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Outcome reporting in randomized controlled trials and systematic reviews of gastroschisis treatment: a systematic review☆,☆☆,★

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ABSTRACT

Background: Core outcome sets (COS) facilitate clinical research by providing an agreed set of outcomes to be measured when evaluating treatment efficacy. Gastroschisis is increasing in frequency and evidence-based treatments are lacking. We aimed to identify initial candidate outcomes for a gastroschisis COS from existing literature.
Methods: Using a sensitive search strategy we identified randomized controlled trials (RCTs) and systematic reviews (SRs) of treatment interventions for gastroschisis. Outcomes were extracted and assigned to the core areas, 'Pathophysiological Manifestations', 'Life Impact', 'Resource Use', 'Adverse Events' and 'Mortality'.
Results: A total of 50 outcomes were identified. RCTs reported 6–9 outcomes each; SRs reported 9–25. The most frequently reported outcomes were 'Length of hospital stay' (reported in 8 studies), 'Duration of ventilation' and 'Time to full enteral feeds' (7 studies). Outcomes identified could be assigned to all five core areas.
Conclusions: There is wide heterogeneity in outcomes reported in studies evaluating treatment interventions for gastroschisis. It is unclear which outcomes are of highest importance across stakeholder groups. Developing a COS to standardize outcome measurement and reporting for gastroschisis is warranted.

Which outcomes are the most important to measure when assessing treatment interventions for infants born with gastroschisis?

As the incidence of gastroschisis continues to increase, so does the need to develop novel treatments and techniques to improve outcome by reducing morbidity, length of stay and treatment costs. For a complex condition such as gastroschisis, there are many candidate outcomes that could be used to assess treatment approaches. These include (among others) duration of ventilation, number of surgical interventions with/without general anesthesia, duration of dependency on parenteral nutrition (PN), and length of inpatient stay. With the exception of mortality, it is unclear which outcomes are the most important to measure when assessing the efficacy of any treatment intervention. Assessing the correct outcomes is important since this determines how the results of research are interpreted by clinicians when they choose how to treat patients under their care. Furthermore when designing efficacy studies it is important that outcomes of importance to patients (and in pediatric conditions, their families) are measured in addition to those of clinicians and researchers. Doing so will likely enhance parental engagement with novel therapies and will help to ensure that the full effects of treatments are not overlooked.

The most notable change in the past 15 years in the treatment of infants with gastroschisis has been the introduction of the preformed silo (PFS) to facilitate abdominal wall closure. The only randomized controlled trial (RCT) to have reported comparative outcomes between infants treated with a PFS and those who had primary abdominal wall closure under general anesthesia selected number of days on a mechanical ventilator as a primary outcome [1]. Secondary outcomes reported were duration of PN, days in hospital, intraabdominal pressure, incidence of positive blood culture, incidence of necrotising enterocolitis (NEC). Which of these outcomes is most important to clinicians and parents is not known.

Core outcomes sets (COS) have been proposed as a means of improving outcome reporting in efficacy studies [2,3]. A COS is an established set of outcomes to be measured when evaluating treatment efficacy for a given condition. The adoption of a COS will ensure that a standardized set of outcome measures is reported as a minimum for a given treatment or pathology thereby minimizing the heterogeneity in outcome reporting between studies. This will likely ensure that outcomes reported are relevant and of importance to multiple stakeholder groups (e.g. researchers, clinicians, patients/parents, treatment commissioners) and improve comparability between studies in quantitative

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data synthesis such as meta-analysis. No COS for gastroschisis exists. We intend to develop a COS for treatment interventions for gastroschisis to improve the quality of outcome research. As the first stage of this process we undertook the current study in which we identified outcomes of treatment interventions aimed at improving outcomes for infants born with gastroschisis, that are important to researchers and clinicians, from the existing literature.

1. Materials and methods

This study was completed in accordance with the PRISMA guidelines for systematic reviews, [4], following a defined protocol and registered with the COMET (Core Outcome Measures in Effectiveness Trials) initiative, (29/06/2015, http://www.comet-initiative.org/studies/details/746) [5]. We performed a systematic review of the existing literature to identify RCTs and SRs relating to treatment interventions for gastroschisis. From these studies we identified outcome(s) reported, the frequency with which they were reported and the provision of definitions of outcomes. Outcomes were then assigned to core areas using the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Filter 2.0, [6].

1.1. Systematic review search strategy

We searched MEDLINE (1946–1st May 2015), the Cochrane Database of Systematic Reviews (CDSR) (to 1st May 2015) and the Cochrane Central Register of Controlled Trials (CENTRAL, 1991–1st May 2015) using the search terms 'gastroschisis', 'trial' and 'systematic review'. No language or date restrictions were applied during the database search. Full details of the search strategy for Medline are available in Appendix A.

1.2. Study selection criteria

Studies were selected for inclusion according to the following predefined criteria.

Types of studies: Systematic reviews of RCTs with or without meta-analysis, and RCTs.

Types of intervention: Any therapeutic intervention given to mother or infant as management aimed to improve outcomes in the infant affected by gastroschisis.

Types of participants: Infants with gastroschisis and mothers of an unborn fetus with gastroschisis.

Exclusion criteria: Studies with no comparator, studies that included other abdominal wall defects and studies written in languages other than English were excluded.

Studies were therefore included in this review if they were a RCT or SR that compared treatment interventions aimed at improving outcomes of infants with gastroschisis. Studies originating from a non-developed country or not in English were excluded at study selection stage as were non-randomized comparison studies.

The results of the search strategy were independently reviewed by two researchers. Articles were assessed initially by title and abstract. Full-texts of articles were retrieved if either reviewer considered the citation potentially relevant with a low threshold for retrieval. Full-texts were then assessed for eligibility. The bibliographies of studies included for full-text review were also evaluated for additional relevant references. The final set of studies included was arrived at by consensus between reviewers.

1.3. Data extraction

Data were extracted independently by each reviewer. The primary (if defined) and other outcome measures reported in each study were extracted in duplicate and compared. Definitions of outcomes were included when reported. Data were extracted as follows: study type (RCT/SR), sample size, intervention/comparator, use and definition of primary outcome, all outcomes reported and definitions if included. An outcome was considered to have been reported if it was included in the methods section, results section, or both. A study was deemed to use a primary outcome if the words 'primary outcome' were stated in the report, if data for a particular outcome were used to generate a sample size for a study, or if the stated aim of a study was to investigate the effect of an intervention on a single specific outcome or single defined composite outcome.

We anticipated some diversity in terminology used to report outcomes and therefore grouped similar outcomes. We identified outcomes that seemed similar or of a similar theme despite differing definitions used across studies and assigned an appropriate term to them. For instance, the outcomes 'proven catheter-related sepsis (line positive blood cultures necessitating antibiotic treatment or catheter removal)' and 'central line infections' were included in the term 'central venous catheter sepsis'.

1.4. Assignment of outcomes to core areas

Each of the outcomes identified was assigned to a core area according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Filter 2.0, [6]. The OMERACT initiative aims to enhance outcome reporting in RCTs by ensuring that a full breadth of outcomes are included during development of a COS. The OMERACT Filter 2.0 includes the core areas 'Mortality', 'Pathophysiological Manifestations', 'Life Impact' and 'Resource Use'. An additional core area of 'Adverse Events' was also used for assignment of outcomes.

1.5. Data synthesis

The total number of studies identified and included, and number of different outcomes identified in included studies were counted. The number of outcomes reported by each study, and variations in definition for each outcome were identified. We identified the number of outcome terms assigned to each core area and the number of core areas covered by each included study. Data are reported descriptively with appropriate summary measures for non-parametric data. Since we did not capture quantitative outcome data from individual studies, instead reporting only which outcomes were selected and reported, assessment of heterogeneity between studies formally using an I^2 statistic or similar was not appropriate.

2. Results

A flow diagram summarizing article selection is shown in Fig. 1. A total of eight articles met the inclusion criteria and all were included. These included three RCTs and five systematic reviews, [1,7–13]. Data from a total of 4398 infants were included. Characteristics of the included studies are shown in Table 1.

A total of 50 distinct outcomes were identified. RCTs reported 6–9 outcomes each; SRs reported 9–25. All the included RCTs and three of the five SRs nominated a primary outcome. The most frequently reported outcome was 'Length of hospital stay' which was reported in all 8 studies. The next most commonly reported were 'Duration of ventilation' and 'Time to full enteral feeds' (7 studies each) and 'Duration of PN', 'NEC' and 'Mortality' (6 studies each). A full description of the outcomes reported in each study is shown in Fig. 2.

Across all included studies only three of the fifty outcomes had any definition provided. 'Time to full enteral feeds' (TTFF) was defined in four studies although three different definitions were used. Line sepsis was defined by one of the two studies that reported it and 'Intra-abdominal pressure' was defined in the single study that reported it, [1]. Variations in definitions used are shown in Table 2.

All of the included studies reported outcomes that could be assigned to the core areas 'Adverse Events', 'Pathophysiological Manifestation'