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Pharmacokinetics and complementary evaluation system-based guidance on prophylaxis of paediatric patients with haemophilia A in China with Kovaltry: protocol of the LEAP study

Huang Kun ,[1] Weiqun Xu,[2] Min Zhou,[3] Xiaojing Li,[4] Zhongjin Xu,[5] Yongjun Fang,[6] Changgang Li,[7] Zhenping Chen,[8] Runhui Wu[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Runhui Wu; runhuiwu@hotmail.com and Dr Zhenping Chen; chenzhenping@outlook.com

ABSTRACT

Introduction Haemophilia A is a rare inherited bleeding disease caused by the deficiency of coagulation factor VIII (FVIII). The main treatment protocol is to administer regular exogenous FVIII concentrate infusions. With the discovery of variability in individualised pharmacokinetics (PK) and bleeding phenotype, the previous weight-based approach needs to be replaced by more advanced PK-tailored prophylaxis with an accurate evaluation system. In this study, we combine individualised PK profiles and a complementary evaluation system to guide prophylaxis in paediatric patients with haemophilia A.

Methods and analysis This is a single-centre, prospective single-arm study. The aim of this study is to assess the effectiveness of a new strategy combining PK and a complementary evaluation system to treat haemophilia A in Chinese paediatric patients. Sixty paediatric patients with haemophilia will be recruited. After PK testing, they will receive a PK-guided stepup prophylaxis in the next 2 years. The dosing regimen will be determined according to individualised PK profiles and complementary evaluation findings. Related indicators at the end of the study will be compared with the values at treatment initiation to examine the effectiveness of this new strategy. The demographic data of the investigated patients will be summarised by descriptive statistics. Quantitative data will be described by summary statistics, including arithmetic median, range, mean and arithmetic SD. Analyses will use t-test to compare indicators such as bleeding rate and imaging score at both ends of the study as well as during follow-up.

Ethics and dissemination The study has been approved by the Ethics Committee of Beijing Children's Hospital (Number 2020-Z-095). The findings will be presented at international meetings such as World Federation of Hemophilia World Congress. Related manuscripts will be submitted to peer-review journals such as *Blood* and *Hemophilia*.

Trial registration number ChiCTR2000037821; Pre-results.

Strengths and limitations of this study

- This study will be the first to combine pharmacokinetic and complementary evaluation in haemophilia therapy.
- The complementary evaluation could provide better joint protection by detecting preclinical lesions.
- The small sample size may limit statistical power for further exploratory analyses.

INTRODUCTION

Haemophilia A is an X-linked inherited bleeding disorder due to the deficiency of coagulation factor VIII (FVIII). Patients with haemophilia have spontaneous bleeds in muscles or joints, which could cause joint disfunction or even death. The main treatment option for haemophilia is to administer regular exogenous FVIII infusions. Compared with on-demand therapy, prophylaxis has been considered an optimised therapy regimen to help patients live a normal life, with enhanced ability to decrease bleeds and maintain the function of joints.[1] Prophylaxis is considered the standard treatment of haemophilia in paediatric patients and should be started as soon as possible once prophylaxis is proposed.[2]

The first prophylaxis regimen was proposed in Sweden and is also known as 'standard prophylaxis'.[3] It aims to keep the trough FVIII level of patients with haemophilia A above 1 IU/dL by giving them regular exogenous FVIII concentrate injections (20–40 IU/kg, three times per week or every other day). The experience of the Malmo protocol in more than 50 years has revealed its clinical effectiveness in treating patients with haemophilia.[4] However, the Malmo protocol has not been widely used in other regions due to the massive consumption of and insufficient access to FVIII concentrate as well as the heavy burden of frequent intravenous

injections. Therefore, other prophylaxis protocols have been developed, including the middle dose prophylaxis in the Netherlands (15–25 IU/kg, 2–3 times per week) and the stepup prophylaxis proposed by Canada.[5 6] In some developing counties, such as China and India, even low-dose prophylaxis was shown to greatly decrease bleeding compared with on-demand therapy.[7]

Currently, prophylactic regimens are determined by a standard weight-based approach, which may cause underdosage or overdosage because of the variability of both FVIII pharmacokinetic (PK) profiles and bleed phenotypes among different patients with haemophilia. According to Chen *et al* FVIII's half-life time varies from 5.52 to 20.02 hour, while in vivo recovery varies from 1.2 IU/kg to 3 IU/kg.[8] Other studies also confirmed great individual variability in PK profile.[9 10] Thus, single weight-based prophylaxis may cause either extra bleeds and joint disfunction due to insufficient treatment or unnecessary FVIII concentrate waste with overdosage. Therefore, it has been recommended that individualised PK profiles should be employed for determining the patient's dose and frequency of routine prophylaxis. In the past, it was hard to obtain individualised PK profiles because of the heavy burden of up to 10 time points after a long washout period and single-dose infusion.[11] With the application of the Bayes approach to population PK (popPK) in haemophilia, it is currently possible to use blood samples collected at only 2–3 time points to determine individualised PK profiles.[11] According to Iorio *et al*, the popPK method is a practical and accurate way to predict individualised PK profiles.[12] Previous studies have revealed the advantages of PK-tailored prophylaxis in haemophilia treatment.[13] In addition, online PK dosing tools such as Web Accessible Population Pharmacokinetics (WAPPS) have been recommended by official organisations to guide routine prophylaxis according to individualised PK profiles.[11]

Besides variability in PK profiles, different bleed phenotypes among patients also need to be taken into consideration in routine therapy. Although Collins *et al* clearly demonstrated that break-through bleeds in prophylaxis are correlated to weekly time spent with low FVIII levels, some patients with high-trough FVIII levels in daily prophylaxis still suffer from bleeds, especially those with target joints.[14] According to the sports guidelines for haemophilia, patients with target joints need to keep higher FVIII levels in the same sport compared with those without joint disfunction. In a Dutch study involving more than 400 patients with haemophilia, it seemed that only trough FVIII levels reached 12 IU/dL should the number of target joints decrease to zero.[15] The target trough FVIII level to reach the goal of zero bleed was 15 IU/dL in another study.[16] Besides the joint state, Den Uijl *et al* also suggested that multiple targets should be considered in determining the routine prophylaxis regimen, including physical activity, the quality of life and cost-effectiveness.[16] The haemophilia care team of Beijing Children's Hospital started a study named CHIPS (Chinese Hemophilia Individualized Prophylaxis Study) in 2016 to explore an evaluation system for paediatric patients with haemophilia, which includes multiple targets such as joint structure assessed by MRI and ultrasound (US) scores, joint function evaluated by Haemophilia Joint Health Score (HJHS) scores, the quality of life assessed by Canadian Hemophilia Outcomes-Kids Life Assessment Tool scores and other aims and scaling scores.[17] In this study, some patients could keep the bleeding rate at 0 in step 1, while others still suffered from frequent bleeds even in step 4, which indicated the variability of bleed phenotype leads to a difference in target trough FVIII levels in routine prophylaxis.

Although some products involving new mechanisms to treat haemophilia are available, most patients around the world are still taking FVIII concentrate for routine prophylaxis, and this situation would not change for a long time.[2] How to use PK data and a complementary evaluation system to individualise prophylaxis in patients with haemophilia, achieving better clinical outcomes and reduced cost, remains a vital question that needs to be addressed urgently.

STUDY OBJECTIVES

Primary objectives

1. To evaluate the effect of PK-based and complementary evaluation system-based instructions for prophylaxis in paediatric patients with haemophilia A (according to US and/or MRI findings).
2. To establish a popPK model for Kovaltry suitable for paediatric patients with haemophilia A in China.

Secondary objectives

1. To study the efficacy and safety of the prophylactic regimen under the guidance of PK and complementary evaluation system.
2. To evaluate the PK parameters of paediatric haemophilia A patients in China administered Kovaltry products in China.

METHODS AND ANALYSIS

Ethics and dissemination

The study was approved by the ethics committee of Beijing Children's Hospital (Number 2020-Z-095). Written informed consent was obtained from each enrolled patient and their legally authorised guardians. The SPIRIT list of this study would be available as supplementary files.

Study design

This is a multicentre, prospective single-arm study, including two stages from January 2021 to January 2024.

Stage I is the popPK period lasting for 6 months. The enrolled paediatric patients will be treated with Kovaltry according to current clinical situation, and the therapeutic regimen and bleeding situation will be recorded. PK indicators will be measured comprehensively.

PopPK model building and verification

At this stage, after obtaining the individual PK information of paediatric patients, the PK and personal information of 30 paediatric patients (aged 1–18 years) will be included in WAPPS to generate the Kovaltry popPK model including the data of paediatric patients in China; meanwhile, the individual PK information of another 30 paediatric patients in China not involved in modelling will be included for external verification to ensure the accuracy and availability of the model. Considering the balanced distribution of paediatric patients in various age groups, age distribution for modelling and verification will be 1–6, 6–12 and 12–18 years old. All enrolled paediatric patients should undergo PK testing prior to the trial period. A washout period of at least 72 hours will be retained before PK testing. A single dose of 50 IU/kg coagulation FVIII concentrate (Kovaltry, BAY81-8973) will be infused, with blood samples collected at different time points before and after infusion to determine FVIII concentration. Blood samples will be taken within half an hour before infusion, and at 1 hour, 3 hours, 9 hours, 24 hours, 48 hours and 72 hours after infusion, centrifuged and tested.[18] PK parameters will be obtained through the WAPPS-Hemo team.[12]

Data collection

After enrolment, patients' data on prophylaxis with Kovaltry in the first 6 months will be collected as baseline data in this study.

Stage II is the clinical stage lasting for 2 years. Patients will receive joint assessment and trough FVIII level test every 3 months and PK monitoring every 6 months.

All eligible patients will receive a dose-escalation prophylactic regimen guided by the results of PK and a complementary evaluation system, including four steps (the first step would be decided according to patients' individualised trough FVIII level in their routine prophylaxis):

Step 1: Maintained trough FVIII concentration=1–2 IU/dL.

Step 2: Maintained trough FVIII concentration=2–3 IU/dL.

Step 3: Maintained trough FVIII concentration=3–4 IU/dL.

Step 4: Maintained trough FVIII concentration=4–5 IU/dL.

Step 5: Maintained trough FVIII concentration >5 IU/dL.

In the above steps, the specific dose and frequency of dosing are not stipulated. The investigators will jointly decide a therapeutic regimen with the subject based on comprehensive assessments and instructions of WAPPS-Hemo PK, the patient's needs for quality of life and other specific conditions.

Prophylactic administration in all eligible patients will be initially (at the seventh month) evaluated as 'insufficient' according to specific criteria (table 1), and the trough FVIII levels of their current prophylaxis will be upgraded to the trough concentrations at the corresponding time. This protocol aims to combine PK and a complementary evaluation system to instruct patients to receive prophylaxis and help them further control bleeding, protecting joint function and improving the quality of life.

Study population

Inclusion criteria

1. Severe haemophilia A (FVIII: C<1%), aged 1–18 years.

Table 1 Escalation criteria determined by the complementary evaluation system

	Parameter	Time	Description	Score
Bleeding (1–18 years)	Bleeding	Every 3 months	No bleeding	0
			1 bleed	+1
			≥2 bleeds	+2
Clinical imaging (1–18 years)	HEAD-US	Every 3 months	No change or improved	0
			HEAD-US scores+1 or new significant haematoma/ joint haematoma/haemosiderosis	+1
			HEAD-US scores+2 or new severe haematoma/ joint haematoma/haemosiderosis	+2
Joint function (4–18 years)	HJHS	Every 3 months	No change or improved	0
			Single joint score increased by ≥1	+1
			Single joint score increased by ≥2	+2
Motion (7–18 years)	FISH	Every 6 months	Total score decreased by <2	0
			Total score decreased by 2–4	+1
			Total score decreased by ≥4	+2

Evaluation:<2 points:maintain the prophylactic dose;≥2 points: increase the prophylactic dose into the next step.
FISH, functional independence score in haemophilia; HEAD-US, Hemophilia Early Arthropathy Dection with Ultrasound; HJHS, Haemophilia Joint Health Score.

2. A history of knee, elbow or ankle bleeding.
3. >50 exposure days (calculated from previous treatments with FVIII products).
4. No FVIII inhibitors at enrolment.
5. Regular clinical visits and medical records available.
6. Informed consent from the legal guardians of patients before enrolment.
7. Prophylaxis with Kovaltry being administered at the time of enrolment and baseline data on prophylaxis with Kovaltry for at least 6 months prior to phase I available.

Exclusion criteria

1. Other haemorrhagic diseases such as von Willebrand disease (VWD).
2. Generation of FVIII inhibitors: >0.6 BU (confirmed by two separate tests).
3. A previous history of inhibitors and presence of FVIII inhibitor at any time in the study period.
4. Planning to participate (or previous involvement) in other Kovaltry-related studies, other interventional studies or any studies expected to affect the study protocol.
5. Using other FVIII concentrates for routine prophylaxis.

Sample size

According to the guidance of the WAPPS team and the number of potential patients available in our centre, the PK data of 60 paediatric patients with haemophilia A would be sufficient for this study. In addition, due to the novelty of this study, the sample size could not be estimated through previous studies.

Study endpoints and outcomes measures

Primary endpoints

1. Percentages of MRI/US scores of joints improved/unchanged from baseline.
2. A valid Kovaltry popPK model established for patients with paediatric haemophilia A in China

Second endpoints

1. Annual bleeding rate, annual joint bleeding rate and annual target joint bleeding rate.
2. Bleeding rates will be calculated according to the routine electronic record of patients.
3. Joint function (HJHS).
4. Joint structure (X-ray Pettersson score) .
5. Motion (functional independence score in haemophilia >7 years of age).
6. Quality of life.
7. Consumption and therapeutic dose regimen of Kovaltry.
8. Assessment of family disease burden.
9. Treatment compliance and reasons for noncompliance of patients in various age groups.

Escalation criteria

According to the criteria detailed in table 1, the prophylactic dose would increase into the next step with a score ≥2 points. Detailed variables and evaluation methods are described in table 2.

The study flowchart is depicted in figure 1.

Statistical analysis plan

Descriptive analysis of all variables will be performed by appropriate statistical methods. Categorical variables will be analysed using frequency distribution tables (absolute and relative frequencies). Continuous variables will be analysed using sample statistics (ie, mean, SD, minimum,

Table 2 Variables and evaluation methods

Study outcomes	Variables and methods
Percentages of MRI/ultrasound scores of representative joints improved/unchanged from baseline at the end of the study.	MRI: IPSG MRI score Ultrasound: HEAD-US score
ABR, AJBR and ATJBR	Annual bleeding and joint bleeding rates
X-ray outcome	Pettersson score
Joint function	HJHS
Motion	FISH (>7 years old)
Quality of life	CHO-KLAT score, China V.2.0
Percentage of patients remaining at each step of administration at the end of this study	Percentage of patients
FVIII consumption	Frequency and volume of FVIII infusion
Inhibitors	Incidence of inhibitors
Treatment compliance	Comparison of the actual infusion volume received with the individualised prevention protocol prescribed by physicians

ABR, annual bleeding rate; AJBR, annual joint bleeding rate; ATJBR, annual target joint bleeding rate; CHOKLAT, Canadian Hemophilia Outcomes-Kids Life Assessment Tool; FISH, functional independence score in haemophilia; HEAD-US, Hemophilia Early Arthropathy Dection with Ultrasound; HJHS, Haemophilia Joint Health Score; IPSG, International Prophylaxis Study Group.

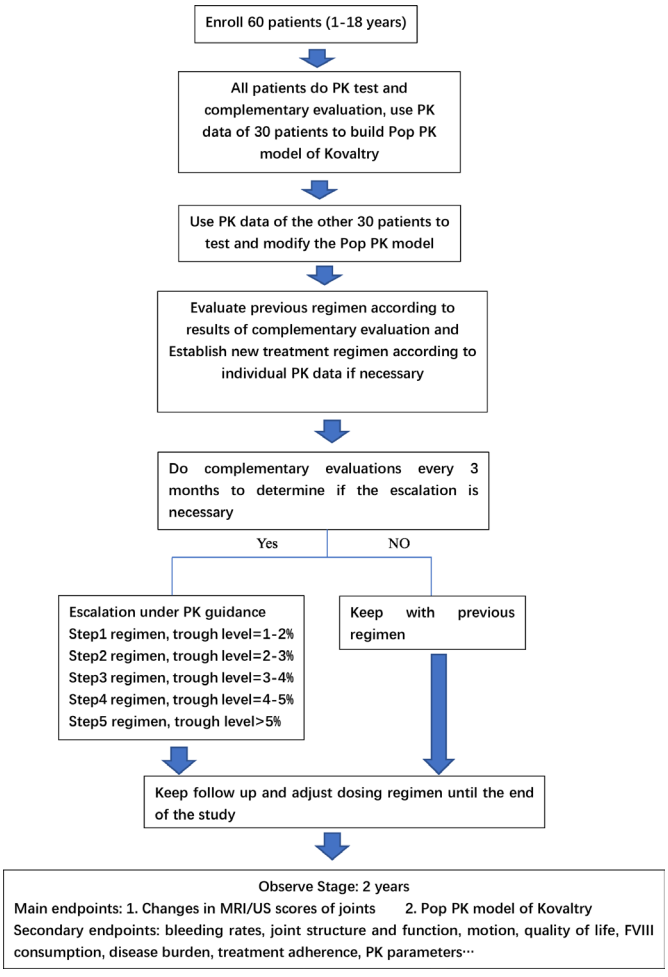

Figure 1 The study flowchart. FVIII, factorVIII; PK, pharmacokinetics.

median, quartile and maximum). Continuous variables will be described using absolute values from each time point and represented as changes from baseline (if applicable). The statistical package for social sciences (SPSS) software V.13.0 will be used for statistical processing. Student's t-test will be performed for the analysis of normally distributed data. The χ^2 test will be carried out for enumeration data. Non-normally distributed data will be analysed by the rank sum test. $p<0.05$ will be considered statistically significant.

Ethics and dissemination

This study has been approved by the Ethics Committee of Beijing Children's Hospital (BCH). Informed consent will be obtained from all boys with severe haemophilia A and their legally authorised guardians. The results will be organised into manuscripts and submitted to peer-review journals as well as international academic meetings. The original data will be stored at Beijing Children's Hospital, and disclosure will only be available on reasonable request by e-mail to the corresponding authors. The main finding will be open to all participants and the Haemophilia Society.

Author affiliations
[1]Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China
[2]Department of Hematology and Oncology, The Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Pediatric Leukemia Diagnostic and Therapeutic Technology Research Center of Zhejiang Province, Zhejiang, China
[3]Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China
[4]Department of Hematology, Chengdu Women & Children's New Century Hospital, Chengdu, China
[5]Department of Hematology, Jiangxi Provincial Children's Hospital, Nanchang, China
[6]Department of Hematology and Oncology, Children's Hospital of Nanjing Medical University School of Medicine, Nanjing, China
[7]Department of Hematology and Oncology, Shenzhen Children's Hospital, Shenzhen, Guangdong, China
[8]Hematologic Disease Laboratory, Hematology Center, Beijing Children's Hospital, Capital Medical University, Beijing, China

Contributors HK proposed the study, defended during ethical review and wrote the manuscript. RW and ZC designed the study, applied for funding and reviewed the manuscript. WX, MZ, XL, ZX, YF and CL discussed on the planning, conduct and reporting of this study and reviewed the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Huang Kun http://orcid.org/0000-0003-1641-1472

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SPIRIT 2013 Checklist for LEAP study

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1&2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	9
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	5c	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	9

	5d	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)	NA
Introduction			
Background and rationale	6a	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&4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	2
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6

Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4&5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	4
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5&9, Figure1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, 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	6,7,8
	18b	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	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7,8
Statistical methods	20a	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	8
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			

Data monitoring	21a	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, an explanation of why a DMC is not needed	NA
	21b	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	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	NA
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	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	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	9
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	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	2
	31b	Authorship eligibility guidelines and any intended use of professional writers	2
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	2,3
Biological specimens	33	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	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & 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.