Outcome reporting in randomised 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 randomised 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 standardise outcome measurement and reporting for gastroschisis is warranted.

**Keywords:** congenital abnormality; paediatric surgery; evidence based medicine; outcomes research; neonatology

**1. Introduction:**

Which outcome measures 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 which could be used to assess treatment approaches. These include (amongst others) duration of ventilation, number of surgical interventions with/without general anaesthesia, 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 paediatric 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 randomised controlled trial (RCT) to have reported comparative outcomes between infants treated with a PFS and those who had primary abdominal wall closure under general anaesthesia selkected number of days on a mechanical ventilator as a primary outcome [1]. Secondary outcomes reported were duration of PN, days in hospital, intra-abdominal 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 standardised set of outcome measures is reported as a minimum for a given treatment or pathology thereby minimising 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 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.

**2. 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].

**2.1 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 1.

**2.2 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-randomised 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.

**2.3 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’.

**2.4 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.

**2.5 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 I2 statistic or similar was not appropriate.

**3. Results**

A flow diagram summarising article selection is shown in Figure 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 Figure 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’ and ‘Resource Use’. Six studies reported ‘Mortality’[8–13] , while only two reported outcomes relating to ‘Life impact’,[9,10]. Only two studies,[9,10] reported outcomes assigned to all five core areas, four studies reported outcomes relating to four core areas,[8,11–13] and two studies,[1, 7] reported outcomes relating to only three of the core areas.

**4. Discussion**

As the initial stage of developing a core outcome set for treatment interventions for gastroschisis we have performed a systematic review of the existing literature with the aim of identifying outcomes reported in studies comparing two or more treatment interventions. We limited our review to existing RCTs or SRs (with or without meta-analysis) since we anticipated that these highest quality studies would have paid the greatest attention to selecting outcomes in their design. Only eight studies were eligible for inclusion, reflecting the paucity of high quality evidence to support current treatments for gastroschisis. The key findings of our review are a wide variation in outcome reporting between studies, a lack of definition for the majority of the outcomes reported and a paucity of outcomes reported within the core area of ‘Life impact’.

**4.1 Variation of OM reporting**

Overall 50 distinct outcomes were identified, with each individual study reporting between 6 and 25. This heterogeneity may reflect the quality of the existing data in this field; few RCTs have been completed, and the majority of reports relating to gastroschisis are of less robust methodology. Only ‘Length of Stay’ was reported consistently across all of the included studies. Other outcomes were inconsistently reported across studies and we found 36 outcomes that were each reported only by a single study.

During study design it is likely that researchers select a primary outcome that represents the outcome they consider to be of greatest importance to researchers and clinicians. Other outcomes offering a lesser influence on treatment selection but which are nonetheless important are likely included as secondary outcomes. A primary outcome was nominated in six of the eight included studies, (Figure 2). Our study suggests that ‘Time to full enteral feeds’ (designated as a primary outcome in three studies and included in seven studies overall) and ‘Duration of ventiliation’ (designated as a primary outcome in two studies and included in seven studies) are outcomes deemed to be of greatest importance by researchers on the basis of frequency of selection. ‘Length of hospital stay’ although included as a primary outcome in only one study, was the only outcome reported in all the included studies. ‘Mortality’ features in most but not all studies (primary outcome in two studies, included in six) but it is not universally reported. This may reflect the reduction in infant mortality in gastroschisis such that survival is now expected in 95% of cases,[14]. However, the wide range of outcomes reported (n=50) and the limited consistency between studies both suggest that in many cases clinicians and researchers remain unclear which outcomes should be reported in treatment interventions for gastroschisis. This underpins the need to develop a COS.

**4.2 Outcome definition**

In these ‘highest level of evidence’ studies, definitions for outcomes were rarely used. Of the 50 outcomes identified, only three had definitions provided. ‘Time to full enteral feeds’, one of the most commonly used outcomes, had three distinct definitions used in the four papers that provided a definition. None of these definitions were complete and unambiguous. For example, for ‘Time to full enteral feeds’, the starting time for each definition is unclear – is it birth, time of abdominal wall closure, time at which feeds were started or another arbitrary timepoint? This lack of detail and the overall lack of definition across all outcomes create methodological inconsistencies that affect the validity of conclusions. These inconsistencies become of greater importance when data from multiple studies are combined (for example in meta-analysis). The use of standardised, agreed definitions for all but the most unambiguous outcomes would improve the transparency of research findings and reduce methodological inconsistencies across research. The development of definitions for outcomes is an important component of COS development.

**4.3 Assignment of outcomes to core areas**

All included studies reported outcomes that were assigned to the OMERACT core areas of ‘Resource use’, ‘Pathophysiological manifestation’ and ‘Adverse events’. This is not an unexpected finding: these domains inform clinicians about the safety and efficacy of an intervention while guiding provision of resources. However, only two studies reported outcomes that could be assigned to the ‘Life Impact’ core area,[9,10]. The paucity of outcome reporting within the ‘Life Impact’ core area is likely a reflection that the included studies were designed to address questions identified only by clinicians and researchers. One possible reason for this is a lack of patient / parent involvement in designing studies. The lack of patient or parental involvement in defining important outcomes for any condition is widely recognised,[15]. In development of a COS it is essential that the views of multiple stakeholder groups (clinicians, surgeons, patients, parents) are included so that the COS reflects a broad spectrum of views.

**4.4 Developing a Core Outcome Set**

The development of a COS will overcome the limitations we have identified in the existing literature. By developing a range of relevant and important outcomes agreed by consensus across multiple stakeholder groups we hope to enable more robust and meaningful assessment of treatment interventions for this condition. The correct use of a COS by individual studies will subsequently facilitate accurate comparison of interventions across multiple RCTs. Importantly in developing the COS we will involve patients and parents in the identification and selection of relevant and important outcomes for inclusion. Only by including these stakeholders in all stages of the COS development process can we be certain that the COS reflects the views of those stakeholders on whom research will inevitably impact. Previous studies have highlighted the importance of engaging with patients and parents in the COS development process and the pitfalls that may result from their exclusion The COS will, for the first time, identify which outcomes of treatment interventions for gastroschisis are prioritised by multiple stakeholder groups, as well as associated definitions and how they should be measured. This will not only enhance clinicans’ ability to make informed treatment decisions but will also help to ensure that research is more meaningful to our patients and their parents.

The principal limitation to this study is that we have selected only RCTs and SRs for review. As a result, it is possible that we have not identified outcomes that have been reported in other types of studies of infants with gastroschisis using alternate methodology. We justify the use of only RCTs and SRs since we believe authors of these types of studies are most likely to have paid the greatest attention to the outcomes they have selected on the basis of their importance and relevance to informing future treatment decisions. In designing a RCT/SR researchers are required to consider, select and justify both primary and secondary outcomes. We acknowledge that this may be considered an assumption but we believe it to be correct and appropriate. It is possible that other outcomes have been reported in the wider literature relating to gastroschisis but we believe through focussing on RCTs and SRs we will have identified those of greatest interest and importance to researchers. The wide range of outcomes we have identified and their contribution to all OMERACT core areas suggests that our approach is unlikely to have missed important outcomes that are only reported otside of RCTs and SRs. At the time of COS creation the process of outcome selection will address the issue of any ‘missed’ outcomes as the other stakeholders perspectives, not included here, will be sought.

**5. Conclusion**

Great heterogeneity exists in the outcomes currently reported when comparing treatment interventions for infants with gastroschisis. Whilst we have identified outcomes that appear to be of greatest importance to clinicians and researchers, it is unclear which outcomes are of highest importance to other stakeholder groups such as patients and parents. Furthermore, we have identified a lack of definitions for existing outcomes. Efforts to develop a core outcome set by identification of relevant and important well defined outcomes across multiple stakeholder groups are warranted. Such a COS would greatly improve the quality of clinical research for gastroschisis.

Figure legends

**Figure 1. PRISMA Flowchart of article selection**

**Figure 2. Matrix of outcomes reported by each study (Black box with X = Primary outcome, Grey box = Secondary outcome). \* - Mortality**

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**Appendix 1 - MEDLINE Search strategy**

Database: Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations < May 2015>

Search Strategy:

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* 1. Gastroschisis/ (1925)
	2. ("gastroschisis"[MeSH Terms] OR "gastroschisis"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "systematic review"[All Fields]) (179)
	3. ("gastroschisis"[MeSH Terms] OR "gastroschisis"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]) (52)
	4. ("gastroschisis"[MeSH Terms] OR "gastroschisis"[All Fields]) AND ("meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]) (14)
	5. ("gastroschisis"[MeSH Terms] OR "gastroschisis"[All Fields]) AND ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] ("gastroschisis"[MeSH Terms] OR "gastroschisis"[All Fields]) AND ("review"[Publication Type] OR "review literature as topic"[MeSH Terms] OR "review"[All Fields]) (8)
	6. or/1-5