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Intraoperative haemodynamic optimisation using the Hypotension Prediction Index and its impact on tissular perfusion: a protocol for a randomised controlled trial

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ABSTRACT

Introduction Intraoperative arterial hypotension is associated with poor postoperative outcomes. The Hypotension Prediction Index (HPI) developed using machine learning techniques, allows the prediction of arterial hypotension analysing the arterial pressure waveform. The use of this index may reduce the duration and severity of intraoperative hypotension in adults undergoing non-cardiac surgery. This study aims to determine whether a treatment protocol based on the prevention of arterial hypotension using the HPI algorithm reduces the duration and severity of intraoperative hypotension compared with the recommended goal-directed fluid therapy strategy and may improve tissue oxygenation and organ perfusion.

Methods and analysis We will conduct a multicentre, randomised, controlled trial (N=80) in high-risk surgical patients scheduled for elective major abdominal surgery. All participants will be randomly assigned to a control or intervention group. Haemodynamic management in the control group will be based on standard haemodynamic parameters. Haemodynamic management of patients in the intervention group will be based on functional haemodynamic parameters provided by the HemoSphere platform (Edwards Lifesciences), including dynamic arterial elastance, dP/dt_{max} and the HPI. Tissue oxygen saturation will be recorded non-invasively and continuously by using near-infrared spectroscopy technology. Biomarkers of acute kidney stress (cTIMP2 and IGFBP7) will be obtained before and after surgery. The primary outcome will be the intraoperative time-weighted average of a mean arterial pressure <65 mm Hg.

Ethics and dissemination Ethics committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Findings will be widely disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT04301102.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A multicentre randomised controlled trial to test whether an Hypotension Prediction Index-based therapeutical protocol reduces intraoperative hypotension (IOH) and affects tissue oxygenation and organ perfusion in non-cardiac surgery.
⇒ The primary outcome is the intraoperative time-weighted average of the mean arterial blood pressure below 65 mm Hg (TWA- mean arterial pressure<65) and other variables related to IOH. Secondary outcomes are intraoperative S_tO_2, as an indicator of tissue oxygenation, postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk), postoperative complications, length of hospital stay and 30-day mortality.
⇒ The study sample size was calculated based on the potential reduction in IOH, not the potential reduction in postoperative complications.
⇒ Although the clinical teams performing the trial interventions will not be blinded to the patient inclusion group, they will not be aware of the perioperative StO_2 and AKIRisk variables. Research staff assessing clinical outcomes will not be aware of treatment group assignment.
⇒ No 1-year mortality follow-up of recruited patients is currently proposed.

INTRODUCTION

Intraoperative monitoring of usual haemodynamic parameters, such as heart rate or blood pressure, is insufficient to ensure adequate oxygen delivery (DO_2) to the tissues and prevent organ hypoperfusion.[1] Moreover, tissue hypoxia is a significant determinant of a surgical patient's outcome.[2] Haemodynamic strategies aimed to optimise DO_2 and prevent organ hypoperfusion, also known as

goal-directed therapies (GDT), have been demonstrated to be superior to the traditional care of patients undergoing surgery. This perioperative haemodynamic optimisation has been associated with a significant reduction in morbidity and mortality.[3]

Moreover, arterial hypotension is a frequent phenomenon during the intraoperative period and has been related to the development of organ hypoperfusion and poor postoperative outcomes.[4] Both the duration and severity of arterial hypotension are significant determinants of the postoperative outcome.[5] Particularly, intraoperative hypotension (IOH) significantly increases acute kidney and myocardial injury.[6]

The Hypotension Prediction Index (HPI) is a recently available index developed from machine learning that predicts the occurrence of arterial hypotension from the analysis of the arterial pressure waveform. The HPI value indicates the likelihood of an arterial hypotension event in the following 5–10 min.[7] The use of this index coupled with a proactive therapeutic attitude may reduce IOH in adults undergoing non-cardiac surgery patients.[8–10] However, not all studies that have used intraoperative HPI-guided therapy have successfully reduced the time and severity of IOH. Particularly, the pilot study by Maheshwari *et al*[11] did not demonstrate a significant reduction in IOH using an HPI-guided therapeutical protocol. Furthermore, all these positive results came from single-centre studies or retrospective analysis of available data, which reduces the external validity of their results.

Moreover, since tissue oxygenation depends not only on DO_2 but also on perfusion pressure, haemodynamic optimisation should be targeted to achieve an adequate blood flow and arterial pressure that ensures normal organ function. We, therefore, hypothesise that an HPI-based therapeutic protocol will reduce the overall duration of intraoperative arterial hypotension and may improve tissue oxygenation and organ perfusion during non-cardiac surgery.

METHODS AND ANALYSIS

This manuscript was written according to the Standard Protocol Items: Recommendations for Interventional Trials guideline (online supplemental file 1) on reporting of interventional trial protocols.[12]

A multicentre, randomised controlled trial, with daily follow-up of patients until hospital discharge and mortality censured at 30 days after surgery, will be conducted. The study will be carried out at five different Spanish hospitals: Juan Ramón Jiménez University Hospital (Huelva), Virgen del Rocío University Hospital (Sevilla), Infanta Leonor University Hospital (Madrid), Hospital Universitario SAS de Jerez (Jerez de la Frontera) and Infanta Cristina University Hospital (Badajoz).

Enrolled patients will be at least 65 years old and/or American Society of Anesthesiologist (ASA) physical status III/IV, scheduled for elective major abdominal surgery (general surgery, urology, or gynaecology, through laparoscopic or open approach), with general or combined anaesthesia. Surgery will be considered to be major if the expected duration is >2 hour, or the estimated blood loss is >15% of blood volume, or if the expected required transfusion is ≥2 packed red blood cells.

Exclusion criteria will be pregnancy, preoperative glomerular filtrate <60 mL/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2009 formula, persistent atrial fibrillation, known cardiac shunts, right ventricular dysfunction, severe valvulopathy, kidney transplant recipient and refusal to participate in the study.

Study protocol

Researchers will screen all patients who present for elective, non-cardiac surgery. Patients will be contacted by the principal investigator (PI) of each hospital and informed if they are eligible. The patient's informed consent will be obtained the day before surgery. Patient demographics and comorbidities will be collected before randomisation. Patients will be assigned by the local PI to the intraoperative HPI algorithm (intervention group) or a GDT algorithm (control group). We will use a computer-generated, variable block randomisation method through age strata. Patients will not be aware of the group allocation. Although intraoperative personnel (anaesthesiologists, surgeons…) will be not blinded to monitoring allocation, data-analysis will remain blinded.

All PIs and collaborators will receive specific training with the monitoring used for haemodynamic management.

A Consolidated Standards of Reporting Trials flow diagram of the study is shown in figure 1. All data will be entered using an electronic Clinical Report Form in Castor EDC, a Good Clinical Practice compliant data management system.[13]

Common perioperative measures

Before the induction and during surgery, all subjects will receive standard of care with a five-lead ECG, pulse oximetry, a peripheral intravenous line and an indwelling radial arterial catheter.

All subjects will receive general or combined anaesthesia, neuraxial analgesia technique (epidural or intradural) will be performed according to the preference of the anaesthesiologist before induction. For pragmatic reasons, the administration of the drugs used in the induction of anaesthesia and neuromuscular relaxants will be at the discretion of the anaesthesiologist. Bispectral-index monitoring (BIS; Medtronic, Dublin, Ireland) will be used to monitor the depth of anaesthesia. Sevoflurane will be used for hypnosis maintenance, with a BIS target range of 40–60. All patients will receive invasive and continuous arterial pressure monitoring with an indwelling radial arterial catheter connected to a FloTrac sensor in the control group or an Acumen IQ sensor in the intervention group (Edwards Lifesciences, Irvine, California, USA).

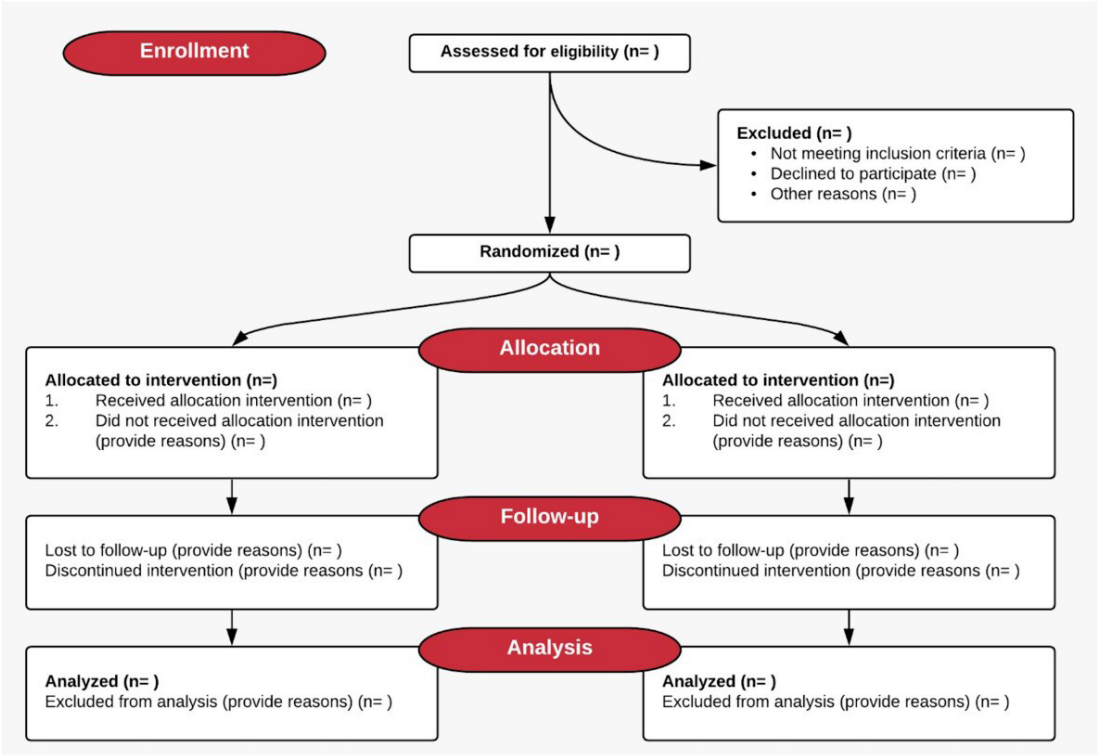

Figure 1 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

All subjects will receive standard measures to maintain oxygen saturation by pulse oximetry >94%, normothermia (>36°C) and heart rate <100 beats/min. Ventilation with an inspired oxygen fraction of 60% will be mechanically controlled to maintain $PaCO_2$ between 4.7 and 6.0 kPa, with a positive end-expiratory pressure of 4–6 mm Hg and a tidal volume of 8 mL/kg. For maintenance fluid therapy, a balanced crystalloid (Isofundin/Plasmalyte) will be administered at 1–3 mL/kg/hour for laparoscopic surgery and 5–7 mL/kg/hour for open surgery. Flow optimisation will be performed with hydroxyethyl starch (Voluven).[14] Packed red blood cells will be transfused if the haemoglobin level is <80 g/L.[15] The choice and dose of the vasopressor and ionotropic drugs will be determined by the anaesthesiologist in charge of the patient in both groups.

Tissue oxygen saturation (StO_2) will be non-invasively and continuously recorded every 2 s placing an adult sensor (ForeSight Elite sensor, model FSESL, Edwards Lifesciences) over the brachioradial muscle by using near-infrared spectroscopy (NIRS) technology (ForeSight Elite tissue oximetry system, Edwards Lifesciences=). Details about this NIRS technology are provided elsewhere.[16] StO_2 values will be hidden from the main screen in both groups but will be recorded internally into the HemoSphere system, so StO_2 values will not be available to clinicians and therefore cannot induce changes in patient management.

The haemodynamic optimisation algorithm will begin 15 min after the start of the surgery, once the haemodynamic impact of anaesthesia and surgery have been stabilised. Meanwhile, the haemodynamic goal in both groups will be to achieve a mean arterial pressure (MAP) >65 mm Hg with the administration of boluses of vasopressors at the choice of the anaesthesiologist. In both groups, haemodynamic data will be recorded every 20 s in the HemoSphere system after starting the haemodynamic optimisation protocols and downloaded after the surgery for offline analysis.

During the surgery, any procedure carried out with repercussions for the haemodynamic status of the patient will be marked and adequately labelled for further identification.

Biomarkers of acute kidney stress in the perioperative period will be measured by the PI and blinded for the rest of the researchers. Urinary (TIMP-2)-(IGFBP7) will be measured with the Astute140 Meter (BioMérieux). This device applies a sandwich immunoassay technique and converts the fluorescent signals from each of the two immunoassays (TIMP-2 and IGFBP7) contained within the Nephrocheck test cartridge into a single numerical risk result (AKIRisk). The result is calculated as the product of the measured concentrations of the two cell-cycle arrest biomarkers and can quantify the stress developed by kidney epithelial cells during surgery, identifying patients at risk of postoperative acute kidney injury (AKI).[17–19]

The first urine sample will be collected when performing the bladder catheterisation after induction. The first postoperative sample will be collected 4 hours after the patient's admission to the Intensive Care Unit for postoperative stay. If the value of this sample is in the grey zone,

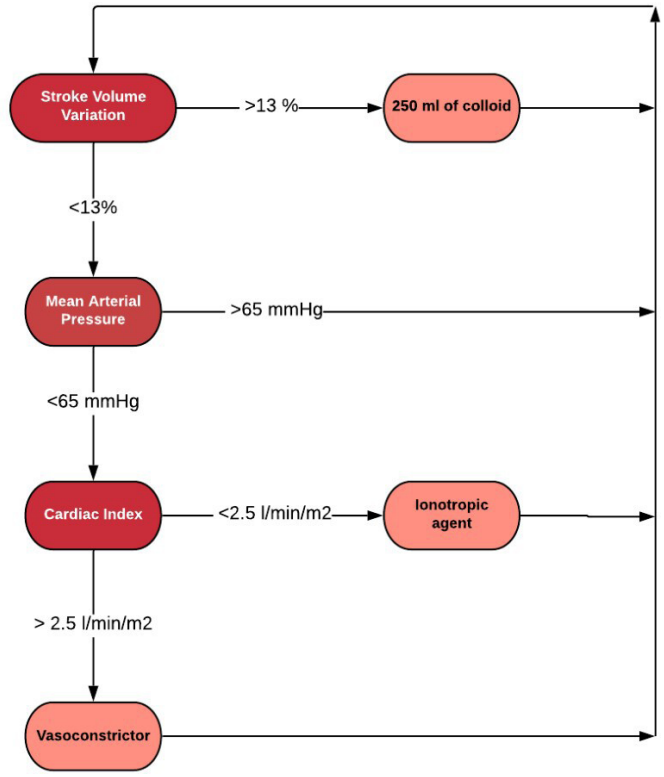

Figure 2 Control group haemodynamic optimisation algorithm.

between 0.3 and 2, a second postoperative sample will be collected 12 hours after the first one.[20]

Arterial blood analyses will be performed after induction of anaesthesia, midway through the surgery, immediately after admission to the intensive care unit, and daily from postoperative day 1–day 5 inclusive.

Haemodynamic management

Control group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the FloTrac sensor, including cardiac index (CI) and stroke volume variation (SVV). The haemodynamic optimisation algorithm on this group is shown in figure 2. If SVV increases above 13%, a fluid bolus of 250 mL of colloid will be performed. MAP will be maintained above 65 mm Hg by a vasoconstrictor drug. An ionotropic agent will be added if the CI persists <2.51/mL/m^2 after previous steps.

Intervention group

Haemodynamic management will be based on the haemodynamic parameters provided by the HemoSphere platform with the Acumen IQ sensor, including CI, SVV and Acumen IQ specific parameters: maximum arterial pressure rise (dP/dt_{max}), dynamic arterial elastance (Ea_{dyn}) and HPI. The haemodynamic optimisation algorithm on the intervention group is based on the three main mechanisms leading to arterial hypotension: hypovolaemia, impaired contractility and vasoplegia (figure 3). When HPI rises above 85, SVV will be checked. If SVV is <13%,

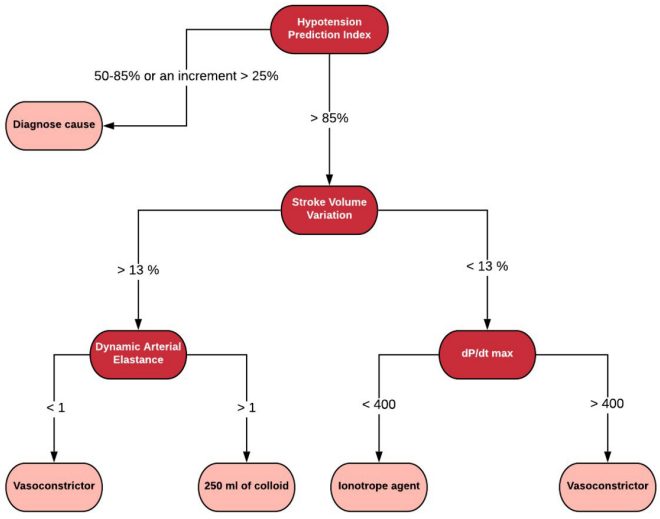

Figure 3 Intervention group haemodynamic optimisation algorithm.

a vasoconstrictor will be administered if dP/dt_{max} value is >400 mm Hg·s, or an inotrope if dP/dt_{max} is <400 mm Hg·s. If SVV is >13%, a 250 mL fluid bolus will be administered if the Ea_{dyn} value is >1, or a vasoconstrictor if Ea_{dyn} <1.

Study outcomes

Primary outcomes

Intraoperative time-weighted average of MAP <65 mm Hg (TWA-MAP <65), calculated as the area between 65 mm Hg threshold and the curve of the MAP measurements (AUC 65 mm Hg) divided by the total continuous reading time:[21]

$$TWA-MAP<65=\frac{\sum_{i=1}^{k}(area_1\ 65)+(area_2\ 65+\ldots+area_k\ 65)}{Total\ time\ of\ measurements}$$

The advantage of using TWA-MAP instead of MAP is that the former combines the severity and duration of the hypotension considering the overall duration of the surgery.

Other variables related to IOH: the number of IOH episodes (defined as an event of MAP <65 mm Hg of at least 1 min duration) and the total time of hypotension per case.

Secondary outcomes

The secondary outcomes include:

- Intraoperative StO_2, as an indicator of tissue oxygenation and wellness of the microcirculation. StO_2 will be non-invasively and continuously recorded in the brachioradial muscle in the arm opposite to the arterial line. We will calculate the time-weighted average of all StO_2 measurement values, the time weighted averaged below an individual specific threshold obtained during the first minute of optimisation and identifying the minimum StO_2, defined as the minimum value sustained at least for 5 min.[22 23]
- Postoperative measurements of the TIMP-2 and IGFBP7 (AKIRisk). We will compare the AKIRisk at baseline and the evolution among both groups.

	STUDY PERIOD				
	Enrolment	Study Intervention			
TIMEPOINT**	d_{-1}	Surgical day (d_0)	Daily follow-up (d_1-d_{hd})	Hospital discharge (d_{hd})	Follow-up (d_{30})
ENROLMENT:					
Eligibility screen	X				
Written and oral project explanation	X				
Written Informed consent	X				
Allocation		X			
Patient demographic/comorbidities	X	X			
INTERVENTIONS:					
Control group		X			
Intervention group]		X			
ASSESSMENTS:					
Primary outcomes		X			
Secondary outcomes		X	X	X	X

Figure 4 Schedule of enrolment, interventions and assessments. ** Specific timepoints listed

At the end of the surgery, data regarding the total fluid therapy during surgery, the accumulated dose of opioids during the intraoperative period, accumulated dose of vasoactive agents during the intraoperative period, accumulated dose of ionotropic drugs during the intraoperative period, other drugs with a haemodynamic impact not included in previous groups, total intraoperative diuresis, and transfusion of total blood products during surgery, will be collected.

Secondary outcomes will also include postoperative complications in accordance with the European Perioperative Clinical Outcome definitions,[24] length of hospital stay and 30-day mortality. Postoperative follow-up of patients will be performed by a collaborating investigator from each centre, blinded for the randomisation. For an overview of the outcome assessments, see figure 4.

Sample size and data analysis

The literature indicates that a cumulative hypotension time of more than 10 min during surgery is clinically relevant.[25] Given the novelty of the HPI parameter and the lack of publications during the design of this study, a pilot study in 31 patients undergoing major surgery was performed at the Virgen del Rocío Hospital. In this preliminary study, two groups were defined: a control group with invasive and continuous arterial pressure monitoring but without the use of HPI; and an intervention group with invasive and continuous blood pressure monitoring, in which the anaesthesiologist also had access to the HPI value and the additional parameters during surgery. In both groups, the haemodynamic objective during the intraoperative period was to maintain the MAP above 65 mm Hg. The results from this preliminary study revealed that in the control group (15 patients), 68.75% of the patients accumulated more than 10 min of hypotension (11 patients), while in the intervention group with HPI (16 patients), only 31.25% of the patients accumulated periods of a MAP <65 mm Hg more than 10 min (5 patients).

Based on this pilot study, to achieve a 90% power, and a significance level of 5%, 72 patients will be required (36 in each group). Assumed a drop-out rate of 10%, a total of 80 patients will be required (40 patients per group).

Statistical analysis

The normality of data distribution was assessed by the D'Agostino-Pearson test and confirmed by inspection of a Q-Q Plot. The results are expressed as the mean±SD when normally distributed or the median (25th–75th IQR). Categorical data were given as frequencies with percentages.

Comparison of quantitative variables between control and intervention group will be performed with the Mann-Whitney U test or the independent *t* test, and the χ^2 test for categorical variables. To establish a relationship between changes IOH management and tissue perfusion, a regression analysis will be performed between TWA-MAP and the perfusion indexes (StO_2 and AKIRisk).

A $p<0.05$ will be considered statistically significant. The statistical analyses will be performed with the SPSS software, V.23.0.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

DISCUSSION

Our goal is to determine whether a goal-directed algorithm based on the prevention of arterial hypotension using the HPI and the aid of the additional parameters, such as arterial dP/dt_{max} and Ea_{dyn}, reduces the duration and severity of IOH when compared with the recommended goal-directed fluid therapy. We also aim to determine whether this optimisation of the systemic perfusion pressure influences intraoperative tissue perfusion and postoperative complications. To achieve this objective, we will include patients with a higher risk of IOH (>65 years old and/or ASA III/IV).

Considering the significant impact of intraoperative arterial hypotension on mortality and morbidity, arterial pressure should be considered as a critical element. Therefore, maintaining blood pressure within a physiological range that ensures tissue perfusion should be considered not an option. Furthermore, the definition of blood pressure as a critical element, also implies a paradigm shift in the current treatment of intraoperative arterial hypotension from a reactive attitude to a proactive action based on predictors, such as HPI. If this proactive attitude associates with a better patient's outcome still needs to be proven clinically. Moreover, the proper correction of arterial hypotension also depends on the adequate identification of the pathophysiological mechanisms leading to low

blood pressure and the choice of the optimal treatment.[9] Accordingly, the clinical benefit of an artificial parameter based on machine learning, such as HPI, should be analysed coupled with the haemodynamic protocol that determines the best treatment according to those physiological mechanisms involved in the development of arterial hypotension. Therefore, if this preemptive haemodynamic protocol affects tissue perfusion is also one of the main goals of our study.

ETHICS AND DISSEMINATION

Ethics Committee approval was obtained from the Ethics Committee of Hospital Gregorio Marañón (Meeting of 27 July 2020, minutes 18/2020, Madrid, Spain). Written informed consent will be obtained from all included patients. Patients will be informed that they may decline to participate or withdraw from the study at any time.

Serious adverse effect of the product which, by its nature, incidence, intensity or consequences has not been identified in the updated version of the risk analysis report.

Regardless of the outcomes, it is our intention to publish the results of this study in a peer-reviewed journal. Findings will also be presented at Spanish and international conferences.

Trial status

Protocol V.1.0; March 2020. Recruitment started in November 2020, and it is expected to be finished on February 2022.

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Disclaimer The design of the study, the writing of this manuscript and the collection and interpretation of data are being carried out independently by the research team, without any intervention from the funding body.

Competing interests JVL: Edwards Lifesciences, Fresenius Kabi, Baxter, Vifor Pharma and bioMérieux conference fees, financial support for Edwards Lifesciences research obtained through the Grant Portal of the company. Economic research support from bioMérieux. IJ: Edwards Lifesciences conference fees. JR-M: Edwards Lifesciences, MSD, Fresenius Kabi and Dextera Medical conference fees. MIM: Clinical consultant for Edwards Lifesciences and Dextera Medical. WW: Employed by Edwards Lifesciences. The rest of the authors declare no conflict of interest.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1 and 4
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1 and 2
	2b	All items from the World Health Organization Trial Registration Data Set	4 and 5
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 15
	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	14
	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)	14 and 15
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	9 and 10
Objectives	7	Specific objectives or hypotheses	8 and 9

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)	4-8
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	4
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)	4 and 5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-8
	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)	15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Figure 2 Figure 3 Page 7-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Figure 2 Figure 3
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	8-9
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)	Figure 4
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	9-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9-10
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	5
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	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5-9
Blinding (masking)	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	5-9
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	Figure 4 Page 8-10
	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	5-7
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	5
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	9-10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10

	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)	9-10
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	14
	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	9
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	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
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)	1 and 13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n.a. (No planned ancillary studies)
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	5
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15

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	5
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	10
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	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	15-16
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	1
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix II.
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	n.a. (No genetic or molecular analyses in the current trial and no planned ancillary studies)

*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.