### SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

<table>
<thead>
<tr>
<th>Section/Item</th>
<th>Item No</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Administrative information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed Line 1</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed Line 48</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Completed throughout document</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol version 3.0 (3.1 in France) 04th February 2020</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protocol version 4.0(4.1 in France) with specific instructions for handling COVID-19 patients – 25th March 2020</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
</tr>
<tr>
<td></td>
<td></td>
<td>This study is supported by Inotrem SA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Line 448</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>See text</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Line 9</td>
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<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dr Jean Jacques Garaud</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INOTREM S.A.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>54 Rue de Ponthieu</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75008 Paris</td>
</tr>
<tr>
<td></td>
<td></td>
<td>France</td>
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</tbody>
</table>
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.

The sponsor or its designated representatives are responsible for study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The sponsor is committed to open access publishing of the trial report.

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).

Coordinating centre: St Luc Clinical coordinating centre (Belgium), Ocean State CCC (Providence, Rhode Island, USA)
Data adjudication committee: (Judgments on a per patient basis on: Appropriate antibiotics, septic shock steroids, septic shock related mortality)
Data Management team: CRO: PPD ltd
Safety and pharmacovigilence: Stragen Services plc

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

See text Line 101

6b Explanation for choice of comparators

See text Line 154

Objectives
7 Specific objectives or hypotheses

See text Line 118

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)

See text Line 219
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
See text
Line 139

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)
See text
Table 1

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
See text
Line 152

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)
See text
Line 296

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
See text
Line 205

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial
See text
Line 152

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
See text
Line 168
### 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)

See text
See Figure 1

### 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

See text
Lines 224 to 233

### Recruitment

15 Strategies for achieving adequate participant enrolment to reach target sample size

See text
Line 141

### Methods: Assignment of interventions (for controlled trials)

**Allocation:**

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

See text
Line 221

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

See text
Line 216

16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

See text
Line 222

17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
17b 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**

<table>
<thead>
<tr>
<th>Subsection</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Data collection methods</strong></td>
<td>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</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Data management</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td>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</td>
</tr>
<tr>
<td>20b Methods for any additional analyses (eg, subgroup and adjusted analyses)</td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analysis Plan available on request
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)

See text

Line 251

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

DMC charter attached as an appendix

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

See text

Line 275

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

See text

Line 209

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Independent audit of selected study centres will be undertaken on at least five occasions during the study period to ensure compliance with study protocol and data quality.

Ethics and dissemination

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

See text

Line 290

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)
Clinical trials databases will be updated with protocol amendments
Study sites will be updated in the event of protocol amendments
IRBs/Regulatory bodies will approve all substantial amendments prior
to implementation

Consent or assent 26a
Who will obtain informed consent or assent from potential trial
participants or authorised surrogates, and how (see Item 32)
See text
Line 147

26b
Additional consent provisions for collection and use of participant data
and biological specimens in ancillary studies, if applicable
See text
Line 296

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
See text
Line 301

Declaration of interests 28
Financial and other competing interests for principal investigators for
the overall trial and each study site
See text
Line 453

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
Consistent with regulatory requirements, the trial data set will be
published online without restriction.

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
All appropriate insurance is in place to manage any trial associated
harm.

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
See text
Line 300

31b
Authorship eligibility guidelines and any intended use of professional
writers
See author contribution text. No use of professional writers is projected at this time.

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Open access publication of the protocol is proposed. The participant level data set and statistical code will not be available.

Appendices

<table>
<thead>
<tr>
<th>Informed consent materials</th>
<th>Model consent form and other related documentation given to participants and authorised surrogates</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>See Appendix for exemplar consent form</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological specimens</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>See appendix</td>
</tr>
</tbody>
</table>

*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.*