Home parenteral nutrition for people with inoperable malignant bowel obstruction (Protocol)

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Home parenteral nutrition for people with inoperable malignant bowel obstruction

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ABSTRACT

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

To assess the effectiveness and safety of home parenteral nutrition in people with inoperable malignant bowel obstruction.

BACKGROUND

Description of the condition

Malignant bowel obstruction (MBO) is caused by mechanical, vascular or neurological dysfunction of the small or large bowel (Anthony 2007; Ripamonti 2008). Patients with MBO experience symptoms such as nausea, vomiting, abdominal distention and pain (Mercadante 1995).

MBO occurs most often in people who have ovarian and gastrointestinal cancers. There is a wide variation in quoted incidence rates of MBO as data has been drawn from small retrospective and autopsy studies, with reported rates varying between 5% to 51% in people with ovarian cancer and 10% to 28% in people with gastrointestinal cancer (Cousins 2016). Other cancers that have been associated with MBO include bladder (3% to 10%) and endometrial (3% to 11%) cancer, as well as metastases from breast cancer and melanoma (Ferguson 2015).

The role of surgery in people with MBO remains contested, but some patients may have disease that is amenable to surgical treatment on first presentation (Cousins 2016; Daniele 2015). However, people who experience subsequent occurrences of MBO are unlikely to benefit from further surgery, at which point they are deemed to have inoperable MBO (Naghibi 2015). These patients can be managed medically using corticosteroids, antiemetics and antisecretory agents (Ferguson 2015). For patients with uncontrolled vomiting, a venting gastrostomy tube may be considered (Brett 1986). People with inoperable MBO are unable to maintain adequate oral intake and may require parenteral nutrition.
Description of the intervention

Parenteral nutrition is the provision of macronutrient, micronutrient and fluid infused as an intravenous solution directly into the venous system. Patients are assessed to calculate their energy, nutrient and fluid requirements. Daily caloric intake is partitioned between protein, carbohydrate and fat; electrolytes, vitamins and occasionally medication will then be added to the solution (Bielawska 2017). This solution is usually administrated to a patient overnight, cycled between 10 to 15 hours, depending on total volume and patient tolerance (Wanten 2011). Short-term parenteral nutrition may be initially administrated via a peripheral or central vein. However, patients generally require delivery of nutrition into a central vein, and also home parenteral nutrition must be delivered by a central venous catheter (Pittiruti 2009). Thus, this Cochrane Review will focus on such nutritional support.

How the intervention might work

In parenteral nutrition, nutrients and fluids are delivered to patients via the venous route. Patients with MBO are unable to tolerate limited, if any, enteral nutrition and thus are unable to meet their nutritional requirements orally. Parenteral nutrition therefore provides a method for these patients to receive nutrients that otherwise would be inaccessible to them. Parenteral nutrition may improve survival (Brard 2006); median survival in people with MBO who receive parenteral nutrition is around 80 days (Abu-Rustum 1997; Naghibi 2015). The treatment may also improve quality of life (QoL) and there have been reports improvement of symptoms after starting parenteral nutrition (Mercadante 1995).

Why it is important to do this review

Parenteral nutrition in people undergoing palliative care is somewhat controversial. There is a fundamental human right to food, which has been recognised by the United Nations (UN) (UN 1948). However, there are clinical, ethical and legal issues for and against the administration of parenteral nutrition, related to both what the patient wants and what is supported by clinical evidence. There is some evidence of benefit in terms of survival, but the treatment is costly to the healthcare provider and burdensome for patients (Abu-Rustum 1997; Brard 2006; DiBaise 2007; Hoda 2005; Naghibi 2015; Pasanisi 2001). There is a lack of consensus on the role of parenteral nutrition in this patient group which is reflected in varying rates worldwide of cancer as the reason for parenteral nutrition (Howard 1995; Smith 2011). In the USA, people with cancer account for 42% of the patients who receive home parenteral nutrition (Dibb 2013). In Europe as a whole this is 39% (Bakker 1999), whereas in the UK cancer is the primary reason for home parenteral nutrition in less than 15% of cases (Smith 2011). This Cochrane Review will examine the potential benefits and disadvantages of parenteral nutrition for people with cancer. We will focus on benefits, such as survival or QoL or both, and disadvantages, which will include any adverse events that result from the treatment. If there is insufficient data to comment on these issues, we will provide suggestions for future research.

OBJECTIVES

To assess the effectiveness and safety of home parenteral nutrition in people with inoperable malignant bowel obstruction.

METHODS

Criteria for considering studies for this review

Types of studies

Quantitative

As we do not envisage that we will identify any randomised controlled trials (RCTs), we will include non-randomised studies including quasi-RCTs, non-randomised controlled trials, prospective and retrospective cohort studies and case series of more than five participants. However, we will exclude case series with less than five participants.

Qualitative

We will include any qualitative studies (phenomenological, ethnographic or grounded theory) that use recognised methods of qualitative data collection (interview, observation, focus group) and analysis.

Types of participants

Inclusion criteria

To be included participants must fulfil each of the following criteria:

- People over 16 years of age with inoperable bowel obstruction caused by malignancy.
- Receiving central parenteral nutrition.
- Receiving or planned to receive parenteral nutrition at home.
- No curative treatment: we will deem any chemotherapy or radiotherapy in these people as palliative.
Exclusion criteria

- Bowel obstruction caused by pseudomyxoma peritonei and desmoid tumours as these tumours are slow growing and patients have more favourable survival.
- Receiving peripheral parenteral nutrition.
- Studies with < 70% patients receiving parenteral nutrition for inoperable bowel obstruction, unless we can extract data on MBO patients.

If it is unclear whether the patients meet the inclusion criteria based on the published data, we will contact the study authors for further information. If we are still unable to establish if the study meets the criteria, then we will exclude it.

Types of interventions

**Intervention**
- Treatment with parenteral nutrition delivered through a central line.

**Control**
- No parenteral nutritional support.
- Other nutritional interventions, such as elemental diet or intravenous fluids alone.

Types of outcome measures

**Primary outcomes**
- Length of survival from diagnosis of bowel obstruction or, if not given, implementation of parenteral nutrition.
- QoL: any measure of QoL completed by patients, carers or an independent rater. However, we will give preference to validated questionnaires, e.g. the European Organisation for Research and Treatment of Cancer QoL Questionnaire (EORTC QLQ-C30).

**Secondary outcomes**
- Measurement of gastrointestinal symptoms e.g. nausea, vomiting, distention, diarrhoea, pain on eating using a validated questionnaire or recorded in a dichotomous form i.e. present/absent.
- Any measure of nutritional status, such as anthropometry. However, we will give preference to validated measures e.g. subjective global assessment.
- Qualitative reports of QoL or symptoms.
- Where multiple time points are recorded, we will give priority to baseline, three month and six month observations.
- Adverse events: line sepsis/hospitalisation due to nutritional support/fluid overload (to include peripheral oedema or ascites), either present or absent.
- Adverse events if they occur at any time point during the administration of parenteral nutrition.
- Health economic outcomes: cost of treatment, any measurement of cost effectiveness of treatment such as quality adjusted life year.

Search methods for identification of studies

**Electronic searches**

We will identify relevant studies by conducting searches of electronic databases, including Ovid MEDLINE, Embase, BNI, CINAHL, Web of Science and NHS Economic Evaluation and Health Technology Assessment. We will conduct searches to incorporate both qualitative and quantitative search terms. We will search for relevant RCTs on the Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue). We will search for any currently recruiting trials in ClinicalTrials.gov (http://clinicaltrials.gov/) and in the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/).

The detailed search strategy for MEDLINE is in Appendix 1. We will amend the search strategy as necessary for searching other databases.

**Searching other resources**

We will handsearch any selected articles to identify any other relevant articles. We will also find all included articles on PubMed and search for other pertinent articles using the ‘related articles’ feature.

Data collection and analysis

We will follow the guidance of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will conduct the analyses using Review Manager 5 (RevMan 5) (RevMan 2014) and SPSS (version 23) (IBM corp 2015), if appropriate.

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to EndNote and we will remove duplicates. Two review authors (AMS and another author: ES, SL, GJ, AC or JS) will independently examine the remaining references. We will exclude those studies that clearly do not meet the inclusion criteria, and will obtain copies of the full-text of potentially relevant articles.
references. Independently, two review authors (AMS and another review author: ES, SL, GJ, AC, CT or JS) will assess the eligibility of the retrieved reports/publications. We will resolve any disagreement through discussion or, if required, we will consult a third review author (SB). We will identify and exclude duplicate reports and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and a 'Characteristics of excluded studies' table (Liberati 2009).

**Data extraction and management**

Two review authors (AMS and another author: ES, AMR, RB, GJ, AC, AT, CT or JS) will independently extract study characteristics and outcome data from included studies using a piloted data collection form. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (SB). One review author (JS) will transfer data to the RevMan 5 file (RevMan 2014). We will double-check that data has been entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (AMS) will 'spot-check' the accuracy of the study characteristics against the trial report.

For included studies, we will extract the following data.

- **Author, year of publication and journal citation (including language).**
- **Country.**
- **Setting.**
- **Inclusion and exclusion criteria.**
- **Study design, methodology.**
- **Source of funding.**
- **Study population:**
  - total number enrolled;
  - age;
  - co-morbidities;
  - performance status at diagnosis of MBO;
  - cancer diagnosis including, if indicated, staging, number and sites of metastasis and treatments received;
  - any data on confounding factors which may improve patient's symptoms of MBO such as administration of steroids, antisecretory medication or prokinetics.
- **Intervention details:**
  - any details of nutrition received: parenteral nutrition nutritional content, number of times given in a week, reason for parenteral nutrition (fluid replacement or nutritional needs or both) and whether any other oral intake is recorded;
  - Primary outcomes and Secondary outcomes as detailed above.
- **Comparison:**
  - whether any oral intake is recorded or intravenous fluids administered;
  - Primary outcomes and Secondary outcomes as detailed above.

- **Risk of bias in study** (see Assessment of risk of bias in included studies section below).
- **Duration of follow-up.**
- **We will note the time points at which outcomes were collected and reported.**

We will extract results as follows.

- For time-to-event data (e.g. survival), we will extract the log of the hazard ratio [log(HR)] and its standard error (SE) from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its SE using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. gastrointestinal symptoms) we will extract the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed at endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. QoL measures), we will extract the final value and standard deviation (SD) of the outcome of interest and the number of participants assessed at endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) between treatment arms and its SE.

**Assessment of risk of bias in included studies**

We will assess and report on the methodological risk of bias of included studies in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011), which recommends the explicit reporting of the following individual elements for RCTs.

- **Selection bias:** random sequence generation and allocation concealment.
- **Performance bias:** blinding of participants and personnel.
- **Detection bias:** blinding of outcome assessment.
- **Attrition bias:** incomplete outcome data, which is less than 80% reported for primary outcomes.
- **Reporting bias:** selective reporting of outcomes.
- **Other:** any other risk of bias.

Two review authors (AMS and another: ES, AMR, RB, GJ, AC, AT, CT or JS) will independently apply the 'Risk of bias' tool and resolve differences by discussion or by appeal to a third review author (SB). We will judge each item as being at either high, low or unclear risk of bias as set out in Higgins 2011, and we will provide a quote from the study report or a statement, or both, as justification for the judgement for each item in the 'Risk of bias' table. We will summarise results in a 'Risk of bias' graph and a 'Risk of bias' summary. When interpreting treatment effects and meta-analyses, we will take into account the risk of bias for the
studies that contribute to that outcome. Where information on risk of bias relates to unpublished data or from correspondence with a trial author, we will note this in the ‘Risk of bias’ table. We will assess the risk of bias in non-randomised controlled trials in accordance with the additional criteria below.

- Details of criteria for assignment of participants to treatments:
  - low risk of bias: yes.
  - high risk of bias: no.
  - unclear risk of bias: if no details provided.
- Comparability of treatment groups: no differences between the two groups or differences controlled for, in particular with reference to age, performance status at diagnosis of MBO, cancer diagnosis, stage, grade, metastasis:
  - low risk of bias: if at least two of these characteristics were reported and any reported differences were controlled for.
  - high risk of bias: if the two groups differed and differences were not controlled for.
  - unclear risk of bias: if fewer than two of these characteristics were reported even if there were no other differences between the groups, and other characteristics had been controlled for.

We define the following endpoints as subjective outcomes: QoL. We define the following endpoints as objective outcomes: survival and adverse events (hospitalisation due to parenteral nutrition).

### Measuring the effect of treatment

We will use the following measures of the effect of treatment.

- For time-to-event data, we will use the hazard ratio (HR), if possible.
- For dichotomous outcomes, we will analyse data based on the number of events and the number of patients assessed in the intervention and comparison groups. We will use these to calculate the RR and 95% confidence interval (CI).
- For continuous outcomes, we will analyse data based on the mean, SD and number of patients assessed for both the intervention and comparison groups to calculate MD between treatment arms with a 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in RevMan 5 (RevMan 2014).

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. We will describe skewed data that are reported as medians and interquartile ranges narratively.

### Unit of analysis issues

We will use participants as the unit of analysis. In case of repeated measurements, we will record data at 1 month, 3 months and 6 months.

### Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome or summary data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise we will analyse data as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias. For missing outcome or summary data, we will not impute missing data and we will report any assumptions in the review.

### Assessment of heterogeneity

Where we consider studies similar enough based on consideration of primary cancer to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots, by estimation of the percentage heterogeneity ($I^2$ statistic) between trials which cannot be ascribed to sampling variation (Higgins 2003), by a formal statistical test of the significance of the heterogeneity ($\chi^2$ test) (Deeks 2001). We will regard heterogeneity to be substantial if the $I^2$ statistic value is greater than 30% and either the $T^2$ value is greater than zero, or there is a low P value (< 0.10) in the $\chi^2$ test for heterogeneity. If there is evidence of substantial clinical, methodological or statistical heterogeneity across included studies, we will not pool results for meta-analysis but instead will use a narrative approach to our data synthesis. In this event, we will investigate and report the possible clinical or methodological reasons for this level of heterogeneity.

### Assessment of reporting biases

If we identify a sufficient number of trials for inclusion, we will explore potential publication bias using a funnel plot (Higgins 2011).

### Data synthesis

#### Quantitative synthesis

If a sufficient number of clinically similar studies (in terms of primary cancer diagnosis) are available to ensure meaningful conclusions, and if statistical heterogeneity is low ($I^2$ statistic < 30%), we will pool their results in meta-analyses using the fixed-effect model in RevMan 5 (RevMan 2014). If there is variability in the primary
cancer diagnosis of included studies, or if statistical heterogeneity is substantial ($I^2$ statistic $> 30$%), we will use the random-effects model with inverse variance for meta-analysis (DerSimonian 1986). We will only include non-randomised studies with two or more comparison groups if statistical adjustments are made for baseline imbalances.

- For time-to-event data, we will pool HRs using the generic inverse variance facility in RevMan 5 (RevMan 2014).
- For any dichotomous outcomes, we will calculate the RR for each study and we will then pool these.
- For continuous outcomes, we will pool the MD between the treatment arms at the end of follow-up, if all trials measure the outcome on the same scale; otherwise we will pool SMD values.

If we are unable to pool the data statistically using meta-analysis, we will conduct a narrative synthesis of the results. We will present the major outcomes and results, organised by whether the patients received parenteral nutrition or not.

**Qualitative synthesis**

We will undertake a meta-synthesis to identify key themes in the data. We will then summarise these themes to give an overview of the key points in the qualitative studies. We will note any comments regarding implications for practice in a table.

**Subgroup analysis and investigation of heterogeneity**

We will perform subgroup analyses, if sufficient data is available to explore the effects of parenteral nutrition in different types of cancers.

**Sensitivity analysis**

If sufficient numbers of studies meet the inclusion criteria of the review, we will undertake a sensitivity analysis to determine if the findings are altered by excluding trials of high risk of bias as determined by Cochrane 'Risk of bias' tool (Higgins 2011). For qualitative studies, we will assess whether any one article is adding disproportionately to the findings.

**Summary of findings' table**

To interpret the findings and to rate the quality of the evidence, two review authors (AMS and either ES, AMR, RB, GJ, AC, AT or JS) will use the GRADE approach (Guyatt 2011) and the guidelines provided in Chapter 12.2 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann 2011). First, we will analyse the overall quality of evidence for each outcome individually, downgrading the evidence from 'high quality' to 'moderate', 'low' or 'very low' depending on the risk of bias, indirectness of evidence, inconsistency, imprecision of effect estimates or potential publication bias. Afterwards, we will take into account this analysis to draft the review conclusions. We will use the GRADEpro GDT software to produce a 'Summary of findings' table with the results of this analysis (GRADEpro 2015). We will consider the following outcomes:

- Survival.
- QoL measured on a validated questionnaire.
- Hospitalisation due to parenteral nutrition adverse events.

If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table format, such as that used by Chan 2011. A template 'Summary of findings' tables is in Table 1.

**Acknowledgements**

We thank Jo Morrison for clinical and editorial advice; and Gail Quinn, Clare Jess and Tracey Harrison for their contributions to the editorial process. Also we are grateful to Jo Platt for designing and executing the search strategy.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancers Group. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, the NIHR, the NHS or the Department of Health.

We thank the referees for many helpful suggestions and comments, including Kathie Godfrey.
Additional references

Abu-Rustum 1997

Anthony 2007

Bakker 1999

Bielawska 2017

Brard 2006

Brett 1986

Chan 2011

Cousins 2016

Daniele 2015

Deeks 2001

DerSimonian 1986

DiBaise 2007

Dibb 2013

Ferguson 2015

GRADEpro 2015 [Computer program]

Guyatt 2011

Higgins 2003

Higgins 2011

Hoda 2005

Howard 1995

IBM corp 2015 [Computer program]

References
Table 1. Summary of findings table

**Parenteral nutrition compared with no parenteral nutrition for inoperable malignant bowel obstruction (MBO)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Number of participants (studies)</th>
<th>Relative effect</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
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<tr>
<td><strong>Illustrative comparative risks</strong></td>
<td>(95% CI)</td>
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<tr>
<td><strong>Assumed risk</strong></td>
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<tr>
<td><strong>Corresponding risk</strong></td>
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<tr>
<td>[experimental]</td>
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</tbody>
</table>

*Indicates the major publication for the study*
### Table 1. Summary of findings table (Continued)

| Survival | | | | | |
| --- | --- | --- | --- | --- | |
| Very low | Moderate | High | |
| Quality of life | | | | | |
| Very low | Moderate | High | |
| Adverse events: hospitalisation due to parenteral nutrition | | | | | |
| Very low | Moderate | High | |

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**Abbreviations:** CI: confidence interval; RR: risk ratio

**GRADE Working Group grades of evidence**

- **High quality:** further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very low quality:** we are very uncertain about the estimate.
Appendix 1. MEDLINE search strategy

1. Neoplasms/
2. (neoplasm* or tumor* or tumour* or cancer* or malignan* or carcinoma* or adenocarcinoma* or carcinosarcoma* or sarcoma*).mp.
3. 1 or 2
4. exp Intestinal Obstruction/
5. ((bowel* or intestin* or gastrointestin* or gastro-intestin* or colon* or colorect* or retrosigmoid*) adj3 (obstruct* or occlu* or fail* or block* or adhes*)).mp.
6. 4 or 5
7. 3 and 6
8. exp Parenteral Nutrition/
9. (total parenteral nutrition* or TPN* or parenteral nutrition* or PN*).mp.
10. ((parenteral* or artificial* or tub* or catheter* or intraven* or IV* or subcutan* or bypass*) adj3 (nutri* or hydration* or feed* or fcd* or treatment* or manag* or method* or car* or support* or diet*)).mp.
11. (home adj3 parenteral*).mp.
12. 8 or 9 or 10 or 11
13. 7 and 12

Key
mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier
pt=publication type
ab=abstract
ti=title
sh=subject heading

WHAT'S NEW

<table>
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<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>28 September 2017</td>
<td>Amended</td>
<td>Author list amended</td>
</tr>
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</table>

CONTRIBUTIONS OF AUTHORS

SB, SL, CT will provide a methodological perspective.
SL, GJ, AC, RB, AT, AMR will provide a clinical perspective:
AMS, SB, GJ have written the protocol
All authors have commented on the protocol.
SB, SL, CT, AC, RB secured funding for the review.
DECLARATIONS OF INTEREST

Anne Marie Sowerbutts: none known
Simon Lal: none known
Andrew Clamp: none known
Chris Todd: none known
Gordon Jayson: none known
Antje Teubner: none known
Anne Marie Raftery: none known
Eileen J Sutton: none known
Jana Sremanakova: none known
Richard Berman: none known
Sorrel Burden: none known

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