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Thromboelastography-guided blood transfusion during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: study protocol for a prospective randomized controlled trial

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Title:

Thromboelastography-guided blood transfusion during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: study protocol for a prospective randomized controlled trial.

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Abstract

Introduction

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a well-established treatment for peritoneal cancer. However, this kind of combination therapy is connected to a high incidence of complications. Moreover, relative studies have indicated that traditional laboratory testing is insufficient to demonstrate the overall haemostatic physiology of CRS/HIPEC. Thromboelastography (TEG), administered by monitoring dynamic changes in haemostasis, has been shown to contribute to reducing transfusion requirements and improving survival. However, there is no evidence to verify whether TEG can be applied to guide transfusion strategies during CRS/HIPEC. Therefore, we aim to investigate whether TEG-guided blood product transfusion (TEG-BT) therapy is superior to traditional blood product transfusion (T-BT) therapy for guiding perioperative blood transfusion treatment and improving the prognosis of patients undergoing CRS/HIPEC.

Methods and analysis

The TEG-BT versus T-BT study is a single-centre, randomized, blinded outcome assessment clinical trial of 162 peritoneal cancer patients aged 18-64 years undergoing CRS/HIPEC. Participants will be randomly allocated to receive TEG-BT or T-BT. The primary outcome will be the evaluation of perioperative blood transfusion, which refers to the total amount of blood transfusion given from the time patients enter the operating room up to 72 hours post-operatively. The secondary outcomes will include the transfusion volume during surgery, total amount of intraoperative infusion, amount of blood lost during the operation, total blood transfusion between 0 and 72 hours after surgery, lowest haemoglobin level within 72 hours after surgery, intensive care unit duration, overall length of stay, total cost of hospitalization and adverse events. Data will be analysed according to the intention-to-treat principle.

Ethical approval and dissemination The study protocol has been approved by the Scientific Research Ethics Committee of Beijing Shijitan Hospital Affiliated with Capital Medical University (Approval Number: sjtkyll-lx-2020-3). The results will be published in peer-reviewed journals.

Trial registration number ChiCTR2000028835

Strengths and limitations of this study

- This is a randomized, controlled, blinded outcome assessment trial to test the efficacy of thromboelastography (TEG)-guided blood transfusion in cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).
- The results of this study will improve a more goal-oriented transfusion strategy to reduce intraoperative blood transfusion, stabilize the perioperative coagulation function and lighten the economic burden.
- Future studies should address the importance of the relationship between transfusion thresholds and TEG parameters for the optimal management of coagulopathy.
- This is a single-centre trial, which may limit the generalization of conclusions; consequently, multicentre clinical studies with a larger sample size will be required.
- Although there is no way for anaesthesiologists to be blinded during the trial, the main outcome evaluators will be blinded.

BACKGROUND

Peritoneal cancer (PC) was previously considered to be a fatal stage of many gastrointestinal malignancies. Patients receiving palliative care had a median survival of 3 to 9 months, depending on the initial stage[1]. Significant progress has been made in the treatment of peritoneal malignancies over the past decade, and increasing evidence supports the use of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in an attempt to eradicate the disease macroscopically or microscopically and reduce peritoneal recurrence[2]. Currently, CRS/HIPEC is a an established treatment for pseudomyxoma peritonei, colorectal cancer, ovarian cancer, and gastric cancer with intraperitoneal metastasis[3]. The number of patients receiving CRS/HIPEC is expected to rise due to the high mortality of PC and the encouraging long-term benefits of treatment[4].

Although positive results have been observed in the treatment of tumour disease, CRS/HIPEC is characterized by a high incidence of complications that challenge both intraoperative and postoperative management[5]. Patients undergo CRS/HIPEC with significant fluid and blood loss, as well as chemotherapy and severe fluctuations in the core temperature[6]. Schmidt et al reported that CRS/HIPEC is a long and intricate surgical procedure accompanied by massive blood and fluid loss, with 51% of patients requiring a blood transfusion[7]. Massive intraoperative bleeding and the above factors will certainly lead to severe coagulation disorders. Intraoperative coagulation is a known complication of extensive surgery and HIPEC and may be caused by a combination of the high fluid requirements for resuscitation, direct effects of intraperitoneal chemotherapy, hepatotoxicity due to antitumour drugs, and direct liver injury[8]. Coagulation problems can be part of a series of events that can lead to massive blood loss during surgery, which can compromise the quality of the procedure, increase the need for blood transfusions, and compromise the patient's postoperative process[9]. Therefore, perioperative management of patients undergoing CRS/HIPEC is a challenge for surgeons, anaesthesiologists and critical care physicians[10].

Regarding the perioperative monitoring of coagulation function, the management of coagulation disorders at 90% of HIPEC centres is guided by standard laboratory tests

(SLTs), such as the activated partial thromboplastin time (APTT), prothrombin time (PT), or international normalized ratio (INR)[11]. Laboratory analysis shows that with an increase in the INR, coagulation disorders are observed, antithrombin III (AT III) and fibrinogen values are reduced, APTT is prolonged, and the number of coagulation cells is reduced[12]. Originally invented by Hartert in 1948, thromboelastography (TEG) is a viscoelastic, haemostatic assay analyser that imitates sluggish venous flow[13]. It is a different test from standard coagulation tests in that it measures the viscoelastic properties of whole blood as it clots, providing comprehensive information about the dynamics of clot development, stabilization and dissolution and assesses both thrombosis and fibrinolysis[14 15]. TEG has been used increasingly in intensive care units (ICUs) and in cases of acute critical surgery to evaluate coagulation disorders and guide the infusion of blood products for critically ill patients[16]. The technique has been tested in clinical scenarios such as heart and liver surgery and transplantation to reduce the number of transfusions and serve as a screening tool for patients managing hypercoagulant and bleeding disorders[17]. One study has shown that the PT, APTT and platelet (PLT) count are insufficient to demonstrate the effect of surgical stress, hyperthermia, chemotherapy and mass fluid transfer on the overall haemostatic physiology of CRS/HIPEC, while more sophisticated TEG monitoring is more accurate for perioperative coagulation function monitoring[18]. Another study reported that although traditional clinical monitoring of coagulation disorders was not meaningful in CRS/HIPEC, TEG monitoring confirmed that epidural analgesia after CRS/HIPEC was safe[19]. However, whether the effect of CRS/HIPEC on coagulation function can be treated according to TEG guidance and the infusion of various blood products can be guided according to changes in TEG and thereby achieve better outcomes for patients has not been fully verified.

Based on the existing literature, we aim to investigate the advantages of TEG-guided blood product transfusion (TEG-BT) in perioperative blood protection during CRS/HIPEC. Our working hypothesis is that compared with traditional blood product transfusion (T-BT) patients, TEG-BT patients receive fewer transfusions of intraoperative blood products and exhibit a more stable perioperative coagulation

function, no reduction in postoperative haemoglobin (HGB) levels and coagulation function, shorter hospital stays, and no increase in the incidence of adverse reactions.

METHODS AND ANALYSIS

Trial design

The trial will be conducted at Beijing Shijitan Hospital, Capital Medical University in Beijing, China. The study started recruiting patients in May 2020 and will continue for one year. The TEG-BT versus T-BT study is a single-centre, randomized, blinded outcome assessment clinical trial that conforms to the Consolidated Standards of Reporting Trials[20]. CRS/HIPEC is planned for two groups of patients, and TEG-BT or T-BT is adopted for perioperative blood transfusion management. The ratio of the two groups is 1:1 (Figure 1).

Objectives

The purpose of this study is to verify whether TEG-BT is better than T-BT for perioperative blood transfusion treatment and the prognosis of patients undergoing CRS/HIPEC.

Participants

Inclusion criteria

Patients who meet all of the following criteria are eligible for inclusion:

1. Age of 18-64 years
2. American Society of Anaesthesiologists (ASA) grade I or II
3. Well-established histologic diagnosis of peritoneal disease
4. Performance of CRS/HIPEC under general anaesthesia
5. Written consent to participate in the study

Exclusion criteria

1. Anaemia
2. Abnormal coagulation function before surgery
3. Uncontrolled systemic infections
4. Long-term anticoagulant or anti-PLT therapy
5. Thrombotic events
6. Severe cardiopulmonary disease

7. Hepatic or renal failure
8. Pregnancy or lactation
9. Patient refusal to sign the informed consent form
10. Patient participation in another clinical-treatment study

Randomization and blinding

All participants will be randomly divided into two groups: TEG-BT for the experimental group and T-BT for the control group. Before the study begins, an independent investigator who is not exposed to any of the participants will use a simple randomized method to divide the two groups in a 1:1 ratio. The random numbers will be saved in sealed opaque envelopes. Before surgery, the anaesthesiologist will evaluate the patient, and after the informed consent form is signed, the envelope will be opened to obtain the grouping information of the patient. Blood transfusion will be performed intraoperatively according to the grouping of the patients. After the operation, independent follow-up staff will collect the data of the patients during and after the operation according to the electronic medical record system. During the whole experiment, the anaesthesiologists will be aware of the patient grouping information, but they will not participate in the postoperative follow-up and data collection. Other individuals and personnel involved, including patients, surgeons, data collectors, etc., will not know the grouping information.

Anaesthesia management

The anaesthesia regimen will be consistent between the two groups. Venous access will be open in all patients in the preparation room, and midazolam will be administered (0.05 mg/kg intravenously) to the patients before they enter the operating room. Upon arrival in the operating room, standard monitoring (pulse oximetry, electrocardiogram, and noninvasive arterial blood pressure monitoring) will be established. Sufentanil 0.5 μg/kg, propofol 2.5 mg/kg and rocuronium 0.6 mg/kg will be adopted for general anaesthesia induction. After endotracheal intubation, the lungs will be aerated with 50% oxygen and 50% air mixture, and the ventilation level will be adjusted to maintain normocapnia. Radial artery and internal jugular vein puncture will be performed to monitor the invasive arterial pressure and central venous pressure. We will perform an

ultrasound-guided bilateral rectus sheath blockade, and 0.375% ropivacaine will be given for analgesia on both sides. Anaesthesia will be maintained with inhalation of sevoflurane and IV remifentanil, and muscle relaxation will be maintained with IV rocuronium. Postoperative intravenous injection of atropine 0.01 mg/kg and neostigmine 0.05 mg/kg will be used to antagonize residual neuromuscular block. Extubation will be performed after confirming that the patient's eyes are open and that he or she exhibits adequate spontaneous breathing and purposeful movement.

Intraoperative intervention

All enrolled patients will be assigned to one of the following two study groups. For patients in the T-BT group, the anaesthesiologist will inject blood products according to his or her clinical judgement. Patients entering the TEG-BT group will undergo TEG monitoring 4 times before surgery, during CRS, before HIPEC and after HIPEC, and blood products such as erythrocytes, plasma, PLTs, prothrombin complex and fibrinogen will be administered according to the monitoring results. The two groups of patients will be given red blood cells (RBCs) to maintain HGB levels of at least 10 g/dl. Blood will be collected from the central vein through a three-way catheter. The first 10 ml of venous blood will be administered to the patient through the peripheral venous pathway, and then 3.5 ml of venous blood will be collected after syringe replacement. According to relevant guidelines, the samples of whole blood should be tested within 5 minutes after collection.

All blood samples will be tested by the same professional TEG operator. The operator of the TEG machine model [TEG 5000 (Haemoscope)] will not know the patient grouping information.

R time is the incubation period from blood entry into the reactive vessels to initial clot formation. The lack of the R time extension prompt factor can be corrected by fresh frozen plasma (FFP)[21]. When the R time value is greater than 10 minutes, the patient will be infused with 2 U of FFP; when the R time value is greater than 15 minutes, the patient will be infused with 4 U of plasma; when the R time value is greater than 20 minutes, the patient will be infused with 6 U[22].

Angle α is the measurement of fibrin cross linkage mechanics or clot strengthening

speed. A low angle may indicate a lack of fibrinogen, which is less affected by the PLT count, and this loss of function may be corrected by the use of FFP or fibrinogen.

MA is a direct effect of fibrin and PLT binding properties of glycoprotein IIb/IIIA (GPIIb/IIIA), representing the strength of fibrin clots. Low MA may be corrected by the administration of PLTs[21]. At Ma < 45, PLT transfusion will begin. LY30 values show the rate of thrombus rupture at 30 minutes after MA. When LY30 > 8%, this indicates hyperfibrinolysis, which can be corrected by tranexamic acid.

Outcomes

Table 1 provides an overview of the outcomes and intervention or assessment time points.

Table 1. Study visits of the TEG-BT vs T-BT trial

Time point	Enrolment Preoperative	Allocation 0 d	Post-allocation T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	Discharged
Enrolment													
Eligibility screen	X												
Informed consent	X												
Allocation		X											
Interventions													
TEG-BT			X	X	X	X							
T-BT													
Assessments													
Demographic data	X	X											
Baseline variables		X											
HGB		X						X	X	X	X	X	
Hct		X						X	X	X	X	X	
PLTs		X						X	X	X	X	X	
PT		X						X	X	X	X	X	
APTT		X						X	X	X	X	X	
INR		X						X	X	X	X	X	
Fibrinogen		X						X	X	X	X	X	
Crystalloid fluid							X						
Artificial colloid fluid							X						
RBCs							X						
FFP							X						
PLTs							X						
Fibrinogen							X						
Prothrombin complex							X						

Albumin	X			
Blood loss	X			
Urine output	X			
The amount of blood lost between 0 and 72 hours after surgery			X	
Total blood transfusion between 0 and 72 hours after surgery			X	
The lowest HGB level			X	
ICU duration				X
Overall length of stay				X
Total cost of the hospitalization				X

T0, entering the operating room; T1, the performance of CRS; T2, before HIPEC; T3, after HIPEC; T4, at the end of surgery; T5, 2 hours after surgery; T6, postoperative day 1; T7, postoperative day 2; T8, postoperative day 3; T9, postoperative day 5.

TEG-BT, thromboelastography-guided blood product transfusion therapy; T-BT, traditional blood product transfusion therapy; HGB, haemoglobin; Hct, haematocrit; PLTs, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, the international ratio; RBCs, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit.

Primary outcome

The primary outcome will be the evaluation of perioperative blood transfusion. The amount of blood transfusion during the perioperative period refers to the total amount of blood transfusion given from the time patients enter the operating room (intra-operative) to 72 hours post-operatively (post-operative), including RBCs, FFP and PLTs.

Secondary outcomes

The secondary results mainly include the following aspects:

- Transfusion volume during the operation: The total amount of RBCs, FFP and PLTs in the two groups.
- The total amount of intraoperative infusion: During the operation, the amount of fluid input from the two groups will include the total amount of crystalloid fluid, artificial colloid fluid, albumin, fibrinogen and prothrombin complex.

- The amount of blood lost during the operation: During the operation, the total output of the two groups will include blood loss and urine output.
- Effects of CRS/HIPEC on TEG： Before and after CRS/HIPEC, TEG monitoring will assess changes in blood coagulation function: including reaction time (R time), thrombosis time (K time), fibrinogen function (α angle), thrombus strength (MA), and fibrinolysis (LY30).
- Effects of surgery on indicators of coagulation function: The influence of surgery on coagulation function. Based on the routine blood cell count and coagulation test, the values of HGB, PLT count, PT, APTT and INR will be recorded 1, 2, 3 and 5 days after the operation.
- The amount of total blood lost between 0 and 72 hours after surgery: total blood lost is calculated using the formula provided by Gross[23], total blood loss = PBV $\times$ (Hct_{pre}−Hct_{post})/Hct_{ave}. The peripheral blood volume (PBV) is then calculated using the formula proposed by Nadler et al.[24]: PBV=k1 $\times$ height(m)^3+ k2 $\times$ weight(kg)+k3, where k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men, and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women.
- Total blood transfusion between 0 and 72 hours after surgery: Within 0-72 hours after the operation, patients will again receive a blood transfusion, including the total amount of RBCs, FFP and PLTs.
- The lowest HGB within 72 hours after surgery: Within three days after the operation, blood samples will be collected every morning to measure the HGB level. Patients who need a second operation due to postoperative bleeding within 72 hours will be excluded from this study.
- ICU duration.
- Overall length of stay.
- Total cost of the hospitalization.

Adverse events

Adverse events in this study will mainly include intraoperative blood transfusion-related adverse reactions: nonhemolytic febrile reactions, allergic reactions, haemolytic reactions, circulatory overload and acid-base imbalance; etc. Once the anaesthesiologist

identifies an adverse event, all patients should be accurately documented and immediately treated. If the condition progresses to severe intraoperative adverse events, such as shock, heart failure and massive blood loss, the patient will be excluded from the study.

Data collection

Throughout the trial, the investigator – the anaesthesiologist involved in the operation – will be completely independent of the data collection staff. Data collection personnel are responsible for collecting preoperative and postoperative patient information and all data required in the trial protocol. Anonymous data will be collected in the case report form (CRF), either numerically or alphabetically. After the completion of the anonymous CRF table, the researcher shall confirm the authenticity and validity of all data, give a reasonable explanation for any missing data, or choose to exclude the test scheme.

Sample size calculation

The Pass 11.0 software package was used for sample size evaluation. According to a small sample (86 cases) observation study in the early stage of the research group, it was found that the allogeneic blood volume used in the operation of PC patients undergoing thermal perfusion chemotherapy was 1664.7 ± 789.3 ml [median: 1600 (1200, 2000)]. It is estimated that the blood volume of allogeneic patients used in thromboelastogram monitoring after intervention could be reduced by 20%, i.e., 1331.8 ± 631.4 ml, with a set α value of 0.05 and a β value of 0.2, and the sample volume of the two groups was 73 cases. However, the index of allogeneic blood volume is non-normally distributed data, and a nonparametric test is planned to be used for analysis. Compared with the t-test, the efficiency of the Wilcoxon rank sum test is estimated to be approximately 95%, which means that the sample size required for the Wilcoxon test is 1.053 times the sample size required for the t-test[25]. Therefore, the number of subjects to be included in the study was increased by 1.053 times, and the drop-out rate was maintained to within 5%. The final target sample size was 81 people in each group (162 people in total).

Statistical analysis

Baseline characteristics

Data analyses will be performed by the statistical software SPSS version 25.0. During the trial, the statistical analyst will be unaware of the participants' personal information and their group assignment. The Kolmogorov-Smirnov test will be used to test the normal distribution of continuous variables. If data values are normally distributed, they will be presented as the mean ± standard deviation (SD) and will be compared using the independent t-test. If data values are not normally distributed, they will be presented as median and interquartile range (IQR) and compared using the nonparametric test. Categorical data will be shown as frequency and percentage and compared using the $\chi 2$ test or Fisher's exact test.

Primary outcome and secondary outcomes

The primary outcome, the total amount of blood transfusion, will be presented as the mean ± SD or median and IQR and compared using the independent t-test or Wilcoxon's rank sum test. For the secondary outcomes (i.e., transfusion volume during the operation, total amount of intraoperative infusion, amount of blood lost during the operation, total blood transfusion between 0 and 72 hours after surgery, and lowest HGB within 72 hours after surgery), the t-test will be used to compare the measurement data, and the rank sum test will be used for ranked data. The $\chi 2$ test or Fisher's exact test will be used to analyse categorical data (adverse events). The effect size, mean differences, and their confidence intervals will be reported to make the results comparable. For repeated variables, a repeated-measures analysis of covariance will be performed with visit time as the repeated factor and group as the non-repeated factor.

All analyses will be performed on the intention-to-treat population of participants who are given the randomized treatment. Missing data will be handled using the multiple imputation method. A complete-case analysis without imputation of missing data will also be performed to determine whether the results are consistent. The significance level that will be used for statistical analysis with two-tailed testing will be 5%. No interim analyses will be performed.

DISCUSSION

The TEG-BT versus T-BT study is a single-centre and randomized clinical trial with

a blinded outcome assessment that aims to verify whether TEG-BT is superior to T-BT in the perioperative blood transfusion treatment and prognosis of patients in CRS/HIPEC. If it can be proven that compared with T-BT, TEG-BT can lead to less intraoperative blood transfusion, more stable perioperative coagulation function, no reduction in postoperative HGB levels and coagulation function, and no increase in the incidence of adverse events, then the treatment and transfusion of various blood products can be guided according to changes in the TEG index to achieve a better prognosis.

CRS/HIPEC is a therapeutic method for patients with colorectal, appendiceal, ovarian, and gastric cancer with peritoneal metastasis and peritoneal mesothelioma[26-28]. A relevant study demonstrated that intraoperative transfusion of RBCs and a possibly increased peritoneal carcinomatosis index (PCI) are associated with abnormal postoperative coagulation, including changes in the PLT count, INR, and partial thromboplastin time (PTT)[4]. Based on the above points, optimal blood product transfusion is of great importance for patients receiving CRS/HIPEC.

SLTs, including the fibrinogen concentration, INR, PT and APTT, were initially used to diagnose intraoperatively acquired coagulopathy and guide the administration of treatment for massive haemorrhage[29 30]. However, relevant data suggest that the PT, APTT and PLT count insufficiently demonstrate the impact of surgical stress, hyperthermia, chemotherapy and considerable fluid shifts on the overall haemostatic physiology of CRS/HIPEC[18]. Routine laboratory testing is performed in PLT-deficient plasma whose results are not available to the clinician for 45–60 minutes[30-32]; in contrast, TEG can make up for the above deficiencies as a bedside analysis tool, estimating the clotting process in whole blood and providing real-time data[33]. Increasing evidence has demonstrated that the application of a TEG-guided transfusion strategy can reduce the demand for blood products and improve the morbidity of bleeding patients, mainly according to trials involving heart surgery with cardiopulmonary bypass and liver transplantation surgery[34 35]. After many clinical experiences and the application of TEG, targeted coagulation therapy has become feasible[36]. A previous prospective study indicated that conventional coagulation measures had no significance for CRS/HIPEC,

but TEG monitoring confirmed the suitability of epidural analgesia after CRS/HIPEC by evaluating perioperative clot kinetics[37]. However, there is no relevant study to verify whether TEG can be applied to guide transfusion strategies for treating coagulation disorders due to CRS/HIPEC. Therefore, it is believed that the use of TEG in guiding perioperative blood transfusion treatment and improving prognosis of patients undergoing CRS/HIPEC is definitely worth exploring.

The current study still has several limitations. First, for various reasons, we did not observe certain long-term outcomes, such as overall mortality, the incidence of reoperation, transfusion-related complications and thrombotic/thromboembolic events. Nevertheless, the influence of TEG-BT on these outcomes is worthy of further exploration. Moreover, due to the design of this trial, it is not available to determine the impact of pathophysiological changes in patients with potential diseases; therefore, we will remove severely ill patients from this study for safety reasons. Additionally, further studies may be required to determine whether TEG-BT combined with T-BT is superior to either alone for guiding the perioperative blood transfusion treatment of patients receiving CRS/HIPEC. Last but not least, this study is a single-centre trial, which may limit its generalisability; consequently, it is of great importance to perform multicentre clinical studies with a larger sample size to provide higher levels of evidence.

The primary outcome of our study is perioperative blood transfusion. As mentioned earlier, patients treated with CRS/HIPEC undergo an extensive abdominal incision, large fluid shifts, hyperthermic insults, and exposure to chemotherapeutic agents, which increases the likelihood of altered coagulation and excessive bleeding[4 38 39]. Therefore, rational transfusion strategies are warranted. Extensive literature notes that allogeneic blood transfusion itself is an independent risk factor for increased morbidity (thrombotic/thromboembolic events, anaemia, nosocomial infections, multiorgan dysfunction syndrome), mortality, hospital stay, hospital costs, etc., in trauma, cardiovascular surgery, and ICU patients[40-43]. Nevertheless, TEG can be performed to monitor dynamic changes in haemostasis, which is thought to enable clinicians to distinguish between a surgical cause of bleeding or coagulopathy, to guide and evaluate the choice of haemostatic treatment, and to reduce transfusion requirements and

improve survival[34]. In contrast, postoperative bleeding and coagulation disorders also increase the transfusion of allogeneic blood products, thereby affecting morbidity and mortality[36]. Hence, to further explore their interaction in patients undergoing CRS/HIPEC, the indicators of coagulation function, lowest value of HGB within 72 hours after surgery, ICU duration, overall length of stay, and costs incurred during the hospital stay will be the secondary outcomes of this study.

To conclude, the TEG-BT versus T-BT trial will be the first single-centre, randomized clinical trial with a blinded outcome assessment undertaken to substantiate the hypothesis that TEG-BT is superior to T-BT for administrating perioperative blood transfusion treatment and improving the prognosis of patients undergoing CRS/HIPEC. If the benefits mentioned in the hypothesis are confirmed, our study will improve a more goal-oriented transfusion strategy to reduce intraoperative blood transfusion, stabilize perioperative coagulation function and lighten the economic burden. Combined with our research results, the potential significance of this trial is that it may influence future guidelines on anaesthesia management of CRS/HIPEC and bring wider application for TEG.

ETHICS AND DISSEMINATION

Ethical and legislative approvals

The TEG-BT vs T-BT study is registered at the Chinese Clinical Trial Registry with the trial identification number ChiCTR2000028835. The research plan was approved by the scientific research ethics committee of Beijing Shijitan Hospital Affiliated with Capital Medical University (Approval Number: sjtkyll-lx-2020-3). We will inform investigators, all participants and the trial registry when there are significant changes to the study protocol. Before each participant enters the study, he/she and the researchers will sign an informed consent form. Patients have the right to refuse or withdraw from the study at any time, which will not affect any of their medical or other interests. The personal information of the participants will be kept confidential, and anonymous personal patient data will be shared according to requirements.

Publication plan

With the consent of the main researchers and methodologists, the research coordinator

will be responsible for preparing scientific statements and reports corresponding to the study. Based on the proportion of contribution to the study, the participating researchers and clinicians as well as biostatisticians and related researchers will be the co-authors of the ensuring report and publication. The rules of publication will be in accordance with international recommendations, and the publications will be submitted to peer-reviewed journals[44].

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Contributors

WS and ZQ contributed equally to this work and should be considered co-first authors. WS and ZQ contributed to the conception and drafting of the first manuscript for this trial. LP is the principal investigator of the entire study and edited the final manuscript. CL and LG contributed to the conception of the research protocol and will participate in the follow-up for this trial. All authors critically revised and modified the protocol and the article. They all approved the final version to be published.

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Competing interests

None declared.

Patient consent for publication

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No additional unpublished data are available.

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Figure 1

Study flow diagram of the TEG-BT vs T-BT trial.

TEG-BT, thromboelastography-guided blood product transfusion therapy; T-BT, traditional blood product transfusion therapy; CRS/HIPEC, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.

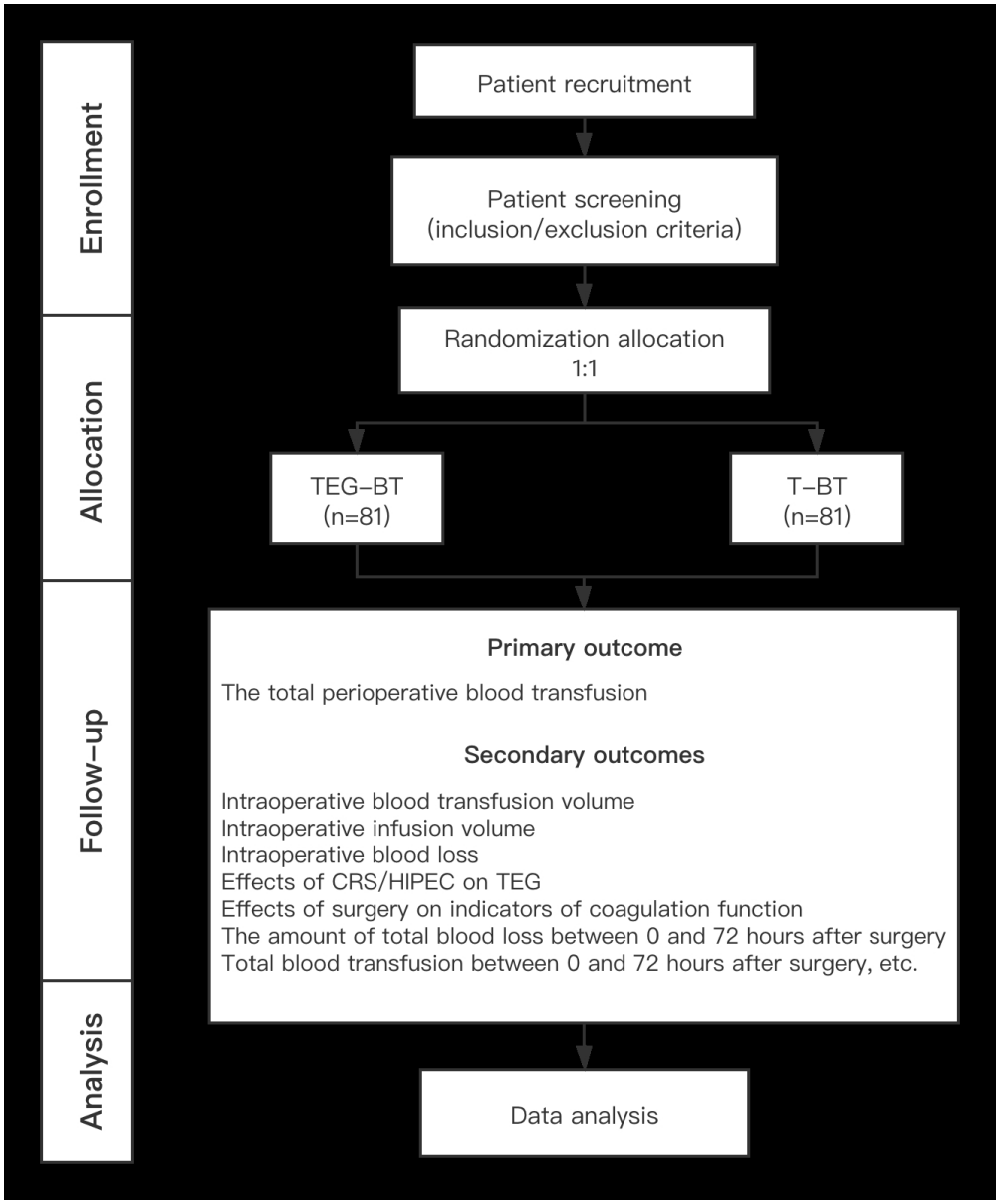

Figure 1. Study flow diagram of the TEG-BT vs T-BT trial.

467x561mm (72 x 72 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
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	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	N/A
	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	N/A
	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)	N/A

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	4-6
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	6
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)	6
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	N/A
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, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	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)	8, 9, 11, 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
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	9, 10, 11
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)	9, 10, 11

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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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	8, 12
	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	N/A

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	N/A
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	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	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)	12-13
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	N/A
	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	N/A
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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	16, 17
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	N/A
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	16, 17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

*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.

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Thromboelastography-guided blood transfusion during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: study protocol for a prospective randomized controlled trial

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Title:

Thromboelastography-guided blood transfusion during cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy: study protocol for a prospective randomized controlled trial.

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Cytoreductive surgery, Hyperthermic intraperitoneal chemotherapy, Thromboelastography, Blood transfusion

Word count: 4027

Abstract

Introduction

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) is a well-established treatment for peritoneal cancer. However, this kind of combination therapy is connected to a high incidence of complications. Moreover, relative studies have indicated that traditional laboratory testing is insufficient to demonstrate the overall haemostatic physiology of CRS/HIPEC. Thromboelastography (TEG), administered by monitoring dynamic changes in haemostasis, has been shown to contribute to reducing transfusion requirements and improving survival. However, there is no evidence to verify whether TEG can be applied to guide transfusion strategies during CRS/HIPEC. Therefore, we aim to investigate whether TEG-guided blood product transfusion (TEG-BT) therapy is superior to traditional blood product transfusion (T-BT) therapy for guiding perioperative blood transfusion treatment and improving the prognosis of patients undergoing CRS/HIPEC.

Methods and analysis

The TEG-BT versus T-BT study is a single-centre, randomized, blinded outcome assessment clinical trial of 162 peritoneal cancer patients aged 18-64 years undergoing CRS/HIPEC. Participants will be randomly allocated to receive TEG-BT or T-BT. The primary outcome will be the evaluation of perioperative blood transfusion, which refers to the total amount of blood transfusion given from the time patients enter the operating room up to 72 hours post-operatively. The secondary outcomes will include the transfusion volume during surgery, total amount of intraoperative infusion, amount of blood lost during the operation, total blood transfusion between 0 and 72 hours after surgery, lowest haemoglobin level within 72 hours after surgery, intensive care unit duration, overall length of stay, total cost of hospitalization and adverse events. Data will be analysed according to the intention-to-treat principle.

Ethical approval and dissemination The study protocol has been approved by the Scientific Research Ethics Committee of Beijing Shijitan Hospital Affiliated with

Capital Medical University (Approval Number: sjtkyll-lx-2020-3). The results will be published in peer-reviewed journals.

Trial registration number ChiCTR2000028835

Strengths and limitations of this study

- This is a randomized, controlled, blinded outcome assessment trial to test the efficacy of thromboelastography (TEG)-guided blood transfusion in cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).
- The results of this study will improve a more goal-oriented transfusion strategy to reduce intraoperative blood transfusion, stabilize the perioperative coagulation function and lighten the economic burden.
- Future studies should address the importance of the relationship between transfusion thresholds and TEG parameters for the optimal management of coagulopathy.
- This is a single-centre trial, which may limit the generalization of conclusions; consequently, multicentre clinical studies with a larger sample size will be required.
- Although there is no way for anaesthesiologists to be blinded during the trial, the main outcome evaluators will be blinded.

BACKGROUND

Peritoneal cancer (PC) was previously considered to be a fatal stage of many gastrointestinal malignancies. Patients receiving palliative care had a median survival of 3 to 9 months, depending on the initial stage[1]. Significant progress has been made in the treatment of peritoneal malignancies over the past decade, and increasing evidence supports the use of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) in an attempt to eradicate the disease macroscopically or microscopically and reduce peritoneal recurrence[2]. Currently, CRS/HIPEC is a an established treatment for pseudomyxoma peritonei, colorectal cancer, ovarian cancer, and gastric cancer with intraperitoneal metastasis[3]. The number of patients receiving CRS/HIPEC is expected to rise due to the high mortality of PC and the encouraging long-term benefits of treatment[4].

Although positive results have been observed in the treatment of tumour disease, CRS/HIPEC is characterized by a high incidence of complications that challenge both intraoperative and postoperative management[5]. Patients undergo CRS/HIPEC with significant fluid and blood loss, as well as chemotherapy and severe fluctuations in the core temperature[6]. Schmidt et al reported that CRS/HIPEC is a long and intricate surgical procedure accompanied by massive blood and fluid loss, with 51% of patients requiring a blood transfusion[7]. Massive intraoperative bleeding and the above factors will certainly lead to severe coagulation disorders. Intraoperative coagulation is a known complication of extensive surgery and HIPEC and may be caused by a combination of the high fluid requirements for resuscitation, direct effects of intraperitoneal chemotherapy, hepatotoxicity due to antitumour drugs, and direct liver injury[8]. Coagulation problems can be part of a series of events that can lead to massive blood loss during surgery, which can compromise the quality of the procedure, increase the need for blood transfusions, and compromise the patient's postoperative process[9]. Therefore, perioperative management of patients undergoing CRS/HIPEC is a challenge for surgeons, anaesthesiologists and critical care physicians[10].

Regarding the perioperative monitoring of coagulation function, the management

of coagulation disorders at 90% of HIPEC centres is guided by standard laboratory tests (SLTs), such as the activated partial thromboplastin time (APTT), prothrombin time (PT), or international normalized ratio (INR)[11]. Laboratory analysis shows that with an increase in the INR, coagulation disorders are observed, antithrombin III (AT III) and fibrinogen values are reduced, APTT is prolonged, and the number of coagulation cells is reduced[12]. Originally invented by Hartert in 1948, thromboelastography (TEG) is a viscoelastic, haemostatic assay analyser that imitates sluggish venous flow[13]. It is a different test from standard coagulation tests in that it measures the viscoelastic properties of whole blood as it clots, providing comprehensive information about the dynamics of clot development, stabilization and dissolution and assesses both thrombosis and fibrinolysis[14 15]. TEG has been used increasingly in intensive care units (ICUs) and in cases of acute critical surgery to evaluate coagulation disorders and guide the infusion of blood products for critically ill patients[16]. The technique has been tested in clinical scenarios such as heart and liver surgery and transplantation to reduce the number of transfusions and serve as a screening tool for patients managing hypercoagulant and bleeding disorders[17]. One study has shown that the PT, APTT and platelet (PLT) count are insufficient to demonstrate the effect of surgical stress, hyperthermia, chemotherapy and mass fluid transfer on the overall haemostatic physiology of CRS/HIPEC, while more sophisticated TEG monitoring is more accurate for perioperative coagulation function monitoring[18]. Another study reported that although traditional clinical monitoring of coagulation disorders was not meaningful in CRS/HIPEC, TEG monitoring confirmed that epidural analgesia after CRS/HIPEC was safe[19]. However, whether the effect of CRS/HIPEC on coagulation function can be treated according to TEG guidance and the infusion of various blood products can be guided according to changes in TEG and thereby achieve better outcomes for patients has not been fully verified.

Based on the existing literature, we aim to investigate the advantages of TEG-guided blood product transfusion (TEG-BT) in perioperative blood protection during CRS/HIPEC. Our working hypothesis is that compared with traditional blood product transfusion (T-BT) patients, TEG-BT patients receive fewer transfusions of

intraoperative blood products and exhibit a more stable perioperative coagulation function, no reduction in postoperative haemoglobin (HGB) levels and coagulation function, shorter hospital stays, and no increase in the incidence of adverse reactions.

METHODS AND ANALYSIS

Trial design

The trial will be conducted at Beijing Shijitan Hospital, Capital Medical University in Beijing, China. The study started recruiting patients in May 2020 and will continue for one year. The TEG-BT versus T-BT study is a single-centre, randomized, blinded outcome assessment clinical trial that conforms to the Consolidated Standards of Reporting Trials[20]. CRS/HIPEC is planned for two groups of patients, and TEG-BT or T-BT is adopted for perioperative blood transfusion management. The ratio of the two groups is 1:1 (Figure 1).

Objectives

The purpose of this study is to verify whether TEG-BT is better than T-BT for perioperative blood transfusion treatment and the prognosis of patients undergoing CRS/HIPEC.

Participants

Inclusion criteria

Patients who meet all of the following criteria are eligible for inclusion:

1. Age of 18-64 years
2. American Society of Anaesthesiologists (ASA) grade I or II
3. Well-established histologic diagnosis of peritoneal disease
4. Performance of CRS/HIPEC under general anaesthesia
5. Written consent to participate in the study

Exclusion criteria

1. Anaemia: HGB<9g/dl
2. Abnormal coagulation function before surgery
3. Uncontrolled systemic infections
4. Antiplatelet or anticoagulant therapy was administered at enrollment or discontinued for less than 7 days prior to study evaluation

5. Thrombotic events: Any blood clot in the vein or artery has been recorded before or at present
6. Severe cardiopulmonary disease
7. Hepatic or renal failure
8. Pregnancy or lactation
9. Patient refusal to sign the informed consent form
10. Patient participation in another clinical-treatment study

Randomization and blinding

All participants will be randomly divided into two groups: TEG-BT for the experimental group and T-BT for the control group. Before the study begins, an independent investigator who is not exposed to any of the participants will use a simple randomized method to divide the two groups in a 1:1 ratio. The random numbers will be saved in sealed opaque envelopes. Before surgery, the anaesthesiologist will evaluate the patient, and after the informed consent form is signed, the envelope will be opened to obtain the grouping information of the patient. Blood transfusion will be performed intraoperatively according to the grouping of the patients. After the operation, independent follow-up staff will collect the data of the patients during and after the operation according to the electronic medical record system. During the whole experiment, the anaesthesiologists will be aware of the patient grouping information, but they will not participate in the postoperative follow-up and data collection. Other individuals and personnel involved, including patients, surgeons, data collectors, etc., will not know the grouping information.

Anaesthesia management

The anaesthesia regimen will be consistent between the two groups. Venous access will be open in all patients in the preparation room, and midazolam will be administered (0.05 mg/kg intravenously) to the patients before they enter the operating room. Upon arrival in the operating room, standard monitoring (pulse oximetry, electrocardiogram, and noninvasive arterial blood pressure monitoring) will be established. Sufentanil 0.5 μg/kg, propofol 2.5 mg/kg and rocuronium 0.6 mg/kg will be adopted for general anaesthesia induction. After endotracheal intubation, the

lungs will be aerated with 50% oxygen and 50% air mixture, and the ventilation level will be adjusted to maintain normocapnia. Radial artery and internal jugular vein puncture will be performed to monitor the invasive arterial pressure and central venous pressure. We will perform an ultrasound-guided bilateral rectus sheath blockade, and 0.375% ropivacaine will be given for analgesia on both sides. Anaesthesia will be maintained with inhalation of sevoflurane and IV remifentanil, and muscle relaxation will be maintained with IV rocuronium. Postoperative intravenous injection of atropine 0.01 mg/kg and neostigmine 0.05 mg/kg will be used to antagonize residual neuromuscular block. Extubation will be performed after confirming that the patient's eyes are open and that he or she exhibits adequate spontaneous breathing and purposeful movement.

Intraoperative intervention

All enrolled patients will be assigned to one of the following two study groups. For patients in the T-BT group, the anaesthesiologist will inject blood products according to his or her clinical judgement. Patients entering the TEG-BT group will undergo TEG monitoring 4 times before surgery, during CRS, before HIPEC and after HIPEC, and blood products such as erythrocytes, plasma, PLTs, prothrombin complex and fibrinogen will be administered according to the monitoring results. The two groups of patients will be given red blood cells (RBCs) to maintain HGB levels of at least 9g/dl.

Blood will be collected from the central vein through a three-way catheter. The first 10 ml of venous blood will be administered to the patient through the peripheral venous pathway, and then 3.5 ml of venous blood will be collected after syringe replacement. According to relevant guidelines, the samples of whole blood should be tested within 5 minutes after collection.

All blood samples will be tested by the same professional TEG operator. The operator of the TEG machine model [TEG 5000 (Haemoscope)] will not know the patient grouping information.

R time is the incubation period from blood entry into the reactive vessels to initial clot formation. The lack of the R time extension prompt factor can be corrected by fresh

frozen plasma (FFP)[21]. When the R time value is greater than 10 minutes, the patient will be infused with 2 U of FFP; when the R time value is greater than 15 minutes, the patient will be infused with 4 U of plasma; when the R time value is greater than 20 minutes, the patient will be infused with 6 U[22].

Angle α is the measurement of fibrin cross linkage mechanics or clot strengthening speed. A low angle may indicate a lack of fibrinogen, which is less affected by the PLT count, and this loss of function may be corrected by the use of FFP or fibrinogen. MA is a direct effect of fibrin and PLT binding properties of glycoprotein IIb/IIIA (GPIIb/IIIA), representing the strength of fibrin clots. Low MA may be corrected by the administration of PLTs[21]. At Ma < 45, PLT transfusion will begin. LY30 values show the rate of thrombus rupture at 30 minutes after MA. When LY30 > 8%, this indicates hyperfibrinolysis, which can be corrected by tranexamic acid.

Outcomes

Table 1 provides an overview of the outcomes and intervention or assessment time points.

Table 1. Study visits of the TEG-BT vs T-BT trial

Time point	Enrolment	Allocation	Post-allocation										
	Preoperative	0 d	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9	Discharged
Enrolment													
Eligibility screen	X												
Informed consent	X												
Allocation		X											
Interventions													
TEG-BT			X	X	X	X							
T-BT													
Assessments													
Demographic data	X	X											
Baseline variables		X											
HGB		X						X	X	X	X	X	
Hct		X						X	X	X	X	X	
PLTs		X						X	X	X	X	X	
PT		X						X	X	X	X	X	
APTT		X						X	X	X	X	X	
INR		X						X	X	X	X	X	

Fibrinogen	X			X	X	X	X	X	
Crystalloid fluid			X						
Artificial colloid fluid			X						
RBCs			X						
FFP			X						
PLTs			X						
Fibrinogen			X						
Prothrombin complex			X						
Albumin			X						
Blood loss			X						
Urine output			X						
The amount of blood lost between 0 and 72 hours after surgery							X		
Total blood transfusion between 0 and 72 hours after surgery							X		
The lowest HGB level							X		
ICU duration									X
Overall length of stay									X
Total cost of the hospitalization									X

T0, entering the operating room; T1, the performance of CRS; T2, before HIPEC; T3, after HIPEC; T4, at the end of surgery; T5, 2 hours after surgery; T6, postoperative day 1; T7, postoperative day 2; T8, postoperative day 3; T9, postoperative day 5.

TEG-BT, thromboelastography-guided blood product transfusion therapy; T-BT, traditional blood product transfusion therapy; HGB, haemoglobin; Hct, haematocrit; PLTs, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; INR, the international ratio; RBCs, red blood cells; FFP, fresh frozen plasma; ICU, intensive care unit.

Primary outcome

The primary outcome will be the evaluation of perioperative blood transfusion. The amount of blood transfusion during the perioperative period refers to the total amount of blood transfusion given from the time patients enter the operating room (intra-operative) to 72 hours post-operatively (post-operative), including RBCs, FFP and PLTs.

Secondary outcomes

The secondary results mainly include the following aspects:

- Transfusion volume during the operation: The total amount of RBCs, FFP and PLTs in the two groups.
- The total amount of intraoperative infusion: During the operation, the amount of fluid input from the two groups will include the total amount of crystalloid fluid, artificial colloid fluid, albumin, fibrinogen and prothrombin complex.
- The amount of blood lost during the operation: During the operation, the total output of the two groups will include blood loss and urine output.
- Effects of CRS/HIPEC on TEG： Before and after CRS/HIPEC, TEG monitoring will assess changes in blood coagulation function: including reaction time (R time), thrombosis time (K time), fibrinogen function (α angle), thrombus strength (MA), and fibrinolysis (LY30).
- Effects of surgery on indicators of coagulation function: The influence of surgery on coagulation function. Based on the routine blood cell count and coagulation test, the values of HGB, PLT count, PT, APTT and INR will be recorded 1, 2, 3 and 5 days after the operation.
- The amount of total blood lost between 0 and 72 hours after surgery: total blood lost is calculated using the formula provided by Gross[23], total blood loss = PBV $\times$ (Hct_{pre}−Hct_{post})/Hct_{ave}. The peripheral blood volume (PBV) is then calculated using the formula proposed by Nadler et al.[24]: PBV=k1 $\times$ height(m)^3+ k2 $\times$ weight(kg)+k3, where k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men, and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women.
- Total blood transfusion in 0-72 hours after operation: If the patient needs a blood transfusion within 0-72 hours after the operation, we will record the total amount of RBCs, FFP and PLTs. If the patient does not receive a blood transfusion, the amount will be recorded as 0.
- The lowest HGB within 72 hours after surgery: Within three days after the operation, blood samples will be collected every morning to measure the HGB level. Patients who need a second operation due to postoperative bleeding within 72 hours will be excluded from this study.
- ICU duration.

- Overall length of stay.
- Total cost of the hospitalization.

Adverse events

Adverse events in this study will mainly include intraoperative blood transfusion-related adverse reactions: nonhemolytic febrile reactions, allergic reactions, haemolytic reactions, circulatory overload and acid-base imbalance; etc. Once the anaesthesiologist identifies an adverse event, all patients should be accurately documented and immediately treated. If the condition progresses to severe intraoperative adverse events, such as shock, heart failure and massive blood loss, we will continue to follow up the patients to observe the final results.

Data collection

Throughout the trial, the investigator – the anaesthesiologist involved in the operation – will be completely independent of the data collection staff. Data collection personnel are responsible for collecting preoperative and postoperative patient information and all data required in the trial protocol. Anonymous data will be collected in the case report form (CRF), either numerically or alphabetically. After the completion of the anonymous CRF table, the researcher shall confirm the authenticity and validity of all data, give a reasonable explanation for any missing data, or choose to exclude the test scheme.

Sample size calculation

The Pass 11.0 software package was used for sample size evaluation. According to a small sample (86 cases) observation study in the early stage of the research group, it was found that the allogeneic blood volume used in the operation of PC patients undergoing thermal perfusion chemotherapy was 1664.7 ± 789.3 ml [median: 1600 (1200, 2000)]. It is estimated that the blood volume of allogeneic patients used in thromboelastogram monitoring after intervention could be reduced by 20%, i.e., 1331.8 ± 631.4 ml, with a set α value of 0.05 and a β value of 0.2, and the sample volume of the two groups was 73 cases. However, the index of allogeneic blood volume is non-normally distributed data, and a nonparametric test is planned to be used for analysis. Compared with the t-test, the efficiency of the Wilcoxon rank sum

test is estimated to be approximately 95%, which means that the sample size required for the Wilcoxon test is 1.053 times the sample size required for the t-test[25]. Therefore, the number of subjects to be included in the study was increased by 1.053 times, and the drop-out rate was maintained to within 5%. The final target sample size was 81 people in each group (162 people in total).

Statistical analysis

Baseline characteristics

Data analyses will be performed by the statistical software SPSS version 25.0. During the trial, the statistical analyst will be unaware of the participants' personal information and their group assignment. The Kolmogorov-Smirnov test will be used to test the normal distribution of continuous variables. If data values are normally distributed, they will be presented as the mean ± standard deviation (SD) and will be compared using the independent t-test. If data values are not normally distributed, they will be presented as median and interquartile range (IQR) and compared using the nonparametric test. Categorical data will be shown as frequency and percentage and compared using the $\chi 2$ test or Fisher's exact test.

Primary outcome and secondary outcomes

The primary outcome, the total amount of blood transfusion, will be presented as the mean ± SD or median and IQR and compared using the independent t-test or Wilcoxon's rank sum test. For the secondary outcomes (i.e., transfusion volume during the operation, total amount of intraoperative infusion, amount of blood lost during the operation, total blood transfusion between 0 and 72 hours after surgery, and lowest HGB within 72 hours after surgery), the t-test will be used to compare the measurement data, and the rank sum test will be used for ranked data. The $\chi 2$ test or Fisher's exact test will be used to analyse categorical data (adverse events). The effect size, mean differences, and their confidence intervals will be reported to make the results comparable. For repeated variables, a repeated-measures analysis of covariance will be performed with visit time as the repeated factor and group as the non-repeated factor.

All analyses will be performed on the intention-to-treat population of participants who

are given the randomized treatment. Missing data will be handled using the multiple imputation method. A complete-case analysis without imputation of missing data will also be performed to determine whether the results are consistent. The significance level that will be used for statistical analysis with two-tailed testing will be 5%. No interim analyses will be performed.

DISCUSSION

The TEG-BT versus T-BT study is a single-centre and randomized clinical trial with a blinded outcome assessment that aims to verify whether TEG-BT is superior to T-BT in the perioperative blood transfusion treatment and prognosis of patients in CRS/HIPEC. If it can be proven that compared with T-BT, TEG-BT can lead to less intraoperative blood transfusion, more stable perioperative coagulation function, no reduction in postoperative HGB levels and coagulation function, and no increase in the incidence of adverse events, then the treatment and transfusion of various blood products can be guided according to changes in the TEG index to achieve a better prognosis.

CRS/HIPEC is a therapeutic method for patients with colorectal, appendiceal, ovarian, and gastric cancer with peritoneal metastasis and peritoneal mesothelioma[26-28]. A relevant study demonstrated that intraoperative transfusion of RBCs and a possibly increased peritoneal carcinomatosis index (PCI) are associated with abnormal postoperative coagulation, including changes in the PLT count, INR, and partial thromboplastin time (PTT)[4]. Based on the above points, optimal blood product transfusion is of great importance for patients receiving CRS/HIPEC.

SLTs, including the fibrinogen concentration, INR, PT and APTT, were initially used to diagnose intraoperatively acquired coagulopathy and guide the administration of treatment for massive haemorrhage[29 30]. However, relevant data suggest that the PT, APTT and PLT count insufficiently demonstrate the impact of surgical stress, hyperthermia, chemotherapy and considerable fluid shifts on the overall haemostatic physiology of CRS/HIPEC[18]. Routine laboratory testing is performed in PLT-deficient plasma whose results are not available to the clinician for 45–60 minutes[30-32]; in contrast, TEG can make up for the above deficiencies as a bedside

analysis tool, estimating the clotting process in whole blood and providing real-time data[33]. Increasing evidence has demonstrated that the application of a TEG-guided transfusion strategy can reduce the demand for blood products and improve the morbidity of bleeding patients, mainly according to trials involving heart surgery with cardiopulmonary bypass and liver transplantation surgery[34 35]. After many clinical experiences and the application of TEG, targeted coagulation therapy has become feasible[36]. A previous prospective study indicated that conventional coagulation measures had no significance for CRS/HIPEC, but TEG monitoring confirmed the suitability of epidural analgesia after CRS/HIPEC by evaluating perioperative clot kinetics[37]. However, there is no relevant study to verify whether TEG can be applied to guide transfusion strategies for treating coagulation disorders due to CRS/HIPEC. Therefore, it is believed that the use of TEG in guiding perioperative blood transfusion treatment and improving prognosis of patients undergoing CRS/HIPEC is definitely worth exploring.

The current study still has several limitations. First, for various reasons, we did not observe certain long-term outcomes, such as overall mortality, the incidence of reoperation, transfusion-related complications and thrombotic/thromboembolic events. Nevertheless, the influence of TEG-BT on these outcomes is worthy of further exploration. Moreover, due to the design of this trial, it is not available to determine the impact of pathophysiological changes in patients with potential diseases; therefore, we will remove severely ill patients from this study for safety reasons. Additionally, further studies may be required to determine whether TEG-BT combined with T-BT is superior to either alone for guiding the perioperative blood transfusion treatment of patients receiving CRS/HIPEC. Last but not least, this study is a single-centre trial, which may limit its generalisability; consequently, it is of great importance to perform multicentre clinical studies with a larger sample size to provide higher levels of evidence.

The primary outcome of our study is perioperative blood transfusion. As mentioned earlier, patients treated with CRS/HIPEC undergo an extensive abdominal incision, large fluid shifts, hyperthermic insults, and exposure to chemotherapeutic agents,

which increases the likelihood of altered coagulation and excessive bleeding[4 38 39]. Therefore, rational transfusion strategies are warranted. Extensive literature notes that allogeneic blood transfusion itself is an independent risk factor for increased morbidity (thrombotic/thromboembolic events, anaemia, nosocomial infections, multiorgan dysfunction syndrome), mortality, hospital stay, hospital costs, etc., in trauma, cardiovascular surgery, and ICU patients[40-43]. Nevertheless, TEG can be performed to monitor dynamic changes in haemostasis, which is thought to enable clinicians to distinguish between a surgical cause of bleeding or coagulopathy, to guide and evaluate the choice of haemostatic treatment, and to reduce transfusion requirements and improve survival[34]. In contrast, postoperative bleeding and coagulation disorders also increase the transfusion of allogeneic blood products, thereby affecting morbidity and mortality[36]. Hence, to further explore their interaction in patients undergoing CRS/HIPEC, the indicators of coagulation function, lowest value of HGB within 72 hours after surgery, ICU duration, overall length of stay, and costs incurred during the hospital stay will be the secondary outcomes of this study.

To conclude, the TEG-BT versus T-BT trial will be the first single-centre, randomized clinical trial with a blinded outcome assessment undertaken to substantiate the hypothesis that TEG-BT is superior to T-BT for administrating perioperative blood transfusion treatment and improving the prognosis of patients undergoing CRS/HIPEC. If the benefits mentioned in the hypothesis are confirmed, our study will improve a more goal-oriented transfusion strategy to reduce intraoperative blood transfusion, stabilize perioperative coagulation function and lighten the economic burden. Combined with our research results, the potential significance of this trial is that it may influence future guidelines on anaesthesia management of CRS/HIPEC and bring wider application for TEG.

ETHICS AND DISSEMINATION

Ethical and legislative approvals

The TEG-BT vs T-BT study is registered at the Chinese Clinical Trial Registry with the trial identification number ChiCTR2000028835. The research plan was approved by the scientific research ethics committee of Beijing Shijitan Hospital Affiliated with

Capital Medical University (Approval Number: sjtkyll-lx-2020-3). We will inform investigators, all participants and the trial registry when there are significant changes to the study protocol. Before each participant enters the study, he/she and the researchers will sign an informed consent form. Patients have the right to refuse or withdraw from the study at any time, which will not affect any of their medical or other interests. The personal information of the participants will be kept confidential, and anonymous personal patient data will be shared according to requirements.

Publication plan

With the consent of the main researchers and methodologists, the research coordinator will be responsible for preparing scientific statements and reports corresponding to the study. Based on the proportion of contribution to the study, the participating researchers and clinicians as well as biostatisticians and related researchers will be the co-authors of the ensuring report and publication. The rules of publication will be in accordance with international recommendations, and the publications will be submitted to peer-reviewed journals[44].

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Contributors

WS and ZQ contributed equally to this work and should be considered co-first authors. WS and ZQ contributed to the conception and drafting of the first manuscript for this trial. LP is the principal investigator of the entire study and edited the final manuscript. CL and LG contributed to the conception of the research protocol and will participate in the follow-up for this trial. All authors critically revised and modified the protocol and the article. They all approved the final version to be

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Competing interests

None declared.

Patient and public involvement

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Patient consent for publication

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No additional unpublished data are available.

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Figure 1

Study flow diagram of the TEG-BT vs T-BT trial.

TEG-BT, thromboelastography-guided blood product transfusion therapy; T-BT, traditional blood product transfusion therapy; CRS/HIPEC, cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy.

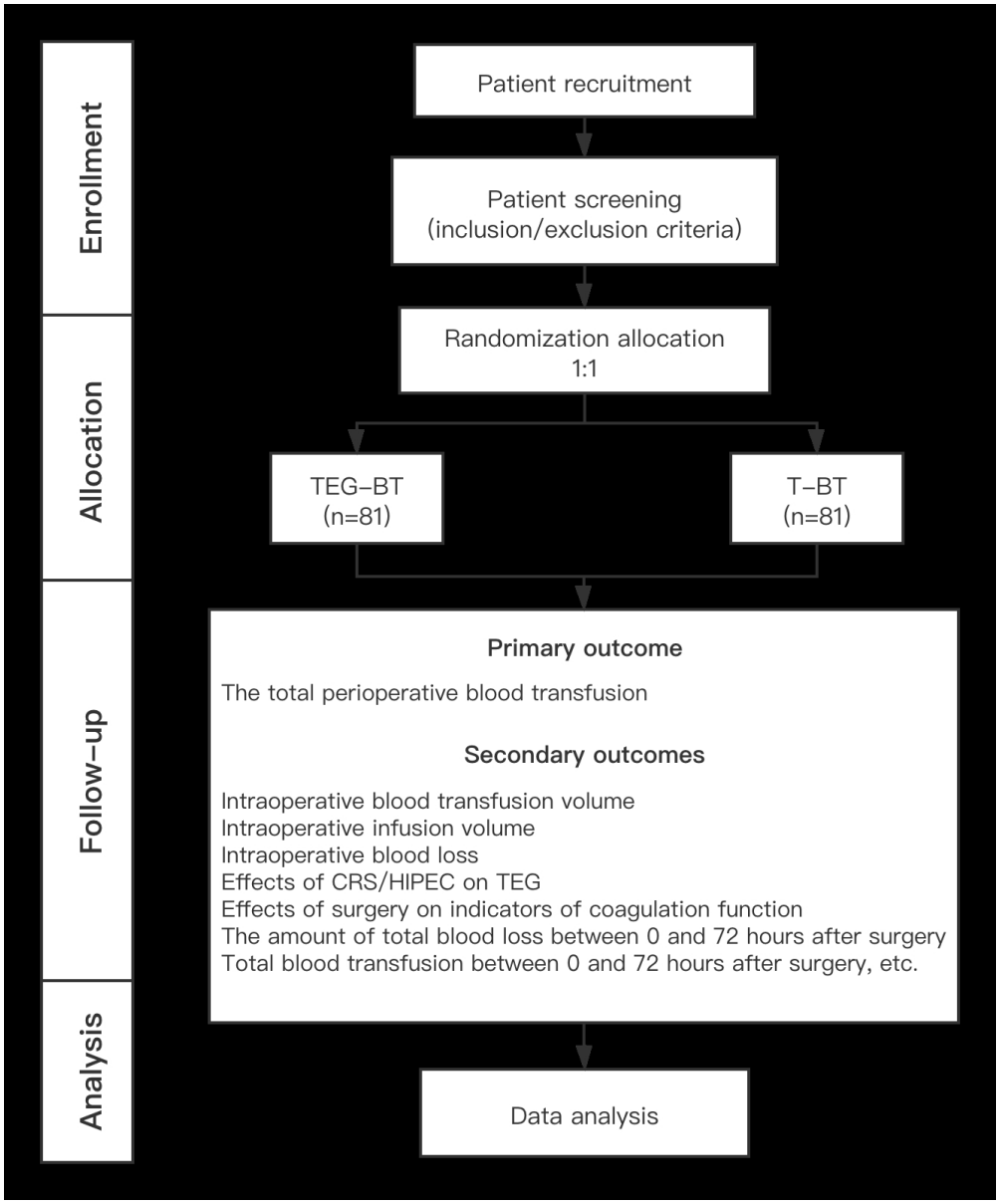

Figure 1. Study flow diagram of the TEG-BT vs T-BT trial.

467x561mm (72 x 72 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
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	3, 16
	2b	All items from the World Health Organization Trial Registration Data Set	3,16
Protocol version	3	Date and version identifier	3,16
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	1,17
	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	1,17
	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)	N/A

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	4-6
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	6
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)	6
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	6
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, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	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)	8,9,11,12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8,
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	9, 10, 11
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)	9, 10, 11

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	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
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	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
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	8-12
	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	8-12

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	8-12
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	12-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12,13
	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)	12-13
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	8-12
	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	8-12
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	11-12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16
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)	16

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	16
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	16
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
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	16, 17
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	N/A
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	16, 17
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

*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.