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*Imp*roving the *R*eporting of Clinical Trials of *In*fertility *T*reatments (IMPRINT): modifying the CONSORT statement†‡

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ABSTRACT: Clinical trials testing infertility treatments often do not report on the major outcomes of interest to patients and clinicians and the public (such as live birth) nor on the harms, including maternal risks during pregnancy and fetal anomalies. This is complicated by the multiple participants in infertility trials which may include a woman (mother), a man (father), and result in a third individual if successful, their offspring (child), who is also the desired outcome of treatment. The primary outcome of interest and many adverse events occur after cessation of infertility treatment and during pregnancy and the puerperium, which create a unique burden of follow-up for clinical trial investigators and participants. In 2013, because of the inconsistencies in trial reporting and the unique aspects of infertility trials not adequately addressed by existing Consolidated Standards of Reporting Trials (CONSORT) statements, we convened a consensus conference in Harbin, China, with the aim of planning modifications to the CONSORT checklist to improve the quality of reporting of clinical trials testing infertility treatment. The consensus group recommended that the preferred primary outcome of all infertility trials is live birth (defined as any delivery of a live infant $\geq$20 weeks gestations) or cumulative live birth, defined as the live birth per women over a defined time period (or number of treatment cycles). In addition, harms to all participants should be systematically collected and reported, including during the intervention, any resulting pregnancy, and during the neonatal period. Routine information should be collected and reported on both male and female participants in the trial. We propose to track the change in quality that these guidelines may produce in published trials testing infertility treatments. Our ultimate goal is to increase the transparency of benefits and risks of infertility treatments to provide better medical care to affected individuals and couples.

Key words: infertility trial / CONSORT / reporting / IMPRINT / modification

Introduction

Clinical trials of infertility treatments are challenging to conduct and to report (Schlaff, 2011). The existing Consolidated Standards of Reporting Trials (CONSORT) statement (Schulz *et al.*, 2010) does not cover all aspects of an infertility trial. For example, trials of infertility treatments generally involve multiple participants, including a potential mother and father one or both of whom may be the target of intervention. In addition, if the intervention succeeds, there is a pregnancy that may or may not lead to an infant (also the primary outcome of interest to all involved).

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Thus at a minimum, a successful outcome involves three individuals, one of whom does not exist at the start of the trial. This creates uncertainty on what to report on whom.

There is a natural time lag between the end of an episode of infertility treatment and the birth of an infant, which may result in loss to follow-up, primarily because obstetric and infant care is delivered by other providers. This contributes to incomplete reporting of outcomes and harms of treatment. Clinical trials in infertility frequently do not report items of critical importance regarding efficacy, such as ongoing pregnancy (Clarke *et al.*, 2010; Dapuzzo *et al.*, 2011) or live birth of a healthy infant, arguably the most important event (Min *et al.*, 2004). Rather they often focus on surrogate outcomes of varying clinical importance, such as ovulation rates, number of oocytes retrieved, embryo fertilization and implantation rates (Legro and Myers, 2004; Johnson, 2006). Reports on the safety of interventions include risks to females and males during infertility treatment, to the mother during the subsequent pregnancy and to fetuses and infants, including preterm delivery. In addition, fetal anomaly rates, developmental delays and other adverse infant outcomes (Wennerholm and Bergh, 2004) are variably reported or not mentioned at all (Dapuzzo *et al.*, 2011). This creates uncertainty on how long to report outcomes and harms in humans after completion of the infertility intervention (Vail and Gardener, 2003).

We sought to improve the quality of reporting of infertility trials by convening an expert conference of key stakeholders in the conduct and publishing of infertility trials to consider how to improve publication by including items of vital interest to infertile couples, clinicians and the public. We achieved a consensus on these items and drafted changes to the 22-item checklist of the CONSORT statement to provide guidance on what to collect on whom and for how long in infertility trials. Such guidance has already been achieved for other specialized types of clinical trials (Gagnier *et al.*, 2006; Piaggio *et al.*, 2006; Boutron *et al.*, 2008; MacPherson *et al.*, 2010).

Methods

We developed these changes in three phases, including a pre-meeting planning phase, the meeting itself and a post meeting review of results based on previous extensions to the CONSORT checklist (Gagnier *et al.*, 2006; Boutron *et al.*, 2008; MacPherson *et al.*, 2010), and published guidance for implementing such change (Moher *et al.*, 2010). In planning for the meeting, we sought to assemble a representative group of experienced investigators in trials of infertility treatments as well as the editors of the leading journals that publish fertility trials, *Fertility & Sterility* and *Human Reproduction*, to participate in the meeting. With the input of the Scientific Committee we framed topics of relevance to clinical trials of infertility and most invited participants were asked to prepare a lecture in their field of expertise for the open part of the meeting.

Invited participants included experts in reproductive medicine and reproductive endocrinology, andrology, maternal-fetal medicine, neonatology, traditional Chinese medicine, biostatistics and clinical trial study design, data safety monitoring and journal Editors. Invited participants ($N = 25$) were queried by email prior to the meeting about their suggested changes to the CONSORT checklist. We received comments from 11 individuals in the following distribution according to the checklist item (in descending order of frequency): Results (22 comments), Intervention (10 comments), Outcomes (9 comments), Introduction (6 comments), Title and Abstract (5 comments), Discussion (5 comments), Participants (3 comments), Sample size (4 comments), Blinding (2 comments), Statistical Methods (4 comments), Randomization (3 comments), Other information (3 comments) and Methods (2 comments).

The meeting was designed as a one and a half day open meeting with public lectures framing issues in infertility trials followed by a one and a half day closed meeting among the invited participants to achieve consensus. The Scientific Committee divided the three half day closed sessions into discussions about: (i) Main outcomes of infertility trials; (ii) Adverse events in infertility trials; and (iii) Participant issues in infertility trials. Each session was led by two members of the Scientific Committee and each suggested modification was discussed until consensus was achieved with a total of 20 modifications finally ($N = 20$). Representatives from the U.S. National Institutes of Health of the United States were unable to attend the meeting due to budgetary sequestration and one representative from China was unable to attend the closed meeting. After the meeting we circulated a draft summary report to all participants to ensure that it accurately represented the deliberations and decisions of the consensus group.

Results

The group recommended a revision to eight items in the CONSORT Checklist (Table I). The full amended CONSORT checklist is shown in Table II. Several of the revisions had multiple components. The item that generated the most discussion was the optimal primary outcome of an infertility trial with options ranging from an ongoing viable intrauterine pregnancy to a healthy child with normal development. The group decided that trials testing infertility treatments should report as the primary outcome: live birth with a definition based on gestational age (i.e. $\geq$20 weeks) reflecting the World Health Organization definition of live birth as a fetus exiting the body displaying signs of life such as movement, breathing or heartbeat (World Health Organization, 1993). While the group acknowledged that the ultimate goal of an infertility trial is a healthy baby who develops normally, and that ideally this outcome should always be reported, the difficulties in tracking this outcome and clearly defining it precluded it as a choice for the primary outcome of an infertility trial. Because most infertility trials involve multiple treatment cycles, cumulative live birth rates should also be reported in this context.

This discussion also overlapped with the potential harms of infertility treatment. The group recommended more complete tracking of potential harms of infertility treatment including ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy as well as adverse events during pregnancy and the neonatal/infancy period, including any fetal anomalies. To aid reporting of such events, the group developed a table of key potential harms to collect and report (Table III).

Discussion

We developed recommendations for modifications of the CONSORT checklist to improve the quality of reporting of trials of infertility treatments. Our suggested revisions were designed to aid transparency of trials, including requiring more complete characterization of the participants in an infertility trial, providing some uniform measure of pregnancy outcome (we chose live birth), and accounting for the major harms and risks to the participants in an infertility trial as well as the resulting fetus (es)/infant (s). While we see this checklist primarily of relevance to larger pragmatic randomized infertility trials, we believe it is also applicable to smaller randomized or prospective non-randomized or single intervention trials which pilot newer treatments. All such trials must be

Table I Summary of Proposed Modifications for Infertility Trials to the Consolidated Standards Of Reporting Trials (CONSORT) 2010 Statement (only items with modifications are included here, while the full checklist is shown in Table II).

Section	Topic	Item number	Current description	Consensus modification
Participants		4a	Eligibility criteria for participants	Characterize how infertility factors in male and female participants were evaluated, describe the definitions used, any preconception screening, and on which participants informed consent was obtained.
Interventions		5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	State the duration of the intervention noting when the treatment started and concluded. State the temporal relation of the intervention with randomization and pregnancy.
Outcomes		6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Clearly define the primary outcome. Reporting live birth (defined as a delivery ≥20 weeks gestation) is preferred (including gestational age, birthweight and sex of infant). When >1 cycle occurs or frozen embryos are transferred, the preferred outcome is cumulative live birth per woman. Secondary pregnancy outcomes that merit reporting are serum pregnancy, ongoing pregnancy (≥12 weeks), multiple pregnancy and an accounting of all pregnancy losses. Both male and female outcomes, other than live birth, could be the primary outcome and should be justified. When live birth is not the primary end-point and infertility treatment is given (for example, embryos are transferred), live birth should still be reported.
Results	Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	Report the numbers of couples who were screened and eligible
	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	State the duration of infertility (including whether it is primary or secondary), relevant obstetric history, and cause of infertility in females and in males.
	Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	The preferred unit of analysis is per randomized individual/couple (and not cycles or oocytes/embryos) for a specified period of time (preferably displayed with life table analysis). If per cycle analysis is used, it should be justified and must account for individuals receiving multiple cycles. Clearly describe what happens to all multiple pregnancies, including fetal reduction and vanishing gestations. Report multiple pregnancy outcome both per woman and per pregnancy. Separate out twin/triplets/quads/etc.
	Harms	19	All important harms or unintended effects in each group (for specific guidance, see CONSORT for harms Legro, Myers, 2004)	Report all important harms or unintended effects in each group (males, females, infants); during treatment (including both male and female partners), during pregnancy and around birth, and in infants after birth. Reportable harms include ovarian hyperstimulation syndrome, infection, bleeding, multiple pregnancy (see also Item 16) and maternal pregnancy complications, and harms or unintended effects on the fetus/newborn including congenital abnormalities, and major neonatal complications as well as infant developmental delays or medical problems.
Discussion	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Balance outcomes and any competing interests of female and male participants and infant.

Table II 2014 checklist of information to include when reporting a randomized trial of infertility treatment.*

Section/topic	Item number	Checklist item	Reported on page number
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants Characterize how infertility factors in male and female participants were evaluated, describe the definitions used, any preconception screening, and on which participants informed consent was obtained.	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered (State the duration of the intervention noting when the treatment started and concluded. State the temporal relation of the intervention with randomization and pregnancy.)	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed Clearly define the primary outcome. Reporting live birth (defined as a delivery ≥20 weeks gestation) is preferred (including gestational age, birthweight and sex of infant). For infertility trials, where >1 cycle occurs or where frozen embryos are transferred the preferred outcome is cumulative live birth per woman. Secondary pregnancy outcomes that merit reporting are serum pregnancy, ongoing pregnancy (≥12 weeks), multiple pregnancy and an accounting of all pregnancy losses. Both male and female outcomes, other than live birth, could be the primary outcome and should be justified. When live birth is not the primary end-point and infertility treatment is given (for example, embryos are transferred), live birth should still be reported.	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome Report the numbers of couples who were screened and eligible	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	

Continued

Table II *Continued*

Section/topic	Item number	Checklist item	Reported on page number
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group State the duration of infertility (including whether it is primary or secondary), relevant obstetric history, and cause of infertility in females and in males if possible.	
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups The preferred unit of analysis is per randomized individual/couple (and not cycles or oocytes/embryos) for specified period of time (preferably displayed with life table analysis). If per cycle analysis is used, it should be justified and must account for individuals receiving multiple cycles. Clearly describe what happens to all multiple pregnancies, including fetal reduction and vanishing gestations. Report multiple pregnancy outcome both per woman and per pregnancy. Separate out twin/triplets/quads/etc.	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) Report all important harms or unintended effects in each group (males, females, infants); during treatment (including both male and female partners), during pregnancy and around birth, and in infants after birth. Reportable harms include ovarian hyperstimulation syndrome, infection, bleeding, multiple pregnancy (see also Item 16) and maternal pregnancy complications, and harms or unintended effects on the fetus/newborn including congenital abnormalities, and major neonatal complications as well as infant developmental delays or medical problems.	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration, as well as the 2014 Harbin Consensus Document Explanation and Elaboration (see the Supplementary data for details) for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

registered with a clinical trial registry prior to enrolling the first patient, so it is possible to *a priori* capture these outcomes in the trial design. It is incumbent on all researchers to capture harms and pregnancy outcomes even in these smaller trials because they may serve as the basis for larger multi-center trials or become incorporated in systematic reviews. Incomplete reporting contributes to gaps in evidence-based infertility treatment (Johnson *et al.*, 2003).

A longer more detailed rationale paper of the suggested changes (The Harbin Consensus Conference Workshop Group, 2014, see Supplementary data for details) includes examples of ideal reporting and serves as an Explanation and Elaboration paper (Moher *et al.*, 2010). We will scrutinize published trials of infertility treatments subsequently to determine if our modifications to the CONSORT checklist have improved the quality of reported information related to participants, outcomes and harms of treatment. We also plan to re-convene a meeting within the next 5 years to formally review our experience and the need for further modifications or revisions to the CONSORT checklist. In the interim, we hope that medical journals will endorse their use, clinical researchers will incorporate the collection of these data into their trial design and reporting, and that ultimately medical care will improve

Table III Potential harms to participants in an infertility trial that merit reporting.

Time	Females*	Males*	Fetus/infant*
Delivery of the infertility intervention	Burden of treatment/stress,† OHSS,** bleeding, infection, adverse oocyte quality†	Burden of treatment/ stress,† adverse semen quality†	N.A.
Pregnancy	Multiple pregnancy, ectopic pregnancy, pregnancy loss (all trimesters), pregnancy-related hypertension,‡ Gestational diabetes,§ abnormal placentation,¶ gestational trophoblastic disease††		Adverse embryo quality,† fetal anomaly, Fetal Growth Restriction (FGR)‡‡
Delivery	Caesarean section/operative deliveries		Small or large for gestational age (SGA/LGA),§§ preterm delivery (PTD),¶¶ anomalies detected by obstetrical screening
Post-partum and neonatal/infancy	Thromboembolism, post-partum depression, lactation rates		Anomalies detected after birth, Neonatal Intensive Care Unit admission, length of stay

*A death of males and female parents and fetus/infant participating in trials should be reported.
**OHSS (Ovarian Hyperstimulation Syndrome) is an exaggerated and symptomatic response to ovulation induction therapy (Practice Committee of the American Society for Reproductive Medicine, 2003).
†There are currently no accepted standards for determining these parameters.
‡Pregnancy related hypertension includes pre-eclampsia defined as new onset hypertension with proteinuria after 20 weeks gestation, eclampsia defined as the development of seizures in a women with pre-eclampsia, and HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) (Bulletins—Obstetrics ACoP, 2002).
§Gestational Diabetes has varying definitions depending on country of origin. The USA uses a two-step screening approach with a 1 h 50 g oral glucose test followed by a 3 h 100 g oral glucose test (Vandorsten *et al.*, 2013), whereas most of the rest of the world uses a 2 h 75 g oral glucose test (International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger *et al.*, 2010).
¶Abnormal placentation includes placentia previa, placental abruption, placenta accreta, increta, and percreta.
††Gestational trophoblastic disease includes Hydatidiform mole (complete or partial), Persistent/invasive gestational trophoblastic neoplasia (GTN), Choriocarcinoma, and Placental site trophoblastic tumors.
‡‡FGR is most commonly defined as an ultrasound determined estimated fetal weight below the third percentile for gestational age (McIntire *et al.*, 1999).
§§SGA is most commonly defined as a weight below the 10th percentile for the gestational age. At term this is $\leq$2500 g. LGA is most commonly defined as a weight above the 10th percentile for the gestational age. At term this is $\geq$4000 g (Battaglia and Lubchenco, 1967).
¶¶PTD is defined by a delivery before 37 weeks gestation (Spong, 2013).

from the increased transparency of the risk/benefit ratio of infertility treatments (Johnson *et al.*, 2003).

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

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Conflict of interest

Dr Xiaoke Wu has received research funding from the National Clinical Trial Base in TCM, National Key Discipline/Specialty and the 'Longjiang Scholars' Program and 'Innovative Team' of Heilongjiang Province Universities. Dr Richard Legro has received funding from the NIH, the 'Longjiang Scholars Program' and the '1000-Plan Scholars' Program of the Chinese Government, has served as a chair of Steering Committee for the National Clinical Trial Base in TCM, a consultant to the NIH, FDA, Ferring Pharmaceuticals, AstraZeneca, and Euroscreen, is a member of the Board of Directors of the American Society of Reproductive Medicine and is an Associate Editor of *Fertility and Sterility* and *Seminars in Reproductive Medicine*, and on the editorial boards of *Endocrinology* and *Endocrine Reviews*. Dr Craig Niederberger, Co-Editor in Chief of *Fertility and Sterility*, Section Editor of *Journal of Urology*, and co-founder and Chief Technology Officer of NexHand. Dr Ernest H. Y. Ng has received research funding from Bayer Healthcare, Ferring, Merck Serono and MSD. Prof. Stefano Palomba is Co-Editor in Chief of *Journal of Ovarian Research*, Editor in Chief of *Current Drug Therapy* and Associate Editor of *Human Reproduction*; and declares no commercial conflict of interest. Dr Heping Zhang has received funding from the NIH, the 1000-plan Scholars Program of the Chinese Government, and served as a consultant to the Heilongjiang University of Chinese Medicine, China. Dr Robert Rebar serves as a Contributing Editor to NEJM Journal Watch Women's Health and has served on several Data Safety Monitoring Committees. Dr Antonio Pellicer is Co-Editor-in-Chief of *Fertility and Sterility* and reports ownership/stock of the following tech companies: BIOMEDICAL SUPPLY, S. L. (DIBIMED); UNISENSE FERTILITECH A/S; IVIOMICS S.L. Dr Richard Reindollar is Executive Director of the American Society of Reproductive Medicine and a recipient of NIH funding. Prof. Bart Fauser has received fees and grant support from the following companies (in alphabetic order); Actavis, Andromed, Ardana, COGI, Euroscreen, Finox Biotech, Ferring, GenOvum, Gedeon-Richter, Merck Serono, MSD, Organon, OvaScience, Pantharei Bioscience, PregLem, Roche, Schering, Schering Plough, Serono, Uteron, Watson

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