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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

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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.

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4 **Trial registration number** ChiCTR2000028835
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7 **Strengths and limitations of this study**
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- 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 stage¹. 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 recurrence². Currently, CRS/HIPEC is an established treatment for pseudomyxoma peritonei, colorectal cancer, ovarian cancer, and gastric cancer with intraperitoneal metastasis³. 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 treatment⁴.

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 management⁵. Patients undergo CRS/HIPEC with significant fluid and blood loss, as well as chemotherapy and severe fluctuations in the core temperature⁶. 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 transfusion⁷. 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 injury⁸. 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 process⁹. Therefore, perioperative management of patients undergoing CRS/HIPEC is a challenge for surgeons, anaesthesiologists and critical care physicians¹⁰.

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

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4 (SLTs), such as the activated partial thromboplastin time (APTT), prothrombin time
5 (PT), or international normalized ratio (INR)¹¹. Laboratory analysis shows that with an
6 increase in the INR, coagulation disorders are observed, antithrombin III (AT III) and
7 fibrinogen values are reduced, APTT is prolonged, and the number of coagulation cells
8 is reduced¹². Originally invented by Hartert in 1948, thromboelastography (TEG) is a
9 viscoelastic, haemostatic assay analyser that imitates sluggish venous flow¹³. It is a
10 different test from standard coagulation tests in that it measures the viscoelastic
11 properties of whole blood as it clots, providing comprehensive information about the
12 dynamics of clot development, stabilization and dissolution and assesses both
13 thrombosis and fibrinolysis^{14 15}. TEG has been used increasingly in intensive care units
14 (ICUs) and in cases of acute critical surgery to evaluate coagulation disorders and guide
15 the infusion of blood products for critically ill patients¹⁶. The technique has been tested
16 in clinical scenarios such as heart and liver surgery and transplantation to reduce the
17 number of transfusions and serve as a screening tool for patients managing
18 hypercoagulant and bleeding disorders¹⁷. One study has shown that the PT, APTT and
19 platelet (PLT) count are insufficient to demonstrate the effect of surgical stress,
20 hyperthermia, chemotherapy and mass fluid transfer on the overall haemostatic
21 physiology of CRS/HIPEC, while more sophisticated TEG monitoring is more accurate
22 for perioperative coagulation function monitoring¹⁸. Another study reported that
23 although traditional clinical monitoring of coagulation disorders was not meaningful in
24 CRS/HIPEC, TEG monitoring confirmed that epidural analgesia after CRS/HIPEC was
25 safe¹⁹. However, whether the effect of CRS/HIPEC on coagulation function can be
26 treated according to TEG guidance and the infusion of various blood products can be
27 guided according to changes in TEG and thereby achieve better outcomes for patients
28 has not been fully verified.

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52 Based on the existing literature, we aim to investigate the advantages of TEG-
53 guided blood product transfusion (TEG-BT) in perioperative blood protection during
54 CRS/HIPEC. Our working hypothesis is that compared with traditional blood product
55 transfusion (T-BT) patients, TEG-BT patients receive fewer transfusions of
56 intraoperative blood products and exhibit a more stable perioperative coagulation
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4 function, no reduction in postoperative haemoglobin (HGB) levels and coagulation
5 function, shorter hospital stays, and no increase in the incidence of adverse reactions.
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7 **METHODS AND ANALYSIS**

8 **Trial design**

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10 The trial will be conducted at Beijing Shijitan Hospital, Capital Medical University in
11 Beijing, China. The study started recruiting patients in May 2020 and will continue
12 for one year. The TEG-BT versus T-BT study is a single-centre, randomized, blinded
13 outcome assessment clinical trial that conforms to the Consolidated Standards of
14 Reporting Trials²⁰. CRS/HIPEC is planned for two groups of patients, and TEG-BT or
15 T-BT is adopted for perioperative blood transfusion management. The ratio of the two
16 groups is 1:1 (Figure 1).
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25 **Objectives**

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

34 **Inclusion criteria**

35 Patients who meet all of the following criteria are eligible for inclusion:
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- 37 1. Age of 18-64 years
- 38 2. American Society of Anaesthesiologists (ASA) grade I or II
- 39 3. Well-established histologic diagnosis of peritoneal disease
- 40 4. Performance of CRS/HIPEC under general anaesthesia
- 41 5. Written consent to participate in the study

42 **Exclusion criteria**

- 43 1. Anaemia
 - 44 2. Abnormal coagulation function before surgery
 - 45 3. Uncontrolled systemic infections
 - 46 4. Long-term anticoagulant or anti-PLT therapy
 - 47 5. Thrombotic events
 - 48 6. Severe cardiopulmonary disease
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- 6 8. Pregnancy or lactation
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- 8 9. Patient refusal to sign the informed consent form
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- 10 10. Patient participation in another clinical-treatment study

11 **Randomization and blinding**

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

26 **Anaesthesia management**

27 The anaesthesia regimen will be consistent between the two groups. Venous access will
28 be open in all patients in the preparation room, and midazolam will be administered
29 (0.05 mg/kg intravenously) to the patients before they enter the operating room. Upon
30 arrival in the operating room, standard monitoring (pulse oximetry, electrocardiogram,
31 and noninvasive arterial blood pressure monitoring) will be established. Sufentanil 0.5
32 µg/kg, propofol 2.5 mg/kg and rocuronium 0.6 mg/kg will be adopted for general
33 anaesthesia induction. After endotracheal intubation, the lungs will be aerated with 50%
34 oxygen and 50% air mixture, and the ventilation level will be adjusted to maintain
35 normocapnia. Radial artery and internal jugular vein puncture will be performed to
36 monitor the invasive arterial pressure and central venous pressure. We will perform an
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4 ultrasound-guided bilateral rectus sheath blockade, and 0.375% ropivacaine will be
5 given for analgesia on both sides. Anaesthesia will be maintained with inhalation of
6 sevoflurane and IV remifentanyl, and muscle relaxation will be maintained with IV
7 rocuronium. Postoperative intravenous injection of atropine 0.01 mg/kg and
8 neostigmine 0.05 mg/kg will be used to antagonize residual neuromuscular block.
9 Extubation will be performed after confirming that the patient's eyes are open and that
10 he or she exhibits adequate spontaneous breathing and purposeful movement.
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17 **Intraoperative intervention**

18 All enrolled patients will be assigned to one of the following two study groups. For
19 patients in the T-BT group, the anaesthesiologist will inject blood products according
20 to his or her clinical judgement. Patients entering the TEG-BT group will undergo TEG
21 monitoring 4 times before surgery, during CRS, before HIPEC and after HIPEC, and
22 blood products such as erythrocytes, plasma, PLTs, prothrombin complex and
23 fibrinogen will be administered according to the monitoring results. The two groups of
24 patients will be given red blood cells (RBCs) to maintain HGB levels of at least 10 g/dl.
25 Blood will be collected from the central vein through a three-way catheter. The first 10
26 ml of venous blood will be administered to the patient through the peripheral venous
27 pathway, and then 3.5 ml of venous blood will be collected after syringe replacement.
28 According to relevant guidelines, the samples of whole blood should be tested within 5
29 minutes after collection.
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42 All blood samples will be tested by the same professional TEG operator. The operator
43 of the TEG machine model [TEG 5000 (Haemoscope)] will not know the patient
44 grouping information.
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48 R time is the incubation period from blood entry into the reactive vessels to initial clot
49 formation. The lack of the R time extension prompt factor can be corrected by fresh
50 frozen plasma (FFP)²¹. When the R time value is greater than 10 minutes, the patient
51 will be infused with 2 U of FFP; when the R time value is greater than 15 minutes, the
52 patient will be infused with 4 U of plasma; when the R time value is greater than 20
53 minutes, the patient will be infused with 6 U²².
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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 PLTs²¹. 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										Discharged
	Preoperative	0 d	T 0	T 1	T 2	T 3	T 4	T 5	T 6	T 7	T 8	T 9	
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						

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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 Gross²³, 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: $PBV = k_1 \times \text{height(m)}^3 + k_2 \times \text{weight(kg)} + k_3$, where $k_1 = 0.3669$, $k_2 = 0.03219$, and $k_3 = 0.6041$ for men, and $k_1 = 0.3561$, $k_2 = 0.03308$, and $k_3 = 0.1833$ 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

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

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

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31 The Pass 11.0 software package was used for sample size evaluation. According to a
32 small sample (86 cases) observation study in the early stage of the research group, it
33 was found that the allogeneic blood volume used in the operation of PC patients
34 undergoing thermal perfusion chemotherapy was 1664.7 ± 789.3 ml [median: 1600
35 (1200, 2000)]. It is estimated that the blood volume of allogeneic patients used in
36 thromboelastogram monitoring after intervention could be reduced by 20%, i.e., 1331.8
37 ± 631.4 ml, with a set α value of 0.05 and a β value of 0.2, and the sample volume of
38 the two groups was 73 cases. However, the index of allogeneic blood volume is non-
39 normally distributed data, and a nonparametric test is planned to be used for analysis.
40 Compared with the t-test, the efficiency of the Wilcoxon rank sum test is estimated to
41 be approximately 95%, which means that the sample size required for the Wilcoxon
42 test is 1.053 times the sample size required for the t-test²⁵. Therefore, the number of
43 subjects to be included in the study was increased by 1.053 times, and the drop-out rate
44 was maintained to within 5%. The final target sample size was 81 people in each group
45 (162 people in total).
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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 \pm 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 χ^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 \pm 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 χ^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

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4 a blinded outcome assessment that aims to verify whether TEG-BT is superior to T-BT
5 in the perioperative blood transfusion treatment and prognosis of patients in
6 CRS/HIPEC. If it can be proven that compared with T-BT, TEG-BT can lead to less
7 intraoperative blood transfusion, more stable perioperative coagulation function, no
8 reduction in postoperative HGB levels and coagulation function, and no increase in the
9 incidence of adverse events, then the treatment and transfusion of various blood
10 products can be guided according to changes in the TEG index to achieve a better
11 prognosis.
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19 CRS/HIPEC is a therapeutic method for patients with colorectal, appendiceal,
20 ovarian, and gastric cancer with peritoneal metastasis and peritoneal mesothelioma²⁶⁻
21 ²⁸. A relevant study demonstrated that intraoperative transfusion of RBCs and a possibly
22 increased peritoneal carcinomatosis index (PCI) are associated with abnormal
23 postoperative coagulation, including changes in the PLT count, INR, and partial
24 thromboplastin time (PTT)⁴. Based on the above points, optimal blood product
25 transfusion is of great importance for patients receiving CRS/HIPEC.
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33 SLTs, including the fibrinogen concentration, INR, PT and APTT, were initially used
34 to diagnose intraoperatively acquired coagulopathy and guide the administration of
35 treatment for massive haemorrhage^{29 30}. However, relevant data suggest that the PT,
36 APTT and PLT count insufficiently demonstrate the impact of surgical stress,
37 hyperthermia, chemotherapy and considerable fluid shifts on the overall haemostatic
38 physiology of CRS/HIPEC¹⁸. Routine laboratory testing is performed in PLT-deficient
39 plasma whose results are not available to the clinician for 45–60 minutes³⁰⁻³²; in contrast,
40 TEG can make up for the above deficiencies as a bedside analysis tool, estimating the
41 clotting process in whole blood and providing real-time data³³. Increasing evidence has
42 demonstrated that the application of a TEG-guided transfusion strategy can reduce the
43 demand for blood products and improve the morbidity of bleeding patients, mainly
44 according to trials involving heart surgery with cardiopulmonary bypass and liver
45 transplantation surgery^{34 35}. After many clinical experiences and the application of TEG,
46 targeted coagulation therapy has become feasible³⁶. A previous prospective study
47 indicated that conventional coagulation measures had no significance for CRS/HIPEC,
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4 but TEG monitoring confirmed the suitability of epidural analgesia after CRS/HIPEC
5 by evaluating perioperative clot kinetics³⁷. However, there is no relevant study to verify
6 whether TEG can be applied to guide transfusion strategies for treating coagulation
7 disorders due to CRS/HIPEC. Therefore, it is believed that the use of TEG in guiding
8 perioperative blood transfusion treatment and improving prognosis of patients
9 undergoing CRS/HIPEC is definitely worth exploring.

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

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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 patients⁴⁰⁻⁴³. 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

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4 improve survival³⁴. In contrast, postoperative bleeding and coagulation disorders also
5 increase the transfusion of allogeneic blood products, thereby affecting morbidity and
6 mortality³⁶. Hence, to further explore their interaction in patients undergoing
7 CRS/HIPEC, the indicators of coagulation function, lowest value of HGB within 72
8 hours after surgery, ICU duration, overall length of stay, and costs incurred during the
9 hospital stay will be the secondary outcomes of this study.
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15 To conclude, the TEG-BT versus T-BT trial will be the first single-centre,
16 randomized clinical trial with a blinded outcome assessment undertaken to substantiate
17 the hypothesis that TEG-BT is superior to T-BT for administering perioperative blood
18 transfusion treatment and improving the prognosis of patients undergoing CRS/HIPEC.
19 If the benefits mentioned in the hypothesis are confirmed, our study will improve a
20 more goal-oriented transfusion strategy to reduce intraoperative blood transfusion,
21 stabilize perioperative coagulation function and lighten the economic burden.
22 Combined with our research results, the potential significance of this trial is that it may
23 influence future guidelines on anaesthesia management of CRS/HIPEC and bring wider
24 application for TEG.
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34 **ETHICS AND DISSEMINATION**

35 **Ethical and legislative approvals**

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

58 With the consent of the main researchers and methodologists, the research coordinator
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4 will be responsible for preparing scientific statements and reports corresponding to the
5 study. Based on the proportion of contribution to the study, the participating researchers
6 and clinicians as well as biostatisticians and related researchers will be the co-authors
7 of the ensuring report and publication. The rules of publication will be in accordance
8 with international recommendations, and the publications will be submitted to peer-
9 reviewed journals⁴⁴.
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30 31 **Contributors**

32
33 WS and ZQ contributed equally to this work and should be considered co-first authors.
34
35 WS and ZQ contributed to the conception and drafting of the first manuscript for this
36 trial. LP is the principal investigator of the entire study and edited the final manuscript.
37
38 CL and LG contributed to the conception of the research protocol and will participate
39 in the follow-up for this trial. All authors critically revised and modified the protocol
40 and the article. They all approved the final version to be published.
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46
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49

50 51 **Competing interests**

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53 None declared.

54 55 **Patient consent for publication**

56
57 Obtained.

58 59 **Provenance and peer review**

60
Not commissioned; externally peer reviewed.

Data sharing statement

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.

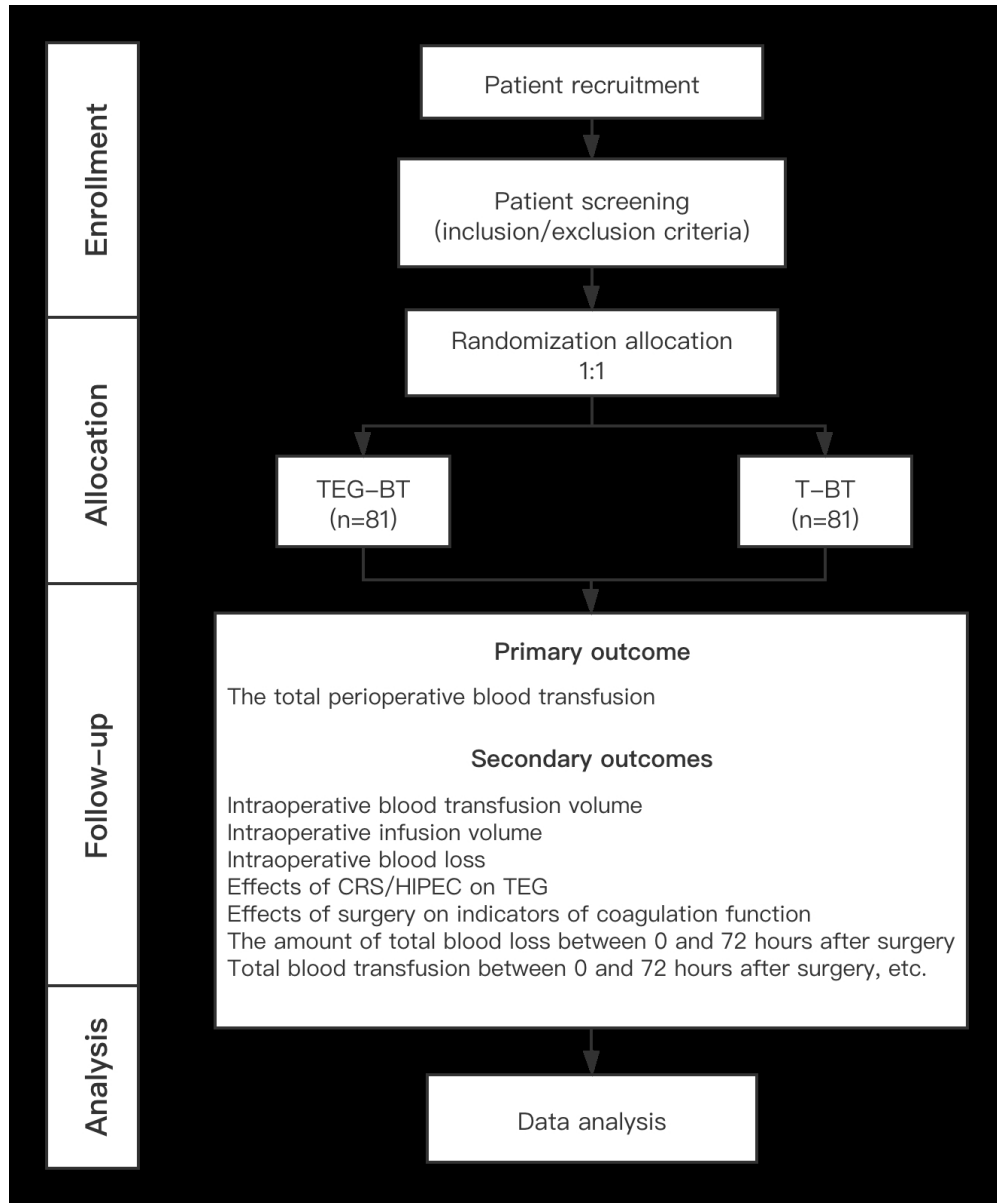


Figure 1. Study flow diagram of the TEG-BT vs T-BT trial.

467x561mm (72 x 72 DPI)



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 ___

1 **Introduction**

2

3 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 _____

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6 6b Explanation for choice of comparators _____ N/A _____

7

8 Objectives 7 Specific objectives or hypotheses _____ 6 _____

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10 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 _____

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14 **Methods: Participants, interventions, and outcomes**

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16 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 _____

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18

19 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 _____

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered _____ 8, 9 _____

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25 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 ___

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28 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) _____ N/A _____

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31 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial _____ N/A _____

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34 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 _____

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40 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 _____

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1 Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including _____ 12 _____
 2 clinical and statistical assumptions supporting any sample size calculations

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 4 Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size _____ N/A _____
 5

6 **Methods: Assignment of interventions (for controlled trials)**

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 8 Allocation:

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 10 Sequence 16a Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any _____ 7 _____
 11 generation factors for stratification. To reduce predictability of a random sequence, details of any planned restriction
 12 (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants
 13 or assign interventions
 14

15
 16 Allocation 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, _____ 7 _____
 17 concealment opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
 18 mechanism
 19

20 Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to _____ 7 _____
 21 interventions
 22

23 Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome _____ 7 _____
 24 assessors, data analysts), and how
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26
 27 17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's _____ N/A _____
 28 allocated intervention during the trial
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 31 **Methods: Data collection, management, and analysis**

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 33 Data collection 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related _____ 8, 12 _____
 34 methods processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of
 35 study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.
 36 Reference to where data collection forms can be found, if not in the protocol
 37

38
 39 18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be _____ N/A _____
 40 collected for participants who discontinue or deviate from intervention protocols
 41

1	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 _____
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3				
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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	_____ 12-13 _____
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____ N/A _____
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)	_____ 12-13 _____
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14	Methods: Monitoring			
15				
16	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 _____
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22		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 _____
23				
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25	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 _____
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____ 12 _____
29				
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32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____ 16 _____
35				
36				
37	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 _____
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____16_____
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3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____N/A_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
11				
12				
13	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_____
14				
15				
16	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_____
17				
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____17_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____18_____
27				
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29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____N/A_____
32				
33				
34	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_____
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
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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

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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 stage¹. 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 recurrence². Currently, CRS/HIPEC is an established treatment for pseudomyxoma peritonei, colorectal cancer, ovarian cancer, and gastric cancer with intraperitoneal metastasis³. 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 treatment⁴.

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 management⁵. Patients undergo CRS/HIPEC with significant fluid and blood loss, as well as chemotherapy and severe fluctuations in the core temperature⁶. 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 transfusion⁷. 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 injury⁸. 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 process⁹. Therefore, perioperative management of patients undergoing CRS/HIPEC is a challenge for surgeons, anaesthesiologists and critical care physicians¹⁰.

Regarding the perioperative monitoring of coagulation function, the management

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4 of coagulation disorders at 90% of HIPEC centres is guided by standard laboratory
5 tests (SLTs), such as the activated partial thromboplastin time (APTT), prothrombin
6 time (PT), or international normalized ratio (INR)¹¹. Laboratory analysis shows that
7 with an increase in the INR, coagulation disorders are observed, antithrombin III (AT
8 III) and fibrinogen values are reduced, APTT is prolonged, and the number of
9 coagulation cells is reduced¹². Originally invented by Hartert in 1948,
10 thromboelastography (TEG) is a viscoelastic, haemostatic assay analyser that imitates
11 sluggish venous flow¹³. It is a different test from standard coagulation tests in that it
12 measures the viscoelastic properties of whole blood as it clots, providing
13 comprehensive information about the dynamics of clot development, stabilization and
14 dissolution and assesses both thrombosis and fibrinolysis^{14 15}. TEG has been used
15 increasingly in intensive care units (ICUs) and in cases of acute critical surgery to
16 evaluate coagulation disorders and guide the infusion of blood products for critically
17 ill patients¹⁶. The technique has been tested in clinical scenarios such as heart and
18 liver surgery and transplantation to reduce the number of transfusions and serve as a
19 screening tool for patients managing hypercoagulant and bleeding disorders¹⁷. One
20 study has shown that the PT, APTT and platelet (PLT) count are insufficient to
21 demonstrate the effect of surgical stress, hyperthermia, chemotherapy and mass fluid
22 transfer on the overall haemostatic physiology of CRS/HIPEC, while more
23 sophisticated TEG monitoring is more accurate for perioperative coagulation function
24 monitoring¹⁸. Another study reported that although traditional clinical monitoring of
25 coagulation disorders was not meaningful in CRS/HIPEC, TEG monitoring confirmed
26 that epidural analgesia after CRS/HIPEC was safe¹⁹. However, whether the effect of
27 CRS/HIPEC on coagulation function can be treated according to TEG guidance and
28 the infusion of various blood products can be guided according to changes in TEG
29 and thereby achieve better outcomes for patients has not been fully verified.

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54 Based on the existing literature, we aim to investigate the advantages of
55 TEG-guided blood product transfusion (TEG-BT) in perioperative blood protection
56 during CRS/HIPEC. Our working hypothesis is that compared with traditional blood
57 product transfusion (T-BT) patients, TEG-BT patients receive fewer transfusions of
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4 intraoperative blood products and exhibit a more stable perioperative coagulation
5 function, no reduction in postoperative haemoglobin (HGB) levels and coagulation
6 function, shorter hospital stays, and no increase in the incidence of adverse reactions.
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9 **METHODS AND ANALYSIS**

11 **Trial design**

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13 The trial will be conducted at Beijing Shijitan Hospital, Capital Medical University in
14 Beijing, China. The study started recruiting patients in May 2020 and will continue
15 for one year. The TEG-BT versus T-BT study is a single-centre, randomized, blinded
16 outcome assessment clinical trial that conforms to the Consolidated Standards of
17 Reporting Trials²⁰. CRS/HIPEC is planned for two groups of patients, and TEG-BT or
18 T-BT is adopted for perioperative blood transfusion management. The ratio of the two
19 groups is 1:1 (Figure 1).
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27 **Objectives**

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

35 **Inclusion criteria**

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37 Patients who meet all of the following criteria are eligible for inclusion:
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- 40 1. Age of 18-64 years
 - 41 2. American Society of Anaesthesiologists (ASA) grade I or II
 - 42 3. Well-established histologic diagnosis of peritoneal disease
 - 43 4. Performance of CRS/HIPEC under general anaesthesia
 - 44 5. Written consent to participate in the study
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50 **Exclusion criteria**

- 51 1. Anaemia: HGB<9g/dl
 - 52 2. Abnormal coagulation function before surgery
 - 53 3. Uncontrolled systemic infections
 - 54 4. Antiplatelet or anticoagulant therapy was administered at enrollment or
55 discontinued for less than 7 days prior to study evaluation
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- 4 5. Thrombotic events: Any blood clot in the vein or artery has been recorded before
- 5 or at present
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- 8 6. Severe cardiopulmonary disease
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- 10 7. Hepatic or renal failure
- 11
- 12 8. Pregnancy or lactation
- 13
- 14 9. Patient refusal to sign the informed consent form
- 15
- 16 10. Patient participation in another clinical-treatment study

17 **Randomization and blinding**

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

32 **Anaesthesia management**

33 The anaesthesia regimen will be consistent between the two groups. Venous access
34 will be open in all patients in the preparation room, and midazolam will be
35 administered (0.05 mg/kg intravenously) to the patients before they enter the
36 operating room. Upon arrival in the operating room, standard monitoring (pulse
37 oximetry, electrocardiogram, and noninvasive arterial blood pressure monitoring) will
38 be established. Sufentanil 0.5 µg/kg, propofol 2.5 mg/kg and rocuronium 0.6 mg/kg
39 will be adopted for general anaesthesia induction. After endotracheal intubation, the
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4 lungs will be aerated with 50% oxygen and 50% air mixture, and the ventilation level
5 will be adjusted to maintain normocapnia. Radial artery and internal jugular vein
6 puncture will be performed to monitor the invasive arterial pressure and central
7 venous pressure. We will perform an ultrasound-guided bilateral rectus sheath
8 blockade, and 0.375% ropivacaine will be given for analgesia on both sides.
9 Anaesthesia will be maintained with inhalation of sevoflurane and IV remifentanyl,
10 and muscle relaxation will be maintained with IV rocuronium. Postoperative
11 intravenous injection of atropine 0.01 mg/kg and neostigmine 0.05 mg/kg will be used
12 to antagonize residual neuromuscular block. Extubation will be performed after
13 confirming that the patient's eyes are open and that he or she exhibits adequate
14 spontaneous breathing and purposeful movement.
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25 **Intraoperative intervention**

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27 All enrolled patients will be assigned to one of the following two study groups. For
28 patients in the T-BT group, the anaesthesiologist will inject blood products according
29 to his or her clinical judgement. Patients entering the TEG-BT group will undergo
30 TEG monitoring 4 times before surgery, during CRS, before HIPEC and after HIPEC,
31 and blood products such as erythrocytes, plasma, PLTs, prothrombin complex and
32 fibrinogen will be administered according to the monitoring results. The two groups
33 of patients will be given red blood cells (RBCs) to maintain HGB levels of at least
34 9g/dl.
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43 Blood will be collected from the central vein through a three-way catheter. The first
44 10 ml of venous blood will be administered to the patient through the peripheral
45 venous pathway, and then 3.5 ml of venous blood will be collected after syringe
46 replacement. According to relevant guidelines, the samples of whole blood should be
47 tested within 5 minutes after collection.
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52 All blood samples will be tested by the same professional TEG operator. The operator
53 of the TEG machine model [TEG 5000 (Haemoscope)] will not know the patient
54 grouping information.
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58 R time is the incubation period from blood entry into the reactive vessels to initial clot
59 formation. The lack of the R time extension prompt factor can be corrected by fresh
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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 U²².

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 PLTs²¹. 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										Discharged
			T 0	T 1	T 2	T 3	T 4	T 5	T 6	T 7	T 8	T 9	
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		

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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 Gross²³, 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

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4 test is estimated to be approximately 95%, which means that the sample size required
5 for the Wilcoxon test is 1.053 times the sample size required for the t-test²⁵.
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7 Therefore, the number of subjects to be included in the study was increased by 1.053
8 times, and the drop-out rate was maintained to within 5%. The final target sample size
9 was 81 people in each group (162 people in total).
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12 **Statistical analysis**

13 **Baseline characteristics**

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15 Data analyses will be performed by the statistical software SPSS version 25.0. During
16 the trial, the statistical analyst will be unaware of the participants' personal
17 information and their group assignment. The Kolmogorov-Smirnov test will be used
18 to test the normal distribution of continuous variables. If data values are normally
19 distributed, they will be presented as the mean \pm standard deviation (SD) and will be
20 compared using the independent t-test. If data values are not normally distributed,
21 they will be presented as median and interquartile range (IQR) and compared using
22 the nonparametric test. Categorical data will be shown as frequency and percentage
23 and compared using the χ^2 test or Fisher's exact test.
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35 **Primary outcome and secondary outcomes**

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37 The primary outcome, the total amount of blood transfusion, will be presented as the
38 mean \pm SD or median and IQR and compared using the independent t-test or
39 Wilcoxon's rank sum test. For the secondary outcomes (i.e., transfusion volume
40 during the operation, total amount of intraoperative infusion, amount of blood lost
41 during the operation, total blood transfusion between 0 and 72 hours after surgery,
42 and lowest HGB within 72 hours after surgery), the t-test will be used to compare the
43 measurement data, and the rank sum test will be used for ranked data. The χ^2 test or
44 Fisher's exact test will be used to analyse categorical data (adverse events). The effect
45 size, mean differences, and their confidence intervals will be reported to make the
46 results comparable. For repeated variables, a repeated-measures analysis of
47 covariance will be performed with visit time as the repeated factor and group as the
48 non-repeated factor.
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60 All analyses will be performed on the intention-to-treat population of participants who

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

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15 The TEG-BT versus T-BT study is a single-centre and randomized clinical trial
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17 with a blinded outcome assessment that aims to verify whether TEG-BT is superior to
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19 T-BT in the perioperative blood transfusion treatment and prognosis of patients in
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21 CRS/HIPEC. If it can be proven that compared with T-BT, TEG-BT can lead to less
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23 intraoperative blood transfusion, more stable perioperative coagulation function, no
24
25 reduction in postoperative HGB levels and coagulation function, and no increase in
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27 the incidence of adverse events, then the treatment and transfusion of various blood
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29 products can be guided according to changes in the TEG index to achieve a better
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31 prognosis.
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33 CRS/HIPEC is a therapeutic method for patients with colorectal, appendiceal,
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35 ovarian, and gastric cancer with peritoneal metastasis and peritoneal
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37 mesothelioma²⁶⁻²⁸. A relevant study demonstrated that intraoperative transfusion of
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39 RBCs and a possibly increased peritoneal carcinomatosis index (PCI) are associated
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41 with abnormal postoperative coagulation, including changes in the PLT count, INR,
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43 and partial thromboplastin time (PTT)⁴. Based on the above points, optimal blood
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45 product transfusion is of great importance for patients receiving CRS/HIPEC.
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47 SLTs, including the fibrinogen concentration, INR, PT and APTT, were initially
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49 used to diagnose intraoperatively acquired coagulopathy and guide the administration
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51 of treatment for massive haemorrhage^{29 30}. However, relevant data suggest that the
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53 PT, APTT and PLT count insufficiently demonstrate the impact of surgical stress,
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55 hyperthermia, chemotherapy and considerable fluid shifts on the overall haemostatic
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57 physiology of CRS/HIPEC¹⁸. Routine laboratory testing is performed in
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59 PLT-deficient plasma whose results are not available to the clinician for 45–60
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61 minutes³⁰⁻³²; in contrast, TEG can make up for the above deficiencies as a bedside

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4 analysis tool, estimating the clotting process in whole blood and providing real-time
5 data³³. Increasing evidence has demonstrated that the application of a TEG-guided
6 transfusion strategy can reduce the demand for blood products and improve the
7 morbidity of bleeding patients, mainly according to trials involving heart surgery with
8 cardiopulmonary bypass and liver transplantation surgery^{34 35}. After many clinical
9 experiences and the application of TEG, targeted coagulation therapy has become
10 feasible³⁶. A previous prospective study indicated that conventional coagulation
11 measures had no significance for CRS/HIPEC, but TEG monitoring confirmed the
12 suitability of epidural analgesia after CRS/HIPEC by evaluating perioperative clot
13 kinetics³⁷. However, there is no relevant study to verify whether TEG can be applied
14 to guide transfusion strategies for treating coagulation disorders due to CRS/HIPEC.
15 Therefore, it is believed that the use of TEG in guiding perioperative blood
16 transfusion treatment and improving prognosis of patients undergoing CRS/HIPEC is
17 definitely worth exploring.

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

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56 The primary outcome of our study is perioperative blood transfusion. As mentioned
57 earlier, patients treated with CRS/HIPEC undergo an extensive abdominal incision,
58 large fluid shifts, hyperthermic insults, and exposure to chemotherapeutic agents,
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4 which increases the likelihood of altered coagulation and excessive bleeding^{4 38 39}.
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6 Therefore, rational transfusion strategies are warranted. Extensive literature notes that
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8 allogeneic blood transfusion itself is an independent risk factor for increased
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10 morbidity (thrombotic/thromboembolic events, anaemia, nosocomial infections,
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12 multiorgan dysfunction syndrome), mortality, hospital stay, hospital costs, etc., in
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14 trauma, cardiovascular surgery, and ICU patients⁴⁰⁻⁴³. Nevertheless, TEG can be
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16 performed to monitor dynamic changes in haemostasis, which is thought to enable
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18 clinicians to distinguish between a surgical cause of bleeding or coagulopathy, to
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20 guide and evaluate the choice of haemostatic treatment, and to reduce transfusion
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22 requirements and improve survival³⁴. In contrast, postoperative bleeding and
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24 coagulation disorders also increase the transfusion of allogeneic blood products,
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26 thereby affecting morbidity and mortality³⁶. Hence, to further explore their interaction
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28 in patients undergoing CRS/HIPEC, the indicators of coagulation function, lowest
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30 value of HGB within 72 hours after surgery, ICU duration, overall length of stay, and
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32 costs incurred during the hospital stay will be the secondary outcomes of this study.

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

52 **ETHICS AND DISSEMINATION**

53 **Ethical and legislative approvals**

54
55 The TEG-BT vs T-BT study is registered at the Chinese Clinical Trial Registry with
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57 the trial identification number ChiCTR2000028835. The research plan was approved
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59 by the scientific research ethics committee of Beijing Shijitan Hospital Affiliated with
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4 Capital Medical University (Approval Number: sjtkyll-lx-2020-3). We will inform
5 investigators, all participants and the trial registry when there are significant changes
6 to the study protocol. Before each participant enters the study, he/she and the
7 researchers will sign an informed consent form. Patients have the right to refuse or
8 withdraw from the study at any time, which will not affect any of their medical or
9 other interests. The personal information of the participants will be kept confidential,
10 and anonymous personal patient data will be shared according to requirements.

17 **Publication plan**

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19 With the consent of the main researchers and methodologists, the research coordinator
20 will be responsible for preparing scientific statements and reports corresponding to
21 the study. Based on the proportion of contribution to the study, the participating
22 researchers and clinicians as well as biostatisticians and related researchers will be the
23 co-authors of the ensuring report and publication. The rules of publication will be in
24 accordance with international recommendations, and the publications will be
25 submitted to peer-reviewed journals⁴⁴.

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48 **Contributors**

49
50 WS and ZQ contributed equally to this work and should be considered co-first
51 authors. WS and ZQ contributed to the conception and drafting of the first manuscript
52 for this trial. LP is the principal investigator of the entire study and edited the final
53 manuscript. CL and LG contributed to the conception of the research protocol and
54 will participate in the follow-up for this trial. All authors critically revised and
55 modified the protocol and the article. They all approved the final version to be
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4 published.

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9

10
11 **Competing interests**

12
13 None declared.

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15 **Patient and public involvement**

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17 No patient involved.

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19 **Patient consent for publication**

20
21 Obtained.

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23 **Provenance and peer review**

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25 Not commissioned; externally peer reviewed.

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27 **Data sharing statement**

28
29 No additional unpublished data are available.
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17 Figure 1

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

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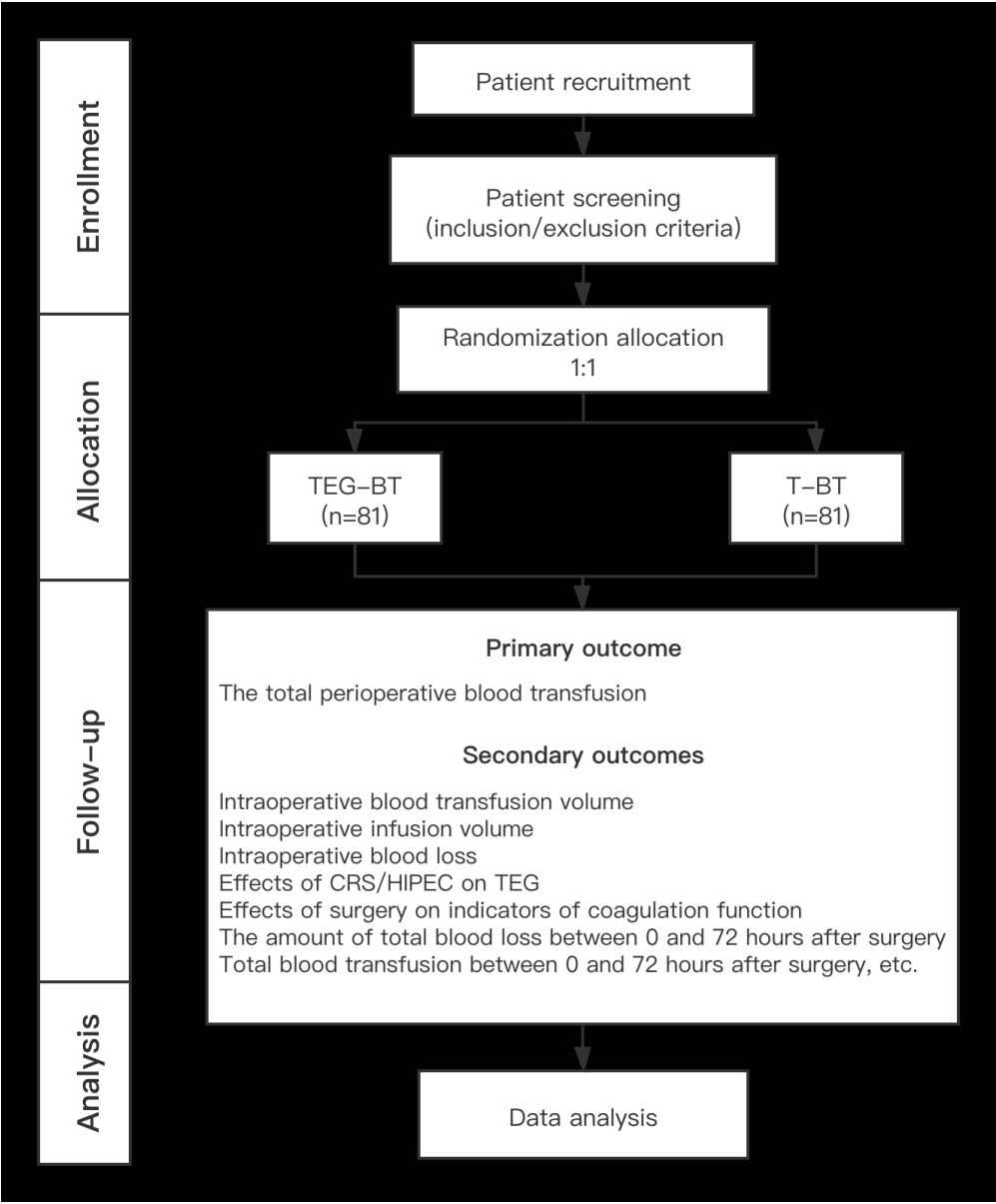


Figure 1. Study flow diagram of the TEG-BT vs T-BT trial.

467x561mm (72 x 72 DPI)



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 ___

1	Introduction			
2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	_____4-6_____
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	_____5-6_____
7				
8	Objectives	7	Specific objectives or hypotheses	_____6_____
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____
12				
13				
14	Methods: Participants, interventions, and outcomes			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	_____6_____
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	_____6, 7_____
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	_____8, 9_____
23			administered	
24				
25		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	___8,9,11,12___
26			change in response to harms, participant request, or improving/worsening disease)	
27				
28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	_____8_____
29			(eg, drug tablet return, laboratory tests)	
30				
31		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____8,_____
32				
33	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	_____9, 10, 11___
34			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
35			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
36			efficacy and harm outcomes is strongly recommended	
37				
38	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	_____9, 10, 11_____
39			participants. A schematic diagram is highly recommended (see Figure)	
40				
41				
42				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____12_____
2				
3				
4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____N/A_____
5				

6 **Methods: Assignment of interventions (for controlled trials)**

7 Allocation:

8				
9				
10	Sequence	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_____
11	generation			
12				
13				
14				
15				
16	Allocation	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_____
17	concealment			
18	mechanism			
19				
20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____7_____
21				
22				
23				
24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____7_____
25				
26				
27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____7_____
28				
29				
30				

31 **Methods: Data collection, management, and analysis**

32				
33	Data collection	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_____
34	methods			
35				
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39		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_____
40				
41				
42				

1	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 ___
2				
3				
4				
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	___ 12-13 ___
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	___ 12,13 ___
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)	___ 12-13 ___
11				
12				
13				
14	Methods: Monitoring			
15				
16	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 ___
17				
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22		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 ___
23				
24				
25	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 ___
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___ 12 ___
29				
30				
31				
32	Ethics and dissemination			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	___ 16 ___
35				
36				
37	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 ___
38				
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____16_____
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____16_____
5				
6				
7	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_____
8				
9				
10	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____17_____
11				
12				
13	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_____
14				
15				
16	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_____
17				
18				
19				
20	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_____
21				
22				
23				
24		31b	Authorship eligibility guidelines and any intended use of professional writers	_____17_____
25				
26		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____18_____
27				
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____N/A_____
32				
33				
34	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_____
35				
36				

*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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.