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Outcome reporting across randomised trials and observational studies evaluating treatments for Twin-Twin Transfusion Syndrome: a systematic review.

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ABSTRACT

Background: Twin-Twin Transfusion syndrome is associated with significant mortality and morbidity. Potential treatments require robust evaluation. The aim of this study was to evaluate outcome reporting across observational studies and randomised controlled trials assessing treatments for twin–twin transfusion syndrome (TTTS).

Methods: Cochrane Central Register of Controlled Trials, EMBASE and Medline were searched from inception to August 2016. Observational studies and randomised controlled trials reporting outcomes following a treatment for TTTS in monochorionic-diamniotic twin pregnancies and monochorionic-triamniotic or dichorionic-triamniotic triplet pregnancies were included. We systematically extracted and categorised outcome reporting.

Results: Six randomised trials and 94 observational studies, reporting data from 20,071 maternal participants and 3,199 children, were included. Six different treatments were evaluated. Included studies reported sixty-two different outcomes, including 10 fetal, 28 neonatal, 6 early childhood and 18 maternal outcomes. The outcomes were inconsistently reported across trials. For example, when considering offspring mortality, 31 studies (31%) reported live birth, 31 studies (31%) reported intrauterine death, 49 studies (49%) reported neonatal mortality, and 17 studies (17%) reported perinatal mortality. Four studies (4%) reported respiratory distress syndrome. Only 19 (19%) of studies were designed for long-term follow-up and 11 of these studies (11%) reported cerebral palsy.

Conclusions: Most studies evaluating treatments for TTTS, have often neglected to report clinically important outcomes, especially neonatal morbidity outcomes. Most studies are not

designed for long-term follow-up. The development of a core outcome set could help standardised outcome collection and reporting in Twin-Twin Transfusion syndrome studies.

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INTRODUCTION

Twin-Twin Transfusion Syndrome (TTTS) is a unique pathology exclusive to monochorionic twin pregnancies whereby unbalanced transfusion across the placental vascular anastomoses leads to amniotic fluid volume imbalance between the twins. In severe TTTS the mortality rate is as high as 90% if untreated.[2, 3] Even with treatment, TTTS is still associated with an increased risk of perinatal mortality and morbidity compared to uncomplicated monochorionic pregnancies, with neurological and cardiac complications reported, as well as a significant risk of preterm birth and its associated complications.[2-8]

The treatment options include fetoscopic laser surgery, amnioreduction, septostomy, expectant management and termination of pregnancy. Fetoscopic laser surgery now forms the mainstay of treatment and different techniques have also been compared.[9] Given the high potential for morbidity and mortality in TTTS, there is a need for robust guidance on the safest course of management, particularly in the refinement of new treatment techniques.

The importance of standardising randomised controlled trial methods has been recognised. However, the selection, collection, and reporting of outcomes has received less attention, despite it being a critical step in the design of randomised trials.[10] Such outcomes should reflect both beneficial and harmful effects and need to be relevant to clinical practice and key stakeholders, including patients, healthcare professionals, and researchers. Evidence synthesis can be further hampered by different methods of measurement or definition, even when outcomes have been consistently collected across trials. For example, childhood neurodevelopmental impairment has been defined using different combinations of clinical

signs and cognitive assessments, performed with a range of tools, by different professionals and at different childhood ages.

There is no consensus amongst key stakeholders on which outcomes should be collected and reported in studies of TTTS treatments. The first step in developing a core outcome set for TTTS requires an evaluation of the reporting of outcomes and outcome measures. The objective of the present study was therefore to assess the consistency of outcome reporting, including the adequacy of information pertaining to definition and measurement, among randomized trials and observational studies evaluating treatments for TTTS.

METHODS

Protocol, eligibility criteria, information sources and search

The protocol for this systematic review was registered prospectively on PROSPERO (International Prospective Register of Systematic Reviews); registration number: CRD42016043999.[11] We have followed the reporting guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12]

We searched Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Medline from inception to August 2016 using MeSH descriptors including "twin-twin transfusion syndrome", "twin-to-twin transfusion syndrome" and "fetofetal transfusion" (Supplementary Table 1). We included all randomised trials and observational studies reporting outcomes following a treatment for TTTS in monochorionic-diamniotic twin pregnancies and monochorionic-triamniotic and dichorionic-triamniotic triplet pregnancies.

We excluded case reports, review articles, meta-analysis, and systematic reviews. We applied no restriction for language or publication date and translated articles where necessary.

Study selection, data collection and data items

Two authors (HP and OU) independently screened all titles and abstracts in the search results. Studies were excluded if they did not fit the eligibility criteria and full texts were obtained for studies that were obviously eligible and those that could not be excluded based on title and abstract alone. These full text articles were critically reviewed for eligibility by two authors and any discrepancies were discussed and resolved with a third author.

Data was extracted from the eligible studies using a standardised data collection tool. Variables collected included year of publication, publishing journal, study design, setting, participants, treatments, stage of TTTS and the funding source (if applicable) for the study. The impact factor was obtained from the International Scientific Institute's Impact Factor List. A quality assessment was performed for each study. For randomised trials we used the Jadad scoring system and for observational studies we used the Newcastle-Ottawa scoring system.[13,14] The size of the study was classified on either maternal or childhood participants, depending on the subject of the study. Due to the large number of relatively small single-centre retrospective observational studies, we decided to include all randomised controlled trials and the largest 94 observational studies in the analysis. After full text review, we did not feel that including more studies would add to the variety of outcomes recorded.

Primary and secondary outcomes were recorded as well as their definition and instruments of measure. We considered and included outcomes listed as 'variables collected' if they were clearly documented in the abstract or methods section and reported in the results section. We did not include outcomes listed for the first time in the results section without any clear justification. An inventory of outcomes was produced and these were organised into the following categories: fetal outcomes, offspring mortality, neonatal outcomes, early childhood outcomes, maternal outcomes and operative complications.

RESULTS

Study selection and characteristics

The search identified 1,209 articles. Forty-six duplicates were removed and 898 articles were considered not to meet inclusion criteria after title and abstract screening. Duplicates were defined as articles with the same title, authors and publishing journal and year. Of the 898 articles that did not meet inclusion criteria 387 were unrelated to TTTS, 483 were not an intervention study (e.g. review, comment, case report) and in 28 cases the narrative did not fit the inclusion criteria (e.g. the paper did not report a discernible outcome). Two hundred and sixty-five articles were identified for full text review. Of these, 35 were further excluded as they either did not meet inclusion criteria (n=32) or full text could not be obtained (n=3). Two hundred and thirty studies were therefore deemed eligible after full text review and all

randomised trials (n=6) [9,15-19] and the largest observational studies (n=94)[20-113] were selected for analysis (Figure 1). There were 13 case-control studies, 32 prospective cohort studies and 49 retrospective cohort studies. The included 100 studies reported data from 20,071 maternal participants and 3199 children.

Synthesis of the results

Six different treatments were evaluated; fetoscopic laser surgery (95 studies; 95%), amnioreduction (15 studies; 15%), septostomy (1 study; 1%), expectant management (5 studies; 5%), selective feticide (2 studies; 2%), and delivery (1 study; 1%). Eighty of the studies evaluated fetoscopic laser surgery alone, with three of these studies comparing different techniques of fetoscopic laser surgery; two studies compared the Solomon technique to the standard technique and one study compared different uterine entry techniques (sheath and trocar, cannula and trocar or cannula and Seldinger). Three studies evaluated adjuncts to fetoscopic laser surgery, including Nifedipine therapy, cervical cerclage and laparoscopic guidance, a single study evaluated amnioreduction alone and the remaining 16 studies compared two or more treatments with one of these studies including the adjunct of Digoxin therapy to amnioreduction. Full details of the studies and their treatments are shown in Table 1.

Included trials reported 62 different outcomes, organised within six domains: six fetal outcomes, seven offspring mortality outcomes, 25 neonatal outcomes, six early childhood outcomes, eight maternal outcomes and 10 operative outcomes (Table 2). Regarding quality assessment, two of the randomised trials scored four out of five on the Jadad score and the remainder scored three out of five. None of them involved blinding due to the nature of the

treatments. Of the observational studies, only seven studies scored eight stars out of nine, nine studies scored seven stars, 38 score six stars, 30 scored six stars and ten scored four stars (Table 1).

Concerning fetal outcomes, only 17 studies (17%) reported recurrence of TTTS (4206 participants; 21.0%) and other fetal outcomes were even less reported. Offspring mortality was the most reported group, however there was inconsistency in the reported outcomes. Thirty-one studies (31%) reported live birth (5219 participants, 26%), 31 (31%) reported intrauterine death (6376 participants; 31.8%), 49 (49%) reported neonatal mortality (8216 participants; 41%) and 17 (17%) reported perinatal mortality (3172 participants; 15.8%). Neonatal morbidity was reported with varying frequency with 33 studies (33%) reporting gestational age at delivery (reporting data from 5583 participants; 27.8%), 16 studies (16%) reporting intraventricular haemorrhage (reporting data from 3430 participants; 17.1%), six studies (6%) reporting necrotising enterocolitis (1023 participants; 5.1%) and four studies (4%) reporting respiratory distress syndrome (reporting data from 620 participants; 3.1%). Childhood outcomes were not commonly reported with only 19 studies reporting on outcomes beyond the neonatal period. Of these, 13 studies (13%) reported neurodevelopmental impairment and 11 studies (11%) reported cerebral palsy (1868 (9.3%) and 1459 (7.3%) participants, respectively).

The most commonly reported maternal outcome was premature rupture of membranes which was reported by 31 studies (31%) (6057 participants; 30.2%). Operative complications were poorly reported with only six studies (6%) reporting haemorrhage (914 participants; 4.6%) and one (1%) study reporting pain (175 participants; 0.9%). The full range of

outcomes reported is shown in Table 3. When considering the five randomised controlled trials and the 20 largest observational studies, 50% reported neonatal mortality, 30% reported premature rupture of the membranes and 15% reported on neurodevelopmental impairment in childhood (Table 4).

There was variation of the definitions of reported outcomes. For neonatal mortality/survival, five different definitions were found, but in 47% of studies where neonatal mortality/survival was reported as an outcome, no definition was given. Seven different definitions were identified for premature rupture of membranes and eight for childhood neurodevelopmental impairment. The full range of variation is demonstrated in Table 5.

DISCUSSION

Summary of main findings

We have found wide variation and inconsistencies in the reporting of maternal and offspring outcomes. Of six randomised controlled trials and 94 observational studies, reporting data from 20,071 maternal participants, less than a third reported live birth or intrauterine death as an outcome. Whilst 49% of studies reported neonatal mortality/survival as an outcome, there were five different definitions of this and almost half of these studies did not define this outcome. Neonatal morbidity was poorly reported with only four studies reporting respiratory distress syndrome, a common morbidity associated with prematurity, as an outcome. Only 19 studies were designed for follow-up beyond the neonatal period and 13 of these reported on childhood neurological outcome. Despite the mainstay of treatments for TTTS being surgical, maternal and operative outcomes were not commonly reported, with haemorrhage only reported by 6% of studies and pain by 1%.

Strengths and Limitations

The strengths of this study are in its robust methodology. Following prospective registration, with pre-determined outcomes, an independent search was performed without limits on date or language and we translated articles where necessary, to be as inclusive as possible. Study selection and data extraction was performed independently by two authors to limit bias.

This study is limited in its ability to garner patient-important outcomes, which may not be best evaluated from randomised controlled trials or observational studies. Further qualitative research, such as structured interview-based studies, is required to overcome this. To

further reduce bias in the review process, we could have blinded the reviewers to details of the articles, such as authors, year of publication and publication journal. By limiting the final analysis to the randomised trials and 94 largest observational studies we may have missed out on outcomes reported by the smaller studies, which were not reported by larger studies. However, with the inclusion of 62 outcomes across seven domains, we feel this review is reflective of current studies of treatment for TTTS. Our study may underestimate consistency in outcome reporting due to our methodology of reporting all studies singularly even if they were from the same centre. It is possible that different publications were used to report different outcomes from the same centres. Similarly, by only including outcomes and recorded variables clearly defined in the abstract and methods section, we may have under-reported some outcomes if they were only mentioned for the first time in the results section. Our rationale for this is that any outcomes that the researchers planned to report would normally be outlined in advance. We had a consistent approach to all studies reviewed and feel we have highlighted that different studies prioritise different outcomes resulting in wide variation in outcome reporting.

Interpretation of findings

Our search only identified six randomised controlled trials reporting outcomes after treatment for TTTS, reflecting the fact that due to the relatively low prevalence of this condition, it is difficult to perform large, good quality trials. With this in mind, it is of paramount importance that any studies that are undertaken collect data on relevant outcomes which can be interpreted in relation to existing literature and results can be easily compared.[114] Previous studies have also found variation and inconsistency in the reporting of outcomes in different areas of women's health including preeclampsia, preterm birth, and endometriosis.[115-119]

One possible reason for this diversity in outcome reporting in TTTS is the emergence of a leading new treatment (fetoscopic laser surgery) over the last 20 years. As the risk of fetal mortality in TTTS is so high, pioneers of this treatment primarily focused on survival to birth as an outcome, with less regard to other outcomes that may be considered important by stakeholders. The fact that many different centres were publishing their results independently as relatively small observational studies probably compounded this effect.

With improving rates of survival to birth, there is now increased interest in the neonatal and longer term morbidity for surviving children and with any treatment for a fetal disease, consideration should also be given to the effects on the mother. This systematic review highlights that to date, these outcomes have not been consistently reported with only 19 of the 100 studies designed to obtain outcomes beyond the neonatal period. We feel that any centre performing treatment for TTTS should have access to neonatal outcomes, yet with the exception of neonatal mortality, these were not commonly reported. Outcomes such as necrotising enterocolitis are likely to be considered important by parents. This issue is not unique to TTTS; in a systematic review of outcome reporting in preterm birth, only one (1%) randomised trial reported composite morbidity in the neonatal period or at follow-up and none reported on maternal morbidity and mortality. Similarly, in a systematic review of outcome reporting in preeclampsia, the authors found that only 6 (7.6%) of randomised trials reported childhood outcomes. [115,116] Bias may be introduced in the selection of primary outcomes in the first place, as researchers are influenced by factors including sample size requirement, time until an outcome can be reported and cost. This can lead to more accessible but less informative outcomes being selected.[120]

The Core Outcomes in Women's and Newborn Health (CROWN) initiative aims to facilitate consistent recording and reporting of outcomes by working closely with journals, researchers, funders and patients to develop core outcome sets for specific diseases.[121, 122] Several core outcome sets are in development across obstetrics including for: gastroschisis, fetal monitoring and stillbirth.[123] The Core Outcome Measures in Effectiveness Trials (COMET) Initiative suggests three stages to developing a core outcome set: (1) identifying potential core outcomes; (2) determining core outcomes using robust consensus methods engaging key stakeholders; and (3) determining how core outcomes should be measured.[124] In line with the CROWN and COMET initiatives, we have previously described our intention to develop a core outcome set for TTTS and the inventory of outcomes identified by this systematic review will be entered into a Delphi Method for the second stage of the process. Key stakeholders including researchers, clinicians and patients will be invited to participate in this consensus-forming exercise.[125] This process has worked successfully in the development of core outcome sets for other related conditions, including abortion, pre-eclampsia, neonatal care, and endometriosis.[126-129] For example, regarding preterm birth, 174 participants from five stakeholder groups reviewed and scored 31 outcomes via Delphi survey. The final core outcome set consisted of 13 outcomes on which consensus was met.[130]

Conclusion

Most studies reporting outcomes following treatment for TTTS are observational in nature and report many different outcomes, with varying definitions. These inconsistencies contribute to an inability to compare, contrast, and combine results and inform decision

making in a clinical context. Developing a clinically relevant core dataset for implementation in future TTTS trials could help to address these issues.

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Figure Legend:

Figure 1: Flow of Studies

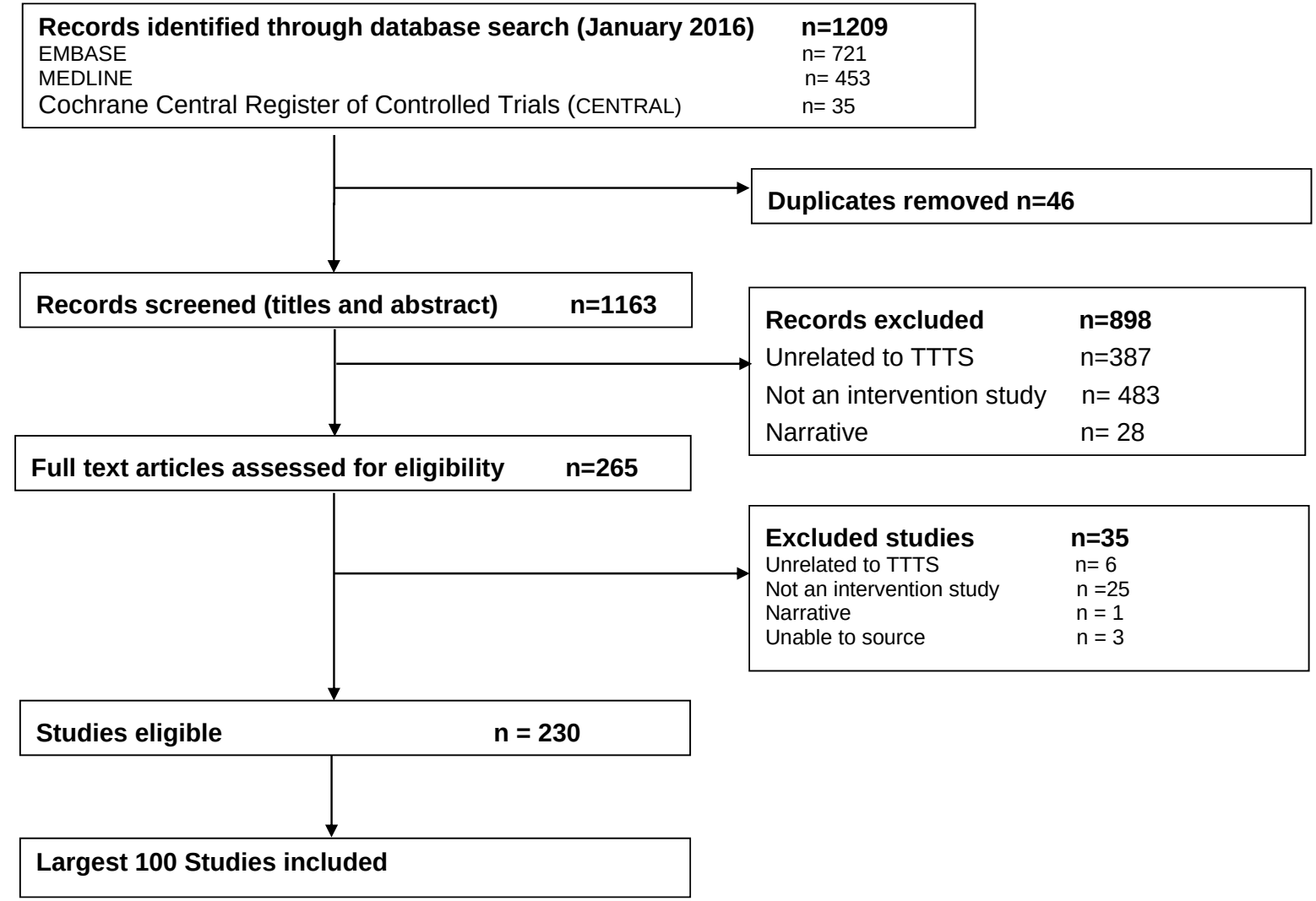

Figure 1. Flow of included studies

Study	Study Design	Inclusion Criteria	Maternal participants (n =20071)	Childhood participants (n= 3199)	Intervention 1	Intervention 2	Intervention 3	Quality Assessment
Randomised trials (n =5)								Jadad Score (max 5)
Van-Klink, 2016	Randomised-controlled trial	TTTS Quintero stage 1-4 up to 26 weeks gestation	156	287	Fetoscopic Laser Surgery (Solomon technique)	Fetoscopic Laser Surgery (standard technique)		4
Slaghekke, 2014	Randomised-controlled trial	TTTS Quintero stage 1-4 up to 26 weeks gestation	274		Fetoscopic Laser Surgery (Solomon technique)	Fetoscopic Laser Surgery (standard technique)		4
Salomon, 2010	Randomised-controlled trial	TTTS Quintero stage 2-4 15-26 weeks gestation	128	120	Fetoscopic Laser Surgery	Amnioreduction		3
Crombleholme, 2007	Randomised-controlled trial	TTTS Quintero stage 2-4 up to 24 weeks gestation	40		Fetoscopic Laser Surgery	Amnioreduction		3
Moise, 2005	Randomised-controlled trial	TTTS Quintero stage 1-4 up to 24 weeks gestation	73		Amnioreduction	Septostomy		3
Senat, 2004	Randomised-controlled trial	TTTS Quintero stage 2-4 15-26 weeks gestation	142	146	Fetoscopic Laser Surgery	Amnioreduction		3
								Newcastle-Ottawa Scale (max 9*)
Observational studies (n =95)								
Zhao, 2016	Case-control study	TTTS cases Quintero stage 1-4 and control monochorionic pregnancies.	124		Fetoscopic Laser Surgery			7*
Ortiz, 2016	Prospective cohort study	TTTS cases Quintero stage 1-4	260		Fetoscopic Laser Surgery			5*
Stirnemann, 2016	Retrospective cohort study	TTTS cases Quintero stage 1-4	1023		Fetoscopic Laser Surgery			5*
Wilson, 2016	Retrospective cohort study	TTTS Quintero stage 1-4 up to 26 weeks gestation	139		Fetoscopic Laser Surgery			5*
Van Kempen, 2016	Case-control study	TTTS cases and control monochorionic pregnancies.	479		Fetoscopic Laser Surgery			8*
Malshe, 2016	Prospective cohort study	TTTS cases Quintero stage 1-4	203		Fetoscopic Laser Surgery			6*
Snowise, 2016	Prospective cohort study	TTTS cases Quintero stage 1-4	154		Fetoscopic Laser Surgery			6*
Emery, 2016	Retrospective cohort study	TTTS cases Quintero stage 1	124		Expectant management	amnioreduction	Fetoscopic laser surgery	5*
Peterson, 2016	Retrospective cohort study	TTTS cases Quintero stage 1-4	673		Fetoscopic Laser Surgery with sheath + trocar uterine entry technique	Fetoscopic Laser Surgery with cannula + trocar uterine entry technique	Fetoscopic Laser Surgery with cannula + Seldinger uterine entry technique	5*
Persico, 2016	Retrospective cohort study	TTTS cases Quintero stage 1-4	106		Fetoscopic Laser Surgery			5*
Eschbach, 2016	Case-control study	TTTS cases Quintero stage 1-4	273		Fetoscopic Laser Surgery			7*
Chmait, 2016	Prospective cohort study	Surviving children after fetoscopic	57	100	Fetoscopic Laser Surgery			5*

		laser surgery for TTTS Quintero stage 1-4						
Van Winden, 2015	Retrospective cohort study	TTTS cases Quintero stage 1-4	369		Fetoscopic Laser Surgery			6*
Pruetz, 2015	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 1-4	54	91	Fetoscopic Laser Surgery			6*
Maggio, 2015	Retrospective cohort study	TTTS cases Quintero stage 2-4	92		Fetoscopic Laser Surgery			6*
Snowise, 2015	Prospective cohort study	TTTS cases Quintero stage 1-4	154		Fetoscopic Laser Surgery			6*
Has, 2014	Retrospective cohort study	TTTS cases Quintero stage 1-4	85		Fetoscopic Laser Surgery			5*
Chai, 2014	Retrospective cohort study	TTTS cases Quintero stage 1-4	103		Amnioreduction	Selective Feticide (Bipolar Cord Coagulation)		4*
Vanderbilt, 2014	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 1-4	57	100	Fetoscopic Laser Surgery			6*
Gapp-Born, 2014	Prospective cohort study	TTTS cases Quintero stage 1-4	90		Fetoscopic Laser Surgery			6*
Lecointre, 2014	Prospective cohort study	TTTS cases Quintero stage 1-4 at < 17 weeks gestation	178		Fetoscopic Laser Surgery			6*
Peeters, 2014	Retrospective cohort study	TTTS cases Quintero stage 1-4	340		Fetoscopic Laser Surgery			7*
Van Klink, 2014	Retrospective cohort study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 1-4	219	318	Fetoscopic Laser Surgery			5*
Michelfelder, 2014	Retrospective cohort study	TTTS cases Quintero stage 2-4	610		Fetoscopic Laser Surgery			4*
Zhao, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	252		Fetoscopic Laser Surgery			5*
Eixarch, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	215		Fetoscopic Laser Surgery			6*
Ngamprasertwong, 2013	Retrospective cohort study	TTTS cases	328		Fetoscopic Laser Surgery			6*
Ruano, 2013	Case-control study	TTTS cases Quintero stage 2-4	102		Fetoscopic Laser Surgery			8*
Papanna, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	134		Fetoscopic Laser Surgery			8*
Baschat, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	147		Fetoscopic Laser Surgery			8*
Baud, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4 at < 17 weeks gestation and > 26 weeks gestation	325		Fetoscopic Laser Surgery			4*
Stirnemann, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	507		Fetoscopic Laser Surgery			6*

Chalouhi, 2013	Case-control study	TTTS cases Quintero stage 3 and monochorionic pregnancies with selective fetal growth restriction	211		Fetoscopic Laser Surgery	Selective Feticide (Bipolar Cord Coagulation)		7*
Barrea, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4 < 28 weeks gestation	81		Fetoscopic Laser Surgery	Amnioreduction		6*
Egawa, 2013	Retrospective cohort study	TTTS cases Quintero stage 1-4	148		Fetoscopic Laser Surgery			5*
Graeve, 2012	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 1-4	200	190	Fetoscopic Laser Surgery			4*
Sundberg, 2012	Prospective cohort study	TTTS cases Quintero stage 1-4	120		Fetoscopic Laser Surgery			6*
Vanderbilt, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4	262		Fetoscopic Laser Surgery			6*
Swiatkowska-Freund, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4	94		Fetoscopic Laser Surgery			5*
Stirnemann, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	648		Fetoscopic Laser Surgery			5*
Spruijt, 2012	Case-control study	TTTS cases Quintero stage 1-4 and dichorionic controls	534		Fetoscopic Laser Surgery			7*
Takahashi, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4	195		Fetoscopic Laser Surgery			4*
Rustico, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4	150	172	Fetoscopic Laser Surgery			6*
Habli, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-2	123		Expectant management	Amnioreduction		5*
Tchirikov, 2012	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	77		Fetoscopic Laser Surgery			6*
Maschke, 2011	Retrospective cohort study	TTTS cases Quintero stage 2-4	196	256	Fetoscopic Laser Surgery			4*
Chmait, 2011	Retrospective cohort study	TTTS cases Quintero stage 2-4	682		Fetoscopic Laser Surgery			6*
Cruz-Martinez, 2011	Retrospective cohort study	TTTS cases Quintero stage 1-4	414		Fetoscopic Laser Surgery			5*
Sago, 2011	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	181	163	Fetoscopic Laser Surgery			5*
Gray, 2011	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 2-4	75	113	Fetoscopic Laser Surgery			5*
Crombleholme, 2010	Case-control study	TTTS cases Quintero stage 1-4	293		Fetoscopic Laser Surgery + Nifedipine			5*
Morris, 2010	Prospective cohort study	TTTS cases Quintero stage 2-4< 26 weeks	164		Fetoscopic Laser Surgery			6*

Quintero, 2010	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	267		Fetoscopic Laser Surgery			5*
Papanna, 2010	Retrospective cohort study	TTTS cases Quintero stage 1-4	97		Fetoscopic Laser Surgery			8*
Chmait, 2010	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	99		Fetoscopic Laser Surgery			6*
Meriki, 2010	Retrospective cohort study	TTTS cases Quintero stage 1-4	79		Fetoscopic Laser Surgery			6*
Habli, 2009	Retrospective cohort study	TTTS cases Quintero stage 1-4, 16-26 weeks gestation	152		Fetoscopic Laser Surgery			6*
Lenclen, 2009	Case-control study	Surviving children after fetoscopic laser surgery or amnioreduction for TTTS born between 24-34 weeks gestation and dichorionic controls	209	312	Fetoscopic Laser Surgery	Amnioreduction		7*
Luks, 2009	Retrospective cohort study	TTTS cases Quintero stage 1-4	98		Expectant Management	Fetoscopic Laser Surgery		5*
Cincotta, 2009	Prospective cohort study	TTTS cases Quintero stage 2-4	100		Fetoscopic Laser Surgery			5*
Lopriore, 2009	Case-control study	Surviving children after fetoscopic laser surgery for TTTS Quintero stage 1-4	212	278	Fetoscopic Laser Surgery			8*
Muratore, 2009	Retrospective cohort study	TTTS cases Quintero stage 1-4	163		Fetoscopic Laser Surgery			5*
Salomon, 2008	Prospective cohort study	TTTS cases Quintero stage 2-4 with cervical length <15mm prior to surgery	272		Fetoscopic Laser Surgery with emergency cervical cerclage	Fetoscopic Laser Surgery without emergency cervical cerclage		5*
Murakoshi, 2008	Retrospective cohort study	TTTS cases Quintero stage 3	82		Fetoscopic Laser Surgery			7*
Chmait, 2008	Retrospective cohort study	TTTS cases Quintero stage 1-4 with dual neonatal survivors born at least 28 days after surgery	211		Fetoscopic Laser Surgery			6*
Winer, 2008	Prospective cohort study	TTTS cases between 15-26 weeks gestation	438		Fetoscopic Laser Surgery			4*
Huber, 2008	Prospective cohort study	TTTS cases Quintero stage 2-4	176		Fetoscopic Laser Surgery			8*
Stirnemann, 2008	Prospective cohort study	TTTS cases Quintero stage 2-4	287		Fetoscopic Laser Surgery			6*
Middeldorp, 2007	Prospective cohort study	TTTS cases Quintero stage 1-4	105		Laparoscopically-guided Fetoscopic Laser Surgery			6*
Quintero, 2007	Prospective cohort study	TTTS cases Quintero stage 1-4, 16-26	193		Fetoscopic Laser Surgery			6*

		weeks gestation						
Quarello, 2007	Retrospective cohort study	TTTS cases Quintero stage 2-4	299		Fetoscopic Laser Surgery	Amnioreduction	Expectant Management	5*
Lenclen, 2007	Case-control study	TTTS cases Quintero stage 2-4 and dichorionic controls	209		Fetoscopic Laser Surgery	Amnioreduction		7*
Middeldorp, 2007	Prospective cohort study	TTTS cases Quintero stage 1-4, 16-28 weeks gestation	100		Fetoscopic Laser Surgery			6*
Lopriore, 2007	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS	82	115	Fetoscopic Laser Surgery			6*
Lopriore, 2007	Case-control study	TTTS cases Quintero stage 1-4 and monochorionic controls	101		Fetoscopic Laser Surgery			5*
Lerullo, 2007	Prospective cohort study	TTTS cases Quintero stage 3-4, <26 weeks gestation	77		Fetoscopic Laser Surgery			6*
Huber, 2006	Prospective cohort study	TTTS cases Quintero stage 1-4, <26 weeks gestation	200		Fetoscopic Laser Surgery			6*
Lopriore, 2006	Case-control study	TTTS cases Quintero stage 1-4 and monochorionic controls	108		Fetoscopic Laser Surgery			6*
Cavicchioni, 2006	Retrospective cohort study	TTTS cases Quintero stage 1-4	120		Fetoscopic Laser Surgery			4*
Robyr, 2006	Retrospective cohort study	TTTS cases where both twins were alive 1 week after treatment	151		Fetoscopic Laser Surgery			6*
Graef, 2006	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS	127	167	Fetoscopic Laser Surgery			5*
Herberg, 2006	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS	73	89	Fetoscopic Laser Surgery			6*
Lopriore, 2005	Case-control study	TTTS cases and monochorionic controls	86		Fetoscopic Laser Surgery			7*
Yamomoto, 2005	Retrospective cohort study	TTTS cases <26 weeks gestation	175		Fetoscopic Laser Surgerv			5*
De Moreira Sa, 2005	Prospective cohort study	TTTS cases with at least 1 survivor after treatment	98		Fetoscopic Laser Surgery			5*
Quintero, 2003	Retrospective cohort study	TTTS cases Quintero stage 1-4	173		Fetoscopic Laser Surgery	Amnioreduction		4*
Banek, 2003	Prospective cohort study	Surviving children after fetoscopic laser surgery for TTTS	73	89	Fetoscopic Laser Surgery			5*
Mari, 2001	Prospective cohort study	TTTS cases <28 weeks gestation	223		Amnioreduction			6*
Hecher, 2000	Prospective cohort study	TTTS cases Quintero stage 2-4, 15-26 weeks	200		Fetoscopic Laser Surgery			6*

		gestation						
Quintero, 2000	Retrospective cohort study	TTTS cases Quintero stage 2-4, 16-26 weeks gestation	92		Fetoscopic Laser Surgery			6*
Dickinson, 2000	Prospective cohort study	All TTTS cases	112		Amnioreduction (with or without adjuvant digoxin)	Expectant Management	Delivery	5*
Hecher, 1999	Retrospective cohort study	TTTS cases Quintero stage 2-4, 17-25 weeks gestation	116		Fetoscopic Laser Surgery	Amnioreduction		6*
De Lia, 1999	Retrospective cohort study	TTTS cases <25 weeks gestation	67	93	Fetoscopic Laser Surgery			4*
Ville, 1998	Prospective cohort study	TTTS cases Quintero stage 2-4, <28 weeks gestation	132		Fetoscopic Laser Surgery			6*

Table 1: Characteristics of included studies

FETAL OUTCOMES	EARLY CHILDHOOD OUTCOMES
Disease progression Recurrence of twin-twin transfusion syndrome **Cardiovascular morbidity** Fetal Echocardiography abnormalities Anaemia **Neurological morbidity** Cerebral Lesions **Other** Amniotic Band Syndrome Twin anaemia polycythaemia syndrome	**Neurodevelopment** Visual impairment Hearing impairment Cerebral palsy Neurodevelopmental Impairment **Cardiovascular morbidity** Hypertension Cardiac dysfunction
OFFSPRING MORTALITY	**MATERNAL OUTCOMES**
Live birth Miscarriage Intrauterine death Neonatal mortality Perinatal mortality Early childhood mortality Termination of Pregnancy	Maternal mortality Mirror syndrome Premature rupture of membranes Chorioamnionitis Abruption Amniotic fluid embolism Preterm birth Pulmonary oedema
NEONATAL OUTCOMES	**OPERATIVE COMPLICATIONS**
Delivery Gestational age at delivery Mode of delivery Birth weight Apgar Scores **Neurological morbidity** Stroke Intraventricular haemorrhage Periventricular leukomalacia Ventriculomegaly Cystic Lesions Retinopathy of prematurity **Cardiovascular morbidity** Pulmonary stenosis Pulmonary atresia Persistent Pulmonary Hypertension of the Newborn Congenital heart disease Hypotension Ischaemic Limb Injury **Respiratory morbidity** Respiratory distress syndrome Chronic lung disease Intubation and ventilation Pulmonary hypoplasia **Gastrointestinal morbidity** Necrotising enterocolitis **Genitourinary morbidity** Renal failure **Infectious morbidity** Sepsis **Interventions to manage morbidity** Parenteral nutrition Resuscitation of the neonate	Pain Hypotension Haemorrhage Blood transfusion Emergency laparotomy Unintentional membrane separation Unintentional septostomy Intra-abdominal amniotic fluid leak Operative Time Admission to intensive care

Table 2: Maternal and offspring outcome reporting across randomised trials and observational studies

Outcome	Reporting studies (n=100)	Number of maternal participants (n=20071)
FETAL OUTCOMES		
Disease progression		
Recurrence of twin-twin transfusion syndrome, n (%)	17 (17)	4206 (21.0)
Cardiovascular morbidity		
Fetal Echo Abnormalities, n (%)	4 (4)	1108 (5.5)
Anaemia, n (%)	1 (1)	120 (0.6)
Neurological morbidity		
Cerebral lesions, n (%)	4 (4)	1592 (7.9)
Other		
Amniotic Band Syndrome, n (%)	4 (4)	1278 (6.4)
Twin anaemia polycythaemia syndrome, n (%)	14 (14)	3738 (18.6)
OFFSPRING MORTALITY		
Live birth, n (%)	31 (31)	5219 (26.0)
Miscarriage, n (%)	11 (11)	1419 (7.1)
Intrauterine death, n (%)	31 (31)	6376 (31.8)
Neonatal mortality/survival, n (%)	49 (49)	8216 (41.0)
Perinatal mortality/survival, n (%)	17(17)	3172 (15.8)
Early childhood mortality, n (%)	9 (9)	1083 (5.4)
Termination of Pregnancy, n (%)	2 (2)	227 (1.1)
NEONATAL OUTCOMES		
Delivery		
Gestational age at delivery, n (%)	33 (33)	5583 (27.8)
Mode of delivery, n (%)	7 (7)	2098 (10.5)
Birth weight, n (%)	14 (14)	2155 (10.7)
Apgar scores, n (%)	3 (3)	365 (1.8)
Neurological morbidity		
Stroke, n (%)	4 (4)	860 (4.3)
Intraventricular haemorrhage, n (%)	16 (16)	3430 (17.1)
Periventricular leukomalacia, n (%)	17 (17)	3594 (17.9)
Ventriculomegaly, n (%)	11 (11)	2297 (11.4)
Cystic Lesions, n (%)	7 (7)	1651 (8.2)
Retinopathy of prematurity, n (%)	3 (3)	510 (2.5)
Cardiovascular morbidity		
Pulmonary stenosis, n (%)	1 (1)	260 (1.3)
Pulmonary atresia, n (%)	1 (1)	260 (1.3)
Persistent Pulmonary Hypertension of the Newborn, n (%)	1 (1)	195 (1.0)
Congenital heart disease, n (%)	1 (1)	101 (0.5)

Hypotension, n (%)	2 (2)	290 (1.4)
Ischaemic Limb Injury, n (%)	2 (2)	360 (1.8)
Respiratory morbidity		
Respiratory distress syndrome, n (%)	4 (4)	620 (3.1)
Chronic lung disease/Bronchopulmonary Dysplasia, n (%)	6 (6)	1044 (5.2)
Intubation and ventilation, n (%)	1 (1)	209 (1.0)
Pulmonary hypoplasia, n (%)	1 (1)	81(0.4)
Gastrointestinal morbidity		
Necrotising enterocolitis, n (%)	6 (6)	1023 (5.1)
Genitourinary morbidity		
Renal failure, n (%)	4 (4)	599 (3.0)
Infectious morbidity		
Sepsis, n (%)	3 (3)	826 (4.1)
Interventions to manage morbidity		
Parenteral nutrition, n (%)	1 (1)	81 (0.4)
Resuscitation of the neonate, n (%)	1 (1)	81 (0.4)
EARLY CHILDHOOD OUTCOMES		
Neurodevelopment		
Visual impairment, n (%)	10 (10)	1430 (7.1)
Hearing impairment, n (%)	9 (9)	1424 (7.1)
Cerebral palsy, n (%)	11 (11)	1459 (7.3)
Neurodevelopmental Impairment, n (%)	13 (13)	1868 (9.3)
Cardiovascular morbidity		
Hypertension, n (%)	1 (1)	54 (0.3)
Cardiac dysfunction, n (%)	1 (1)	73 (0.4)
MATERNAL OUTCOMES		
Maternal mortality, n (%)	2 (2)	409 (2.0)
Mirror syndrome, n (%)	3 (3)	578 (2.9)
Premature rupture of membranes, n (%)	31 (31)	6057 (30.2)
Chorioamnionitis, n (%)	8 (8)	2078 (10.4)
Placental abruption, n (%)	6 (6)	1346 (6.7)
Amniotic fluid embolism, n (%)	1 (1)	142 (0.7)
Preterm birth, n (%)	8 (8)	1857 (9.3)
Pulmonary oedema, n (%)	3 (3)	718 (3.6)
OPERATIVE COMPLICATIONS		
Pain, n (%)	1 (1)	175 (0.9)
Hypotension, n (%)	1 (1)	328 (1.6)

Haemorrhage, n (%)	6 (6)	914 (4.6)
Blood transfusion, n (%)	3 (3)	794 (4.0)
Emergency laparotomy, n (%)	1 (1)	176 (0.9)
Unintentional membrane separation, n (%)	5 (5)	830 (3.3)
Unintentional septostomy, n (%)	4 (4)	814 (4.1)
Intraabdominal amniotic fluid leak, n (%)	5 (5)	753 (3.8)
Admission to intensive care, n (%)	3 (3)	651 (3.2)
Operative Time, n (%)	3 (3)	552 (2.8)

Table 3: Maternal and offspring outcome reporting across randomised trials and observational studies.

	Fetal Outcomes						Offspring Mortality							Operative Complications								Maternal Outcomes							Neonatal Outcomes									Childhood Outcomes			
Outcome	Recurrence of twin-twin transfusion syndrome	Fetal Echo Abnormalities	Anaemia	Cerebral lesions	Amniotic Band Syndrome	Twin anaemia polycythaemia syndrome	Live birth	Miscarriage	Intrauterine death	Neonatal mortality	Perinatal mortality	Early childhood mortality	Termination of Pregnancy	Operator Performance	Hypotension	Haemorrhage	Blood transfusion	Unintentional membrane separation	Unintentional septostomy	Intraabdominal amniotic fluid leak	Admission to intensive care	Mirror syndrome	Premature rupture of membranes	Chorioamnionitis	Abruption	Amniotic fluid embolism	Preterm birth	Pulmonary oedema	Gestational age at delivery	Mode of delivery	Birth weight	Apgar scores	Intraventricular haemorrhage	Periventricular leukomalacia	Ventriculomegaly	Cystic Lesions	Sepsis	Visual impairment	Hearing impairment	Cerebral palsy	Neurodevelopmental Delay
Study																																								
Randomised trials																																								
Van-Klink, 2016																																					X	X	X	X
Slaghekke, 2014	X				X	X					X					X		X					X	X						X		X	X	X	X					
Salomon, 2010											X																										X		X	X
Crombleholme, 2007										X																														
Moise, 2005							X			X																			X											
Senat, 2004								X	X	X	X	X				X				X				X	X	X							X	X			X	X		
Observational studies																																								
Stirnemann, 2016	X			X		X																																		
Chmait, 2011									X	X																														
Peterson, 2016																						X				X														
Stirnemann, 2012	X					X			X	X													X	X				X				X	X							
Michelfelder, 2014		X					X																																	
Spruijt, 2012																																	X	X	X	X				
Stirnemann, 2013											X																													
Vankempen, 2016																						X						X	X	X						X			
Winer, 2008									X													X						X											
Cruz-Martinez, 2011					X				X										X			X						X	X										
Van Winden, 2015									X	X																X			X											
Peeters, 2014											X			X																										
Lenclen, 2009																																					X	X	X	X
Ngamprasertwong, 2013							X								X																									
Baud, 2013							X			X							X				X	X						X												
Quarello, 2007				X			X		X	X																														

Crombleholme, 2010		X					X										X							X															
Stirnemann, 2008	X									X																														
Eschbach, 2016									X																															
Salomon, 2008										X													X	X					X											

Table 4: Inconsistency in outcome reporting across randomised trials and the 20 largest observational studies.

Outcome Measure	Number (%)	Number (%)
Total	**100**	**20071**
Live birth	31 (31)	5219 (26.0)
Survival to birth	10 (10)	1865 (9.3)
Not defined	21 (21)	3354 (16.7)
Miscarriage	11 (11)	1419 (7.1)
Pregnancy loss < 24 weeks	6 (6)	828 (4.1)
Not defined	5 (5)	591 (2.9)
Intrauterine Death	31 (31)	6376 (31.8)
Absence of fetal heart activity on ultrasonography after the procedure and before the onset of labour	1 (1)	154 (0.8)
Death occurring between diagnosis and birth	1 (1)	81 (0.4)
Death within 7 days of surgery	1 (1)	215 (1.1)
Not defined	28 (28)	5926 (29.5)
Neonatal Mortality/Survival	49 (49)	8216 (41.0)
Survival to discharge	4 (4)	527 (1.9)
Death within 7 days of birth	2 (2)	415 (2.1)
Number of fetuses surviving 6 months postnatally	1 (1)	82 (0.4)
Death between birth and 28 days postnatally	13 (13)	2450(7.4)
Survival to 30 days postnatally	6(6)	1727 (7.2)
Not defined	23 (23)	3015(13.9)
Perinatal mortality/Survival	17 (17)	3172 (15.8)
Number of fetuses who died at >20 weeks of gestation together with infants who died at <28 days of life	1 (1)	209 (1.0)
Death between diagnosis and 28 days post-natally	3 (3)	730 (3.6)
Survival at 30 days	1 (1)	193 (1.0)
Either fetal demise or neonatal death	2 (2)	352 (1.8)
Survival to 28 days or beyond	2 (2)	654 (3.3)
Not defined	8 (8)	1034 (5.2)
Early childhood mortality	9 (9)	1083 (5.4)
Alive at 6 months	3 (3)	488 (2.4)
Alive at 7-12 months	1 (1)	142 (0.7)
Alive at 12 months	3 (3)	255 (1.3)
Not defined	2 (2)	198 (1.0)
Termination of Pregnancy	2 (2)	227 (1.1)
Not defined	2 (2)	227 (1.1)

PROM	31 (31)	6057 (30.2)
Rupture of membranes < 24 hours post procedure, within 7 days and within 1-4 weeks of procedure	2 (2)	218 (1.1)
Rupture of membranes within 3 weeks of procedure	1 (1)	267 (1.3)
Rupture of membranes diagnosed clinically ≤ 34 weeks' gestation and prior to the onset of spontaneous labour	7 (7)	982 (4.9)
Rupture of membranes < 32 weeks gestation	2 (2)	592 (2.9)
Rupture of membranes before the beginning of the first stage of labour	1 (1)	94 (0.5)
Rupture of membranes > 24 weeks	1 (1)	150 (0.7)
Rupture of membranes < 37 weeks	1 (1)	164 (0.8)
Not defined	16 (16)	3590 (14.1)
Neurodevelopmental development		
Visual impairment	10 (10)	1430 (7.1)
Bilateral blindness	5 (5)	878 (4.4)
Complete blindness	1 (1)	150 (0.7)
Previous clinical report or Amiel-Tison examination	1 (1)	57 (0.3)
Not defined	3 (3)	345 (1.7)
Hearing impairment	9 (9)	1424 (7.1)
Bilateral deafness requiring amplification	5 (5)	1000 (5.0)
Complete deafness	1 (1)	150 (0.7)
Previous clinical report or Amiel-Tison examination	1 (1)	57 (0.3)
Not defined	2 (2)	217 (1.1)
Cerebral palsy	11 (11)	1459 (7.3)
According to the European CP Network definition	6 (6)	1006 (5.0)
According to the criteria of Mutch et al.	1 (1)	75 (0.4)
On Amiel-Tison Neurodevelopmental Examination	1 (1)	57 (0.3)
Not defined	3 (3)	321 (1.6)
Neurodevelopmental Delay	13 (13)	1868 (9.9)
A Bayley BSID-II score > 2SD below mean = severe delay and >1SD below mean= mild/moderate delay	1 (1)	156 (0.8)
Presence of cerebral palsy, cognitive impairment, bilateral blindness, or deafness requiring amplification with hearing aids	2 (2)	157 (0.8)
Presence of cerebral palsy, a mental developmental indices score below 70, a psychomotor development indexes score below 70 (Bayley BSID-II), bilateral blindness, or bilateral deafness requiring amplification	2(2)	431 (2.2)
Having bilateral blindness (unable to fix on or track an object), bilateral deafness (requiring amplification), cerebral palsy (based on physical exam), and/or a Battelle Developmental Inventory, Second Edition (BDI-2) Total Developmental Quotient of <70	2 (2)	114 (0.6)
An Ages and Stages Questionnaire (ASQ) score <2 SD below the established average score	1 (1)	209 (1.6)
A score of > 2 SD below the mean on Snijders–Oomen non-verbal intelligence test or Griffiths' developmental test	2 (2)	323 (1.6)
Cerebral palsy with neurological abnormalities including hemiparesis, spastic quadriplegia, and blindness	1 (1)	128 (0.6)

Motor deficits impairing their ability to walk, complete blindness or deafness, Griffiths DQ (developmental quotient) < 70 and/or severe behavioral disorder	1 (1)	150 (0.7)
Not defined	1 (1)	200 (1)

Table 5: Variation in outcome definitions across randomised trials and observational studies.