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# Stopping feeds for prevention of transfusion-associated necrotising enterocolitis in preterm infants (Protocol)

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# Stopping feeds for prevention of transfusion-associated necrotising enterocolitis in preterm infants

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## A B S T R A C T

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

To assess the benefits and risks of stopping feed compared to continuing feed management before, during and after blood transfusion in preterm newborn infants. We also plan to assess the effects of stopping feeds versus continuing feed in the following subgroups of infants: infants of different gestations, infants with symptomatic and asymptomatic anaemia, infants who received different feeding schedule, type of feed and methods of feed delivery, infants who were transfused with different blood products, different blood volume, route of delivery, and those who received blood transfusion with and without co-interventions such as the use of diuretics.

# B A C K G R O U N D

## Description of the condition

Necrotising enterocolitis (NEC) is a serious inflammatory condition of the intestine that affects up to 10 percent of very low birth weight (VLBW) infants, leading to increased risk for mortality and significant morbidities (Stoll 2010; Yee 2012). Many factors have been associated with the occurrence of NEC but the pathogenesis has not been clearly elucidated. Transfusion-associated NEC (TANEC) is used to describe NEC episodes that are temporally related to the transfusion of packed red blood cells, typically within 48 hours after the transfusion (McGrady 1987;

Stritzke 2013). In a meta-analysis of observational studies, exposure to blood transfusion was reported to double the risk of NEC (Mohamed 2012).

The incidence of TANEC has been estimated to comprise between 20% to 35% of infants with NEC (Gephart 2012). Compared with NEC unrelated to blood transfusions, infants with TANEC were more likely to require surgical interventions, have higher mortality, and longer hospitalisations (Josephson 2010; Mohamed 2012; Paul 2011). Several mechanisms have been proposed to contribute to the development of TANEC, including severe anaemia that leads to impaired gut blood flow, exposure to immunological mediators in transfused blood that may trigger an immune reaction in gut mucosa, and ischaemia/reperfusion injury associ-

ated with blood transfusion (Blau 2011; Christensen 2010; Marin 2014).

## Description of the intervention

One intervention that has been suggested to reduce the risk of TANEC is stopping of feeds around the time of a blood transfusion (El-Dib 2011). The types of alterations to feeding during blood transfusions include the following: withholding of feeding hours before blood transfusion, during the transfusion, and after transfusion (Keir 2013). However, there are concerns that withholding of feeding during this period may result in lower caloric intake, disruption to feeding progress, and metabolic instability of the infant. Considerations in studies and protocols have also been made to alter the type of milk feed and fortifications during the period of blood transfusion (Christensen 2010; Le 2017).

## How the intervention might work

Although the pathogenesis of TANEC is not well elucidated, withholding of feeding surrounding the time of blood transfusion may decrease the additional effect of any postprandial changes in blood flow and intestine mucosal injury that occurs after feeding in the preterm infant (El-Dib 2011). In a study utilizing Doppler ultrasound, premature infants who were fed during blood transfusion were noted to lack the typical postprandial increase in blood flow of the mesenteric arteries (Krimmel 2009). Feeding surrounding blood transfusion has also been shown to exarcebate mucosal inflammation that may occur as a result of the underlying anaemia in the preterm infant (Le 2017).

## Why it is important to do this review

The potential impact of this intervention on reducing the risk of developing TANEC needs to be evaluated as VLBW infants are among the most transfused patients in hospital settings (Ekhaguere 2016; Widness 1996). There is a lack of evidence-based guidance concerning the benefits and safety of stopping feeds during blood transfusion for preterm infants, especially in relation to the risk of NEC, as no systematic review has been published on this topic to date. .

## O B J E C T I V E S

To assess the benefits and risks of stopping feed compared to continuing feed management before, during and after blood transfusion in preterm newborn infants. We also plan to assess the effects of stopping feeds versus continuing feed in the following subgroups of infants: infants of different gestations, infants with

symptomatic and asymptomatic anaemia, infants who received different feeding schedule, type of feed and methods of feed delivery, infants who were transfused with different blood products, different blood volume, route of delivery, and those who received blood transfusion with and without co-interventions such as the use of diuretics.

## M E T H O D S

## Criteria for considering studies for this review

### Types of studies

Randomised controlled trials (RCTs), cluster-RCTs, and quasi-RCTs.

### Types of participants

Preterm infants (< 37 weeks' gestation) and low birth weight infants (< 1500 g) who are receiving oral feed (any amount) and receiving transfusion of any blood product (such as whole blood, packed cells, or platelets) for any indication during their stay in the neonatal intensive care unit (NICU).
We will exclude infants receiving full or partial exchange transfusion; we believe that these infants have different levels of risk for NEC, which would be best examined is a separate review, should there be any RCT that assesses these infants. However, we consider this unlikely as the current practice is to fast the infants during these exchange transfusion procedures.

### Types of interventions

#### Intervention

- Temporary stopping of feeds before, during, or after transfusion of all blood products. In this review, we will consider the affected feeds as all feeds that would overlap with the administration of blood product should they be given as per feeding schedule. This includes any feed that is scheduled to be given before blood transfusion but would continue during transfusion, and any feed that is to be commenced as per schedule during transfusion, and to be completed either during or after transfusion.

**Control**

- Continuation of feeding as per routine schedule.

We will accept all feeding regimens as implemented by the study authors, including various feed intervals (continuous feed, hourly, once every two hours, once every three hours, or other intervals of bolus feed), types of feed (breast milk, formula milk, or mixed), methods of feed delivery (direct oral or oro/nasogastric tube feed, push or gravity feed), and ways of stopping feeds as appropriate to each feeding regimen, as long as enteral feed is suspended during the process of blood transfusion, as elaborated above.

We will also accept all blood transfusion regimen implemented by the study authors, including the following.

- Type of blood product given: packed cell or whole blood throughout all transfusion episodes or a mixture.
- Volume of blood transfused: up to 10 mL/kg or higher throughout all transfusion episodes or a mixture.
- Route of delivery: umbilical catheter, long line, or peripheral catheter throughout all transfusion episodes or a mixture.
- Presence or absence of co-intervention such as diuretic administration during blood transfusion throughout all transfusion episodes or a mixture.

### Types of outcome measures

Outcomes will be measured within 48 hours of transfusion, or when an episode of NEC occurs subsequent to transfusion, or at discharge/death.

### Primary outcomes

- Number of infants with necrotising enterocolitis (as defined by the modified Bell Stage II or III (Bell 1978), modified Bell staging system, or investigator defined variations of the Bell staging system) within 48 hours after transfusion.
- Number of infants with necrotising enterocolitis (as defined by the modified Bell Stage II or III (Bell 1978), modified Bell staging system, or investigator defined variations of the Bell staging system): any episode(s) after the first blood transfusion. We will consider infants with one or more episodes of NEC as an event.
- Mortality to 44 weeks' of postmenstrual age.

### Secondary outcomes

- Length of hospital stay (days).
- Total number of days to achieve full oral feed since commencement of oral feeding. Full oral feed is defined as defined as ingestion of all nutrient volumes in a 24-hour period without gavage (McCain 2001).
- Incidence of feed intolerance during NICU stay. Feed intolerance is defined as symptoms that arises from

gastrointestinal disturbance, such as: vomiting; diarrhoea; excessive abdominal distension or abnormal gastric aspirates that necessitates ceasing of the oral feed, or both (Young 2012).

- Growth (as defined by weight measured at a defined period in the study, e.g. at 44 weeks' of postmenstrual age; rate of weight gain (g/kg/day) or time to regain birth weight, or both).

## Search methods for identification of studies

We will follow the search strategy as used by the Cochrane Neonatal Group.

### Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, current issue).
- MEDLINE (PubMed (National Library of Medicine)) (1950 to present).
- Embase (1980 to present).
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to present).

We have outlined the detailed search strategies for each of the above databases in Appendix 1, Appendix 2, Appendix 3, and Appendix 4 respectively.

We will also search ongoing clinical trials and unpublished studies via the following websites.

- http://www.clinicaltrials.gov
- http://www.controlled-trials.com
- http://clinicalstudyresults.org

We will not apply any language restrictions.

### Searching other resources

We will search the references cited in relevant studies, Cochrane Reviews, guidelines, review articles, and conference proceedings, including abstracts from Annual Meetings of the Pediatric Academic Societies (American Pediatric Society/Society for Pediatric Research and European Society for Paediatric Research) and the Perinatal Society of Australia and New Zealand. We will also contact experts if necessary to identify further relevant studies.

## Data collection and analysis

### Selection of studies

We will employ the standard Cochrane methods, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Two review authors (NML and KTY) will independently search for relevant studies. Two review authors (JYK and KTY) will then independently screen these studies for inclusion in the review by title/abstract using the predefined inclusion and exclusion criteria. They will resolve any disagreements with the help of a third review author who will act as an arbiter (NML). We will obtain the full-text of any potentially relevant studies and assess these for inclusion.

We will include published and unpublished studies available in full-text article or abstract form. We will contact the authors of unpublished studies and studies available only as abstracts to request additional information not provided in the available reports, including details such as: methods of sequence generation, allocation and blinding, participant withdrawal and prespecified outcomes, and full outcome data. We will list any studies excluded after full-text assessment and their reason for exclusion in a 'Characteristics of excluded studies' table. We will illustrate the study selection process in a PRISMA diagram.

### Data extraction and management

Two review authors (JYK and KTY) will independently extract and code all data from each included study using a pro forma designed specifically for this Cochrane Review. We will screen for duplicate entry of participants by matching the initial number of participants recruited against the total numbers at each step in the study. If we discover a discrepancy, we will try to identify an explanation in the article, e.g. multiple enrolment of the same participants during different transfusion episodes and, if this is the case, we will exclude the study. We will contact the study authors for clarification if necessary. We will resolve any differences in our data by discussion leading to a consensus.

### Assessment of risk of bias in included studies

Two review authors (NML and JYK) will independently assess each included study for risk of bias according to the six criteria stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

- Sequence generation.
- Allocation concealment.
- Blinding.
- Incomplete outcome data.
- Selective outcome reporting.
- Other issues (e.g. extreme baseline imbalance).

We will accord a judgement of low, high, or unclear risk of bias, with justifications based on the information obtained from the papers. A detailed description on how we judge the study according to each criterion is provided in Appendix 5. We will assess the blinding of data for objective and subjective outcomes separately where possible. We will complete a 'Risk of bias' table for each eligible study and present our overall 'Risk of bias' assessment using

a 'Risk of bias' graph and 'Risk of bias' summary. Any disagreement among the review authors will be resolved by discussion to achieve a consensus.

### Measures of treatment effect

We will report the outcome estimates for categorical data using risk ratios (RRs), risk differences (RDs), the number needed to treat for an additional beneficial outcome (NNTB), and the number needed to treat for an additional harmful outcome (NNTH); for continuous data we will use weighted mean differences (WMDs) with their respective 95% confidence intervals (CIs). If pooled analyses are not possible due to reasons such as major discrepancies in study characteristics or outcome reporting, as detailed under the 'Assessment of heterogeneity' section, we will report the results of the studies individually.

### Unit of analysis issues

One unit of analysis issue that we expect is how each study handles multiple transfusion episodes in an infant. We anticipate that the individual studies may adopt one of the following two approaches.

- Randomise infants to either withholding feed or continuing feed at the first blood transfusion, and maintain the same intervention for the randomised infants at all subsequent transfusions, or
- Randomise infants to either withholding feed or continuing feed at each blood transfusion episode.

If this approach is used, each infant may have their feed withheld during one transfusion episode and continued during another transfusion episode. In this review, we will include only studies that adopt the first approach, namely, each infant receives the allocated intervention before the first transfusion, with the same intervention applied during subsequent transfusion episodes. We will exclude studies that adopt the second approach due to the likelihood of contamination secondary to period effect (withholding or continuing feed during blood transfusion may have different effect in different post-menstrual age and different stages in the infants feeding regimen) as well as carry-over effect (the effect of withholding or continuing feed may persist beyond the period of first and subsequent blood transfusion episodes), similar to the issues that may arise in a cross-over trial.

For cluster-RCTs (e.g. trials in which the assignment to intervention or control group was made at the NICU level), we will assess whether adjustment has been made for the effects of clustering in order to account for non-independence among the participants in a cluster via the use of an appropriate analysis model such as the Generalised Estimating Equation (GEE) model. If the study authors do not state the unit of analysis, we plan to inspect the width of the standard error (SE) or 95% CI of the estimated treatment effects. If we find an inappropriately small SEs or a narrow 95%

CI, we will ask the study authors to provide information on the unit of analysis.

If no adjustment is made for the effects of clustering, we will perform adjustment by multiplying the SEs of the final effect estimates by the square root of the 'design effect', represented by the formula "1 + (M-1) x ICC", where M is the average cluster size (number of infants per cluster) and ICC is the intracluster correlation. We will determine the average cluster size (M) from each trial by dividing the total number of infants by the total number of clusters. We will use a relatively large assumed ICC of 0.10 that is commonly used and is considered a realistic estimate in general (Campbell 2001). We will combine the adjusted final effect estimates from each trial with their SEs in meta-analysis using generic inverse-variance methods, as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If the determination of the unit of analysis is not possible, we will include the studies concerned in a meta-analysis using the effect estimates reported by the study authors. We will then perform a sensitivity analysis to assess how the overall results are affected by these studies.

### Dealing with missing data

If a study has a 20% or higher rate of missing data, we will judge the study as having high risk of bias for incomplete outcome data. If a study has lower than 20% missing data, we will adopt a 'worse-case scenario' approach in judging the drop-out rate. If there is an important difference in the effect estimate for the particular outcome after applying the 'worst-case scenario', e.g. markedly different effect size or a reverse of the direction of the effect, we will judge the study has having high risk of bias in incomplete outcome data. If we consider the missing data to be critical to the final estimates in our meta-analysis, we will contact the study authors for further data.

We will perform sensitivity analyses to assess how the overall results are affected by the inclusion of studies with a high risk of attrition bias from incomplete outcome data.

### Assessment of heterogeneity

We will use the $I^2$ statistic to quantify the degree of inconsistency in the results (Higgins 2011a). We will use the following cut-offs for the reporting of heterogeneity, following the Cochrane Neonatal Group's recommendations: less than 25%, negligible heterogeneity; 25% to 49%, low heterogeneity; 50% to 74%, moderate heterogeneity; and 75% or higher, high heterogeneity. If we find a moderate or high degree of heterogeneity, we will evaluate the studies in terms of their clinical and methodological characteristics using the criteria listed as follows to determine whether the degree of heterogeneity may be explained by differences in those characteristics, and whether a meta-analysis is appropriate. We will assess the following criteria.

- Characteristics of the participants (e.g. postmenstrual age, birth weight, indication for blood transfusion, type of blood product received - packed cells or whole blood).
- Clinical settings of the studies (e.g. tertiary or secondary NICU).
- Co-interventions.
- Risk of bias (as detailed in the 'Assessment of risk of bias in included studies' section).

### Assessment of reporting biases

We will use a funnel plot to screen for publication bias if there are at least 10 studies included in the analysis of the relevant outcomes. If publication bias is suggested by a significant asymmetry of the funnel plot, we will include a statement in our results with a corresponding note of caution in our discussion.

### Data synthesis

We will perform meta-analyses using a fixed-effect model in Review Manager 5 (RevMan 5) (RevMan 2014). Our primary data analyses will follow the intention-to-treat principle; namely, all infants in whom relevant outcome data are available will be analysed in the group originally allocated. We will express our results as RRs, RDs, NNTB, NNTH, and MDs with their respective 95% CIs, as detailed in the 'Measures of treatment effect' section. For cluster-RCTs, our proposed methods of analysis are detailed in the 'Unit of analysis issues' section.

### Quality of the evidence

We will assess the quality of evidence for the main comparison at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Schünemann 2013). This methodological approach considers evidence from randomised controlled trials as high quality that may be downgraded if there is at least a serious concern on each of these five areas: risk of bias, inconsistency across studies (heterogeneity), indirectness of the evidence, imprecision of estimates, and suspicion or presence of publication bias (Schünemann 2013). A serious concern on either of these areas will result in downgrading of the quality of evidence by one level, and a very serious concern will result in downgrading of the quality of evidence by two levels. We will create a 'Summary of findings' table to display with quality of the evidence for the major outcomes in this review, as detailed below, using the GRADEpro Guideline Development Tool (GRADEpro GDT 2015).

The GRADE approach results in an assessment of the quality of a body of evidence to one of four grades (Schünemann 2013).

- 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.

Each decision to downgrade the quality of evidence will be accompanied by an explanation, which we will display as a footnote in the 'Summary of findings' table.

Depending on the availability of the data, we plan to include the following outcomes into our 'Summary of findings' table: NEC (within 48 hours after transfusion), NEC (any episode), and mortality to discharge, as detailed under the 'Primary outcomes' section; and length of hospital stay, days to achieve full feed, incidence of feed intolerance, and growth, as detailed under the 'Secondary outcomes' section.

### Subgroup analysis and investigation of heterogeneity

If suitable data are available, we will explore potential sources of clinical heterogeneity through the following subgroup analyses.
- Population:
  - gestational age at enrolment (early preterm defined as < 28 completed weeks' gestation, moderate preterm (28 to 32 completed weeks' gestation) and late preterm (33 to 36 completed weeks' gestation) (Mangham 2009);
  - indications for blood transfusion: symptomatic or asymptomatic anaemia throughout all transfusion episodes, or a mixture of both;
  - feeding schedule: continuous feed, one-hourly, two-hourly, three-hourly or at other intervals, applied consistently throughout all transfusion episodes or a mixture along different transfusion episodes;
  - type of feed: breast milk, formula throughout all transfusion episodes or a mixture;
  - methods of feed delivery: oral or via naso- or orogastric tube throughout all transfusion episodes or a mixture.
- Intervention:
  - type of blood product given: packed cell or whole blood throughout all transfusion episodes or a mixture;
  - volume of blood transfused: up to 10 ml per kg or higher throughout all transfusion episodes or a mixture;
  - route of delivery: umbilical catheter, long line or peripheral catheter throughout all transfusion episodes or a mixture;
  - presence or absence of co-intervention such as diuretic administration during blood transfusion throughout all transfusion episodes or a mixture.

### Sensitivity analysis

We will perform sensitivity analyses for the primary outcomes and any secondary outcomes for which sufficient numbers of studies are available to assess the impact of excluding studies with a high risk of the following.
- Selection bias (for either criterion or both criteria of random sequence generation and allocation concealment).
- Attrition bias (incomplete outcome data).

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* *Indicates the major publication for the study*

# APPENDICES

## Appendix 1. CENTRAL search strategy

1. MeSH descriptor: [Infant, newborn] explode all trees
2. newborn*: ti,ab,kw
3. neonat*: ti,ab,tw
4. infant*: ti,ab,kw
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Transfusion, blood] explode all trees
7. transfus*: ti,ab,kw
8. #6 OR #7
9. feed*: ti,ab,kw
10. Mesh descriptor: [enteral nutrition] explode all trees
11. Mesh descriptor: [feeding behaviour] explode all trees
12. #9 OR #10 OR #11
13. #5 AND #8 AND #12

## Appendix 2. MEDLINE search strategy

1. Search "Infant, newborn"[Mesh]
2. Search newborn* [TIAB]
3. Search neonat* [TIAB]
4. Search infant* [TIAB]
5. Search #1 OR #2 OR #3 OR #4
6. Search blood transfusion [Mesh]
7. Search transfus* [TIAB]
8. Search #6 OR #7
9. Search feed* [TIAB]
10. Search enteral feeding[MeSH Terms]
11. Search feeding pattern[MeSH Terms]
12. Search #9 OR #10 OR #11
13. Search clinical trial [PT]
14. Search clinical trials [Mesh]

15. Search randomized [TIAB]
16. Search randomly [TIAB]
17. Search trial [TI]
18. Search #13 OR #14 OR #15 OR #16 OR #17
19. Search #5 AND #8 AND #12 AND #18


## Appendix 3. Embase search strategy

1. Explode: "Infant, newborn"/all subheadings
2. (newborn*) in TI, AB
3. (neonat*) in TI, AB
4. (infant*) in TI, AB
5. Search #1 OR #2 OR #3 OR #4
6. Explode "transfusion, blood"/all subheadings
7. (transfus*) in TI, AB
8. Search #6 OR #7
9. (feed*) in TI, AB
10. Explode: "enteral feeding"/all subheadings
11. Explode: "feeding pattern"/all subheadings
12. Search #9 OR #10 OR #11
13. Explode "RANDOMIZED-CONTROLLED-TRIAL"/ all subheadings
14. Explode "RANDOMIZATION"/ all subheadings
15. Explode "CONTROLLED-STUDY"/ all subheadings
16. Explode "MULTICENTER-STUDY"/ all subheadings
17. Explode "DOUBLE-BLIND-PROCEDURE"/ all subheadings
18. Explode "SINGLE-BLIND-PROCEDURE"/ all subheadings
19. (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB
20. (SINGL* or DOUBL* or TREBL* or TRIPL*) AND (BLIND* or MASK*) in TI,AB
21. Search #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20
22. Search #5 AND #8 AND #12 AND #21


## Appendix 4. CINAHL search strategy

1. MH "Infant, newborn"
2. TI newborn* or AB newborn*
3. TI neonat* or AB neonat*
4. TI infant* or AB infant*
5. #1 OR #2 OR #3 OR #4
6. MH "blood transfusion"
7. TI transfus* or AB transfus*
8. #6 OR #7
9. TI feed* or AB feed*
10. MH "feeding, enteral"
11. MH "feeding pattern"
12. #9 OR #10 OR #11
13. PT Clinical trial
14. TI randomised or AB randomised or AB random*
15. TI trial
16. MH "Clinical Trials"
17. #13 OR #14 OR #15 OR #16
18. #5 AND #8 AND #12 AND #17

## Appendix 5. 'Risk of bias' domains and judgment

| 'Risk of bias' judgement | Criteria for this judgement |
| --- | --- |
| **Random sequence generation: selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence** | |
| Low risk of bias | The investigators describe a random component in the sequence generation process such as:<br>• referring to a random number table;<br>• using a computer random number generator;<br>• coin tossing;<br>• shuffling cards or envelopes;<br>• throwing dice;<br>• drawing of lots;<br>• minimization*.<br>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random |
| High risk of bias | The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:<br>• sequence generated by odd or even date of birth;<br>• sequence generated by some rule based on date (or day) of admission;<br>• sequence generated by some rule based on hospital or clinic record number.<br>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:<br>• allocation by judgement of the clinician;<br>• allocation by preference of the participant;<br>• allocation based on the results of a laboratory test or a series of tests;<br>• allocation by availability of the intervention. |
| Unclear risk of bias | Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk' |
| **Allocation concealment: selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment** | |
| Low risk of bias | Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:<br>• central allocation (including telephone, web-based and pharmacy-controlled randomisation);<br>• sequentially numbered drug containers of identical appearance;<br>• sequentially numbered, opaque, sealed envelopes. |
| High risk of bias | Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:<br>• using an open random allocation schedule (e.g. a list of random numbers);<br>• assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);<br>• alternation or rotation;<br>• date of birth; |

*(Continued)*

| | |
|---|---|
| | • case record number;<br>• any other explicitly unconcealed procedure. |
| Unclear risk of bias | Insufficient information to permit judgement of 'low risk' or 'high risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement - e.g. if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed |

**Blinding of participants and personnel: performance bias due to knowledge of the allocated interventions by participants and personnel during the study**

| | |
|---|---|
| Low risk of bias | Any one of the following:<br>• no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;<br>• blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| High risk of bias | Any one of the following:<br>• no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;<br>• blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. |
| Unclear risk of bias | Any one of the following:<br>• insufficient information to permit judgement of 'low risk' or 'high risk';<br>• the study did not address this outcome. |

**Blinding of outcome assessment: detection bias due to knowledge of the allocated interventions by outcome assessors**

| | |
|---|---|
| Low risk of bias | Any one of the following:<br>• no blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;<br>• blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |
| High risk of bias | Any one of the following:<br>• no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;<br>• blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. |
| Unclear risk of bias | Any one of the following:<br>• insufficient information to permit judgement of 'low risk' or 'high risk';<br>• the study did not address this outcome. |

**Incomplete outcome data: attrition bias due to amount, nature or handling of incomplete outcome data**

| | |
|---|---|
| Low risk of bias | Any one of the following:<br>• no missing outcome data;<br>• reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); |

|  | • missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;<br>• for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;<br>• for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;<br>• missing data have been imputed using appropriate methods. |
|---|---|
| High risk of bias | Any one of the following:<br>• reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;<br>• for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;<br>• for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;<br>• 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;<br>• potentially inappropriate application of simple imputation. |
| Unclear risk of bias | Any one of the following:<br>• insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided);<br>• the study did not address this outcome. |

**Selective reporting: reporting bias due to selective outcome reporting**

| Low risk of bias | Any of the following:<br>• the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;<br>• the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). |
|---|---|
| High risk of bias | Any one of the following:<br>• not all of the study's pre-specified primary outcomes have been reported;<br>• one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;<br>• one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);<br>• one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;<br>• the study report fails to include results for a key outcome that would be expected to have been reported for such a study. |
| Unclear risk of bias | Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that most studies will fall into this category |

**Other bias: bias due to problems not covered elsewhere in the table**

| Low risk of bias | The study appears to be free of other sources of bias. |
|---|---|
| High risk of bias | There is at least one important risk of bias. For example, the study:<br>• had a potential source of bias related to the specific study design used; or<br>• has been claimed to have been fraudulent; or<br>• had some other problem. |
| Unclear risk of bias | There may be a risk of bias, but there is either:<br>• insufficient information to assess whether an important risk of bias exists; or<br>• insufficient rationale or evidence that an identified problem will introduce bias. |

# CONTRIBUTIONS OF AUTHORS

All authors participated in writing the protocol.

# DECLARATIONS OF INTEREST

NML has no known conflicts of interest.

AS has no known conflicts of interest.

KT has no known conflicts of interest.

KTY has no known conflicts of interest.

JYK has no known conflicts of interest.