patient and public involvement**

53 275 No patients will be involved.

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57 277 **DISCUSSION**

59 278 Due to the limited number of RCTs, observational studies are a great source of
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4 279 potentially high-quality data. Furthermore, observational studies have additional
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6 280 benefits that may justify the evidence obtained from RCTs. We will include RCTs and
7
8 281 observational studies in this review because of the limited number of relevant RCTs
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10 282 examining neonates with thrombocytopaenia. We will separately combine the results
11
12 283 of RCTs and observational studies. To the best of our knowledge, this review will be
13
14 284 the most recent systematic review determining the best PT threshold for neonates with
15
16 285 thrombocytopaenia who are admitted to NICUs. We expect to provide the best
17
18 286 available evidence for neonatologists and guideline developers on PT, which will help
19
20 287 both clinical practice and further study design.
21
22 288

23 289 **Contributors**

24
25 290 TX contributed to the conception of the study. The framework of the systematic
26
27 291 review was developed by all authors. The search strategy was designed by TX and
28
29 292 will be completed by YY and DJL, who will further independently screen the relevant
30
31 293 records, extract data from the included studies and assess the risk of bias. JLW will
32
33 294 perform data synthesis. TX and JT will arbitrate in cases of any disagreement and
34
35 295 ensure that no errors occur during the study. The manuscript describing this protocol
36
37 296 was drafted by DJL and revised by TX. All authors have approved the publication of
38
39 297 this protocol.

40 298 **Competing interests**

41
42 299 None declared.

43 300 **Patient consent**

44
45 301 Not required.

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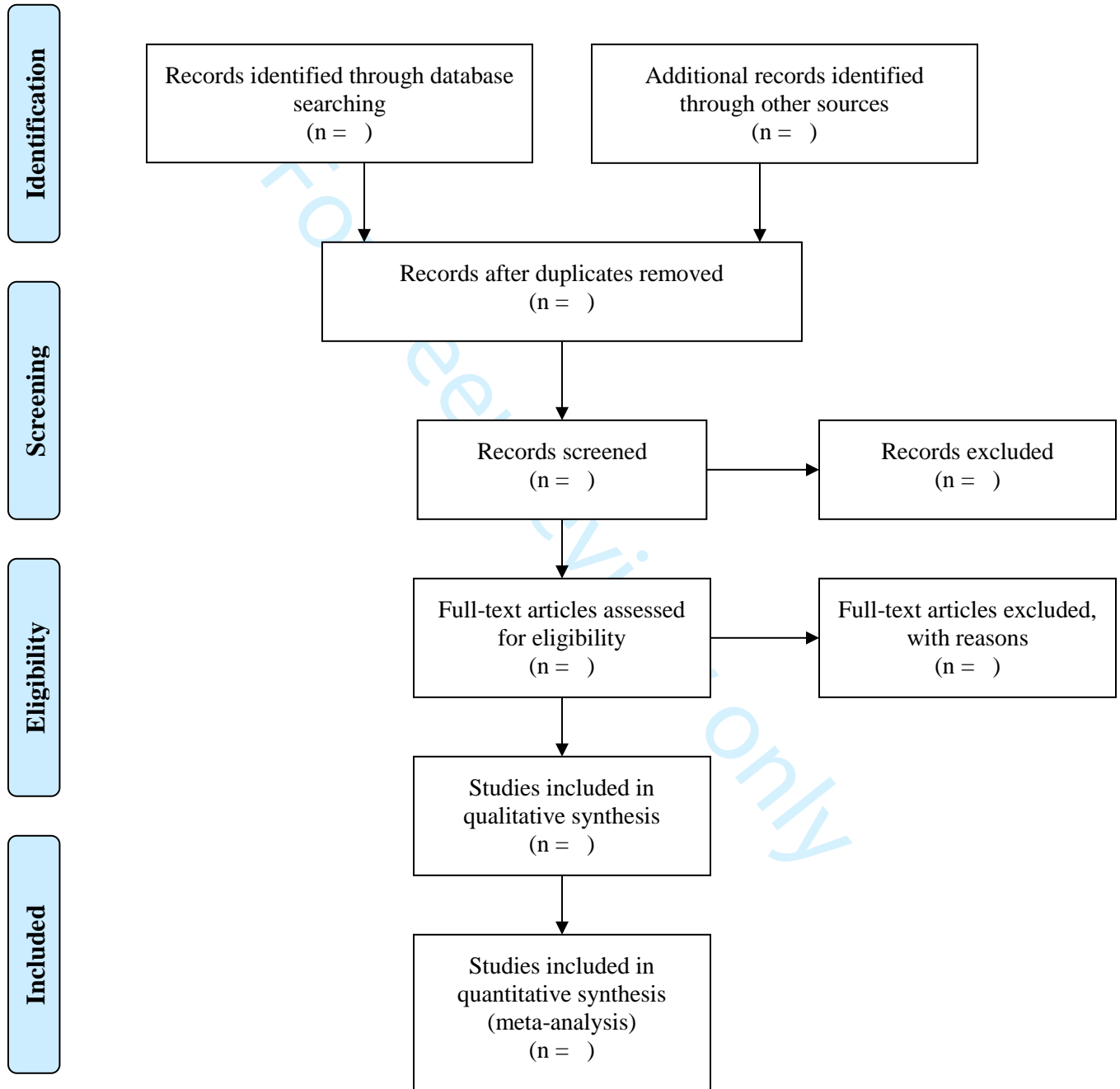
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Supplemental Figure 1. Flow Diagram of Studies Selected for Inclusion in the Systematic Review (PRISMA 2009 Flow Diagram)



**Supplemental Table 1. Search strategy used for the following databases:
PubMed, the Cochrane Central Register of Controlled Trials and Embase**

Table 1.1 PubMed

Query	
#1	“Platelet Transfusion” [MeSH]
#2	platelet transfus*
#3	platelet infus*
#4	platelet administrat*
#5	PT
#6	thrombocyte transfus*
#7	thrombocyte infus*
#8	thrombocyte administrat*
#9	“Thrombocytopenia” [MeSH]
#10	thrombocytopen*
#11	NT
#12	“Infant, Newborn” [MeSH]
#13	infant
#14	newborn
#15	neonat*
#16	preterm
#17	prematur*
#18	#1 or #3 or #4 or #5 or #6 or #7 or #8
#19	#9 or #10 or #11
#20	#12 or #13 or #14 or #15 or #16 or #17
#21	18 and #19 and #20 Filters: Humans

Table 1.2 The Cochrane Central Register of Controlled Trials

Query	
#1	MeSH descriptor: [Platelet Transfusion] explode all trees
#2	(platelet transfus*): ti, ab, kw (word variations have been searched)
#3	(platelet infus*): ti, ab, kw (word variations have been searched)
#4	(platelet administrat*): ti, ab, kw (word variations have been searched)
#5	(PT): ti, ab, kw (word variations have been searched)
#6	(thrombocyte transfus*): ti, ab, kw
#7	(thrombocyte infus*): ti, ab, kw
#8	(thrombocyte administrat*): ti, ab, kw
#9	MeSH descriptor: [Thrombocytopenia] explode all trees
#10	(thrombocytopeni*): ti, ab, kw (word variations have been searched)
#11	(NT): ti, ab, kw (word variations have been searched)
#12	MeSH descriptor: [Infant, Newborn] explode all trees
#13	(infant): ti, ab, kw
#14	(newborn): ti, ab, kw
#15	(neonat*): ti, ab, kw
#16	(preterm): ti, ab, kw
#17	(premat*): ti, ab, kw
#18	#1 or #3 or #4 or #5 or #6 or #7 or #8
#19	#9 or #10 or #11
#20	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#21	18 and #19 and #20 in Trials

Table 1.3 Embase

Query	
#1	'thrombocyte transfusion'/exp
#2	thrombocyte transfus*
#3	thrombocyte infus*
#4	thrombocyte administrat*
#5	'platelet transfusion'/exp OR 'platelet transfusion'
#6	platelet transfus*
#7	platelet infus*
#8	platelet administrat*
#9	pt
#10	'thrombocytopenia'/exp
#11	thrombocytopen*
#12	nt
#13	'newborn'/exp
#14	infant
#15	newborn
#16	neonat*
#17	preterm
#18	prematur*
#19	#1 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#20	#10 or #11 or #12
#21	#13 or #14 or #15 or #16 or #17 or #18
#22	#19 AND #20 AND #21 AND ('clinical article'/de OR 'clinical study'/de OR 'clinical trial'/de OR 'clinical trial topic'/de OR 'cohort analysis'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'feasibility study'/de OR 'human'/de OR 'human experiment'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'multicenter study'/de OR 'observational study'/de OR 'open study'/de OR 'outcomes research'/de OR 'phase 2 clinical trial'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de OR 'retrospective study'/de)

Supplemental Table 2. Definitions of outcome measures

Outcome measures	Definitions	Minimum follow-up
IVH	<p>The presence of blood inside the ventricles on CT or cranial ultrasonography</p> <p>Grading of IVH (as described by J. Volpe):</p> <p>Grade I: bleeding confined to the periventricular area (germinal matrix)</p> <p>Grade II: intraventricular bleeding (10-50% of the ventricular area on a sagittal view)</p> <p>Grade III: intraventricular bleeding (>50% of the ventricular area or distends the ventricle)</p> <p>Grade IV: intra-parenchymal echodensity (IPE) represents periventricular haemorrhagic infarction and is often referred to as Grade IV IVH</p>	3 d
ICH	The presence of blood within the skull on CT or cranial ultrasonography	3 d
PH	The presence of frank tracheal blood and multi-lobular opacity on chest X-ray	3 d
Frank rectal bleeding	Macroscopic faecal bleed	3 d
PDA	<p>PDA: open ductus arteriosus on echocardiography or associated Doppler studies after 15 postnatal hours</p> <p>Clinically significant PDA was suspected in the presence of 2 or more of the following:</p> <ol style="list-style-type: none"> (1) heart murmur, (2) hyperdynamic precordium, (3) bounding pulses, (4) persistent tachycardia (>160 beats per minute), (5) wide pulse pressure, (6) new-onset or increase in ventilator requirements, (7) systemic hypoperfusion (poor pulses, prolonged capillary refill time, decreased urine output, or 	3 d

	<p>hypotension),</p> <p>(8) chest radiographic evidence, i.e., pulmonary congestion or cardiomegaly (a cardiothoracic ratio >60%) with increased pulmonary flow.</p> <p>Echocardiographic hs-PDA was defined as the presence of transductal diameter ≥ 1.5 mm at the pulmonary end plus 1 of the following:</p> <ol style="list-style-type: none"> (1) left-atrium/aorta ratio ≥ 1.4, (2) ductal velocity <2 metres per second, (3) antegrade left pulmonary artery diastolic flow >30 centimetres per second, (4) E-wave/A-wave ratio >1, (5) isovolaemic relaxation time ≤ 45 milliseconds, (6) absent or reversed diastolic blood flow pattern in the descending thoracic aorta. 	
BPD	<p>Treated with more than 21% oxygen for at least 28 days;</p> <p>Diagnostic criteria for bronchopulmonary dysplasia (as described by National Institutes of Health):</p> <p>Mild BPD:</p> <ol style="list-style-type: none"> (1) breathing room air at 36 weeks post-menstrual age or discharge (for those with GA <32 weeks) (2) breathing room air by 56 days postnatal age or discharge (for those with GA ≥ 32 weeks) <p>Moderate BPD:</p> <ol style="list-style-type: none"> (1) need for <30% O₂ at 36 weeks post-menstrual age, or discharge (for those with GA <32 weeks) (2) need for <30% O₂ to 56 days postnatal age, or discharge (for those with GA ≥ 32 weeks) <p>Severe BPD:</p> <ol style="list-style-type: none"> (1) need for >30% O₂, with or without positive pressure ventilation or continuous positive pressure at 36 weeks post-menstrual age, or discharge (for those with GA <32 weeks) (for those with GA ≥ 32 weeks) 	28 d

	(2) need for >30% O ₂ with or without positive pressure ventilation or continuous positive pressure at 56 days postnatal age, or discharge (for those with GA ≥32 weeks)	
Sepsis	A bacterial bloodstream infection (blood culture-proven infection)	7 d
NEC	<p>At least one clinical finding (bilious gastric aspirate or emesis, abdominal distension, or occult or gross blood in the stool in the absence of anal fissures) and at least one radiographic finding (pneumatosis intestinalis, hepatobiliary gas, or pneumoperitoneum) are required to secure the diagnosis.</p> <p>Bell's stages of necrotizing enterocolitis:</p> <p>I. Suspected disease</p> <p>(1) Mild systemic signs (apnoea, bradycardia, temperature instability)</p> <p>(2) Mild intestinal signs (abdominal distention, gastric residuals, bloody stools)</p> <p>(3) Non-specific or normal radiological signs</p> <p>II. Definite disease</p> <p>(1) Mild to moderate systemic signs</p> <p>(2) Additional intestinal signs (absent bowel sounds, abdominal tenderness)</p> <p>(3) Specific radiologic signs (pneumatosis intestinalis or portal venous air)</p> <p>(4) Laboratory changes (metabolic acidosis, thrombocytopenia)</p> <p>III. Advanced disease</p> <p>(1) Severe systemic illness (hypotension)</p> <p>(2) Additional intestinal signs (striking abdominal distention, peritonitis)</p> <p>(3) Severe radiological signs (pneumoperitoneum)</p> <p>(4) Additional laboratory changes (metabolic and respiratory acidosis, disseminated intravascular</p>	7 d

	coagulopathy)	
ROP	Diagnosed by the ophthalmologist according to the International Classification of Retinopathy of Prematurity, first published in 1985 and revised in 2005.	28 d

IVH: intraventricular haemorrhage; CT: computed tomography; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; PDA: patent ductus arteriosus; hs-PDA: haemodynamically significant patent ductus arteriosus; BPD: bronchopulmonary dysplasia; GA: gestational age; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity

Supplemental Table 3.1 Data extraction sheet for RCTs

Publication and study details						
Authors						
Year of publication						
Country						
Study design						
Number of participants						
Groups	Experimental platelet count threshold (*10 ³ /μL)			Control platelet count threshold (*10 ³ /μL)		
Clinical characteristics						
	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
GA (w)						
BW (g)						
Platelet count (*10 ⁻³ per cubic millimeter)						
Number of platelet transfusions						
Primary outcomes						
	Experimental event	Experimental total	Control event	Control total		
In-hospital mortality or major bleeding events						
Bleeding episodes						
IVH						
ICH						
PH						
Frank rectal bleeding						
Other bleeding						
Secondary outcomes						
Major morbidity						
	Experimental	Experimental	Control event	Control total		

	event	total				
PDA						
BPD						
Sepsis						
NEC						
ROP						
Other outcome measures						
LOS (days)	Experimental median (or mean)	Experimental IQR (or SD)	Experimental total	Control median (or mean)	Control IQR (or SD)	Control total
Adverse effects of transfusion	Experimental event	Experimental total	Control event		Control total	
Other information						
Type and dose of platelet component						
Any sponsorship or funding						

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.2 Data extraction sheet for cohort studies

Publication and study details									
Authors									
Year of publication									
Country									
Study design									
Number of participants									
Groups	Group 1 platelet count threshold (*10 ³ /μL)	Group 2 platelet count threshold (*10 ³ /μL)			Group N platelet count threshold (*10 ³ /μL)				
Clinical characteristics									
	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
GA (w)									
BW (g)									
Platelet count (*10 ³ per cubic millimetre)									
Number of platelet transfusions									
Primary outcomes									
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
In-hospital mortality or major bleeding events									
Bleeding episodes									
IVH									
ICH									
PH									
Frank rectal bleeding									
Other bleeding									
Secondary outcomes									

Major morbidity									
	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
PDA									
BPD									
Sepsis									
NEC									
ROP									
Other outcome measures									
LOS (days)	Group 1 median (or mean)	Group 1 IQR (or SD)	Group 1 total	Group 2 median (or mean)	Group 2 IQR (or SD)	Group 2 total	Group N median (or mean)	Group N IQR (or SD)	Group N total
Adverse effects of transfusion	Group 1 event	Group 1 total	Group 2 event	Group 2 total	Group N event	Group N total			
Other information									
Type and dose of platelet component									
Any sponsorship or funding									

IQR: interquartile range; SD: standard deviation; GA: gestational age; BW: birth weight; IVH: intraventricular haemorrhage; ICH: intracranial haemorrhage; PH: pulmonary haemorrhage; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; LOS: length of stay

Supplemental Table 3.3 Data extraction sheet for case-control studies

Publication and study details		
Authors		
Year of publication		
Country		
Study design		
Number of participants		
Outcome measure^a		
Clinical characteristics		
	Case	Control
GA (w)		
BW (g)		
Platelet count (*10 ³ /μL)		
Platelet transfusion		
Platelet transfusion threshold 1 (*10 ³ /μL) ^b		
Platelet transfusion threshold 2 (*10 ³ /μL) ^b		
Number of platelet transfusions		
Other information		
Type and dose of platelet component		
Any sponsorship or funding		

a The outcome measure to distinguish the case and the control groups include: in-hospital mortality or bleeding episodes [including intraventricular haemorrhage (IVH), intracranial haemorrhage (ICH), pulmonary haemorrhage (PH), frank rectal bleeding, and other bleeding], morbidity [including patent ductus arteriosus (PDA), sepsis, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), etc.] and adverse effects of transfusion.

b If the different platelet transfusion thresholds cannot be obtained, we will record only “platelet transfusion” or “without platelet transfusion”.

Supplemental Table 4. The risk of bias assessment tool for randomized controlled studies

Supplemental Table 4.1 The risk of bias table

Item	Judgement	Support for judgement
Random sequence generation (selection bias)		
Allocation concealment (selection bias)		
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data addressed (attrition bias)		
Selective reporting (reporting bias)		
Other bias		

Supplemental Table 4.2 The recommended list of items in the risk of bias tool

Bias domain	Source of bias	Support for judgment	Review authors' judgment (assess as low, unclear or high risk of bias)
Selection bias	Random sequence generation	Describes the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to the inadequate generation of a randomised sequence
	Allocation concealment	Describes the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen before or during enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment
Performance bias	Blinding of participants and personnel*	Describes all measures used, if any, to blind trial participants and researchers from knowledge of which intervention a participant received. Provides any information related to	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study

		whether the intended blinding was effective.	
Detection bias	Blinding of outcome assessment*	Describes all measures used, if any, to blind outcome assessments from knowledge of which intervention a participant received. Provides any information related to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessment
Attrition bias	Incomplete outcome data*	Describes the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. States whether attrition and exclusions were reported, the numbers in each intervention group (compared with the total number of randomised	Attrition bias due to the amount, nature, or handling of incomplete outcome data

		participants), reasons for attrition or exclusions where reported, and any reinclusions in analyses for the review.	
Reporting bias	Selective reporting	States how selective outcome reporting was examined and what was found.	Reporting bias due to selective outcome reporting
Other bias	Anything else, ideally prespecified	States any important concerns about bias not covered in the other domains of the tool.	Bias due to problems not covered elsewhere

*Assessments of each main outcome or class of outcomes should be performed.

Supplemental Table 4.3 Approach to formulating summary assessments of the risk of bias for each important outcome (across domains) within and across trials

Risk of bias	Interpretation	Within a trial	Across trials
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	A low risk of bias for all key domains	Most information is obtained from trials at low risk of bias
Unclear risk of bias	A risk of bias that raises some doubt about the results	A low or unclear risk of bias for all key domains	Most information is obtained from trials at low or unclear risk of bias
High risk of bias	Bias may substantially alter the results	A high risk of bias for one or more key domains	The proportion of information from trials at high risk of bias is sufficient to affect the interpretation of results

Supplemental Table 5. The Newcastle-Ottawa Scale (NOS) for cohort studies and case control studies

Supplemental Table 5.1 The Newcastle-Ottawa Scale (NOS) for cohort studies

Study	Item & score							
	Selection				Comparability	Outcome		
	Representativeness of the exposed cohort (1)	Selection of the non-exposed cohort (1)	Ascertainment of exposure (1)	Demonstration that the outcome of interest was not present at start of study (1)	Compare the ability of cohorts based on the design or analysis (2)	Assessment of outcome (1)	Was the follow-up period long enough for outcomes to occur (1)	Adequacy of the follow-up of cohorts (1)

Supplemental 5.2 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars are possible for Comparability.

Selection

1) Representativeness of the exposed cohort

- a) truly representative of the average _____ (describe) in the community *
- b) somewhat representative of the average _____ (describe) in the community *
- c) selected group of users, e.g., nurses and volunteers
- d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

- a) drawn from the same community as the exposed cohort *
- b) drawn from a different source
- c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

- a) secure record (e.g., surgical records) *
- b) structured interview *
- c) written self-report
- d) no description

4) Demonstration that the outcome of interest was not present at the start of the study

- a) yes *
- b) no

Comparability

1) Comparability of cohorts based on the design or analysis

- a) study controls for _____ (select the most important factor) *
- b) study controls for any additional factor * (This criteria could be modified to indicate a specific control for a second important factor.)

Outcome

1) Assessment of outcome

- a) independent blinded assessment *
- b) record linkage *
- c) self-report
- d) no description

2) Was the follow-up period long enough for outcomes to occur

- a) yes (selected an adequate follow-up period for the outcome of interest) *
- b) no

3) Adequacy of the follow-up of cohorts

- a) complete follow up - all subjects accounted for *
- b) subjects lost to follow-up, unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those individuals lost to follow-up) *
- c) follow-up rate < ____ % (select an adequate %) and no description of those individuals lost to follow-up
- d) no statement

Supplemental Table 5.3 The Newcastle-Ottawa Scale (NOS) for case control studies

Study	Item & score							
	Selection				Comparability	Exposure		
	Is the case definition adequate? (1)	Representativeness of the cases (1)	Selection of Controls (1)	Definition of Controls (1)	Comparability of cases and controls based on the design or analysis (2)	Ascertainment of exposure (1)	Same method of ascertainment for cases and controls (1)	Non-response rate (1)

Supplemental 5.4 NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE FOR CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars is possible for Comparability.

Selection

- 1) Is the case definition adequate?
 - a) yes, with independent validation *
 - b) yes, e.g., record linkage or based on self-reports
 - c) no description
- 2) Representativeness of the cases
 - a) consecutive or obviously representative series of cases *
 - b) potential for selection bias or not stated
- 3) Selection of Controls
 - a) community controls *
 - b) hospital controls
 - c) no description
- 4) Definition of Controls
 - a) no history of disease (endpoint)
 - b) no description of the source

Comparability

- 1) Comparability of cases and controls based on the design or analysis
 - a) study controls for _____ (Select the most important factor.) *
 - b) study controls for any additional factor * (This criteria could be modified to indicate a specific control for a second important factor.)

Exposure

- 1) Ascertainment of exposure
 - a) secure record (e.g., surgical records) *
 - b) structured interview where the interviewer was blinded to the case/control status *
 - c) interviewer was not blinded to the case/control status
 - d) written self-report or medical record only
 - e) no description
- 2) Same method of ascertainment for cases and controls
 - a) yes *
 - b) no
- 3) Non-response rate
 - a) same rate for both groups *
 - b) non-respondents described
 - c) rates differed and no designation was provided

Supplemental Table 6. The GRADE approach

Supplemental Table 6.1 The summary of findings table

Outcomes	Illustrates comparative risks (95% CI)		Relative effect (95% CI)	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Overall results
	Assumed risk Group 1	Corresponding risk Group 2				

Supplemental Table 6.2 GRADE evidence profile

Quality assessment							No. of patients		Effect	Quality
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Group 1	Group 2	Relative (95% CI)	
Outcome 1										
Outcome 2										
Outcome 3										
Outcome 4										

Supplemental Table 6.3 Quality of evidence grades

Grade	Definition
High	We are very confident that the true effect lies is similar to the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but it may be substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

Supplemental Table 6.4 Factors that may reduce the quality of the evidence

Factor	Consequence
Limitations in the study design or execution (risk of bias)	↓ 1 or 2 levels
Inconsistency of the results	↓ 1 or 2 levels
Indirectness of the evidence	↓ 1 or 2 levels
Imprecision	↓ 1 or 2 levels
Publication bias	↓ 1 or 2 levels

Supplemental Table 6.5 Factors that may increase the quality of the evidence

Factor	Consequence
Large magnitude of effect	↑ 1 or 2 levels
All plausible confounding factors would reduce the described effect or increase the effect if no effect was observed	↑ 1 level
Dose-response gradient	↑ 1 level

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	2
Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1

1	Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	12
2				
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5	Amendments			
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7		#4	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	2
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14	Support			
15				
16	Sources	#5a	Indicate sources of financial or other support for the review	1
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18	Sponsor	#5b	Provide name for the review funder and / or sponsor	1
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21	Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	1
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24				
25	Introduction			
26				
27	Rationale	#6	Describe the rationale for the review in the context of what is already known	5-6
28				
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30				
31	Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
32				
33				
34				
35				
36	Methods			
37				
38	Eligibility criteria	#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	7-8
39				
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43				
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45	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	6-7
46				
47				
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49				
50				
51	Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	7
52				
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54				
55				
56	Study records - data management	#11 a	Describe the mechanism(s) that will be used to manage records and data throughout the review	2, 8
57				
58				
59				
60				

1	Study records -	#11	State the process that will be used for selecting studies (such	8
2	selection process	b	as two independent reviewers) through each phase of the	
3			review (that is, screening, eligibility and inclusion in meta-	
4			analysis)	
5				
6				
7				
8	Study records -	#11	Describe planned method of extracting data from reports	8-9
9	data collection	c	(such as piloting forms, done independently, in duplicate),	
10	process		any processes for obtaining and confirming data from	
11			investigators	
12				
13				
14	Data items	#12	List and define all variables for which data will be sought	8-9
15			(such as PICO items, funding sources), any pre-planned data	
16			assumptions and simplifications	
17				
18				
19				
20	Outcomes and	#13	List and define all outcomes for which data will be sought,	8-9
21	prioritization		including prioritization of main and additional outcomes, with	
22			rationale	
23				
24				
25	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	9
26	individual studies		individual studies, including whether this will be done at the	
27			outcome or study level, or both; state how this information	
28			will be used in data synthesis	
29				
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31				
32	Data synthesis	#15	Describe criteria under which study data will be quantitatively	10
33		a	synthesised	
34				
35				
36	Data synthesis	#15	If data are appropriate for quantitative synthesis, describe	10
37		b	planned summary measures, methods of handling data and	
38			methods of combining data from studies, including any	
39			planned exploration of consistency (such as I ² , Kendall's τ)	
40				
41				
42				
43	Data synthesis	#15	Describe any proposed additional analyses (such as	10-11
44		c	sensitivity or subgroup analyses, meta-regression)	
45				
46				
47	Data synthesis	#15	If quantitative synthesis is not appropriate, describe the type	10
48		d	of summary planned	
49				
50				
51	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	10
52			publication bias across studies, selective reporting within	
53			studies)	
54				
55				
56	Confidence in	#17	Describe how the strength of the body of evidence will be	11
57	cumulative		assessed (such as GRADE)	
58	evidence			
59				
60				

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