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Early full enteral feeding for preterm or low birth weight infants (Protocol)

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[Intervention Protocol]

Early full enteral feeding for preterm or low birth weight infants

Verena Walsh[1], Jennifer Valeska Elli Brown[2], Bethany R Copperthwaite[3], Sam J Oddie[4], William McGuire[1]

[1]Centre for Reviews and Dissemination, University of York, York, UK. [2]Mental Health and Addiction Research Group, Department of Health Sciences, University of York, York, UK. [3]Hull York Medical School, York, UK. [4]Bradford Royal Infirmary, Bradford, UK

Contact address: William McGuire, Centre for Reviews and Dissemination, University of York, York, Y010 5DD, UK. william.mcguire@york.ac.uk.

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ABSTRACT

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

We aim to assess the benefits and harms of early full enteral nutrition versus progressive introduction of enteral feeds in preterm or low birth weight (LBW) infants.

Where data are available, we will undertake subgroup analyses of very preterm or very low birth weight (VLBW) infants (versus infants born after a longer gestation or with higher birth weight), infants who are 'small for gestational age' at birth (versus those deemed 'appropriate for gestation'), infants fed with human milk only (versus formula-fed infants), and trials set in low- or middle-income countries (versus high-income countries).

BACKGROUND

This Cochrane Review will appraise and synthesise data from randomised controlled trials that compared early full enteral feeding with delayed or gradual introduction of enteral feeds (combined with parenteral fluids or nutrition) for preterm or low birth weight infants.

Description of the condition

Preterm or low birth weight (LBW; less than 2500 g) infants, especially very preterm or very low birth weight (VLBW: less than 1500 g) infants, have few nutrient reserves at birth and are subject to physiological and metabolic stresses that increase their nutrient needs. Recommendations on nutrient requirements for preterm or LBW infants assume that the optimal rate of postnatal growth should be similar to that of uncompromised fetuses of an equivalent gestational age (Tsang 1993; Agostoni 2010). Such levels of nutrient input and growth are rarely achieved and most very preterm or VLBW infants accumulate nutrient deficits during their initial hospital stay (Embleton 2001; Horbar 2015). By the time they are ready to go home, many of these infants are growth restricted compared to their term-born peers (Clark 2003; Dusick 2003). Growth deficits can persist through childhood and adolescence, and are associated with adverse neurodevelopmental, cognitive, and educational outcomes (Hack 1991; Ford 2000; Cooke 2003; Doyle 2004; Farooqi 2006; Bracewell 2008; Leppänen 2014).

Necrotising enterocolitis

Necrotising enterocolitis (NEC), a syndrome of acute intestinal necrosis of unknown aetiology, affects about one-in-twenty very preterm or VLBW infants (Gagliardi 2008; Holman 1997; Moro 2009). Infants who develop NEC experience more infections, have lower levels of nutrient intake, grow more slowly, and have longer durations of intensive care and hospital stay than gestation-comparable infants who do not develop NEC (Bisquera 2002; Guthrie 2003). The associated mortality rate is greater than 20% (Fitzgibbons 2009). Compared with their peers, infants who develop NEC have a higher incidence of long-term neurological disability, which may be a consequence of infection and undernutrition during a critical period of brain development (Berrington 2012; Pike 2012; Rees 2007).

In addition to low gestational age at birth, the major risk factor for NEC is intrauterine growth restriction, especially if it is associated with absent or reversed end-diastolic flow velocities in Doppler studies of the fetal aorta or umbilical artery (Dorling 2005; Samuels 2017). Most very preterm or VLBW infants who develop NEC have received enteral milk feeds (Ramani 2013). Feeding with artificial formula rather than human milk increases the risk of developing NEC (Quigley 2019; Walsh 2019). However, the available data from randomised controlled trials do not provide evidence that delaying the introduction of progressive enteral feeds beyond four days after birth, or advancing feed volumes more slowly than 24 mL/kg/day, affects the risk of NEC and associated morbidities or mortality in very preterm or VLBW infants (Morgan 2013; Morgan 2014; Oddie 2017).

Early enteral feeding strategies

Evidence exists that early enteral feeding strategies — particularly the timing of introduction and the rate of advancement of milk feeds — affect important outcomes in preterm or LBW infants, including nutrient intake, the risk of NEC, and growth and development (Embleton 2013). Approaches to early enteral feeding vary by the gestational age and clinical condition of the infant (Hay 2008; Klingenberg 2012). Stable preterm infants born at or more than 32 weeks' gestation, or with a birth weight of 1500 g or greater, are generally treated similarly to well term infants; all fluid and nutrition is supplied enterally from birth, either orally or via an intra-gastric feeding tube. In contrast, newborn infants who are extremely preterm (born before 28 weeks' gestation) or of extremely low birth weight (ELBW; less than 1000 g) are commonly affected by respiratory distress, have delayed gastric emptying and inefficient intestinal motility, and are at high risk of developing NEC. These infants tend to be supported with parenteral fluids and nutrition during the first few days after birth. Enteral milk feeds are then introduced in sub-nutritional volumes (trophic feeds) during the first week after birth, ideally as colostrum or expressed breast milk, and the volume of feeds is increased gradually over the next one to two weeks as the volume of parenteral nutrition is decreased.

There remains substantial variation in practice with regard to early enteral feeding strategies for those preterm infants born at gestations between approximately 28 and 32 weeks (or with birth weights between approximately 1000 g and 1500 g). This variation reflects ongoing uncertainty about whether these infants should be treated in the same way as those infants born at a later gestation (that is, with full enteral feeds from birth), or more similarly to extremely preterm or ELBW infants (that is, delayed introduction and gradual advancement of milk feeds while supporting nutritional needs with parenteral nutrition). In many high-income countries, policy and practice has tended to favour the conservative approach to introducing and advancing enteral feeds for these infants because of concerns that early full enteral feeding might increase the risk of feed intolerance, gastro-oesophageal reflux and aspiration of stomach contents, hypoglycaemia, and NEC in very preterm or VLBW infants (Maas 2018; Klingenberg 2012; Leaf 2013; de Waard 2018). However, in low- and middle-income countries with fewer resources for neonatal care, practice is more pragmatic and tends to favour early introduction and advancement of enteral feeds (sometimes facilitated by "kangaroo" mother care) for stable infants born at 28 weeks' gestation or greater, or with a birth weight of 1000 g or more (Sankar 2008; Conde-Agudelo 2016).

Description of the intervention

Early (sometimes termed "immediate") full enteral feeding means that newborn infants receive all of their prescribed nutrition as milk feeds (either human milk or formula) and do not receive any supplemental parenteral fluids or nutrition from birth (Nangia 2018). This approach for feeding preterm infants has been advocated since the earliest days of modern neonatology but has tended to be reserved for clinically stable preterm infants of gestational age at birth of more than approximately 32 weeks (Smallpeice 1964; Klingenberg 2012). In most neonatal care facilities, particularly in high-income countries, the more common practice is to introduce enteral milk feeds for very preterm or VLBW infants at low volume (trophic feeds or minimal enteral nutrition) and to then advance the feed volume slowly during the next one to two weeks. During this time, infants receive most of their fluids and nutrition parenterally, usually in the form of

commercially-available solutions containing amino acids, glucose, minerals, vitamins, and fats (Klingenberg 2012).

There are potential disadvantages associated with conservative enteral feeding regimens (Flidel-Rimon 2004; Flidel-Rimon 2006). Because gastrointestinal hormone secretion and motility are stimulated by milk feeds, delaying full enteral feeding may diminish the functional adaptation of the gastrointestinal tract and disrupt the patterns of microbial colonisation (Embleton 2017). Intestinal dysmotility and dysbiosis might exacerbate feed intolerance and delay the establishment of enteral feeding independently of parenteral nutrition (Pammi 2017). Prolonging the duration of parenteral nutrition is associated with infectious and metabolic complications that increase mortality and morbidity, prolong hospital stay, and adversely affect growth and development (Embleton 2013). Due to cost and equipment implications, parenteral nutrition is less easily available in low- and middle-income countries. In high-income settings, earlier achievement of full enteral feeds and an associated reduction of length of hospital stay could be associated with considerable resource savings (Embleton 2014).

How the intervention might work

The aims of early full enteral feeding are to avoid the risks and costs associated with provision of parenteral nutrition and to accelerate gastrointestinal physiological, endocrine and metabolic maturity and so allow infants to attain nutrient intakes to optimise growth and development. Early full enteral feeding in this vulnerable population might reduce the risk of infection associated with intravascular devices used to deliver parenteral nutrition (Flidel-Rimon 2004). Early provision of breast milk might promote successful expression and lactation and help establish maternal breast milk feeding as the primary source of infant nutrition (Hay 2008; Senterre 2014). However, there is some concern that exclusive enteral nutrition might not be sufficient to maintain normal blood glucose levels during the early metabolic transition phase in very preterm or VLBW infants, particularly in growth-restricted infants with limited nutrient reserves at birth (Klingenberg 2012). Furthermore, any beneficial effects may be negated if early full enteral feeding increases the risk of feed intolerance or NEC in very preterm or VLBW infants (Chauhan 2008; Samuels 2017).

Why it is important to do this review

This review is the first to focus on the comparison of early full enteral feeding versus gradual introduction of progressive enteral feeding in combination with parenteral fluids. Other Cochrane Reviews have addressed the questions of whether delaying the introduction of any enteral milk feeding or restricting feed volumes to trophic levels (minimal enteral nutrition) affect the risk of NEC in very preterm or VLBW infants (Morgan 2013; Morgan 2014). The findings of this review will complement these existing reviews of early enteral feeding strategies and might inform policy, practice, or research in this field (Chauhan 2008).

OBJECTIVES

We aim to assess the benefits and harms of early full enteral nutrition versus progressive introduction of enteral feeds in preterm or low birth weight (LBW) infants.

Where data are available, we will undertake subgroup analyses of very preterm or very low birth weight (VLBW) infants (versus infants born after a longer gestation or with higher birth weight), infants who are 'small for gestational age' at birth (versus those deemed 'appropriate for gestation'), infants fed with human milk only (versus formula-fed infants), and trials set in low- or middle-income countries (versus high-income countries).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials, including cluster-randomised controlled trials.

Types of participants

Infants that are preterm (born at less than 37 weeks' gestation) or low birth weight (less than 2500 g).

Types of interventions

Intervention: full enteral feeds from birth without parenteral fluids or nutrition. Early full enteral nutrition will be defined as sufficient volumes of milk being fed orally or via a naso- or oro-enteric feeding tube from soon after birth, without parenteral supplementation at any point.

Comparison: any other feeding regimen, such as delayed initiation of full milk feeds and gradual advancement of feed volumes while receiving supplemental fluid or nutrients parenterally.

Types of outcome measures

Primary outcomes

1. In hospital rate of weight gain (g/kg/day) until term equivalent
2. In hospital rate of head circumference growth (cm/week) until term equivalent
3. Growth restriction: z-score and proportion of infants who remain below the 10th percentile for the index population distribution of weight at term equivalent
4. Necrotising enterocolitis, confirmed at surgery or autopsy or diagnosed by at least two of the following clinical features (Kliegman 1987)
   a. Abdominal radiograph showing pneumatosis intestinalis or gas in the portal venous system or free air in the abdomen
   b. Abdominal distension with abdominal radiograph with gaseous distension or frothy appearance (or both) of bowel lumen
   c. Blood in stool
   d. Lethargy, hypotonia or apnoea (or combination of these)

Secondary outcomes

1. Feed intolerance during the trial intervention period that results in cessation in enteral feeding for more than four hours
2. Episodes of hypoglycaemia (investigator defined) requiring treatment with enteral supplement (including milk feed or buccal dextrose gel) or with intravenous fluids (including dextrose solution)
3. Invasive infection, as determined by culture of bacteria or fungus from blood, cerebrospinal fluid, or from a normally sterile body space
4. Duration of birth hospitalisation (days)

5. All-cause mortality up to 36 to 44 weeks' post-menstrual age and one year post-term
6. Growth parameters assessed beyond infancy: weight, height or head circumference and proportion of infants who remain below the 10th percentile for the index population's distribution, and measures of body composition (lean/fat mass) and body mass index
7. Severe neurodevelopmental disability, assessed beyond infancy until adulthood: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean and blindness (visual acuity less than 6/60) or deafness (any hearing impairment requiring or unimproved by amplification)

Search methods for identification of studies

We will use the standard search strategy of Cochrane Neonatal.

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL; 2019, current issue), MEDLINE Ovid (1946 to date), Embase Ovid (1974 to present), Maternity & Infant Care Database Ovid (1971 to present), and the Cumulative Index to Nursing and Allied Health Literature (1982 to present), using a combination of text words and MeSH terms, as described in Appendix 1. We will limit the search outputs with the relevant search filters for clinical trials as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will not apply any language restrictions.

We will search ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform (www.who.int/ictrp/en/), for completed or ongoing trials.

Searching other resources

We will examine the reference lists of studies identified as potentially relevant. We will search the abstracts from annual meetings of the Pediatric Academic Societies (1993 to 2019), the European Society for Paediatric Research (1995 to 2019), the UK Royal College of Paediatrics and Child Health (2000 to 2019) and the Perinatal Society of Australia and New Zealand (2000 to 2019). We will consider trials reported only as abstracts to be eligible if sufficient information is available from the report, or from contact with study authors, to fulfil the inclusion criteria (see Dealing with missing data for further details).

Data collection and analysis

We will use the standard methods of Cochrane Neonatal.

Selection of studies

Two review authors (JB, BC, or VW) will independently screen the titles and abstracts of all studies and assess the full articles of all potentially relevant trials. We will exclude those studies that do not meet all of the inclusion criteria and we will state the reason(s) for exclusion. We will discuss any disagreements until consensus is achieved, with referral to WM for a final decision as necessary.

Data extraction and management

Two review authors (JB, BC, or VW) will use a form to independently extract data on design, methodology, participants, interventions, outcomes and treatment effects from each included study. We will discuss any disagreements until we reach a consensus. The data extraction form will be based on forms used previously by the author team, with adaptations made to meet the requirements of this review.

Assessment of risk of bias in included studies

Two review authors (JB, BC, or VW) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017); see Appendix 2 for details.

We will resolve disagreements by discussion or by including WM for final decisions. We will not exclude trials on the basis of risk of bias, but we will conduct sensitivity analyses, if applicable, to explore the consequences of synthesising evidence of variable quality.

Measures of treatment effect

We will analyse the treatment effects in the individual trials and report the risk ratio (RR) and risk difference (RD) for dichotomous data and the mean difference (MD) for continuous data, with 95% confidence intervals (CIs). We will determine the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) for analyses with a statistically significant difference in the RD.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomised trials and the neonatal unit (or sub-unit) for cluster-randomised trials.

For cluster-randomised trials, we will undertake analyses at the level of the individual while accounting for clustering in the data using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

Where data are missing without explanation, and cannot be derived as described above, we will approach the analysis as follows.

1. Where we have concerns about the extent of missing data or potential bias in missing data, we will contact the original study investigators to request the missing data for primary outcomes only, for studies published within the past 10 years where an email address is easily available from the published papers.
2. Where possible, we will impute missing standard deviations (SDs) using the coefficient of variation (CV), or calculate this from other available statistics including standard errors, confidence intervals, t values and P values.
3. If the data are assumed to be missing at random, we will analyse the data without imputing any missing values.
4. If data cannot be assumed to be missing at random then we will impute the missing outcomes with replacement values, assuming all to have a poor outcome, and conduct sensitivity analyses to assess any changes in the direction or magnitude of effect resulting from data imputation.

Assessment of heterogeneity

Two review authors (JB, VW, or WM) will assess clinical heterogeneity, and a meta-analysis will only be conducted when

both authors agree that study participants, interventions and outcomes are sufficiently similar.

We will examine the treatment effects of individual trials and heterogeneity between trial results by inspecting the forest plots. We will calculate the I^2 statistic for each analysis to quantify inconsistency across studies and describe the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. If we detect high levels of heterogeneity (an I^2 value greater than 75%), we will explore the possible sources (for example, differences in study design, participants, interventions or completeness of outcome assessments).

Assessment of reporting biases

If more than 10 trials are included in a meta-analysis, we will examine a funnel plot for asymmetry.

Data synthesis

We will use the fixed-effect model in Review Manager 5 for meta-analyses (Review Manager 2014).

Certainty of evidence

We will assess the certainty of the body of evidence for the main comparisons at the outcomes level using GRADE methods (Schünemann 2013). Two review authors (JVEB and WM) will independently assess the certainty of the evidence for the pre-specified primary outcomes (Primary outcomes). We will consider evidence from randomised controlled trials as high-certainty but will downgrade the evidence by one level for serious (or two levels for very serious) limitations based upon: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. The GRADE approach results in an assessment of the certainty of the evidence in one of the following four grades, which we will present in a 'Summary of findings' table, using GRADEpro GDT.

1. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate certainty: 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.
3. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
4. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Where data are available, we will undertake the following subgroup analyses for the primary outcomes.

1. Trials in which infants received human milk only (maternal expressed breast milk or donor breast milk) versus those where formula could be given instead of or as a supplement to human milk
2. Very preterm infants (born at less than 32 weeks' gestation) versus infants born at 32 weeks' gestation or greater
3. Very low birth weight infants (less than 1500 g) versus infants with a birth weight of 1500 g or greater
4. Infants with a birth weight below the 10th percentile for the reference population ('small for gestation') versus infants with a birth weight at or above the 10th percentile ('appropriate for gestation')
5. Trials set in low- or middle-income countries versus trials set in high-income countries (for classification, see datahelpdesk.worldbank.org/knowledgebase/articles/906519#High_income (accessed 18th April 2019))

Sensitivity analysis

We will undertake sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (low risk of bias), defined as those studies with adequate randomisation and allocation concealment, blinding of intervention and measurement, and less than 10% loss to follow-up.

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APPENDICES

Appendix 1. Electronic search strategy

Indicative strategy developed and tested for Ovid MEDLINE(R) ALL <1946 to 7 March 07, 2019>

[To be adapted for Embase, Maternity & Infant Care Database (MIDIRS), and CINAHL Plus]

Search Strategy:

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1 exp Infant, Newborn/ (579674)
2 Premature Birth/ (11867)
3 (neonat$ or neo nat$).ti,ab. (245905)
4 (newborn$ or new born$ or newly born$).ti,ab. (157152)
5 (preterm or preterms or pre term or pre terms).ti,ab. (67629)
6 (preemie$ or premie or premies).ti,ab. (157)

7 (prematur$ adj3 (birth$ or born or deliver$)).ti,ab. (14688)
8 (low adj3 (birthweight$ or birth weight$)).ti,ab. (32259)
9 (lbw or vlbw or elbw).ti,ab. (7686)
10 infan$.ti,ab. (409955)
11 (baby or babies).ti,ab. (65499)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (998371)

13 Enteral Nutrition/ (18635)
14 (enteral adj2 (nutrition or feed$)).ti,ab. (12909)
15 ((oral or sip or tube) adj2 feeding$).ti,ab. (9343)
16 ((nasogastric or gastrostomy or jejunostomy) adj2 tube$).ti,ab. (7950)
17 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteral feed$).ti,ab. (1497)
18 ((advanc$ or aggressive$ or delay$ or early or fast or full or increas$ or minimal or progress$ or prolonged or rapid$ or routine$ or speed $ or slow$ or volume$) adj3 enteral nutrition).ti,ab. (1297)
19 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 feed$).ti,ab. (2638)
20 ((aggressive$ or fast or rapid$ or slow$ or speed$) adj3 volume$).ti,ab. (3589)
21 trophic feeding$.ti,ab. (85)
22 ((gut or gastrointestinal) adj2 priming).ti,ab. (30)
23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (40147)

24 12 and 23 (6420)

25 Parenteral Nutrition/ae [Adverse Effects] (2675)
26 Enterocolitis, Necrotizing/ep, et, pc [Epidemiology, Etiology, Prevention & Control] (1434)
27 ((prevent$ or risk$) adj3 necrotising enterocolitis).ti,ab. (118)
28 ((prevent$ or risk$) adj3 necrotizing enterocolitis).ti,ab. (527)
29 Infection/ep [Epidemiology] (3709)
30 25 or 26 or 27 or 28 or 29 (8110)

31 12 and 30 (2962)

32 24 or 31 (8867)

33 randomized controlled trial.pt. (477193)
34 controlled clinical trial.pt. (92945)
35 randomized.ab. (436251)
36 placebo.ab. (195836)
37 drug therapy.fs. (2088187)
38 randomly.ab. (306614)
39 trial.ab. (455752)
40 groups.ab. (1887119)
41 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (4389362)
42 exp animals/ not humans.sh. (4554122)
43 41 not 42 (3795778)

44 32 and 43 (2483)

Appendix 2. 'Risk of bias' tool

1. Random sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or classes of outcomes. We will categorise the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or classes of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion (where reported), and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we will explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

All authors contributed to developing the protocol.

DECLARATIONS OF INTEREST

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VW: none known
BC: none known
SO: Dr Oddie is co Chief Investigator of the PREVAIL trial, funded by the UK NIHR HTA to conduct a trial in this area.
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