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Keywords:	Paraquat poisoning, Hemopurification, Hemodialysis, Hemoperfusion

The Efficacy of Initial Hemopurification Strategy for Acute Paraquat Poisoning in Adults: Study Protocol for a Randomized Controlled Trial (HeSAPP)

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Abstract

Introduction

Paraquat (PQ) is a widely used herbicide, which is inexpensive and easily accessible for people in rural areas. A small amount of PQ ingestion could be lethal, yet currently the optimal treatment is still controversial. Extracorporeal therapies (ECTR) have been practiced in paraquat poisoning management, though limited evidence could be obtained to suggest its superiority over conservative therapy. Hemodialysis (HD) and hemoperfusion (HP) are most commonly used, while some institutions also choose HP-HD concurrent therapy. The object of the present trial is to investigate whether hemopurification therapy can reduce mortality compared with conservative therapy.

Methods and analysis

This is a planned single-center, non-blinded, randomized controlled trial (RCT). Acute paraquat poisoned adults who have orally ingested paraquat within 24 hours would be recruited. A total of 360 patients would be recruited and randomly assigned to four groups, i.e. HP, HD, concurrent HP-HD and control, at a 1:1:1:1 ratio. Subjects would be also stratified by their urine dithionite test results. Primary outcome is 28-day all-cause mortality. Secondary outcomes include survival time, all-cause mortality at the 3rd, 7th and 60th day, rate of major complications, APACHE II score and PSS score, etc.

Ethics and dissemination

The protocol and informed consent documents have been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University in September, 2017 (approval number: 2017-KY-10). The result of this trial would be submitted to peer-reviewed journal.

Trial registration number: NCT03314909

Key words: Paraquat poisoning, Hemopurification, Hemodialysis, Hemoperfusion

Strengths and limitations of this study

This is the first parallel random controlled trial (RCT) to directly compare the therapeutic effective of hemodialysis, hemoperfusion, hemodialysis- hemoperfusion concurrent treatment and conservative therapy in acute paraquat poisoning.
Patients would be stratified by the result of urine dithionite test.
In order to reduce bias, several potential cofounders such as urine dithionite result and time lapse from PQ ingestion to treatment would be explored in subgroup analysis.
Serum paraquat concentration is not available in our clinical setting due to lack of equipment and funding.

Introduction

Among 1.6 million violent deaths every year in the world, half are suicidal and 63% of these occur in Asia-Pacific region[1]. Pesticide suicide accounts for up to one third of all suicides worldwide every year [2]. Being inexpensive and easily accessible, paraquat (PQ), a water soluble toxic organic herbicide (1,1-dimethyl-4,4-bipyridine cationic salt) is still widely consumed in some countries like China, and occasionally serves as poison[3].
A very small amount of PQ can cause death in human. A study of 375 participants reports that patients with a plasma PQ concentration higher than 3.44 μg/mL died[4], though some other studies indicate a relative higher upper limit for survivors[5 6].The mortality of PQ is remarkably high (ranging from 42.7% to 90% [7-9]), but unfortunately there is still no effective treatment for confirmed PQ poisoning. The main mechanism of PQ intoxication is generation of free radicals and oxidative stress, and some studies claim that immunosuppressive therapy can improve survival rate[9 10]. Considering the physical characteristics of PQ, e.g. relatively low volume of distribution (1.2-1.6L/kg)[3], low molecular weight and low protein binding rate, it is reasonable to propose that extracorporeal treatment (ECTR) may benefit patients with PQ poisoning.
Hemodialysis (HD) purifies blood by filtering poisonous molecules through a selectively permeable membrane, especially molecules with a small molecular weight and low protein binding rate. It can also correct acid-base disturbance in patients. Theoretically, HD should be the ideal treatment for acute PQ poisoning in view of its physical characteristics. However, HD is not widely applied in practice, and the Expert Consensus on Acute PQ Poisoning in China recommends HD as a supplementary therapy for patients complicated with acid-base disturbance[11].
Little evidence could be obtained in HD for PQ poisoning treatment in the last 30 years. In an experimental model, it is demonstrated that after 90 mins' of HD, PQ clearance remains static in vitro (179 ml/min)[12]. Compared with the high apparent renal clearance of PQ (1.17 L/h) in vivo[13], HD seems to have a limited effect on PQ clearance, probably due to the limitation of HD filter material. With the improvement in filter, HD has a two-fold increase in small molecule clearance compared with 40 years ago[14], thus further research is needed to evaluate the treatment effect of HD in PQ poisoning management.
Hemoperfusion (HP) removes blood toxicants by absorbing them though a column and is another choice for PQ poisoning treatment. As it has a superior PQ clearance over HD in vivo[12], it has become the standard treatment for PQ intoxication in many countries [11,15]. Several retrospective studies report that HP could significantly improve PQ plasma clearance and reduce mortality

compared with control groups[16,17], while other studies point out that patients would benefit from HP only when it is administered early from the onset of poisoning[12,18 19].In one prospective clinical trial, Li *et. al.* reports that HP could enhance PQ clearance, but no conclusion was drawn on mortality[20]. In addition, the toxicokinetics of paraquat during HP are poorly understood. Although some evidence from China suggests that HP and HD concurrent therapy (HP-HD) can significantly reduce mortality[21,22,23,24 25], it is not a standard therapy in paraquat poisoning. High costs and long therapeutic duration may have hindered its application in clinical practice.

The hypothesis of the present study is that early hemopurification therapies may reduce mortality in acute PQ poisoned patients. This is a single-center, parallel non-blinded randomized controlled trial to investigate the superiority of HD, HP and HP-HD concurrent therapy compared with conservative therapy during acute PQ poisoning. Allocation ratio of each group is 1:1:1:1.

Methods and analysis

Study setting

Patient recruitment would be completed in The First Affiliated Hospital of Zhengzhou University, a comprehensive tertiary medical center in Henan Province, China with 50 beds in emergency intensive care units (EICU). The estimated number of admitted acute paraquat poisoned patients ranges from 50-200 persons per year. To assist participant enrolment, after acceptance of this protocol, a notice of this trial would be sent to the Emergency Room (ER) of all secondary hospitals in Henan Province to improve transference to the First Affiliated Hospital of Zhengzhou University. Considering the fact that intervention would be administered in ER setting, and the relatively short duration of assigned hemopurification, adherence of patients is promising. Patients' families would receive full explanation of treatment plan and continuous follow-up in order to promote adherence.

Study population

Upon admission to ER, patients suspected with PQ intoxication would receive a urine dithionite test, and only those with a positive result would be invited to participate in this trial. The urine dithionite test would be measured by Spectrophotometer Type 721, and the minimal measurable concentration of paraquat is 0.2 μg/ml. Detailed inclusion and exclusion criteria are listed as follows.

Inclusion criteria

Patients meeting with all of the following criteria would be included in this trial: (1) Suspected paraquat ingestion history (intended or accidental), which is confirmed by positive urine dithionite result (light blue, navy blue and dark blue). (2) Arriving at the ER within 24 hours after PQ digestion. (3) Age: 18 ~-70 years old. (4) No known current pregnancy or lactation. (4) Absence of cardiac arrest after poisoning, and no previous or present history of chronic kidney disease, chronic liver disease, respiratory failure, COPD, asthma, heart failure, pancreatic disease, acute coronary syndrome (ACS) or stoke. (5) No known combined ingestion with other poisons or alcohol. (6) No previous blood purification treatment prior to admission. (8) No known participation in other medical trials. (9) Agreement on informed consent.

Exclusion criteria

Patients in any one of the following conditions would be excluded: (1) Patients who are unable to comply with the procedures of the present trial, including those who change therapy or withdraw treatment. (2) Patients who develop severe allergic response to HP materials. (3) Patients who do not receive intervention within 4 hours after admission in reality.

Allocation randomization and concealment

All participants would be randomly stratified into three blocks according to the result of urine dithionite test, i.e. light blue, navy blue and dark blue. Block length is set at 12. With the help of SAS 9.3, patients in different blocks would be allocated to four groups, namely the hemodialysis group (HD group), hemoperfusion group (HP group), concurrent hemodialysis and hemoperfusion group (HP-HD group), and conservative therapy group (control group), at a 1:1:1:1 ratio(Figure 1).

Due to the apparently different equipment of the interventions, it would be impractical to blind the present trial, therefore both patients and physicians would be aware of the exact treatment that the patients would receive. A sealed envelope with the allocation information would then be sent to the physician in charge of the patient after stratified grouping. To reduce assessor bias, blood samples and chest radiograph would be collected and examined by staff independent of this study.

Intervention

The intervention under investigation includes conservative therapy, hemoperfusion alone, hemodialysis alone, and hemoperfusion and hemodialysis concurrent therapy under the Guideline of Chinese Blood Purification for Acute Paraquat Poisoning Patients[26].

Study procedure

Physicians involved in the study would receive standardized training in carrying out this trial. Upon enrollment, informed consent, basic demographic information and collateral history would be taken from the patients or their next of kin (Table 1). PQ ingestion volume would be estimated as follows: 1 mouthful of liquid for women= 22 ml and 1 mouthful for men =28 ml [27]. PQ ingestion amount, defined as PQ concentration × PQ ingestion volume, would be calculated. Physicians would also assess the participants by various scores (Table 2), including Acute Physiologic and Chronic Health Evaluation (APACHE II) score and Poisoning Severity Score (PSS).

Table 1 The form of basic demographic information and collateral history

Patient ID number	Date	Patient name	Age	Gender	Time of ingestion (to nearest minute)	PQ ingestion volume (ml)	Concentration of PQ (%)	PQ ingestion amount	Source of information	Recording physician

Table 2 The form of initial assessment

Patient ID number	
Date	
Group	
Time to intervention	
Urine test result	
Complete blood count	
BMI	
Smoking history	
Alcohol history	
Blood gas analysis result	
Liver function	
Pancreatic function	
Kidney function	
Lactase	
Diabetes history	
Hypertension history	
APACHEII score	
Poisoning Severity Score (PSS)	

Upon suspected diagnosis of PQ poisoning, all patients would receive gastric lavage with room warm water (≥5L), and 1g/kg active charcoal via nasogastric tube. After confirmed diagnosis by urine dithionite test, intervention would be initiated upon acquisition of informed consent and randomized allocation, which would take less 1 h after admission ideally. Subsequent treatment varies by groups:

(1) **HD group**: participants would receive 4 hours of HD therapy a day for three consecutive days.
(2) **HP group**: participants would receive 4 hours of HP a day for three consecutive days.
(3) **HP-HD** group: participants in this group would receive 4 hours' hemoperfusion and hemodialysis concurrent therapy for consecutively three days.
(4) **Control group**: participants in this group would receive conservative treatment (see below).

According to the Chinese Guideline on Management of Paraquat Poisoning[11], all patients groups would receive standard treatment as follow. Methylprednisolone 15mg/kg/d together with cyclophosphamide 15mg/kg/d would be administered for the first week. After the first week, methylprednisolone would be reduced by 40 mg every 3 days, while no more cyclophosphamide would be given. Patients would be given supplemental oxygen only if their PaO_2 falls below 40mmHg or in the cases of Acute Respiratory Dyspnea Syndrome (ARDS).

Procedure of HD

(1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or place a dual-lumen catheter in the femoral vein if needed. Equip the hemodialysis machine (HD machine: Fresenius 4008s. Cartridge: Fresenius Fx60. Both by Fresenius Medical Care AG Co, Germany). Rinse the pipeline with 1L of normal saline (NS) at a speed of 100 ml/min. Set the volume of dialysis at 300 ml, and run the dialysis machine in close loop for 10 min.

(2) Anticoagulation: Inject 60-80 IU/kg low molecular weight heparin (LMWH) 20-30 min before hemodialysis.

(3) Therapy and surveillance: connect the pipeline to the catheter, and run the dialysis machine at a speed (ml/min) 4 times as the patient's weight (kg). Dialysis solution speed should be set at 500 ml/min. Run hemodialysis for 4 hours meanwhile closely monitor the patients' vital signs. During HD, anticoagulation function should be monitored by transmembrane pressure (TMP) of dialyzer. If TMP > 250mmHg, additional LMWH should be added.

Procedure of HP

(1) Preparation: Establish a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed. Equip the hemoperfusion machine (HP machines: Jafron model JF-800. Cartridge: HA330. Both by Jafron biomedical.co.). Rinse the whole pipeline with 5% glucose solution at a speed of 100 ml/min until the pipeline is filled with glucose solution. Then rinse pipeline with NS at a speed of 200 ml/min. The total volume used for rinsing is 2000 ml.

(2) Anticoagulation: Rinse the pipeline with 500ml NS mixed with 4 mg/dl heparin. Ten minutes later, rinse the pipeline with 300 ml NS. Connect the pipeline to the catheter on the patient. Inject 0.5-1.0 mg/kg heparin, then add heparin at a speed of 10-20 mg/h based on coagulation status (keep activated partial thromboplastin time (APTT) 50% above upper limit of normal). Stop adding heparin 30 min before the end of each course.

(3) Surveillance: Run HP for 4 hours a day. Monitor vital signs during HP and prevent hypotension. Optimal flow velocity of extracorporeal blood flow ranges from 100 to 200 ml/min. Change the hemoperfusion cartridge as soon as any charcoal appears in the blood flow.

Procedure of HP-HD

(1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed in ER. Equip the blood purification machines (HP and HD machines and cartridges as mentioned above). The outlet of the HP cartridge should be connected with the inlet of HD machine. Rinse HP pipeline and HD pipeline with 1L of NS mixed with 3000 IU heparin at a speed of 100-150 ml/min, followed by 600ml of NS containing 3000 IU heparin.

(2) Anticoagulation: Inject LMWH 50-60 IU/kg as loading dose, then maintain at a speed of 400 IU/h and adjust dose according to transmembrane pressure (keep TMP≤250mmHg).

(3) Run HP-HD: Connect the inlet of the HP cartridge to the catheter, and run the machine for 4 hours. Blood flow speed ranges from 100 to 200 ml/min. Dialysis solution speed is 500 ml/min. Hemoperfusion cartridge should be changed as soon as any charcoal appears. Patients' virtual signs should be monitored during treatment.

Sample size and study power

The hypothesis of the present trial is that all of the active arms, i.e. HP, HD, HP-HD concurrent therapy has a lower mortality compared with conservative therapy in PQ poisoning treatment. Based on this assumption, we searched on several data bases, i.e. Pubmed, EMBASE, SCI, Wanfang Data and CNKI, and found no research had compared HP, HD, HP-HD and conservative therapy for PQ poisoning in one trial, hence data from different studies are adopted for sample size calculation. Studies of bigger sample size and those that have a similar design to our research

are preferentially selected for reference. Gao *et. al.* compared HP (n=458) and HP+CVVH (n=226) in PQ poisoning treatment, and reported that the mortality of HP was 57.4% [19]. Park and colleagues investigated in the efficacy of HP-HD consecutive therapy (n=347) and concurrent therapy (n=383) and found that HP-HD concurrent therapy had a lower mortality (57.9% v.s. 81.8%)[28] . In a Chinese study by Liu *et. al.*, the mortality of conservative therapy for PQ poisoned patients was 78.2% (n=87) [29]. Even less evidence could be obtained in HD treatment for PQ poisoning in the last 30 years. Proudfoot *et. al.* investigated in the efficacy of HD in clearing PQ, but since both hemodialysis and peritoneal dialysis were included in the active arm[30], it is not considered for sample size estimation. Eventually a Chinese study by Yang[31] is adopted, and they concluded that mortality of HD was as low as 38.10% (n=26), as compared to 88.24% in control group (n=17). Though the absolute sample size was small, it is the largest that we could find, and the investigated intervention did not include peritoneal dialysis, thus it is selected for reference. With the 28-day mortality being the primary outcome, and $p<0.05$ defined as significantly different, the Z test with pooled variance [32-36] is applied to calculate the sample size (study power 80%). Based on these data, at least 78，13 and 81 subjects would be needed for HP, HD and HP-HD group respectively. As the subjects in each group is set at a 1：1：1：1 ratio, a sample size of 81 per group is adopted. With an estimated drop-out rate of 10%, 90 patients would be enrolled for each group eventually.

Monitoring

Arterial blood gas test, complete blood count, coagulation function test, liver function, pancreatic function would be performed and urine volume would be taken every day before hemopurification (if there is any). Urine dithionite test result would be recorded every 4-6 hours from admission until there are three consecutive negative results. Renal function would be tested daily[10]. Chest radiographs would be taken once a week or as soon as the patient deteriorates. If any patient develops fever or sepsis during treatment, they would be investigated to identify potential catheter-related bloodstream infection. Ultrasound for lower limb deep veins would be administered for patients with notable increase of calf/thigh circumference to identify thrombogenesis.

Outcomes

28-day mortality would be the primary endpoint for this trial, which is a commonly used measurement [19 28 29 31 37] as most death events occur during this period[11].The result would be presented in the term of percentage and 95% confidence interval.

Secondary outcomes include: (1) survival time (from the time of PQ ingestion to the time of death), all-cause mortality at the 3rd, 7th and 60th day; (2) rate of necessary oxygen uptake and rate of mechanical ventilation; (3) in-hospital length of stay and ICU length of stay; (4) APACHE II score and PSS score; (5) rate of general complications, such as respiratory failure, acute kidney injury (AKI), acute liver failure, pancreas function abnormality and Multiple Organ Failure (MOF); (6) rate of intervention related complications, such as catheter placement related complications, thrombocytopenia and deep venous thrombosis; (7) rate of adverse events, which include unexpected death, severe hemorrhage or edema, unplanned extubation, coagulation in the extracorporeal circulation, blockage of cartridge, incorrect pipe connection, etc.. These results would be presented in the form of mean value and 95% confidence interval. (4) would be assessed

at admission. (2), (3), (5), (6) and (7) would be recorded during hospitalization and reviewed by the time of discharge or in-hospital death. Death events would be recorded during hospitalization. Patients who are discharged would receive a followed-up phone call at the 60th day from PQ intoxication. All death events would be recorded by date to calculate survival time and mortality at 3rd, 7th, 28th and 60th day. For patients who discontinue or change therapy, data would be collected at the termination of assigned treatment.

Participant Timeline

The study would start after the manuscript is accepted, and it is expected to be completed in 3 years or more depending on actual enrollment. The timeline of participant is listed in **Table 3**.

Table 3 Participant timeline

	Enrollment	Discharge from hospital	Day 60
Check the inclusion and exclusion criteria	√		
Sign informed consents	√		
Allocation and intervention	√		
Assessment			
Report and fill the case report forms		√	
Survival status		√	√
Follow-up			√

Data collection and management

All participants would be given a study ID, and all information would be saved by study ID in an electronic data base. All data in this trial would be recorded and saved as electronic case report form (eCRF), kept and managed by the Emergency Department of Peking Union Medical College Hospital. There would be two databases containing information of this trial, one of which (Data Base 1) only contains information of the ID number, name and intervention of each participant, while another (Data Base 2) contains the ID number, grouping information and clinical data of the patient without intervention details. Statisticians only have access to Data Base 2. Front line physicians would have restricted access only to the data of the patients that they are directly involved with. Data Base 1 would be managed by an independent person who has no interest of conflict in this study. All of the envelopes given to physicians with assignment information would be preserved and kept in a locker by the chief data manager. All clinical data including adverse events collected during hospitalization can be obtained from electronic medical record system or paper notes. Contact information of patients and their family members would be required when patients on admission. Information on patient deaths can be obtained from medical records and follow-up calls.

Statistical analysis

Considering the high cost of each participant, intention to treat (ITT) analysis would be adopted to fully use the data. Drop-out rate, which may increase the bias of ITT analysis, would stay low in this trial with the relatively short course of disease. To obtain a relatively conservative result, the last observation carried forward (LOCF) method would be used to fill up missing and drop out data. The missing data of survival would be carried forward as death, so as to reduce potential treatment effect bias induced by the active arms. Results would be calculated by Statistical Analysis System (SAS) 9.3, and P <0.05 is defined as statistically significant. The Cox regression model (5% significance level) would be applied to examine the relationship between 28-day mortality and intervention group, paraquat ingestion amount, urine dithionite test results, time lapse from intoxication to treatment, age and the acid-base or electrolyte status on admission. For secondary outcome (2), (5), (6) and (7), RxC contingency tables would be used to test the difference of these indicators in four groups. If significant differences are found, Bonferroni test would be performed to find treatment effect differences between each group. As for length of stay and scores, one way ANOVA would be applied. Exploratory subgroup analysis would be performed to investigate treatment effect in different patients. Patients would be divided into subgroups by these factors: urine dithionite test result (light blue, navy blue and dark blue), and time from ingestion to treatment (⩾4 h and <4 h). The survival time of each group would also be analyzed with the help of log-rank test, Cox regression and Kaplan-Meier survival curve.

Data monitoring

The data monitoring committee (DMC) consists of three independent physicians and one statistician. It is responsible for regular review of accumulating trial data on efficacy and safety. It can also suggest to trial sponsor and investigator on trial continuation, modification or cessation based on benefit-risk assessment. Every four months, the DMC would hold a meeting to review statistical reports presented by Statistical Data Analysis Center (SDAC), which is composed of a group of statisticians. The DMC would have access to unmasked results on 28-day mortality, survival time, rate of Multiple Organ Failure (MOF) and rate of severe complications. These outcomes would be kept confidential by DMC unless a clear difference is observed among groups and DMC requests trial termination. It would also review the occurrence of serious adverse events, which include unexpected death, severe hemorrhage or edema, etc. Adverse events would be collected by self-report by physicians and nurses in charge of the subjects on eCRF system. The DMC would evaluate these events in the meetings and decide if an early end to the trial should be applied. Inter-rater agreement would be assessed by κ analysis.

Definitions

Chronic kidney disease (CKD) is defined according to Kidney Disease Outcomes Quality Initiative (KDOQI) Guideline as damage or decrease of kidney function[38], which presents as urinary albumin excretion ⩾30mg/d or eGFR⩽60ml/min/1.73m^2 for three months or more. According to Kidney Disease Improving Global Outcomes (KDIGO) classification[39], acute kidney injury (AKI) is diagnosed in patients who meet any criteria of the following: (1) Increase in serum creatinine ⩾0.3mg/dl in 48 hours. (2) The serum creatinine has increased to more than 1.5 times than baseline within 7 days. (3) The volume of urine is lease than 0.5ml/kg/h for 6 hours. Chronic obstructive pulmonary disease (COPD) is defined according to the Global Initiative for Chronic Obstructive Lung Disease(GOLD) criteria[40]. Patients whose spirometry result indicates

air flow limitation ($FEV_1/FVC<0.7$) after bronchodilator inhalation without alternative explanation for patients' symptoms can be diagnosed as COPD.

Respiratory failure can be diagnosed in the patients with an arterial oxygen partial pressure (PaO_2) <60mmHg in air pressure of sea level, with or without $PaCO_2$>50mmHg.

Chronic liver disease is defined as diseases of liver lasting longer than six months. Cirrhosis, chronic liver inflammation caused by infection or autoimmune disease are included in chronic liver disease. Cirrhosis is defined according the National Institute for Health and Care Excellence (NICE) 2016 guideline[41],in which patients can be diagnosed as cirrhosis with typical imaging, laboratory results together with risk factors, or with biopsy confirmation alone.

Acute liver failure is defined as acute damage in liver function without obvious history of liver disease or cirrhosis within 26 weeks. Patients who meet all the following criteria can be diagnosed as acute liver failure[42]: (1) elevated aminotransferases. (2) mental alteration (hepatic encephalopathy). (3) INR（international normalized ratio）≥1.5.

Acute coronary syndrome (ACS) is associated with myocardial ischemia, which includes ST Elevation Myocardial Infarction (STEMI), Unstable Angina (UA) and Non-ST Elevation Myocardial Infarction (NSTEMI).

Acute respiratory distress syndrome (ARDS) is defined according to Berlin definition[43].Patients who meet all the criteria below can be diagnosed as ARDS: (1) The respiratory symptoms must occur within 1 week of noticed clinical disease, or patients' present new symptoms or respiratory symptoms deteriorate in last week. (2) Chest X- ray or CT shows signs of pneumonedema in both sides of lungs which can't be fully explained by pleural effusion, atelectasis, lobe collapse or pulmonary nodules. (3) Heart failure and fluid overload cannot completely explain the respiratory failure. (4) The patient must present with moderate to severe oxygen impairment which can be defined by ratio of PaO_2/FiO_2. When the positive end-expiratory pressure (PEEP) is set as $5cmH_2O$ or more, the PaO_2/FiO_2 is less than 300mmHg.

Abnormal pancreatic function is defined as serum amylase >220U/L, which can be classified into two degrees, mildly elevated (220U/L-660U/L) and elevated (>660U/L)[20].

Multi-organ dysfunction is defined according to the Sepsis-3 definition: patients with Sequential Organ Failure Assessment (SOFA) score≥2 are determined to have multi-organ dysfunction or multiple organ failure(MOF)[44].

Ethics and dissemination

The study protocol and informed consent have been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University in September, 2017 (2017-KY-10). The trial has also been registered in Clinicaltrials.gov (NCT03314909). If important modifications or decision are made, the Ethics Committee of the First Affiliated Hospital of Zhengzhou University would be informed, and new protocols would be uploaded to Clinicaltrials.gov.

All eligible participants and their family members would be given inform consents documents with adequate time to consider and communicate with physicians. Consent provisions for collection and use of participant data and biological specimens in potential ancillary studies are also included in the informed consent. Refusal to participate in this trial would not influence the care they receive under any circumstances. Discontinuation or modification of treatment could be requested by patients and their families, or in the cases of allergic responses to hemopurification materials. Serious events and unexpected adverse events would be recorded and reported to the

Ethics Committee of the First Affiliated Hospital of Zhengzhou University and DMC. An independent audit would be held every 6 months to supervise trial conduct. Three toxicologists and three independent statisticians would be invited to the audit. Personal contact information would be accessible only to the research team members who are in charge of follow-up. Full protocol would be accessible to the public on BMJ Open. The results of the present study would be published in international peer-review journals. Original research data could be requested by contact to corresponding author.

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Competing interest

No declare.

Author Contributions

Yi Li, Yan-Xia Gao, Xuezhong Yu, Huadong Zhu raised the idea and developed the plan for the trial. Yi Li and Yan-Xia Gao formulated the intervention plan. Jian-Wei Cui, Yinyan Xu wrote the original paper. Jian-Wei Cui, Yinyan Xu, Xin Lu, Shiyuan Yu, Yong Ma collected the reference data for the trial and designed the Case Report form (CRF). Yan-Xia Gao, Yibo Wang, Ding Yuan, Lu Che, Pei Sun prepared the documents for ethical review and obtained the research ethical approvals. Shigong Guo revised the paper and work in English. Meng Wang reviewed the reference data, calculated the sample size and helped design the analysis plan. Yi Li reviewed and embellished the original paper, and confirmed the final protocol.
All authors reviewed the final version of manuscript.

Figure 1 Diagram of the protocol (planned).

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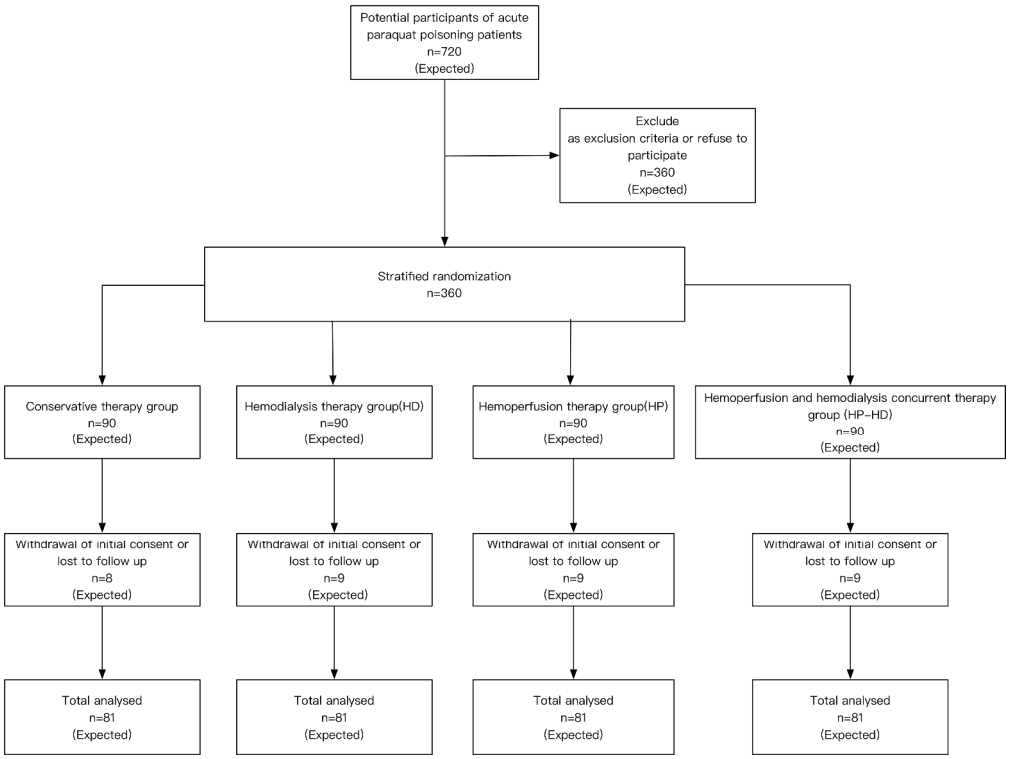

Figure 1 diagram of protocol

356x266mm (300 x 300 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Yes
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	12
	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	12
	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)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	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)	11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, Table 3

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	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	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	9

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	9
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	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	10
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	10,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
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	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
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	8

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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The Efficacy of Initial Hemopurification Strategy for Acute Paraquat Poisoning in Adults: Study Protocol for a Randomized Controlled Trial (HeSAPP)

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Secondary Subject Heading:	Emergency medicine
Keywords:	Paraquat poisoning, Hemopurification, Hemodialysis, Hemoperfusion

The Efficacy of Initial Hemopurification Strategy for Acute Paraquat Poisoning in Adults: Study Protocol for a Randomized Controlled Trial (HeSAPP)

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Abstract

Introduction

Paraquat (PQ) is a widely used herbicide, which is inexpensive and easily accessible for people in rural areas. A small amount of PQ ingestion could be lethal, yet currently the optimal treatment is still controversial. Extracorporeal therapies (ECTR) have been practiced in paraquat poisoning management, though limited evidence could be obtained to suggest its superiority over conservative therapy. Hemodialysis (HD) and hemoperfusion (HP) are most commonly used, while some institutions also choose HP-HD concurrent therapy. The object of the present trial is to investigate whether hemopurification therapy can reduce mortality compared with conservative therapy.

Methods and analysis

This is a planned single-center, non-blinded, randomized controlled trial (RCT). Acute paraquat poisoned adults who have orally ingested paraquat within 24 hours would be recruited. A total of 360 patients would be recruited and randomly assigned to four groups, i.e. HP, HD, concurrent HP-HD and control, at a 1:1:1:1 ratio. Subjects would be also stratified by their urine dithionite test results. Primary outcome is 28-day all-cause mortality. Secondary outcomes include survival time, all-cause mortality at the 3rd, 7th and 60th day, rate of major complications, APACHE II score and PSS score, etc.

Ethics and dissemination

The protocol and informed consent documents have been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University in September, 2017 (approval number: 2017-KY-10). The result of this trial would be submitted to peer-reviewed journal.

Trial registration number: NCT03314909

Key words: Paraquat poisoning, Hemopurification, Hemodialysis, Hemoperfusion

Strengths and limitations of this study

This is the first parallel RCT to compare the efficacy of HP, HD, concurrent HP-HD and non-hemopurification treatment in acute paraquat poisoning.
Patients will be stratified by the result of urine dithionite test.
The primary outcome is 28-day mortality.
Subgroup analysis based on time lapse from PQ ingestion to treatment may provide reference for initiation time of hemopurification.
The limitation of this study is the unavailability of serum paraquat concentration.

Introduction

Among 1.6 million violent deaths every year in the world, half are suicidal and 63% of these occur in Asia-Pacific region[1]. Pesticide suicide accounts for up to one third of all suicides worldwide every year [2]. Being inexpensive and easily accessible, paraquat (PQ), a water soluble toxic organic herbicide (1,1-dimethyl-4,4-bipyridine cationic salt) is still widely consumed in some countries like China, and occasionally serves as poison[3].
A very small amount of PQ can cause death in human. A study of 375 participants reports that patients with a plasma PQ concentration higher than 3.44 μg/mL died[4], though some other studies indicate a relative higher upper limit for survivors[5 6].The mortality of PQ is remarkably high (ranging from 42.7% to 90% [7-9]), but unfortunately there is still no effective treatment for confirmed PQ poisoning. The main mechanism of PQ intoxication is generation of free radicals and oxidative stress, and some studies claim that immunosuppressive therapy can improve survival rate[9 10]. Considering the physical characteristics of PQ, e.g. relatively low volume of distribution (1.2-1.6L/kg)[3], low molecular weight and low protein binding rate, it is reasonable to propose that extracorporeal treatment (ECTR) may benefit patients with PQ poisoning.
Hemodialysis (HD) purifies blood by filtering poisonous molecules through a selectively permeable membrane, especially molecules with a small molecular weight and low protein binding rate. It can also correct acid-base disturbance in patients. Theoretically, HD should be the ideal treatment for acute PQ poisoning in view of its physical characteristics. However, HD is not widely applied in practice, and the Expert Consensus on Acute PQ Poisoning in China recommends HD as a supplementary therapy for patients complicated with acid-base disturbance[11].
Little evidence could be obtained in HD for PQ poisoning treatment in the last 30 years. In an experimental model, it is demonstrated that after 90 mins' of HD, PQ clearance remains static in vitro (179 ml/min)[12]. Compared with the high apparent renal clearance of PQ (1.17 L/h) in vivo[13], HD seems to have a limited effect on PQ clearance, probably due to the limitation of HD filter material. With the improvement in filter, HD has a two-fold increase in small molecule clearance compared with 40 years ago[14], thus further research is needed to evaluate the treatment effect of HD in PQ poisoning management.
Hemoperfusion (HP) removes blood toxicants by absorbing them though a column and is another choice for PQ poisoning treatment. As it has a superior PQ clearance over HD in vivo[12], it has become the standard treatment for PQ intoxication in many countries [11,15]. Several retrospective studies report that HP could significantly improve PQ plasma clearance and reduce mortality compared with control groups[16,17], while other studies point out that patients would benefit from

HP only when it is administered early from the onset of poisoning[12,18 19].In one prospective clinical trial, Li *et. al.* reports that HP could enhance PQ clearance, but no conclusion was drawn on mortality[20]. In addition, the toxicokinetics of paraquat during HP are poorly understood. Although some evidence from China suggests that HP and HD concurrent therapy (HP-HD) can significantly reduce mortality[21,22,23,24 25], it is not a standard therapy in paraquat poisoning. High costs and long therapeutic duration may have hindered its application in clinical practice.
The hypothesis of the present study is that early hemopurification therapies may reduce mortality in acute PQ poisoned patients. This is a single-center, parallel non-blinded randomized controlled trial to investigate the superiority of HD, HP and HP-HD concurrent therapy compared with conservative therapy during acute PQ poisoning. Allocation ratio of each group is 1:1:1:1.

Methods and analysis

Study setting

Patient recruitment would be completed in The First Affiliated Hospital of Zhengzhou University, a comprehensive tertiary medical center in Henan Province, China with 50 beds in emergency intensive care units (EICU). The estimated number of admitted acute paraquat poisoned patients ranges from 50-200 persons per year. To assist participant enrolment, after acceptance of this protocol, a notice of this trial would be sent to the Emergency Room (ER) of all secondary hospitals in Henan Province to improve transference to the First Affiliated Hospital of Zhengzhou University. Considering the fact that intervention would be administered in ER setting, and the relatively short duration of assigned hemopurification, adherence of patients is promising. Patients' families would receive full explanation of treatment plan and continuous follow-up in order to promote adherence.

Study population

Upon admission to ER, patients suspected with PQ intoxication would receive a urine dithionite test, and only those with a positive result would be invited to participate in this trial. The urine dithionite test would be measured by Spectrophotometer Type 721, and the minimal measurable concentration of paraquat is 0.2 μg/ml. Detailed inclusion and exclusion criteria are listed as follows.

Inclusion criteria

Patients meeting with all of the following criteria would be included in this trial: (1) Suspected paraquat ingestion history (intended or accidental), which is confirmed by positive urine dithionite result (light blue, navy blue and dark blue). (2) Arriving at the ER within 24 hours after PQ digestion. (3) Age: 18 ~-70 years old. (4) No known current pregnancy or lactation. (4) Absence of cardiac arrest after poisoning, and no previous or present history of chronic kidney disease, chronic liver disease, respiratory failure, COPD, asthma, heart failure, pancreatic disease, acute coronary syndrome (ACS) or stoke. (5) No known combined ingestion with other poisons or alcohol. (6) No previous blood purification treatment prior to admission. (8) No known participation in other medical trials. (9) Agreement on informed consent.

Exclusion criteria

Patients in any one of the following conditions would be excluded: (1) Patients who are unable to comply with the procedures of the present trial, including those who change therapy or withdraw

treatment. (2) Patients who develop severe allergic response to HP materials. (3) Patients who do not receive intervention within 4 hours after admission in reality.

Allocation randomization and concealment

All participants would be randomly stratified into three blocks according to the result of urine dithionite test, i.e. light blue, navy blue and dark blue. Block length is set at 12. With the help of SAS 9.3, patients in different blocks would be allocated to four groups, namely the hemodialysis group (HD group), hemoperfusion group (HP group), concurrent hemodialysis and hemoperfusion group (HP-HD group), and conservative therapy group (control group), at a 1:1:1:1 ratio(Figure 1).

Due to the apparently different equipment of the interventions, it would be impractical to blind the present trial, therefore both patients and physicians would be aware of the exact treatment that the patients would receive. A sealed envelope with the allocation information would then be sent to the physician in charge of the patient after stratified grouping. To reduce assessor bias, blood samples and chest radiograph would be collected and examined by staff independent of this study.

Intervention

The intervention under investigation includes conservative therapy, hemoperfusion alone, hemodialysis alone, and hemoperfusion and hemodialysis concurrent therapy under the Guideline of Chinese Blood Purification for Acute Paraquat Poisoning Patients[26].

Study procedure

Physicians involved in the study would receive standardized training in carrying out this trial. Upon enrollment, informed consent, basic demographic information and collateral history would be taken from the patients or their next of kin (Table 1). PQ ingestion volume would be estimated as follows: 1 mouthful of liquid for women= 22 ml and 1 mouthful for men =28 ml [27]. PQ ingestion amount, defined as PQ concentration × PQ ingestion volume, would be calculated. Physicians would also assess the participants by various scores (Table 2), including Acute Physiologic and Chronic Health Evaluation (APACHE II) score and Poisoning Severity Score (PSS).

Table 1 The form of basic demographic information and collateral history

Patient ID number	Date	Patient name	Age	Gender	Time of ingestion (to nearest minute)	PQ ingestion volume (ml)	Concentration of PQ (%)	PQ ingestion amount	Source of information	Recording physician

Table 2 The form of initial assessment

Patient ID number	
Date	

Group	
Time to intervention	
Urine test result	
Complete blood count	
BMI	
Smoking history	
Alcohol history	
Blood gas analysis result	
Liver function	
Pancreatic function	
Kidney function	
Lactase	
Diabetes history	
Hypertension history	
APACHEII score	
Poisoning Severity Score (PSS)	

Upon suspected diagnosis of PQ poisoning, all patients would receive gastric lavage with room warm water (≥5L), and 1g/kg active charcoal via nasogastric tube. After confirmed diagnosis by urine dithionite test, intervention would be initiated upon acquisition of informed consent and randomized allocation, which would take less 1 h after admission ideally. Subsequent treatment varies by groups:

(1) **HD group**: participants would receive 4 hours of HD therapy a day for three consecutive days.
(2) **HP group**: participants would receive 4 hours of HP a day for three consecutive days.
(3) **HP-HD** group: participants in this group would receive 4 hours' hemoperfusion and hemodialysis concurrent therapy for consecutively three days.
(4) **Control group**: participants in this group would receive conservative treatment (see below).

According to the Chinese Guideline on Management of Paraquat Poisoning[11], all patients groups would receive standard treatment as follow. Methylprednisolone 15mg/kg/d together with cyclophosphamide 15mg/kg/d would be administered for the first week. After the first week, methylprednisolone would be reduced by 40 mg every 3 days, while no more cyclophosphamide would be given. Patients would be given supplemental oxygen only if their PaO_2 falls below 40mmHg or in the cases of Acute Respiratory Dyspnea Syndrome (ARDS).

Procedure of HD

(1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or place a dual-lumen catheter in the femoral vein if needed. Equip the hemodialysis machine (HD machine: Fresenius 4008s. Cartridge: Fresenius Fx60. Both by Fresenius Medical Care AG Co, Germany). Rinse the pipeline with 1L of normal saline (NS) at a speed of 100 ml/min. Set the volume of dialysis at 300 ml, and run the dialysis machine in close loop for 10 min.
(2) Anticoagulation: Inject 60-80 IU/kg low molecular weight heparin (LMWH) 20-30 min before hemodialysis.

(3) Therapy and surveillance: connect the pipeline to the catheter, and run the dialysis machine at a speed (ml/min) 4 times as the patient's weight (kg). Dialysis solution speed should be set at 500 ml/min. Run hemodialysis for 4 hours meanwhile closely monitor the patients' vital signs. During HD, anticoagulation function should be monitored by transmembrane pressure (TMP) of dialyzer. If TMP > 250mmHg, additional LMWH should be added.

Procedure of HP

(1) Preparation: Establish a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed. Equip the hemoperfusion machine (HP machines: Jafron model JF-800. Cartridge: HA330. Both by Jafron biomedical.co.). Rinse the whole pipeline with 5% glucose solution at a speed of 100 ml/min until the pipeline is filled with glucose solution. Then rinse pipeline with NS at a speed of 200 ml/min. The total volume used for rinsing is 2000 ml.

(2) Anticoagulation: Rinse the pipeline with 500ml NS mixed with 4 mg/dl heparin. Ten minutes later, rinse the pipeline with 300 ml NS. Connect the pipeline to the catheter on the patient. Inject 0.5-1.0 mg/kg heparin, then add heparin at a speed of 10-20 mg/h based on coagulation status (keep activated partial thromboplastin time (APTT) 50% above upper limit of normal). Stop adding heparin 30 min before the end of each course.

(3) Surveillance: Run HP for 4 hours a day. Monitor vital signs during HP and prevent hypotension. Optimal flow velocity of extracorporeal blood flow ranges from 100 to 200 ml/min. Change the hemoperfusion cartridge as soon as any charcoal appears in the blood flow.

Procedure of HP-HD

(1) Preparation: Place a dual-lumen catheter in the internal jugular vein, or in the femoral vein if needed in ER. Equip the blood purification machines (HP and HD machines and cartridges as mentioned above). The outlet of the HP cartridge should be connected with the inlet of HD machine. Rinse HP pipeline and HD pipeline with 1L of NS mixed with 3000 IU heparin at a speed of 100-150 ml/min, followed by 600ml of NS containing 3000 IU heparin.

(2) Anticoagulation: Inject LMWH 50-60 IU/kg as loading dose, then maintain at a speed of 400 IU/h and adjust dose according to transmembrane pressure (keep TMP≤250mmHg).

(3) Run HP-HD: Connect the inlet of the HP cartridge to the catheter, and run the machine for 4 hours. Blood flow speed ranges from 100 to 200 ml/min. Dialysis solution speed is 500 ml/min. Hemoperfusion cartridge should be changed as soon as any charcoal appears. Patients' virtual signs should be monitored during treatment.

Sample size and study power

The hypothesis of the present trial is that all of the active arms, i.e. HP, HD, HP-HD concurrent therapy has a lower mortality compared with conservative therapy in PQ poisoning treatment. Based on this assumption, we searched on several data bases, i.e. Pubmed, EMBASE, SCI, Wanfang Data and CNKI, and found no research had compared HP, HD, HP-HD and conservative therapy for PQ poisoning in one trial, hence data from different studies are adopted for sample size calculation. Studies of bigger sample size and those that have a similar design to our research are preferentially selected for reference. Gao *et. al.* compared HP (n=458) and HP+CVVH (n=226) in PQ poisoning treatment, and reported that the mortality of HP was 57.4% [19]. Park and

colleagues investigated in the efficacy of HP-HD consecutive therapy (n=347) and concurrent therapy (n=383) and found that HP-HD concurrent therapy had a lower mortality (57.9% v.s. 81.8%)[28] . In a Chinese study by Liu *et. al*., the mortality of conservative therapy for PQ poisoned patients was 78.2% (n=87) [29]. Even less evidence could be obtained in HD treatment for PQ poisoning in the last 30 years. Proudfoot *et. al*. investigated in the efficacy of HD in clearing PQ, but since both hemodialysis and peritoneal dialysis were included in the active arm[30], it is not considered for sample size estimation. Eventually a Chinese study by Yang[31] is adopted, and they concluded that mortality of HD was as low as 38.10% (n=26), as compared to 88.24% in control group (n=17). Though the absolute sample size was small, it is the largest that we could find, and the investigated intervention did not include peritoneal dialysis, thus it is selected for reference. With the 28-day mortality being the primary outcome, and $p<0.05$ defined as significantly different, the Z test with pooled variance [32-36] is applied to calculate the sample size (study power 80%). Based on these data, at least 78， 13 and 81 subjects would be needed for HP, HD and HP-HD group respectively. As the subjects in each group is set at a 1：1：1：1 ratio, a sample size of 81 per group is adopted. With an estimated drop-out rate of 10%, 90 patients would be enrolled for each group eventually.

Monitoring

Arterial blood gas test, complete blood count, coagulation function test, liver function, pancreatic function would be performed and urine volume would be taken every day before hemopurification (if there is any). Urine dithionite test result would be recorded every 4-6 hours from admission until there are three consecutive negative results. Renal function would be tested daily[10]. Chest radiographs would be taken once a week or as soon as the patient deteriorates. If any patient develops fever or sepsis during treatment, they would be investigated to identify potential catheter-related bloodstream infection. Ultrasound for lower limb deep veins would be administered for patients with notable increase of calf/thigh circumference to identify thrombogenesis.

Outcomes

28-day mortality would be the primary endpoint for this trial, which is a commonly used measurement [19 28 29 31 37] as most death events occur during this period[11].The result would be presented in the term of percentage and 95% confidence interval.

Secondary outcomes include: (1) survival time (from the time of PQ ingestion to the time of death), all-cause mortality at the 3rd, 7th and 60th day; (2) rate of necessary oxygen uptake and rate of mechanical ventilation; (3) in-hospital length of stay and ICU length of stay; (4) APACHE II score and PSS score; (5) rate of general complications, such as respiratory failure, acute kidney injury (AKI), acute liver failure, pancreas function abnormality and Multiple Organ Failure (MOF); (6) rate of intervention related complications, such as catheter placement related complications, thrombocytopenia and deep venous thrombosis; (7) rate of adverse events, which include unexpected death, severe hemorrhage or edema, unplanned extubation, coagulation in the extracorporeal circulation, blockage of cartridge, incorrect pipe connection, etc. These results would be presented in the form of mean value and 95% confidence interval. (4) would be assessed at admission. (2), (3), (5), (6) and (7) would be recorded during hospitalization and reviewed by the time of discharge or in-hospital death. Death events would be recorded during hospitalization.

Patients who are discharged would receive a followed-up phone call at the 60th day from PQ intoxication. All death events would be recorded by date to calculate survival time and mortality at 3rd, 7th, 28th and 60th day. For patients who discontinue or change therapy, data would be collected at the termination of assigned treatment.

Patient involvement

No patients were involved in the development of the research questions or the outcome measures, nor were they invited to develop the plans for design, recruitment or conduction of the study. No patients were asked to assess the burden of intervention. The result will not be disseminated to participants or the relevant communities.

Participant Timeline

The study would start after the manuscript is accepted, and it is expected to be completed in 3 years or more depending on actual enrollment. The timeline of participant is listed in **Table 3**.

Table 3 Participant timeline

	Enrollment	Discharge from hospital	Day 60
Check the inclusion and exclusion criteria	√		
Sign informed consents	√		
Allocation and intervention	√		
Assessment			
Report and fill the case report forms		√	
Survival status		√	√
Follow-up			√

Data collection and management

All participants would be given a study ID, and all information would be saved by study ID in an electronic data base. All data in this trial would be recorded and saved as electronic case report form (eCRF), kept and managed by the Emergency Department of Peking Union Medical College Hospital. There would be two databases containing information of this trial, one of which (Data Base 1) only contains information of the ID number, name and intervention of each participant, while another (Data Base 2) contains the ID number, grouping information and clinical data of the patient without intervention details. Statisticians only have access to Data Base 2. Front line physicians would have restricted access only to the data of the patients that they are directly involved with. Data Base 1 would be managed by an independent person who has no interest of conflict in this study. All of the envelopes given to physicians with assignment information would be preserved and kept in a locker by the chief data manager. All clinical data including adverse events collected during hospitalization can be obtained from electronic medical record system or paper notes. Contact information of patients and their family members would be required when

patients on admission. Information on patient deaths can be obtained from medical records and follow-up calls.

Statistical analysis

Considering the high cost of each participant, intention to treat (ITT) analysis would be adopted to fully use the data. Drop-out rate, which may increase the bias of ITT analysis, would stay low in this trial with the relatively short course of disease. To obtain a relatively conservative result, the last observation carried forward (LOCF) method would be used to fill up missing and drop out data. The missing data of survival would be carried forward as death, so as to reduce potential treatment effect bias induced by the active arms. Results would be calculated by Statistical Analysis System (SAS) 9.3, and P <0.05 is defined as statistically significant. The Cox regression model (5% significance level) would be applied to examine the relationship between 28-day mortality and intervention group, paraquat ingestion amount, urine dithionite test results, time lapse from intoxication to treatment, age and the acid-base or electrolyte status on admission. For secondary outcome (2), (5), (6) and (7), RxC contingency tables would be used to test the difference of these indicators in four groups. If significant differences are found, Bonferroni test would be performed to find treatment effect differences between each group. As for length of stay and scores, one way ANOVA would be applied. Exploratory subgroup analysis would be performed to investigate treatment effect in different patients. Patients would be divided into subgroups by these factors: urine dithionite test result (light blue, navy blue and dark blue), and time from ingestion to treatment (⩾4 h and <4 h). The survival time of each group would also be analyzed with the help of log-rank test, Cox regression and Kaplan-Meier survival curve.

Data monitoring

The data monitoring committee (DMC) consists of three independent physicians and one statistician. It is responsible for regular review of accumulating trial data on efficacy and safety. It can also suggest to trial sponsor and investigator on trial continuation, modification or cessation based on benefit-risk assessment. Every four months, the DMC would hold a meeting to review statistical reports presented by Statistical Data Analysis Center (SDAC), which is composed of a group of statisticians. The DMC would have access to unmasked results on 28-day mortality, survival time, rate of Multiple Organ Failure (MOF) and rate of severe complications. These outcomes would be kept confidential by DMC unless a clear difference is observed among groups and DMC requests trial termination. It would also review the occurrence of serious adverse events, which include unexpected death, severe hemorrhage or edema, etc. Adverse events would be collected by self-report by physicians and nurses in charge of the subjects on eCRF system. The DMC would evaluate these events in the meetings and decide if an early end to the trial should be applied. Inter-rater agreement would be assessed by κ analysis.

Definitions

Chronic kidney disease (CKD) is defined according to Kidney Disease Outcomes Quality Initiative (KDOQI) Guideline as damage or decrease of kidney function[38], which presents as urinary albumin excretion ⩾30mg/d or eGFR⩽60ml/min/1.73m^2 for three months or more. According to Kidney Disease Improving Global Outcomes (KDIGO) classification[39], acute kidney injury (AKI) is diagnosed in patients who meet any criteria of the following: (1) Increase in serum

creatinine ⩾0.3mg/dl in 48 hours. (2) The serum creatinine has increased to more than 1.5 times than baseline within 7 days. (3) The volume of urine is lease than 0.5ml/kg/h for 6 hours.

Chronic obstructive pulmonary disease (COPD) is defined according to the Global Initiative for Chronic Obstructive Lung Disease(GOLD) criteria[40]. Patients whose spirometry result indicates air flow limitation ($FEV_1/FVC<0.7$) after bronchodilator inhalation without alternative explanation for patients' symptoms can be diagnosed as COPD.

Respiratory failure can be diagnosed in the patients with an arterial oxygen partial pressure (PaO_2) <60mmHg in air pressure of sea level, with or without $PaCO_2$>50mmHg.

Chronic liver disease is defined as diseases of liver lasting longer than six months. Cirrhosis, chronic liver inflammation caused by infection or autoimmune disease are included in chronic liver disease. Cirrhosis is defined according the National Institute for Health and Care Excellence (NICE) 2016 guideline[41],in which patients can be diagnosed as cirrhosis with typical imaging, laboratory results together with risk factors, or with biopsy confirmation alone.

Acute liver failure is defined as acute damage in liver function without obvious history of liver disease or cirrhosis within 26 weeks. Patients who meet all the following criteria can be diagnosed as acute liver failure[42]: (1) elevated aminotransferases. (2) mental alteration (hepatic encephalopathy). (3) INR（international normalized ratio）⩾1.5.

Acute coronary syndrome (ACS) is associated with myocardial ischemia, which includes ST Elevation Myocardial Infarction (STEMI), Unstable Angina (UA) and Non-ST Elevation Myocardial Infarction (NSTEMI).

Acute respiratory distress syndrome (ARDS) is defined according to Berlin definition[43].Patients who meet all the criteria below can be diagnosed as ARDS: (1) The respiratory symptoms must occur within 1 week of noticed clinical disease, or patients' present new symptoms or respiratory symptoms deteriorate in last week. (2) Chest X- ray or CT shows signs of pneumonedema in both sides of lungs which can't be fully explained by pleural effusion, atelectasis, lobe collapse or pulmonary nodules. (3) Heart failure and fluid overload cannot completely explain the respiratory failure. (4) The patient must present with moderate to severe oxygen impairment which can be defined by ratio of PaO_2/FiO_2. When the positive end-expiratory pressure (PEEP) is set as $5cmH_2O$ or more, the PaO_2/FiO_2 is less than 300mmHg.

Abnormal pancreatic function is defined as serum amylase >220U/L, which can be classified into two degrees, mildly elevated (220U/L-660U/L) and elevated (>660U/L)[20].

Multi-organ dysfunction is defined according to the Sepsis-3 definition: patients with Sequential Organ Failure Assessment (SOFA) score⩾2 are determined to have multi-organ dysfunction or multiple organ failure(MOF)[44].

Ethics and dissemination

The study protocol and informed consent have been approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University in September, 2017 (2017-KY-10). The trial has also been registered in Clinicaltrials.gov (NCT03314909). If important modifications or decision are made, the Ethics Committee of the First Affiliated Hospital of Zhengzhou University would be informed, and new protocols would be uploaded to Clinicaltrials.gov.

All eligible participants and their family members would be given inform consents documents with adequate time to consider and communicate with physicians. Consent provisions for collection and use of participant data and biological specimens in potential ancillary studies are

also included in the informed consent. Refusal to participate in this trial would not influence the care they receive under any circumstances. Discontinuation or modification of treatment could be requested by patients and their families, or in the cases of allergic responses to hemopurification materials. Serious events and unexpected adverse events would be recorded and reported to the Ethics Committee of the First Affiliated Hospital of Zhengzhou University and DMC. An independent audit would be held every 6 months to supervise trial conduct. Three toxicologists and three independent statisticians would be invited to the audit. Personal contact information would be accessible only to the research team members who are in charge of follow-up. Full protocol would be accessible to the public on BMJ Open. The results of the present study would be published in international peer-review journals. Original research data could be requested by contact to corresponding author.

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Competing interest

No declare.

Author Contributions

Yi Li, Yan-Xia Gao, Xuezhong Yu, Huadong Zhu raised the idea and developed the plan for the trial. Yi Li and Yan-Xia Gao formulated the intervention plan. Jian-Wei Cui, Yinyan Xu wrote the original paper. Jian-Wei Cui, Yinyan Xu, Xin Lu, Shiyuan Yu, Yong Ma collected the reference data for the trial and designed the Case Report form (CRF). Yan-Xia Gao, Yibo Wang, Ding Yuan, Lu Che, Pei Sun prepared the documents for ethical review and obtained the research ethical approvals. Shigong Guo revised the paper and work in English. Meng Wang reviewed the reference data, calculated the sample size and helped design the analysis plan. Yi Li reviewed and embellished the original paper, and confirmed the final protocol.
All authors reviewed the final version of manuscript.

Figure 1 Diagram of the protocol (planned).

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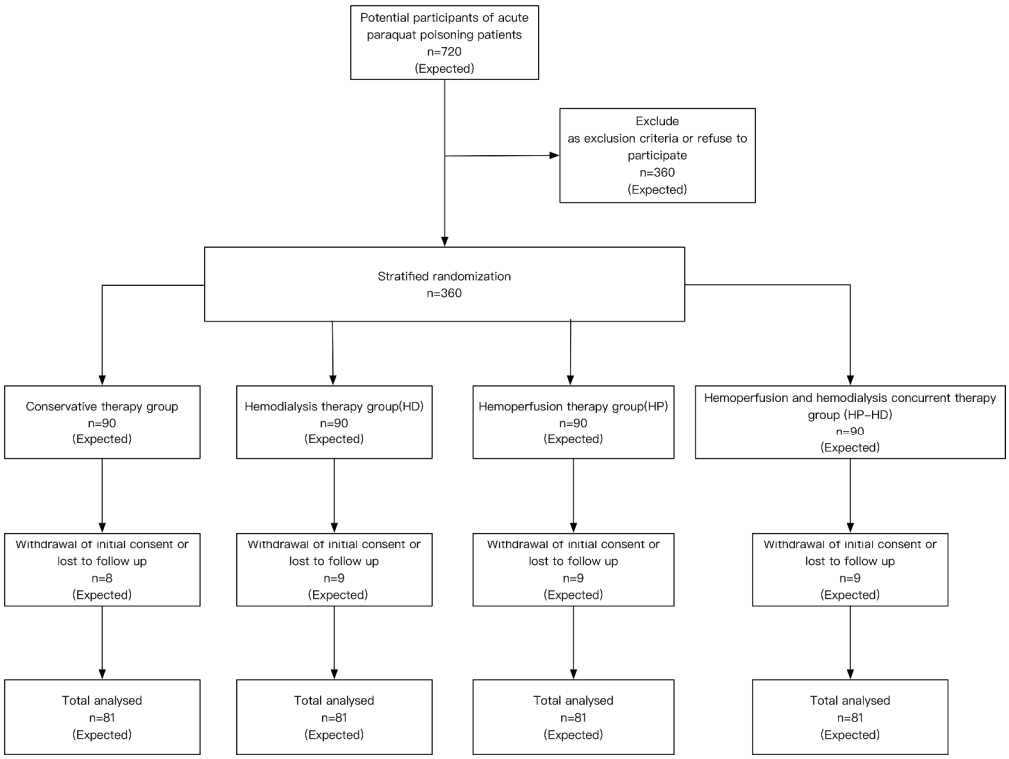

Figure 1 diagram of protocol

356x266mm (300 x 300 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	2
	2b	All items from the World Health Organization Trial Registration Data Set	Yes
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 12
	5b	Name and contact information for the trial sponsor	12
	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	12
	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)	10

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4-5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5-7
	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)	11-12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	4
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9, Table 3

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	7-8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	4
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9
	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	9

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	9
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	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)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	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	10
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	10,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	11

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5,11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
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	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes
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	8

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.