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Protocol

Protocol of randomized controlled trial comparing T piece resuscitator versus self-inflating bag for resuscitation in the delivery room in preterm neonates

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ABSTRACT

Background: Neonatal resuscitation is a critical process for a newborn with effective ventilation as its key component. Three manual ventilation devices, including self-inflating bags (SIB), flow-inflating bags (FIB), and T-piece resuscitator (TPR) are recommended for positive pressure ventilation (PPV) in the delivery room. To date, there is insufficient evidence regarding the optimal device for establishing effective ventilation in newborns. This study is planned to compare the effectiveness of TPR and SIB during resuscitation.
Methods: This will be a single centre, open-label, randomized controlled trial. Study participants will be preterm ≤34 of gestation needing PPV at birth as per NRP algorithm. Newborns will be randomly assigned to two groups (TPR or SIB). SpO_2 at 2 and 5 min, time to reach heart rate >100/min by pulse oximetry, and duration of PPV will be recorded. Primary outcome is need of delivery room intubation. Intention to treat analysis will be done using STATA version 17.0. A priori defined subgroup for purpose of analysis will be gestation ≤30 and 31-34 weeks. Trial will be done as per good clinical practice guidelines.
Conclusions: If PPV with TPR is proven to be more efficacious in terms of less delivery room intubation, there would be a way towards finalizing the TPR as primary device for providing PPV during delivery room resuscitation at birth. This study has potential to bring down need of delivery room intubation with less duration of mechanical ventilation and morbidity in form of IVH, BPD and composite outcome of BPD and death.
Trial registration: CTRI number: CTRI/2023/01/048660.

Keywords: TPR, SIB, Delivery room resuscitation, Delivery room intubation

INTRODUCTION

The vast majority of newborns, approximately 90% need little assistance to successful transition from intrauterine to extrauterine life. Approximately 10% of infants require some assistance for normal transition at birth. Of these, roughly 3-6% need assisted ventilation, and less than 1% require extensive resuscitation.[1,2] The most important action in resuscitation of a newborn in the delivery room is to establish effective ventilation. Most widely used devices for manual ventilation are SIB and TPR, flow inflating bag is another device with uncommon usage.

To date, there is insufficient evidence regarding the optimal device for establishing effective ventilation in newborns at birth. Current ILCOR and American academy of paediatrics (AAP)/American heart association (AHA) recommendations state that ventilation of neonates can be performed effectively with a flow-inflating bag, a SIB, or TPR.[3]

TPR have an intrinsic ability to provide positive end expiratory pressure (PEEP). In addition, it has been shown to deliver more accurate and consistent peak inspiratory pressure (PIP) when compared with SIB.[4] It is

also hypothesized that there will be lower chances of air leak while using TPR as pressures are controlled and pre-set, with little variations while using this device when compared with SIB.

Several studies have compared the effectiveness of these devices on mannequins and found that the resulting pressures are lower and more consistent when using the TPR.[4,5–7] But to extrapolate data from studies on mannequin in live scenario needs validation.

Studies in newborn infants inside the delivery room have found decreased intubation rates and duration of PPV while using TPR when compared with SIB.[8-10] however in these studies randomization method was not used, sample size was small, and cases were not equally distributed. More evidence is needed from adequately powered studies addressing various confounders.

Need for this study: We hypothesized that the use of TPR during resuscitation in preterm neonates would successfully improve ventilation in terms of less intubation in the delivery room, similar to the effect seen in simulation scenarios with mannequins.[4-7]

The finding of this study could have immense impact on how neonatal care is practiced. By finding out which device is superior, health care providers can prioritize using that one to ensure that newborns get the best possible start to life.

Objective

Primary objective is to evaluate the efficacy of TPR compared to SIB in terms of delivery room intubation rate in neonates requiring PPV at birth. Secondary objectives are to compare:(1) Duration of PPV, (2) SpO_2 at 2 and 5 minutes, (3) Time to reach HR ≥ 100 b/m, (4) Time to spontaneous breathing, (5) Need of chest compression and medications and (6) Apgar score at 1,5- and 10-minutes during delivery room resuscitation of preterm neonates at birth using either TPR or SIB.

METHODS

Study design

This is a single centre, open label, randomized controlled trial.

Study settings

The study will be carried out in department of neonatology, government medical college and hospital, Chandigarh, India.

Study protocol development and conduct

It has been approved by institutional ethics committee and is registered prospectively as TIDe NEO under CTRI. The study will be reported in accordance with CONSORT (consolidated standards of reporting trials) recommendation.

The study will be carried over 18 months period from January 2023 to July 2024, including 1 month of staff training and 2 months of data analysis. The participant's informed written consent will be sought prior to enrolment. The consent process involves written, prospective consent from parents for inclusion of their infant in the study. Eligible participants will be parturient mother admitted in labour/delivery area of hospital with gestation age ≤ 34 weeks. Written consent will be taken from mother after explaining the details of study and answering queries if any. Information sheet will be provided to parents explaining the detail of study. In case mother is in active labour, informed consent will be taken from husband.

Outcome

Primary outcome will be determined by the difference in need of intubation in delivery room in neonates requiring PPV during resuscitation at birth, when resuscitated using TPR vs SIB.

Randomization

The randomization sequence uses random permuted blocks with block sizes of 4 and 6. Allocation concealment will be done by sequentially numbered, opaque, sealed envelopes. To avoid any delay in resuscitation, all newborns will be randomized before birth by approaching all expected mothers admitted in labour/delivery area of hospital with gestation ≤34 weeks. Allocated group TPR or SIB will be clearly mentioned on mother's file with color coding. The randomization sequence will be generated by independent person not involved in study form department of neonatology, government medical college, Chandigarh.

Blinding

The group allocation is unblinded, due to nature of intervention.

Sample size calculation

As per our previous year's records endotracheal intubation (ETI) rate was 30% in neonates of gestation age >26-34 weeks while using TPR and approximately 55% in those resuscitated with SIB as a resuscitation device, hence the sample size required with an α error of 0.05 and power of 80%, is 60 in each group, with total 120 newborns.

Framework

The TIDE Neo study is investigating the superiority of TPR, compared to SIB for primary outcome.

Data collection and management

Each qualified participant's demographic information will be entered into study Performa. Using the randomly assigned device, each resuscitation will be carried out following NRP. The senior resident present during resuscitation will record SpO_2 at 2 and 5 min, time to reach HR>100/min, duration of PPV, time to spontaneous respiration and need of intubation in study Performa. The investigator will periodically cross-check the SpO_2 and HR from data stored in Masimo pulse oximeter.

After data entry, records will be reviewed for any missing data.

Trial population

All the mothers with gestation ≤34 weeks will be assessed for eligibility for inclusion in the trial. The CONSORT flow diagram in Figure 1. will be used to detail enrolment, randomization, treatment allocation, follow up and analysis.

Inclusion criteria

Neonates born in the hospital will be eligible for enrolment if they fulfil the following inclusion criteria: Neonates with gestation age ≤ 34 weeks not breathing after completion of initial steps and requiring PPV at birth in the delivery room

Exclusion criteria

Neonates with any of the following conditions will be excluded: (1) major congenital malformation and (2) refusal to give consent.

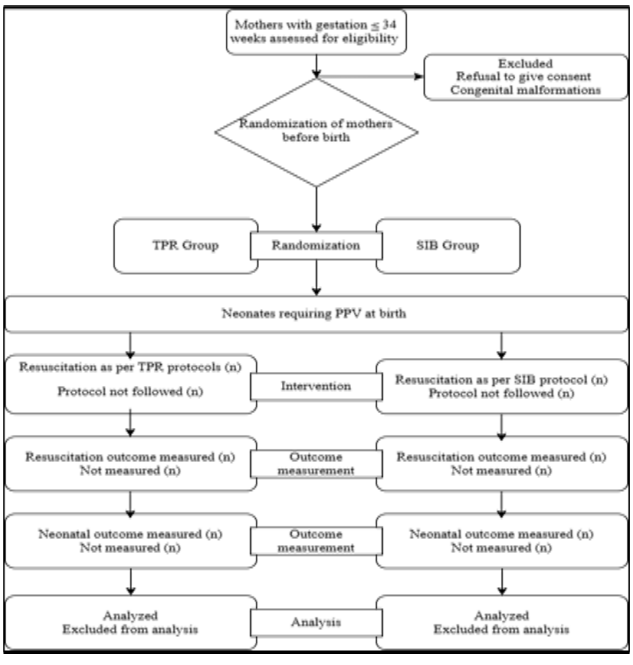

Figure 1: CONSORT diagram.

Withdrawal/follow up

Those who will not receive PPV will be treated as post randomization exclusion.

Baseline characteristics at randomization

The following baseline characteristics will be summarised (Table 1).

Table 1: Baseline characteristics at randomization.

Variables	TPR groups	SIB group
Mothers		
Age (In Years)		
Schooling		
At least 3 antenatal visits		
Multiple gestation (2 or more)		
GDM		
Pre-eclampsia		
Eclampsia		
PPROM		
Oligohydramnios		
APH		
AEDF/REDF		
MSL		
Clinical chorioamnionitis		
LSCS		
Infants		
Gestation		
Birth Weight		
Male		
SGA		
Full coarse of antenatal steroids		

GDM: Gestational diabetes mellitus, MSL: Meconium-stained liquor, SGA: Small for gestation age, PPROM: Preterm premature rupture of membrane, APH: Antepartum haemorrhage, AEDF/REDF: Absent end diastolic flow/Reversed end diastolic flow, LSCS: Lower segment caesarean section,

Intervention

After obtaining informed consent yet to be born neonates will be randomized to one of the study groups, (1) TPR group/(2) SIB group using computer generated random numbers with block of varying sizes 4, 6 and 8. After birth, standard neonatal resuscitation program algorithm will be followed as per international liaison committee on resuscitation ILCOR.[4] Pulse oximeter probe will be attached to neonate's right hand. Time taken for baby to reach heart rate>100 and oxygen saturation at 2 and 5 min of age will be recorded by use of stop clock and pulse oximeter using Masimo technology. Neonates requiring PPV at birth will be identified as per standard resuscitation algorithm by international liaison committee on resuscitation (ILCOR).[1]

TPR group

Those assigned to the TPR group will be provided PPV with Pigeon TPR (Model-A83000-TPB, no.-200811B015) with a flow of 10-12 L/min, starting PIP of 20 cm H_2O, PEEP of 5 cm H_2O, and FiO_2 of 21-30%. Mask size 0 or 00 will be used after insuring proper fit and absence of leak (Figure 2).

Figure 2: Pigeon TPR.

SIB group

Those assigned to the SIB group will be resuscitated using self-inflating bag (240 ml) with a pop off valve of limit 20-30 cm H_2O and starting FiO_2 of 21-30%, using an appropriate size mask (Figure 3).

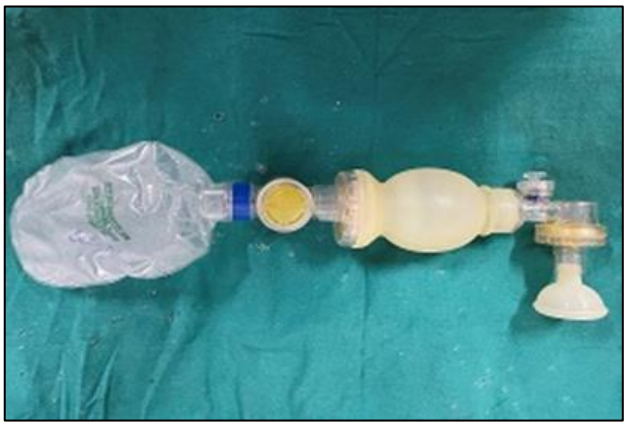

Figure 3: SIB (240 ml) with preterm mask and reservoir.

All resuscitation measures will be done in accordance with resuscitation algorithm defined by ILCOR and American heart association (AHA). Number of babies requiring delivery room intubation and chest compressions/drugs will be noted. Any need for oxygen therapy, need of surfactant and mechanical ventilation will be noted. No cross over will be allowed. After intubation same device will be used for providing PPV (Table 2 and 3).

Table 2: Resuscitation details.

SpO_2	At 2 min	At 5 min
Time to achieve HR >100/min		
Time to spontaneous respiration		
Duration of PPV		
Need of intubation in delivery room	Yes	No
Need for surfactant	Yes	No
Need of chest compression	Yes	No
Need of medications	Yes	No

Table 3: Expanded and combined Apgar score.

	Sign	0	1	2	Combined	1 min	5 min	10 min
APGAR score	Color	Blue or pale	Acrocyanosis	pink	C=CPAP			
	HR	Absent	<100	>100	O=Oxygen			
	Reflex activity	No response	Grimace	Cry or active withdrawal	M-B Mask and bag			
	Tone	Limb	Some flexion	Active motion	I= Intubation			
	Respiration	Absent	Weak cry/ hypoventilation	Good, crying	N=Neonatal chest compression			
					E=Exogenous surfactant			
					D=Drugs			
Total score: Expanded Apgar and combined Apgar								

Combined Apgar: Score (0) if intervention was performed, score (1) if no intervention performed.

Training on the appropriate use of both devices will be imparted by the principal investigator to all paediatric and neonatology residents. Instructions will be displayed through posters in the delivery room and also personally conveyed to the residents on duty regarding the study. Standard post-resuscitation care will be provided to both groups as per hospital protocols.

Statistical analysis

Study data is collected using a specially designed and pre-tested proforma. Data will be entered in a spreadsheet. Data collected will be checked for accuracy and incompleteness. Continuous variables will be expressed as mean and standard deviation if normally distributed and as median and interquartile range if non-normally distributed. Categorical variables will be expressed as number and proportion. Quantitative data with normal distribution will be compared using Student t test and those with skewed distribution will be analysed using Mann-Whitney U test. Categorical data will be compared using chi-square or Fischer exact test as applicable. A $p<0.05$ will be considered significant. Time to event will be analysed using the Kaplan-Meier survival analysis. Subgroup analysis will be done as per pre-defined criteria based on gestation age. Analysis will be by intention to treat principle.

RESULTS

Primary outcome measure will be to find the incidence of endotracheal intubation in the delivery room among the neonates resuscitated with TPR or self-inflating bag. Secondary outcome measures will include outcome measures inside delivery room and outcome measures outside delivery room (Table 4 and 5).

Table 4: Outcome measures inside delivery room.

Outcomes	TPR group	SIB group	95% CI
Primary outcome			
Intubation in DR			
Secondary outcomes			
Duration of PPV			
SpO2 at 2 min			
SpO2 at 5 min			
Time to HR> 100/min			
Need for chest compression			
Need for medication			
COMBINED Apgar@ 5 min			
Duration of DRCPAP			

TPR: T Piece resuscitator, SIB: Self inflating bag, HR: Heart rate, Min: Minute

Late onset sepsis is defined as sign and symptoms of sepsis or culture positive sepsis after 72 hours of life, BPD at 36 weeks, retinopathy of prematurity: maximum severity at any time, PVL any grade, NEC any stage as defined by modified bell's criteria.

Table 5: Outcome measures outside delivery room.

Outcome measures outside delivery room	TPR group	SIB group	95% CI
Need of mechanical ventilation in first 72 hours			
Incidence of respiratory distress in first 72 hours			
Need of surfactant administration in first 72 hours			
Air leaks in first 24 hours			
Duration of oxygen			
Duration of mechanical ventilation (Invasive and non-invasive)			
Incidence of hypoxic ischemic encephalopathy			
Intraventricular haemorrhage (IVH) grade 2 or more			
Incidence of periventricular leukomalacia (PVL)			
Incidence of late onset sepsis			
Incidence of necrotising enterocolitis (NEC)			
Incidence of retinopathy of prematurity (ROP)			
Death and BPD as composite outcome			

DISCUSSION

Although there are multiple studies comparing the TPR and SIB, in which TPR has shown to be better than SIB when compared for intubation in the delivery room, duration of PPV, SpO_2 at 2 min and 5 min, time to reach HR >100/min, need and duration of mechanical ventilation, incidence of BPD and mortality during hospital stay. A recent systematic review and metanalysis have failed to recommend TPR over SIB, because of the paucity of level 1 and 2 evidence for the above-mentioned outcomes as the primary outcome.[10] The current study is planned as a randomized superiority trial (i.e., level 1 evidence) to estimate the endotracheal intubation rate during delivery room resuscitation of preterm neonates using TPR vs SIB.

CONCLUSION

If efficacy of TPR over SIB will be proved, it would provide way to formulate a standard guideline to use TPR as primary device for resuscitation. This will bring down overall cost by reducing need of intubation and advanced resuscitation in preterm neonates and better short-term outcomes in form of less need of mechanical ventilation and oxygen requirement. This will also decrease the long-term morbidities in form of ROP, IVH, BPD. Hence, we will have better device for providing PPV to preterm neonates with less complications, good short-term outcomes, less morbidity and helping preterm babies to achieve as much possible as their term counterparts.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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APPENDIX

Parent informed consent form

Patient identification number for this study: _____

Title of study: T piece resuscitator versus Self Inflating bag for resuscitation in the delivery room in preterm neonates: A randomized controlled trial

Name of Investigator: Dr. Harshit Kumar Mob. No. 0000000000

The contents of the information sheet that was provided have been read carefully by me /explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks/ benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my child's participation is voluntary and that I am free to withdraw my child at any time, without giving any reason, without my medical care being affected.

I understand that the information collected about me from my child's participation in this research and sections of any of my medical notes may be looked at by investigators. I give permission for these individuals to have access to my child's records.

I agree for my baby's participation in the above study.

……. Date:

(Signature/Left thumb impression) Place: Chandigarh

Daughter/Son of: _____

Name of the baby's mother/ father: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

…….. Date:

(Signature of the Investigator)

1) Witness-1 …… 2) Witness -2 ……..

Signature Signature

Table 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents.*

Section/item	Page no.	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	1	Trial identifier and registry name. If not yet registered, name of intended registry
	NA	All items from the World Health Organization Trial Registration Data Set
Protocol version	1	Date and version identifier
Funding	1	Sources and types of financial, material, and other support
Roles and responsibilities	1	Names, affiliations, and roles of protocol contributors
	NA	Name and contact information for the trial sponsor
	NA	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	NA	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	3	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	3	Explanation for choice of comparators
Objectives	3	Specific objectives or hypotheses
Trial design	4	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)
Methods: Participants, interventions, and outcomes		
Study setting	4	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	5	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
Interventions	8	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	9	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)
	9	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	9	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	13, 14	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	6	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	4	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	5, 6	Strategies for achieving adequate participant enrolment to reach the target sample size

Continued.

Section/item	Page no.	Description
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	4	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism	4	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	4	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	4	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how
	NA	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
Methods: Data collection, management, and analysis		
Data collection methods	5	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	5	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	5	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	12	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	12	Methods for any additional analyses (e.g., subgroup and adjusted analyses)
	12	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)
Methods: Monitoring		
Data monitoring	NA	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, explanation of why DMC is not needed
	NA	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	NA	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions/trial conduct
Auditing	NA	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	17	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	NA	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	18	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	18	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Continued.

Section/item	Page no.	Description
Confidentiality	17	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	17	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	17	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	NA	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	NA	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	NA	Authorship eligibility guidelines and any intended use of professional writers
	NA	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	18	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	NA	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 explanation and elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT group under the creative commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.