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DOI:
10.1016/j.ejogrb.2021.04.025

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Farmer, N, Hillier, M, Kilby, M, Hodgetts-Morton, V & Morris, RK 2021, 'Outcomes in intervention and management of multiple pregnancies trials: a systematic review', *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 261, pp. 178-192. https://doi.org/10.1016/j.ejogrb.2021.04.025

European Journal of Obstetrics & Gynecology and Reproductive Biology 261 (2021) 178–192

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review article

Outcomes in intervention and management of multiple pregnancies trials: A systematic review

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ARTICLE INFO

Article history:
Received 12 March 2021
Accepted 19 April 2021
Available online xxx

Keywords:
Core-outcome set
Twin pregnancy
Obstetrics
Multiple pregnancy

ABSTRACT

Objectives: Twin pregnancy has risks of adverse outcomes for mother and baby. Data synthesis is required to gain evidence to aid recommendations but may be hampered by variations in outcome reporting.
Study design: Systematically review outcomes reported in twin pregnancy trials (PROSPERO - CRD42019133805). Searches were performed in MEDLINE, EMBASE, CINHAL, Cochrane library (inception-January 2019) for randomised control trials or their follow-up studies reporting prediction, prognosis, intervention or management outcomes in twin pregnancy. The study characteristics, outcomes definitions and measurements were extracted and descriptively analysed.
Results: 49 RCTs and 8 follow-up studies evaluated 21 interventions, 1257 outcomes, categorised into 170 unique outcomes. 65 % of trials included all twin pregnancies, 12 % DCDA and 11 % MCDA only or MCMA and MCDA. Five (9 %) papers were prediction/ prognosis RCT's and 52 (91 %) related to an intervention. Of interventions, 40 (77 %) were medical, 34 (85 %) for preterm birth; 12 (23 %) surgical, 6 (50 %) related to TTTS interventions (83 % for monochrorionic studies). Commonest domains were: 'Neonatal' 77 %, 'Delivery' 70 % and 'Survival' 67 %. Least reported were longer term outcomes for 'Infant' or 'Parental'.
Conclusions: Twin pregnancy outcomes are diverse and complex. This is related to the need to address maternal, single and double fetal outcomes and different types of chorionicity. The lack of outcome standardisation in selection, definition and reporting hinders evidence synthesis and the selection of outcomes important to women and health care professionals thus limiting the effectiveness of research.

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Abbreviations: DCDA, dichorionic/diamniotic; MCDA, monochorionic/diamniotic; MCMA, monochorionic/monoamniotic; sIUGR, selective growth restriction; TRAP, twin reverse arterial perfusion sequence; TAPS, twin anemia-polythaemia sequence; TTTS, twin-to-twin transfusion syndrome; RCT, randomised control trial; COS, core outcome set.

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https://doi.org/10.1016/j.ejogrb.2021.04.025

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Introduction

The prevalence of multiple pregnancy varies between 0.7 %–3.34 % of women worldwide [1–4]. Currently, 1.54 % of women in England and Wales have a twin pregnancy [5], in the United States it is more than double, at 3.34 % [6]. The variation is largely related to an increased use of assisted reproductive techniques, maternal age and parity leading to a rise in dizygotic, and to a lesser extent monozygotic, twinning. Following the introduction of ovulation induction and multiple embryo transfer fertility therapies, twin pregnancy rates increased by 50 % between 1975–2002 in England and Wales [7] and 90 % in the Netherlands [7]. Changes in policy advising single-embryo transfer [8] has resulted in twin pregnancy rates stabilising [9]. Although zygosity is important, clinical relevance and risk is inferred by chorionicity and amnionicity [10–16].

Twin pregnancy remains a common occurrence with an increased risk of adverse outcomes for mother and baby(s). Excess maternal risks include anemia, urinary tract infection, hypertension, gestational diabetes, hamorrhage and maternal mortality and as such require greater surveillance compared to singleton pregnancies [10–13]. It is important to differentiate between dichorionic/diamniotic (DCDA), monochorionic/diamniotic (MCDA) and monochorionic/monoamniotic (MCMA) pregnancies, as complications can be unique to each type. DCDA twins have the lowest risk of complications but remain at an increased risk compared to singleton pregnancies DCDA [10–12]. In addition, 20 % of dichorionic twins are monozygotic. Monochorionic twins are at higher fetal risk than their dichorionic counterparts and monoamnionicity carries additional risks of fetal loss from complex congenital malformations and umbilical cord entanglement. The prime and common risks are secondary to placental vascular anastomoses and/or unequal placental sharing. These unique complications include selective growth restriction (sIGR), twin reverse arterial perfusion sequence (TRAP), twin-to-twin transfusion syndrome (TTTS) and twin anemia-polythaemia sequence (TAPS) [10,13,14] which significantly increase the risk of fetal morbidity and mortality [15,16] and also make research in twins difficult as there is a large variation in reported outcomes.

The heterogeneity in outcome reporting makes analysis of observational studies and randomised control trials (RCTs) of interventions for effectiveness particularly difficult causing major barriers for data meta-analysis and or comparisons. This is further hampered by the use of different methods of measurement or definitions for an outcome. This in turn, limits the applicability of findings for clinical guidance as it reduces the meaningfulness of evidence based guidelines. Whilst there has been a substantial amount of attention towards standardising RCT methods, the selection, collection and reporting of outcomes has been overlooked [17]. Consequently, there is no consensus regarding the minimum that should be collected and reported. Selecting appropriate outcomes that not only capture the efficacy and safety of potential interventions, but also includes outcomes that are important to patients is crucial. Therefore, to improve the quality of research a standardised core outcome set (COS) for twin pregnancy is vital. COS are agreed, clearly defined outcomes that are measured in a standardised manner and reported consistently as a minimum in all research trials within a specific discipline [18] and are advocated by relevant institutions [19,20].

This systematic review is the initial step in the development of a COS for clinical trials in twin pregnancy and establishes the outcomes used in RCTS of intervention and management.

Materials and methods

This systematic review was registered on PROSPERO (CRD42019133805) and COMET database. It was performed according to recommended methods and reported according to PRISMA and COMET guidance [21] (Supplementary Material for protocol and PRISMA checklist).

Data sources

Electronic database searches were executed to obtain articles reporting RCTs of intervention or management in twin pregnancies. The search was completed in MEDLINE (database inception – 25 Jan 2019), CINHAL (database inception – 25 Jan 2019), EMBASE (database inception – 25 Jan 2019) and the Cochrane library (database inception – 02 Feb 2019) using a pre-defined search strategy. The Web of Science was used to search for grey literature.

The pre-defined search strategy based on our eligibility criteria incorporated all relevant keywords and variations. 'Twin pregnancy' OR 'twin pregnancies' were combined with more twin specific definitions 'monoamniotic' OR 'monochorionic' OR 'diamniotic' OR 'dichorionic' and limited to 'randomised control trials' and 'clinical trials' if the database allowed (Supplementary Material). The reference lists of included studies were cross-checked and authors were contacted for further information where necessary.

Eligibility criteria for selecting studies

Studies were eligible if they reported a specific therapeutic intervention (medical or surgical) in pregnancy and/or a management pathway (e.g. ultrasound screening) in twin pregnancies and were of RCT design. Planned RCT follow-up studies, documented in the original protocol, were also included to capture longer-term outcomes. This is unlike systematic reviews and meta-analysis of effectiveness where participant duplication in statistical analysis is an issue, as it is only outcomes being captured and not their numerical value. Secondary analyses investigating a new hypothesis were not included.

All three variations of twin pregnancy were included i.e. DCDA, MCDA, MCMA, but trials including higher order multiples (e.g. triplets) were excluded as these pregnancies include variations of dichorionic and monochorionic placentation. All therapeutic interventions and comparators were considered regardless of

type, setting or mode of administration and all outcomes were included and collected. No dates, country of origin or language restrictions were applied. Studies that met the eligibility criteria following review of their title and abstract were selected for full manuscript review.

Data extraction and analysis

Manuscripts were reviewed independently in duplicate to confirm eligibility and data extraction was performed using a piloted data extraction proforma. The following study characteristics were extracted: study design, year of study, place of study, sample size, multicentre vs. single centre, intervention, comparator as well as outcome definition, measurement and classification.

To overcome differing definitions, outcomes were categorised into unique outcomes with the same semantic meaning e.g. admission to the neonatal unit and admission to a level three unit was grouped into one unique outcome. Outcomes that were defined at different time points but had the same meaning were also grouped into a unique outcome e.g. neonatal death before discharge and neonatal death before 28 days was grouped as 'neonatal death'. Likewise, authors were mindful not to over aggregate outcomes during a categorisation as this may have resulted in crucial outcomes being lost. For instance, RCTs often reported the number of babies with one or more specified condition as a single composite outcome and would also report each condition that formed the composite outcome as an outcome in itself. It was agreed that composite outcomes would be separated into the measures/definitions used within it to form separate unique outcomes as each had a different semantic meaning.

Unique outcomes were grouped according to the OMERACT 2.0 framework which consists of four core areas – life impact, pathophysiological/manifestations, resource use/economical and death. Dodd et al. [22] was considered for outcome taxonomy, however as there is a maternity specific sub-classification, the majority of unique outcomes may have potentially been placed in a single l sub-classification and therefore the OMERACT 2.0 framework was utilised. There was also plan to further organise into domains within each main area if needed. Each grouping and categorisation was agreed by all the authors who are experts in research and twin pregnancy and by our patient representative. Raw data were inputted into Microsoft EXCEL.

Quality assessment

Studies were subjected to methodological quality assessment using the Cochrane Tool for RCTs (RoB2) [23]. The quality assessment was performed independently in duplicate.

Funding

The research costs of the systematic review and NF were funded by a bursary from the British Maternal and Fetal Medicine Society and Twins Trust. The funder has no role in the design or conduct of the study, the collection, management, analysis or interpretation of data or manuscript preparation.

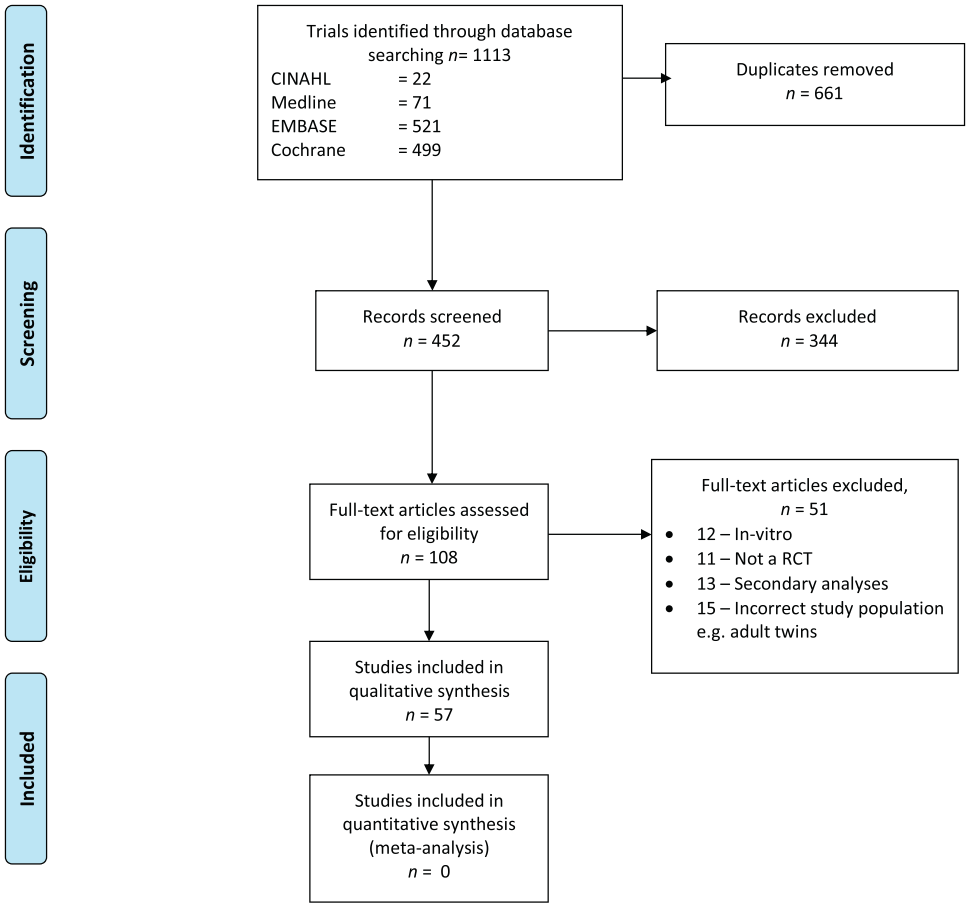

Fig. 1. PRISM flow diagram.

Results

Fig. 1 shows the process of selection for inclusion with a total of 1113 citations identified in the electronic search; 57 were deemed eligible for inclusion following full paper review. There were 48 RCTS and 9 follow-up studies.

Study characteristics

The majority of trials (61 %) were published between 2011–2019 (Table 1). 59 % recruited participants from multiple centres and 21 % recruited across multiple continents including low, middle and high incomes countries. Sample sizes ranged from 12 to 4603 participants with 51 % having a sample size between 101–500 participants. 65 % of the trials included all twin pregnancies, 12 % included DCDA twin pregnancies, 12 % included MCDA and DCDA twin pregnancies, and 11 % included only MCDA or MCMA and MCDA twin pregnancies. Intervention and prediction/ prognosis RCTs were both reported; 5 (9 %) papers were prediction/ prognosis RCTs and 52 (91 %) were intervention RCTs. Of the 52 intervention RCTs, 40 (77 %) were medical management and 12 (23 %) surgical management. Of those reporting medical interventions, 34 (85 %) related to interventions for preterm birth; RCTs investigating progesterone accounted for 28 % of all trials. Of the 12 RCTs reporting a surgical intervention, 6 (50 %) were related to interventions for TTTS (83 % of those whose inclusion criteria were MCMA or MCDA related to laser coagulation). Table 2 reports detailed characteristics of each included trial. 44 (77 %) trials followed up their participants within six months (77 %) and 3 (5 %) trials followed up their participants for more than two years, the maximum length of follow up was eight years.

Table 1
Summary of study characteristics.

		No. of trials (n = 57)	%
Year of publication	1971–1980	2	4
	1981–1990	8	14
	1991–2000	3	5
	2001–2010	9	16
	2011–2019	35	61
Multi-centre		33	59
Continent	Africa	9	16
	Asia	7	12
	Australia	1	2
	Europe	17	30
	North America	10	17
	South America	1	2
	Multiple continents	12	21
Sample size	< 50	11	19
	51–100	5	9
	101–200	13	23
	201–500	16	28
	501–2000	6	11
	2001–5000	4	7
	not documented	2	3
Twin type	All twins	37	65
	DCDA	7	12
	MCDA & DCDA	7	12
	MCDA	2	4
	MCMA & MCDA	4	7
RCT type	Prediction/ Prognosis	5	9
	Intervention	52	91
	- Medical	40	77
	- Surgical	12	23
Maximum length of follow up	0 months - ≤ 6 months	44	77
	> 6 months - ≤ 12 months	1	2
	> 12 months - ≤ 24 months	4	7
	> 24 months	3	5

Outcomes

There were 1257 verbatim outcomes reported within 57 trials between the years 1971–2019.

Outcome classification

Of the 1257 outcomes, 20 % were classified as primary outcomes, 64 % as secondary outcomes and 16 % were unclassified which was seen in 16/57 trials (28 %). Outcome classification has increased over recent years from 0 to 50 % between 1971–2000 to 78–83 % between 2001–2019.

Outcome domains: and unique outcomes

The 1257 outcomes were then grouped and classified into outcome domains according to the OMERACT 2.0 filter and further classified into 170 unique outcomes. The core area 'Life impact' consisted of 2 outcome domains: - 'Parental' which had 8 unique outcomes and 'Infant' which has 7 unique outcomes. The core area 'Pathophysiology/Manifestations' comprised of the 5 outcome domains labelled as: - 'Fetal' which has 12 unique outcomes; 'Delivery' which has 29 unique outcomes; 'Neonatal' which has 50 unique outcomes; 'Maternal Investigations' which has 9 unique outcomes and 'Maternal Morbidity' which has 29 unique outcomes. The core area 'Resource use/Economical impacts' consists of 12 outcomes. The core area 'Death' has 13 unique outcomes. (Table 3 Summarises the outcomes classified according to OMERACT 2.0)

Fig. 2 shows the proportion of outcome domains that were reported by trials within different timeframes. Initially only four outcome domains were reported (Neonatal, Delivery, Survival, and Maternal Investigations) this increased over time and consequently nine domains have been reported. The most frequent and consistent domains reported by trials are 'Neonatal' which was reported in 44/57 (77 %) of trials, 'Delivery' which was reported in 40/57 (70 %) of trials and 'Survival' which was reported in 38/57 (67 %) of trials (Fig. 3). The outcome domains that are least reported by trials are 'Infant' which has been reported in 10/57 trials (18 %) and 'Parental' which was reported in 5/57 (9 %) trials (Table 2). The outcomes within these domains are long term outcomes and/ or patient reported outcomes and it wasn't until 2001 that both Infant and Parental outcomes were reported more frequently (Fig. 2).

As shown in Table 4 the three most frequently reported outcomes were 'Side effects from the intervention' which was reported 85/1257 (7 %) times by 12/57 (21 %) trials and was measured in 72 different ways. 'Preterm Birth' was reported 77/1257 (6 %) times in 26/57 (45 %) trials and measured in 18 different ways; and 'Mode of Delivery' was reported 54/1257 (4 %) times in 24/57 (42 %) trials and measured in 16 different ways (Table 6 shows the different measurement variations and definitions used for each of the three most reported outcomes). Is it important to note that the number of times an outcome is reported will not correlate to the number of trials that have reported the outcome; this is because each trial will often use more than one outcome measure to report a unique outcome. For instance one trial may have measured 'Mode of Delivery' as the number of cesarean sections and the number of vaginal births; in this case one trial will have reported the outcome 'Mode of Delivery' twice. Therefore, if unique outcomes' measures are heterogeneous it may appear to be more frequently reported e.g. 'Side effects from intervention' is the most heterogeneous with 72 different measures and although it has been reported 85 times is has only been reported by 12 trials. Thus, it is important to evaluate which outcomes were most commonly reported by each trial. As seen in ,Table 5 the three outcomes reported most by trials are: - 'Birthweight', which was

Table 2
Detailed Study Characteristics per trial.

First Author	Year of Publication	Study Type	Type of RCT	Type of intervention	Sample size (n)	Country of Origin	Multi-Continent	Twin Type	Topic	Interventions
Marivate	1977	RCT	Intervention	Medical	46	South Africa	No	All Twin Types	Preterm labour	Fenterol
O'Connor	1979	RCT	Intervention	Medical	49	Ireland	?	All Twin Types	pregnancy prolongation	Ritodrine
Skjaerris	1983	RCT	Intervention	Medical	50	Sweden	No	All Twin Types	Preterm birth	Turbutaline
Saunders	1985	RCT	Intervention	Medical	212	Zimbabwe	Yes	All Twin Types	pregnancy prolongation	Hospital admission
Rabinovici	1987	RCT	Intervention	Surgical	33	Israel	No	All Twin Types	poor outcomes	Cesarean section
Crowther	1990	RCT	Intervention	Medical	118	Zimbabwe	No	All Twin Types	Pregnancy duration	Hospital admission
MacLennan	1990	RCT	Intervention	Medical	141	Australia	Yes	All Twin Types	Preterm birth	Hospital admission
Knuppel	1990	RCT	Prediction/ Prognosis	n/a	58	America	Yes	All Twin Types	Preterm labour detection	Home uterine activity monitoring
Saari-Kemppainen, A	1990	RCT	Prediction/ prognosis	n/a	148	Finland	Yes	All Twin Types	Poor outcomes	UUS
Ashworth	1990	RCT	Intervention	Medical	160	United Kingdom	No	All Twin Types	Preterm birth	Salbutamol
Italian Study of Aspirin in Pregnancy	1993	RCT	Intervention	Medical	1106	Italy	Yes	All Twin Types	PIH/IUGR	Asprin
Caspi	1994	RCT	Intervention	Medical	47	Israel	No	All Twin Types	PIH/IUGR	Asprin
Suzuki	1999	RCT	Intervention	Medical	36	Japan	No	All Twin Types	Birth outcomes	Induction of Labour
Giles	2003	RCT	Prediction/ Prognosis	n/a	539	Multiple Countries		All Twin Types	Poor outcomes	Doppler USS
Senat	2004	RCT	Intervention	Surgical	142	Multiple Countries		MCMA or MCDA	TTTS	Laser coagulation VS Amnioreduction
Moise	2005	RCT	Intervention	Surgical	73	America	Yes	MCMA or MCDA	TTTS	Amnioreduction VS Septostomy
Crombleholme	2007	RCT	Intervention	Surgical	42	America	Yes	MCMA or MCDA	TTTS	Amnioreduction VS Laser coagulation
Olsen	2007	RCT	Intervention	Medical	367	Multiple Countries		All Twin Types	Pregnancy duration	Fish oil
Norman	2009	RCT Follow up study	Intervention	Medical	500	United Kingdom	Yes	All Twin Types	Preterm birth	Progesterone
Briery	2009	RCT	Intervention	Medical	30	America	No	All Twin Types	Preterm birth	Progesterone
Eddama	2010	RCT Follow up study	Intervention	Medical	500	United Kingdom	Yes	All Twin Types	Cost effectiveness	Progesterone
Elsheikhah	2010	RCT	Intervention	Medical	100	Eygpt	?	All Twin Types	Preterm birth	Progesterone
Cetingoz	2011	RCT	Intervention	Medical	150	Turkey	No	All Twin Types	Preterm birth	Progesterone
Coombs	2011	RCT	Intervention	Medical	240	America	Yes	DCDA	Preterm birth	Progesterone
Lim	2011	RCT	Intervention	Medical	671	Netherlands	Yes	All Twin Types	Preterm birth	Progesterone
Rode	2011	RCT	Intervention	Medical	677	Multiple Countries		DCDA	Preterm birth	Progesterone
Dodd	2012	RCT	Intervention	Surgical	235	Multiple Countries		All Twin Types	Poor outcomes	Elective birth
Aboulghar	2012	RCT	Intervention	Medical	313	Eygpt	No	DCDA	Preterm birth	Progesterone
Serra	2012	RCT	Intervention	Medical	290	Spain	Yes	DCDA	Preterm birth	Progesterone
Barrett	2013	RCT	Intervention	Surgical	2804	Multiple Countries		DCDA or MCDA	Poor outcomes	Cesarean section
Liem	2013	RCT	Intervention	Medical	813	Netherlands	Yes	All Twin Types	Poor outcomes	Pessary
Senat	2013	RCT	Intervention	Medical	165	France	Yes	DCDA or MCDA	Pregnancy duration	Progesterone
Priyadarshini	2013	RCT	Intervention	Medical	12	India	No	All Twin Types	Preterm labour	Ritodrine VS Nifedipine
Carrick-Sen	2014	RCT	Intervention	Medical	162	United Kingdom	Yes	All Twin Types	Depression	Parent Education Classes
Awwad	2014	RCT	Intervention	Medical	293	America	No	All Twin Types	Preterm birth	Progesterone
Slaghekke	2014	RCT	Intervention	Surgical	274	Multiple Countries		MCDA	TTTS	Soloman technique VS Laser coagulation
Fahmy	2015	RCT	Intervention	Medical	60	Eygpt	No	All Twin Types	PPH	Carbetocin
Hutton	2015	RCT Follow up study	Intervention	Surgical	2570	Multiple Countries		DCDA	Long-term outcomes	Cesarean section

Table 2 (*Continued*)

First Author	Year of Publication	Study Type	Type of RCT	Type of intervention	Sample size (n)	Country of Origin	Multi-Continent	Twin Type	Topic	Interventions
Gliozheni	2015	RCT	Intervention	Medical	218	?	?	All Twin Types	Preterm birth	Pessary
Brizot	2015	RCT	Intervention	Medical	390	America	No	DCDA or MCDA	Preterm birth	Progesterone
McNamara	2015	RCT Follow up study	Intervention	Medical	?	United Kingdom	Yes	All Twin Types	Long-term outcomes	Progesterone
Asztalos	2016	RCT Follow up study	Intervention	Surgical	4603	Multiple Countries		DCDA or MCDA	Long-term outcomes	Cesarean section
Gordon	2016	RCT	Prediction/ Prognosis	n/a	125	America	Yes	DCDA or MCDA	Pregnancy duration	TV cervical length scan
Goya	2016	RCT	Intervention	Medical	137	Spain	Yes	All Twin Types	Preterm birth	Pessary
Nicolaides	2016	RCT	Intervention	Medical	1180	Multiple Countries		All Twin Types	Preterm birth	Pessary
El-Refaie	2016	RCT	Intervention	Medical	322	Eygpt	No	DCDA or MCDA	Preterm birth	Progesterone
Vedel	2016	RCT Follow up study	Intervention	Medical	498	Danish	Yes	DCDA	Preterm brith	Progesterone
Van Klink	2016	RCT Follow up study	Intervention	Surgical	216	Multiple Countries		MCDA	Long-term outcomes	Soloman technique VS Laser coagulation
Shinar	2017	RCT	Intervention	Medical	87	Israel	No	All Twin Types	Anaemia	Iron
Ali	2017	RCT	Intervention	Medical	120	Eygpt	No	All Twin Types	Amemia	Iron
Quintero	2017	RCT	Intervention	Surgical	20	America	?	MCMA or MCDA	long term outcomes	Laser coagulation
Berghella	2017	RCT	Intervention	Medical	46	America	Yes	DCDA or MCDA	Preterm birth	Pessary
Mikami	2017	RCT	Intervention	Medical	171	Brazil	No	All Twin Types	Breastfeeding	Prenatal breastfeeding councelling
Dang	2018	RCT	Intervention	Medical	300	Vietnam	No	All Twin Types	Preterm birth	Cervical pessay VS Vaginal progesterone
Brocklehurst	2018	RCT	Prediction/ Prognosis	n/a	?	United Kingdom	Yes	All Twin Types	Poor outcomes	Computerised CTG interpretation
Hutton	2018	RCT Follow up study	Intervention	Surgical	2305	Multiple Countries		DCDA	Urinary incontinence	Cesarean section
Van 't Hooft	2018	RCT Follow up study	Intervention	Medical	133	Netherlands	Yes	All Twin Types	Long-term outcomes	Pessary

reported by 29/57 (50 %) trials and was reported 42/1257 (3 %) times using 7 different measures; 'Gestation at delivery' which was reported in 29/57 (50 %) trials and was reported 34/1257 (3 %) times using 7 different measures; 'Neonatal death' was reported by 27/57 (47 %) trials and was reported 36/1257 (3 %) times using 13 different measures (Table 7 shows the variation in their outcome measures).

The large variety of outcome measurements and definitions is seen across all unique outcomes with no single measure or definition being utilised for any of the 170 unique outcomes that were reported more than once. Furthermore, 23 % of verbatim outcomes had not been defined; and those that were defined, were poorly defined and often not based on any standardised measurement. This was further complicated as some trials reported their outcomes as a continuous variable whilst others reported the outcome dichotomised. For instance, preterm birth was measured by the number of gestational weeks the baby was at birth and others reported the number of babies that were born before 37 weeks. Trials also differed in their choice of common denominator, as some trials reported the number of pregnancies and others reported the number of babies that were affected by an outcome.

Quality assessment

Fig. 4 shows that 18 % of trials scored at a low risk of bias, with the area at highest risk of bias being outcome measures and selection of the reported result. This reflects the findings that most trials did not clearly define their outcome and report it.

Discussion

Main findings

Our review highlights the complexities and heterogeneity of outcomes in twin pregnancy clinical trials and a lack of standardisation of outcomes and their measures. Of note, this review identified that longer term outcomes for mother and baby(s) are rarely collected and long-term parent related outcomes have only been included in research since 2001. Furthermore, the inconsistencies within the outcome definitions and measurements identified and use of denominators for reporting of results introduces further diversity and bias. The three most reported outcomes were 'side effects of intervention', 'Pre-term delivery' and 'Mode of delivery'. The three most frequently reported outcomes by trials were 'Birth weight', 'Gestation at delivery' and 'Neonatal death'.

Strengths and limitations

To our knowledge this review is the first to provide a comprehensive summary and analysis of all outcome reporting in twin pregnancy RCTs and RCT follow-up studies and the strength lies within the methodology employed.

Currently there is on-going work aiming to establish the most efficient methodology for systematic reviews for COS development. It has been suggested that it may not be necessary to search multiple databases as outcome saturation can be reached regardless. Furthermore, it has also been suggested that outcomes

Table 3
Outcome classified according to OMERACT 2.0, their characteristics and reported percentages.

Area	Domain	Outcome	Reporting Frequency				Definition Reporting			Outcome Classcifcation		
			No. of trials that reported the outcome (n = 57)	%	No. of times the outcome was reported (n = 1257)	%	No. of outcomes that were defined	No. of different definitions used	No. of outcomes that were not defined	Primary	Secondary	Not stated
Pathophysiology/ Manifestations	**Delivery**	Preterm delivery	26	45.6	77	6.1	77	18	0	12	58	7
		Mode of delivery	24	42.1	54	4.3	54	16	0	2	46	7
		Preterm prolonged rupture of membranes	11	19.3	11	0.9	1	1	10	0	11	0
		Spontaneous preterm delivery	9	15.8	16	1.3	16	12	0	4	12	0
		Induction of labour	8	14.0	16	1.3	9	5	7	0	7	1
		Duration of treatment	6	10.5	7	0.6	7	7	0	2	3	2
		Elective preterm delivery	5	8.8	6	0.5	6	4	0	2	4	0
		Postpartum Haemorrhage	5	8.8	8	0.6	7	5	1	2	6	0
		Spontaneous labour	5	8.8	6	0.5	2	2	4	0	4	2
		Preterm labour	4	7.0	5	0.4	4	4	1	1	4	0
		Spontaneous delivery	4	7.0	4	0.3	3	3	1	1	2	1
		Duration of labour	3	5.3	9	0.7	9	9	0	0	7	2
		Blood loss	2	3.5	3	0.2	2	2	1	0	0	2
		Genital tract injury	2	3.5	9	0.7	9	9	0	0	9	0
		Intraoperative damage to the bladder, ureter or bowel	2	3.5	4	0.3	4	4	0	0	4	0
		Meconium at delivery	2	3.5	2	0.2	0	0	2	0	1	1
		Spontaneous rupture of membranes	2	3.5	2	0.2	2	2	0	0	2	0
		Amniotic fluid embolism	1	1.8	1	0.1	0	0	1	0	1	0
		Cardiotocogram abnormality during labour	1	1.8	1	0.1	1	1	0	0	1	0
		Duration of induction	1	1.8	2	0.2	2	2	0	0	0	2
		Epidural	1	1.8	1	0.1	0	0	1	0	1	0
		Hysterectomy resulting from birth	1	1.8	1	0.1	1	1	0	0	1	0
		Placental weight	1	1.8	1	0.1	0	0	1	0	0	1
		Prolonged rupture of membranes	1	1.8	1	0.1	0	0	1	0	0	1
		Reduced isoflurane concentration	1	1.8	1	0.1	0	0	1	0	0	1
		Required methergine	1	1.8	1	0.1	0	0	1	0	0	1
		Uterine hyperactivity	1	1.8	1	0.1	0	0	1	0	0	1
		Uterine rupture	1	1.8	1	0.1	1	1	0	0	0	1
		Uterine tone after delivery	1	1.8	2	0.2	2	2	0	0	0	2
	Neonatal	Birthweight	29	50.9	42	3.3	21	6	21	3	24	29
		Gestation at delivery	29	50.9	34	2.7	7	6	27	5	19	10
		Admission to higher level of care	27	47.4	37	2.9	37	14	0	7	24	6
		Respiratory distress syndrome	19	33.3	22	1.8	5	5	17	6	13	3
		Intraventricular haemorrhage	17	29.8	20	1.6	15	10	5	8	12	0
		Low apgar score	16	28.1	26	2.1	25	16	1	3	16	7
		Low birthweight	16	28.1	43	3.4	43	13	0	1	29	13
		Necrotizing Enterocolitis	16	28.1	17	1.4	8	8	9	6	11	0
		Sepsis	15	26.3	16	1.3	10	7	6	5	11	0
		Intrauterine growth restriction	11	19.3	14	1.1	13	9	1	4	7	3
		Retinopathy of prematurity	11	19.3	12	1.0	2	2	10	2	10	0
		Bronchopulmonary dysplasia	8	14.0	8	0.6	4	4	4	4	5	0
		Duration of admission to higher level of care	8	14.0	10	0.8	10	6	0	1	9	0
			7	12.3	8	0.6	8	7	0	4	4	0

Table 3 (*Continued*)

Area	Domain	Outcome	Reporting Frequency				Definition Reporting			Outcome Classcifcation		
			No. of trials that reported the outcome (n = 57)	%	No. of times the outcome was reported (n = 1257)	%	No. of outcomes that were defined	No. of different definitions used	No. of outcomes that were not defined	Primary	Secondary	Not stated
		Intubation and mechanical ventilation										
		Patent ductus arteriosus	7	12.3	7	0.6	1	1	6	1	6	0
		Apgar	6	10.5	10	0.8	10	7	0	0	2	8
		Pneumonia	6	10.5	6	0.5	1	1	5	2	4	0
		Respiratory support	5	8.8	6	0.5	3	3	3	1	5	0
		Seizures	5	8.8	5	0.4	2	2	3	2	3	0
		Assisted ventilation	4	7.0	7	0.6	4	4	3	4	3	0
		Jaundice	4	7.0	5	0.4	3	3	2	0	5	0
		Periventricular leukomalacia	4	7.0	6	0.5	1	1	5	2	4	0
		Poor cord gas results	4	7.0	5	0.4	5	5	0	3	2	0
		Chronic lung disease	3	5.3	3	0.2	2	2	1	2	1	0
		Cystic pericentricular leukomalacia	3	5.3	4	0.3	2	2	2	4	0	0
		Hypoglycaemia	3	5.3	3	0.2	0	0	3	0	2	1
		Resuscitation	3	5.3	4	0.3	3	3	1	2	2	0
		Ischemic injury	2	3.5	2	0.2	1	1	1	2	0	0
		Neonatal encephalopathy	2	3.5	2	0.2	2	2	0	2	0	0
		Neonatal treatments	2	3.5	4	0.3	4	4	0	2	2	0
		Severe birth trauma	2	3.5	10	0.8	10	9	0	10	0	0
		Transient tachypnea	2	3.5	2	0.2	0	0	2	1	0	1
		Abnormal consciousness level	1	1.8	2	0.2	2	2	0	2	0	0
		Anaemia	1	1.8	1	0.1	1	1	0	0	1	0
		Blood transfusion	1	1.8	2	0.2	2	2	0	0	2	0
		Congenital abnormalities at birth	1	1.8	4	0.3	4	3	0	0	4	0
		Head circumference	1	1.8	1	0.1	1	1	0	0	1	0
		Hemodynamic instability	1	1.8	1	0.1	1	1	0	0	1	0
		Hyperbilirubinemia	1	1.8	1	0.1	0	0	1	0	1	0
		Infection	1	1.8	1	0.1	1	1	0	0	1	0
		Life threatening events	1	1.8	1	0.1	0	0	1	0	1	0
		Meconium aspiration	1	1.8	1	0.1	0	0	1	1	0	0
		Meningitis	1	1.8	1	0.1	1	1	0	1	0	0
		Metabolic acidosis	1	1.8	1	0.1	0	0	1	0	1	0
		Neonatal morbidity	1	1.8	1	0.1	0	0	1	0	0	1
		Pneumothorax	1	1.8	1	0.1	0	0	1	1	0	0
		Porencephalic or parenchymal cyst	1	1.8	1	0.1	1	1	0	1	0	0
		Secondary apnoea	1	1.8	1	0.1	0	0	1	0	0	1
		Stroke	1	1.8	1	0.1	0	0	1	1	0	0
		Ventricular dilatation	1	1.8	1	0.1	1	1	0	1	0	0
	Fetal	Fetal malformations	7	12.3	14	1.1	11	10	3	0	13	1
		Fetal complications	2	3.5	2	0.2	0	0	2	0	0	2
		Abnormal umbilical artery Doppler	1	1.8	1	0.1	1	1	0	0	1	0
		Amniondelhiscence (membrane seperation)	1	1.8	1	0.1	0	0	1	0	1	0
		Amniotic band injury	1	1.8	1	0.1	0	0	1	1	0	0
		Arterial infarction	1	1.8	1	0.1	1	1	0	1	0	0
		Bizygotic	1	1.8	1	0.1	0	0	1	0	0	1
		Gestation age at treatment	1	1.8	1	0.1	1	1	0	0	0	1
		Iatrogenic monoamnioticity	1	1.8	1	0.1	0	0	1	0	1	0
		Monozygotic	1	1.8	1	0.1	0	0	1	0	0	1
		Twin-to-Twin Transfusion Syndrome (TTTS)	1	1.8	1	0.1	1	1	0	1	0	0
		Twin Anemia Polycythemia Sequence (TAPS)	1	1.8	1	0.1	1	1	0	1	0	0
			13	22.8	16	1.3	8	7	8	1	14	1

Table 3 (*Continued*)

Area	Domain	Outcome	Reporting Frequency				Definition Reporting			Outcome Classcifcation		
			No. of trials that reported the outcome (n = 57)	%	No. of times the outcome was reported (n = 1257)	%	No. of outcomes that were defined	No. of different definitions used	No. of outcomes that were not defined	Primary	Secondary	Not stated
	Maternal Morbidity	Hypertensive disorders										
		Side effects from intervention	12	21.1	85	6.8	85	72	0	0	85	0
		Diabetes	7	12.3	7	0.6	6	5	1	0	7	0
		Intrauterine infection	7	12.3	10	0.8	1	1	9	0	10	0
		Thromboembolic event	6	10.5	10	0.8	6	6	4	3	7	0
		Haematological disturbances	5	8.8	7	0.6	7	6	0	0	6	1
		Genitourinary infection	3	5.3	4	0.3	2	2	2	0	4	0
		Antepartum haemorrhage	2	3.5	2	0.2	1	1	1	0	2	0
		Bowel obstruction after delivery	2	3.5	2	0.2	2	2	0	0	2	0
		Obstetric Cholestasis	2	3.5	2	0.2	1	1	1	0	2	0
		Paralytic ileus	2	3.5	2	0.2	1	1	1	0	2	0
		Pneumonia	2	3.5	2	0.2	1	1	1	1	1	0
		Primary pulmonary hypertension	2	3.5	2	0.2	0	0	2	1	1	0
		Sepsis	2	3.5	3	0.2	2	2	1	2	1	0
		Wound infection	2	3.5	8	0.6	8	6	0	4	4	0
		Urinary, fecal or flatal incontinence	2	3.5	2	0.2	2	2	0	0	1	1
		Acute respiratory distress	1	1.8	1	0.1	0	0	1	1	0	0
		Bleeding at placental surface	1	1.8	1	0.1	0	0	1	0	1	0
		Liver disease	1	1.8	1	0.1	1	1	0	0	0	1
		Maternal complications	1	1.8	1	0.1	1	1	0	0	0	1
		Maternal morbidity	1	1.8	1	0.1	0	0	1	0	0	1
		Neurological disturbances	1	1.8	1	0.1	1	1	0	0	1	0
		Polyhydramnios	1	1.8	1	0.1	0	0	1	0	1	0
		Pulmonary odema	1	1.8	1	0.1	0	0	1	0	1	0
		Renal insufficiency	1	1.8	1	0.1	1	1	0	0	1	0
		Respiratory arrest	1	1.8	1	0.1	0	0	1	0	1	0
		Respiratory depression syndrome	1	1.8	1	0.1	0	0	1	0	1	0
		Maternal disability or incapacity	1	1.8	1	0.1	0	0	1	0	1	0
		Stroke	1	1.8	1	0.1	1	1	0	0	1	0
	Maternal Investigations	Cervical measurement	4	7.0	11	0.9	10	10	1	0	3	8
		Ferritin	2	3.5	3	0.2	3	3	0	0	3	0
		Haemoglobin	2	3.5	7	0.6	7	7	0	2	5	0
		Increased liver enzymes	2	3.5	2	0.2	0	0	2	0	2	0
		Haematocrit	1	1.8	2	0.2	2	2	0	1	1	0
		Maternal weight gain during pregnancy	1	1.8	1	0.1	0	0	1	0	0	1
		Mean arterial blood pressure at delivery	1	1.8	11	0.9	11	11	0	0	0	11
		Mean heartrate value at delivery	1	1.8	11	0.9	11	11	0	0	0	11
		Number of observations	1	1.8	1	0.1	1	1	0	0	0	1
Death		Neonatal death	27	47.4	36	2.9	23	12	13	8	27	1
		Intrauterine death	24	42.1	33	2.6	16	12	17	9	21	3
		Perinatal death	13	22.8	14	1.1	6	5	8	3	7	4
		Live births	10	17.5	16	1.3	15	11	1	0	15	1
		Infant death	4	7.0	4	0.3	3	3	1	2	2	0
		Intrapartum death	4	7.0	5	0.4	5	5	0	1	4	0
		Maternal death	4	7.0	4	0.3	4	4	0	0	3	1
		Neonatal survival	4	7.0	11	0.9	11	11	0	7	4	0
		Infant survival	2	3.5	7	0.6	7	7	0	6	1	0
		Miscarriage	2	3.5	2	0.2	1	1	1	0	0	2
			1	1.8	1	0.1	0	0	1	1	0	0

Table 3 (*Continued*)

Area	Domain	Outcome	Reporting Frequency				Definition Reporting			Outcome Classcifcation		
			No. of trials that reported the outcome (n = 57)	%	No. of times the outcome was reported (n = 1257)	%	No. of outcomes that were defined	No. of different definitions used	No. of outcomes that were not defined	Primary	Secondary	Not stated
		Death or survival with neurodevelopmental disability										
		Perinatal and infant death	1	1.8	1	0.1	0	0	1	0	1	0
		Sudden infant death syndrome	1	1.8	1	0.1	0	0	1	0	1	0
Life Impact	**Parental**	Breastfeeding	4	7.0	10	0.8	10	10	0	4	5	1
		Psychological health	2	3.5	22	1.8	22	22	0	1	19	2
		Relationship health	2	3.5	5	0.4	3	3	2	0	3	2
		Satisfaction with motherhood	2	3.5	4	0.3	4	4	0	0	3	1
		Paternal psychological health	1	1.8	2	0.2	2	2	0	0	2	0
		Quality of life	1	1.8	2	0.2	2	2	0	0	0	2
		Satisfaction with method of delivery	1	1.8	1	0.1	1	1	0	0	0	1
		Sleep	1	1.8	3	0.2	3	3	0	0	3	0
	Infant	Neurodevelopmental impairment	10	17.5	37	2.9	37	36	0	28	4	5
		Poor health	3	5.3	20	1.6	20	17	0	9	0	11
		Cerebral palsy	2	3.5	4	0.3	4	4	0	4	0	0
		Hearing impairment	2	3.5	2	0.2	2	2	0	1	0	1
		Growth impairment	1	1.8	5	0.4	5	5	0	0	0	5
		Physiological impairment	1	1.8	9	0.7	9	9	0	9	0	0
		Visual impairment	1	1.8	1	0.1	1	1	0	0	0	1
Resource Use/ Economical		Corticosteriods for lung maturation	11	19.3	11	0.9	11	11	0	0	11	0
		Tocolytic therapy	11	19.3	12	1.0	12	2	0	0	12	0
		Antenatal hospitalisation	10	17.5	14	1.1	14	11	0	1	6	7
		Duration of hospitalisation	8	14.0	4	0.3	4	4	0	0	4	0
		Cerclage placed	4	7.0	4	0.3	1	1	3	0	4	0
		Blood transfusion	3	5.3	3	0.2	0	0	3	0	2	2
		Hospitalisation	2	3.5	2	0.2	0	0	2	0	2	0
		Activity restriction	1	1.8	2	0.2	1	1	1	0	2	0
		Laparotomy	1	1.8	1	0.1	1	1	0	0	1	0
		Magnesium sulphate for neuro protection	1	1.8	1	0.1	1	1	0	0	1	0
		Postnatal hospitalisation	1	1.8	5	0.4	5	4	0	0	0	5
		Intervention cost difference	1	1.8	8	0.6	8	8	0	8	0	0

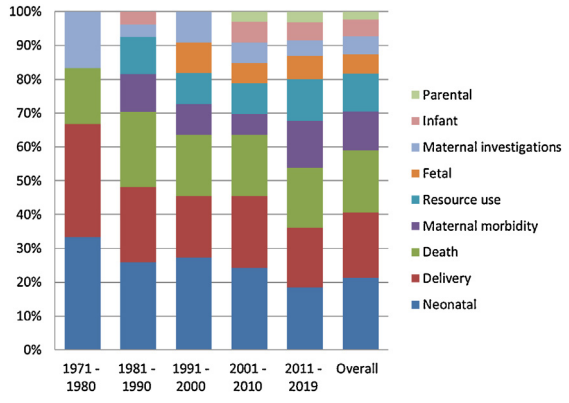

Fig. 2. Proportion of outcome domains reported by trials within each timeframe.

need only be collected by one reviewer as there is a low risk of error when collecting outcomes as opposed to numerical data [24]. However, our review has followed the standardised data collection within systematic review methodology as we wanted to ensure a rigorous approach. Additionally, all outcomes were collected regardless of classification. Some COS developers have collected primary outcome data only; deeming them to be of upmost importance, yet of the 1257 outcomes collected in this review, 80 % were not classified as primary outcomes and therefore would have been missed. Furthermore, bias would also be introduced during the data collection as outcome classification has only been adopted recently meaning the outcomes gathered would only be from the latter years. However, it could be argued that older outcomes may be outdated as they reflect the interventions/ complications of that era and that as medicine advances the complications of that era change and outcomes that are reported will adapt to this. Nevertheless, if outcomes have truly become outdated they will be eliminated during the Delphi survey.

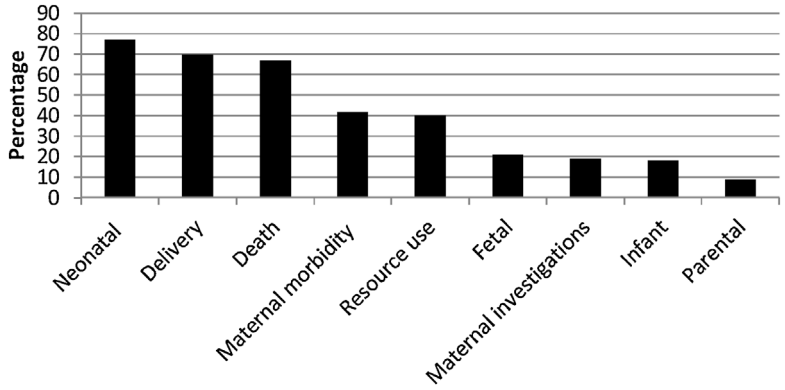

Fig. 3. Percentage of trials that reported each outcome domain.

Table 4
Outcomes most frequently reported.

Outcome Domain	Outcome	Number of times reported (Total number outcomes *n* = 1257)	Number of trials that reported the outcome (Total number of studies *n* = 57)	Number of different definitions/measures
Maternal morbidity	Side effects from intervention	85 (7 %)	12 (21 %)	72
Delivery	Preterm delivery	77 (6 %)	26 (45 %)	18
Delivery	Mode of delivery	54 (4 %)	24 (42 %)	16

Table 5
Outcomes that were reported in the most trials .

Outcome Domain	Outcome	Number of trials that reported the outcome (Total number of studies *n* = 57)	Number of times reported (Total number of outcomes *n* = 1257)	Number of different definitions/ measures
Neonatal	Birthweight	29 (50 %)	42 (3 %)	6
Neonatal	Gestation at delivery	29 (50 %)	34 (3 %)	6
Survival	Neonatal death	27 (47 %)	36 (3 %)	12

A limitation of this review is that we restricted the inclusion criteria to RCTs and RCT follow up studies; it could be argued that some outcomes may only be present in observational studies. However, RCTs are considered to be of the highest quality and so are most likely to influence clinical practice, therefore outcomes reported in these trials should be the most important and relevant. In addition, during the Delphi Survey twin experts will have the opportunity to suggest outcomes that they feel were missed which will minimise this risk. Moreover, the RCT follow up trials included within this review identified important long term patient reported outcomes such as' infant neurodevelopmental impairment', 'Cerebral Palsy', and 'visual impairment'. These outcomes may be crucial as they not only have lifelong consequences for the child and their family but will also increase health care costs significantly.

Another limitation of this review was the degree of subjectivity when categorising verbatim outcomes into unique outcomes as many were poorly defined or closely inter-related. For instance, one trials' outcome may have been postpartum hemorrhage measured by the requirement of a blood transfusion however another trial may have reported blood transfusion as an outcome but not defining its measure i.e. a blood transfusion due to postpartum hemorrhage. This was exacerbated by the use of neonatal composite outcomes which was an unforeseen challenge during categorisation. To overcome this we made consensus-led clear decisions involving all authors and our patient representative. At the time of outcome categorisation there was no clear guidance for COS developers clarifying or standardising the way in which outcomes were categorised. However, literature has since been published which discusses the importance of verbatim outcomes being categorised into outcomes with the same 'original meaning' [25] and so supports the method used.

Interpretation

This review suggests that outcomes likely to be of importance to parents and long term outcomes are not well incorporated within research. One possible reason for this is the lack of patient involvement when trials are designed. Our research supports this, as the outcome domains most frequently and consistently reported by trials were 'Neonatal', 'Delivery' and Survival' and these outcomes reflect the questions identified by clinicians and researchers. The lack of patient involvement has become widely recognised and the importance of engaging them in research is being increasingly acknowledged [24,26–29]. This is vital as researchers can only be certain that interventions are being evaluated in a way that is relevant to the target population if parents' perspectives are considered [30]. Likewise, it is debatable whether trials have followed up their participants for long enough to understand the effects of the intervention as only three trials followed up their participants for more than two years and prior to 2014 no trials had followed up their participants for more than six months. Fortunately, the scope of research has widened and researchers have recognised the importance of long-term follow

Table 6
Outcome measures used to evaluate the three most frequently reported outcomes.

1. Side effects of intervention Outcome measure (n = 72)	No. times reported (n)
Abdomen pain at 24 weeks gestation	1
Abdomen pain at 36 weeks gestation	1
Black staining to stool at 24 weeks gestation	1
Black staining to stool at 36 weeks gestation	1
Diarrhoea at 24 weeks gestation	1
Diarrhoea at 36 weeks gestation	1
Loss of appetite at 24 weeks gestation	1
Loss of appetite at 36 weeks gestation	1
Metallic taste in the mouth at 24 weeks gestation	1
Metallic taste in the mouth at 36 weeks gestation	1
Nausea and vomiting at 24 weeks gestation	1
Nausea and vomiting at 36 weeks gestation	1
No side effects at 24 weeks gestation	1
No side effects at 36 weeks gestation	1
Acne	1
Allergic reactions	1
Any side effects	1
Bloating	1
Breast tenderness	1
Bruising	1
Cervical tear from pessary	1
Delay in labour	1
Depression	1
Difficulty sleeping	1
Discharge and pain	1
Discomfort	1
Leading to discontinuation of study drug	1
Dizziness	1
Drowsiness	1
Excessive hair growth	1
Excessive weight gain	1
Fever	1
Fever or signs of infections	1
Fluid retention	1
Gastrointestinal upset	1
Gastrointestinal side effect	2
Generalised pruritus	1
Hair loss	1
Headache	3
Heavy bleeding from pessary	1
Injection site bruising	1
Injection site itching	1
Injection site pruritus	1
Injection site soreness	1
Itching	2
Jaundice	1
Joint pain	1
Nausea	1
Nausea, vomiting, and diarrhoea	1
Necrosis	1
Pain	2
Pelvic discomfort	1
Pessary replacement	1
Pessary repositing	1
Pessary repositioning without removal	1
Pruritus	1
Pubic pain	1
Rash	1
Reproductive system and breasts side effects	1
Rupture of the cervix	1
Skin rashes	1
Skin side effects	1
Soreness	1
Suspected fetal distress	1
Swelling	1
Systemic reaction	1
Uterine rupture	1
Virginal discharge	7
Vaginal discomfort	1
Vaginal infection	1
Vaginal irritation	1
Vaginal itching	3

2. Preterm delivery Outcome measure (n = 18)	No. times reported (n)
Delivered <22 weeks of gestation	1
Delivered <24 weeks of gestation	3
Delivered <27 weeks of gestation	1
Delivered <28 weeks of gestation	9
Delivered <30 weeks of gestation	3
Delivered <31 weeks of gestation	1
Delivered <32 weeks of gestation	14
Delivered <33 weeks of gestation	1
Delivered <34 weeks of gestation	15
Delivered <34 weeks of gestation(gestational age calculated before 20/40 at USS)	1
Delivered <35 weeks of gestation	4
Delivered <37 weeks of gestation	17
Spontaneous delivery <37 weeks of gestation (Gestational age calculated based on last menstrual period)	1
Spontaneous or induced delivery <37 weeks of gestation spontaneous or induced (Gestational age calculated based Dodowitz score)	2
Delivered between 30–34 weeks of gestation	1
Delivered between 34–35 weeks of gestation	1
Delivered between 34–37 weeks of gestation	1
Preterm delivery after failed tocolysis	1

3. Mode of delivery Outcome measure (n = 16)	No. times reported (n)
Delivered by cesarean section	18
Instrumental delivery or cesarean section	1
Delivered by elective cesarean section	7
Delivered by emergency cesarean section	7
Breech delivery	1
Instrumental delivery	5
Vaginal delivery	5
Vontouse delivery	2
Forceps delivery	1
Lower segment cesarean section	1
Cesarean section of the second twin	1
Labouring cesarean section	1
Emergency cesarean section for the second twin	1
Cesarean section for arrest in labour - 2 h with no cervical change and arrest of descent as 1 h without fetal decent despite ARM or antenatal oxytocin	1
Delivered by cesarean section for fetal distress	1
Cesarean section for maternal infection - maternal temperature of ≥38C, white blood count of ≥20,000/mm3 and C-reactive protein of ≥2	1

up with one trials' follow up being over eight years. However, as this gains momentum COS developers need to be mindful as implementing such methods can be costly on resources and time.

The heterogeneity and inconsistencies within outcome definitions and measurements reduces the quality of the results produced by data synthesis, which ultimately affects the validity of conclusions and reduces the meaningfulness of evidence-based guidelines. The use of different common denominators in twin pregnancy research, introduces bias as it will significantly affect the overall percentages. This is relatively unique to multiple pregnancy research. Therefore, even if trials' utilise the same outcome definitions, evidence could not be synthesised because of the diversity within the variable reporting.

The COS will overcome the inadequacies of current practice by developing a range of approved outcomes with agreed definitions, measurements, and common denominators which will be reported as a minimum in all trials. The outcomes gathered in this review are those that are deemed important by clinicians and researchers

Table 7
Outcome measures used to evaluate the three outcome reported most by trials.

1. Birthweight	
Outcome measure (n = 6)	No. times reported (n)
Birthweight of both twins	4
Birthweight of twin 1	7
Birthweight of twin 2	7
Birthweight of twins >38/40	1
Birthweight of recipient twin up to 30 days	1
Birthweight of donor twin	1
Not defined	21

2. Gestation at birth	
Outcome measure (n = 6)	No. times reported (n)
Last menstrual period, ovulation or ovum picked up in IVF cases and confirmed by 1 st or 2nd trimester USS	1
USS or last menstrual period using Naegeles rule	1
Maternal menstrual history, confirmed by USS - fetal crown rump length at 9–11 weeks	1
Menstrual history and confirmed by USS - crown-rump measurement of the bigger fetus at 11–13 weeks	1
Dubowitz scoring	2
Last menstrual period	1
Not defined	27

3. Neonatal Death	
Outcome measure (n = 12)	No. times reported (n)
Death <24 h	1
Death before discharge	4
Death between 2–7 days	1
Death between 8–28 days	1
Death <27 days	1
Death <28 days after delivery	5
Death <28 days after delivery excluding abnormalities	1
< 6 weeks after expected term date	1
Early neonatal death	2
Early neonatal death excluding abnormalities	1
Death of the donor twin	1
Death of the recipient twin	1
Not defined	13

and were collected from RCTs in low, middle and high income countries which will aid the international generalisability of the COS.

The next step in the COS development is identifying outcomes that are important to parents via interviews. The outcomes identified will be combined with the outcomes from this review to form a comprehensive outcome inventory. The outcomes for the COS will be determined using the modified Delphi method and a consensus meeting, with all stakeholders, will take place to finalise the measurements and common denominators for each outcome [18,19].

The development of a COS for twin pregnancy will ultimately improve patient care as it will enable clinicians to make better informed decisions and ensure that research is meaningful to patients. However, it is important that clinicians also recognise that the COS for twin pregnancy will provide an overview of all twin pregnancies. This systematic review details the difficulty of assessing outcomes in twin pregnancy which was mainly due to the vast number of variables e.g. outcomes could evaluate the pregnancy as whole or they could evaluate each individual baby or they could depend on the type of twin pregnancy. Therefore, there is also a need for a COS relevant to unique conditions to be developed - such as a COS for Twin-to-Twin Transfusion syndrome [31] to further aid data synthesis in such conditions. Researchers also need to be aware of the complexities of statistical analysis related to outcomes in multiple pregnancies [32].

Conclusion

Our review has demonstrated the complexity of outcome reporting in twin pregnancy clinical trials and the clear deficiency of patient-centred outcomes and long-term outcomes for the babies. The heterogeneity of outcome selection results from the need to address maternal, single fetal, double fetal and different types of twinning.

Contribution to authorship

NF – study design; acquisition, analysis and interpretation of data, drafting and editing of manuscript

MH – second reviewer, data acquisition, editing of manuscript

VHM –study concept and design, second reviewer, data acquisition, analysis and interpretation; editing of manuscript

MK – study concept, editing of manuscript

RKM – study concept and design, third reviewer, data analysis and interpretation, editing of manuscript.

Funding

Funded by The British Maternal and Fetal Medicine Society and Twins Trust.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We would like to acknowledge Derek Yates, Clinical Librarian Birmingham Women's and Children's Hospital NHS Trust, for his

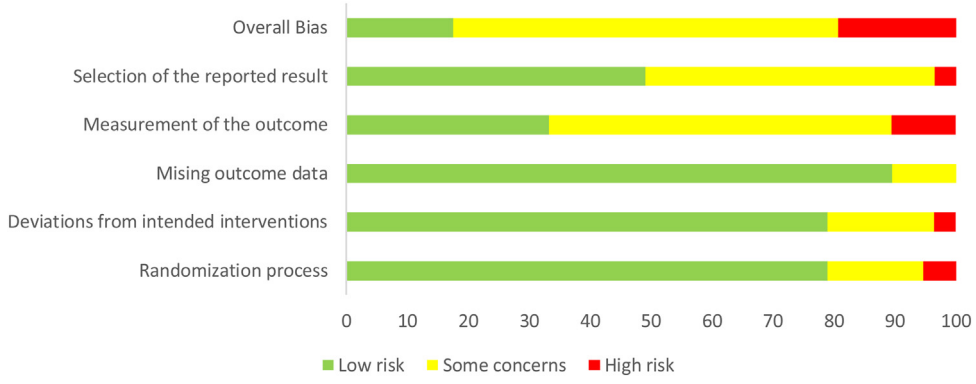

Fig. 4. RoB2 Assessment of 'risk of bias'.

assistance with the database searches and Alison Davies, Director of Quality Improvement Birmingham Women's and Children's Hospital NHS Trust for proof reading the review.

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