Improving the Reporting of Clinical Trials of Infertility Treatments (IMPRINT): modifying the CONSORT statement

Harbin Consensus Conference Workshop Group

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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 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 creates 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 after $\geq$20 weeks' gestation) 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 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. (Fertil Steril® 2014;102:952-9. ©2014 by American Society for Reproductive Medicine.)

Key Words: Infertility trial, CONSORT, reporting, IMPRINT, modification

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Clinical trials of infertility treatments are challenging to conduct and to report (1). The existing Consolidated Standards of Reporting Trials (CONSORT) statement (2) 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 of whom one or both 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). 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 obstetrical and infant care are delivered by other providers. This

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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 (3, 4) or live birth of a healthy infant, arguably the most important event (5). Rather, they often focus on surrogate outcomes of varying clinical importance, such as ovulation rates, number of oocytes retrieved embryo, and fertilization and implantation rates (6, 7). Reports on the safety of interventions include risks to women and men 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 (8) are variably reported or not mentioned at all (4). This creates uncertainty on how long to report outcomes and harms in humans after completion of the infertility intervention (9).

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 (10, 11, 12, 13).

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 (10, 11, 12) and published guidance for implementing such change (14). 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 and 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 e-mail before 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 1.5-day open meeting with public lectures framing issues in infertility trials followed by a 1.5-day closed meeting among the invited participants to achieve consensus. The Scientific Committee divided the three half-day closed sessions into discussions about: 1) Main outcomes of infertility trials: 2) Adverse events in infertility trials; and 3) 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 final total of 20 modifications ($n = 20$). Representatives from the National Institutes of Health of the United States were unable to attend the meeting owing 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 1). The full amended CONSORT checklist is shown in Table 2. 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 heart beat (15). Although 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 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 3)

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). Although we see this checklist primarily of relevance to larger pragmatic randomized infertility trials, we think it is also applicable

TABLE 1

Summary of proposed modifications for infertility trials to the Consolidated Standards of Reporting Trials (CONSORT) 2010 Statement (only items with modifications are included here; the full checklist is shown in Table 2).

Section	Topic	Item no.	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 from which participants informed consents were 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 to randomization and pregnancy.
Outcomes		6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥20 weeks' gestation) is preferred (including gestational age, birthweight, and sex of infant). When more than one 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 obstetrical history, and cause of infertility in women and men.
	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 (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, (7)	Report all important harms or unintended effects in each group (men, women, 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.

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TABLE 2

2014 checklist of information to include when reporting a randomized trial of infertility treatment.[a]

Section/topic	Item no.	Checklist item	Reported on page no.
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 from which participants informed consents were 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 to randomization and pregnancy.)	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed. Clearly define the primary outcome. Reporting live birth (defined as a delivery after ≥20 weeks' gestation) is preferred (including gestational age, birthweight, and sex of infant). For infertility trials, where more than one 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 (e.g., 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			

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TABLE 2

Continued.

Section/topic	Item no.	Checklist item	Reported on page no.
Title and abstract			
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	
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 obstetrical history, and cause of infertility in women and men 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 (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.	
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 prespecified 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	

[a] 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 Supplemental Material, (available online) for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomized trials, noninferiority and equivalence trials, nonpharmacologic 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.

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TABLE 3

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

Time	Women[a]	Men[a]	Fetus/Infant[a]
Delivery of the infertility intervention	Burden of treatment/stress,[c] OHSS,[b] bleeding, infection, adverse oocyte quality[c]	Burden of treatment/stress,[c] adverse semen quality[c]	
Pregnancy	Multiple pregnancy, ectopic pregnancy, pregnancy loss (all trimesters), pregnancy-related hypertension,[d] gestational diabetes,[e] abnormal placentation,[f] gestational trophoblastic disease[g]		Adverse embryo quality,[c] fetal anomaly, fetal growth restriction (FGR)[h]
Delivery	Cesearean section/operative deliveries		Small or large for gestational age (SGA/LGA),[i] preterm delivery (PTD),[j] anomalies detected by obstetrical screening
Postpartum and neonatal/infancy	Thromboembolism, postpartum depression, Lactation rates		Anomalies detected after birth, neonatal intensive care unit admission, length of stay

[a] A death of male or female parent or fetus/infant participating in trials should be reported.
[b] OHSS (ovarian hyperstimulation syndrome) is an exaggerated and symptomatic response to ovulation induction therapy (16).
[c] There are currently no accepted standards for determining these parameters.
[d] Pregnancy-related hypertension includes preeclampsia defined as new-onset hypertension with proteinuria after 20 weeks' gestation, eclampsia defined as the development of seizures in a women with preeclampsia, and HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (17).
[e] Gestational Diabetes has varying definitions depending on country of origin. The USA uses a two-step screening approach with a 1-hour 50-g oral glucose test followed by a 3-hour 100-g oral glucose test (18), whereas most of the rest of the world uses a 2-hour 75-g oral glucose test (19).
[f] Abnormal placentation includes placentia previa, placental abruption, placenta accreta, increta, and percreta.
[g] Gestational trophoblastic disease includes hydatidiform mole (complete or partial), persistent/invasive gestational trophoblastic neoplasia, choriocarcinoma, and placental site trophoblastic tumors.
[h] FGR is most commonly defined as an ultrasound-determined estimated fetal weight below the 3rd percentile for gestational age (20).
[i] SGA is most commonly defined as a weight below the 10th percentile for the gestational age. At term this is ≤2,500 g. LGA is most commonly defined as a weight above the 10th percentile for the gestational age. At term this is ≥4,000 g (21).
[j] PTD is defined by a delivery before 37 weeks' gestation (22).

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to smaller randomized or prospective nonrandomized or single-intervention trials that pilot newer treatments. All such trials must be registered with a clinical trial registry before 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 multicenter trials or become incorporated in systematic reviews. Incomplete reporting contributes to gaps in evidence-based infertility treatment (23).

A longer more detailed rationale paper of the suggested is available online, which includes examples of ideal reporting and serves as an Explanation and Elaboration paper (14). 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 regarding participants, outcomes, and harms of treatment. We also plan to reconvene 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, that clinical researchers will incorporate the collection of these data into their trial design and reporting, and ultimately that medical care will improve from the increased transparency of the risk-benefit ratio of infertility treatments (23).

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CONFLICTS OF INTEREST

Dr. Wu has received research funding from the National Clinical Trial Base in Traditional Chinese Medicine (TCM), National Key Discipline/Specialty, and the Longjiang Scholars Program and Innovative Team of Heilongjiang Province Universities. Dr. Legro has received funding from the National Institutes of Health (NIH), the Longjiang Scholars Program, and the 1000-Plan Scholars Program of the Chinese Government, has served as a chair of the Steering Committee for the National Clinical Trial Base in TCM, a consultant to the NIH, Food and Drug Administration, Ferring Pharmaceuticals, Astra Zeneca, and Euroscreen, is a member of the Board of Directors of the American Society of Reproductive Medicine (ASRM), is an Associate Editor of *Fertility and Sterility* and *Seminars in Reproductive Medicine*, and is on the editorial boards of *Endocrinology* and *Endocrine Reviews*. Dr. Niederberger is Co-Editor-in-Chief of *Fertility and Sterility*, Section Editor of *Journal of Urology*, and co-founder and Chief Technology Officer of Nexhand. Dr. Ng has received research funding from Bayer Healthcare, Ferring, Merck Serono, and MSD. Prof. Palomba is Co-Editor-in-Chief of *Journal of Ovarian Research,* Editor-in-Chief of *Current Drug Therapy*, and Associate Editor of *Human Reproduction*. Dr. 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. Dr. Rebar serves as a Contributing Editor to NEJM *Journal Watch Women's Health* and has served on several Data Safety Monitoring Committees. Dr. Pellicer is Co-Editor-in-Chief of *Fertility and Sterility* and reports ownership/stock of Biomedical Supply (Dibimed), Unisense Fertilitech, and Iviomics. Dr. Reindollar is Executive Director of the ASRM and a recipient of NIH funding. Prof. Fauser has received fees and grant support from 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 Laboratories, and Wyeth. Prof. Tapanainen has received funding from the Academy of Finland and the Sigrid Juselius Foundation and is chairman of the European Society for Human Reproduction and Embryology (ESHRE) and chairman of the Publication Subcommittee of ESHRE. Dr. Barnhart has received funding from NIH, has served as a consultant to Bayer, Pfizer, and Swiss Precision Diagnostics, is an Associate Editor for *Fertility and Sterility*, and is a member of the Board of Directors of the ASRM. Dr. Evers is Editor-in-Chief of *Human Reproduction*. Dr. Silver has received research funding from NIH. Prof. Mol has received fees for lecturing and consultancy from Ferring Pharmaceuticals, MSD, and Besins Healthcare. Prof. Norman has received travel support from Merck Serono and Merck Sharp and Dohme. Prof. Farquhar, Prof. Shankaran, and Dr. van der Poel have nothing to disclose.

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SUPPLEMENTAL MATERIAL

The 2014 Harbin Consensus Document with Explanation and Elaboration of the Modification of the CONSORT statement can be viewed online.

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