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Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalaemia Management (PLATINUM): Design of a Multicentre, Randomised, Double-blind, Placebo-controlled, Parallel Group Study

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Abstract

(299/300 words)

Introduction: Hyperkalaemia is common, life-threatening, and often requires emergency department (ED) management, however no standardised ED treatment protocol exists. Common treatments transiently reducing serum potassium (K^+) (including albuterol, glucose and insulin) may cause hypoglycaemia. We outline the design and rationale of the Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalaemia Management (PLATINUM) study, which will be the largest ED randomised controlled hyperkalaemia trial ever performed, enabling assessment of a standardised approach to hyperkalaemia management, as well as establishing a new evaluation parameter (net clinical benefit) for acute hyperkalaemia treatment investigations.

Methods and analysis: Platinum is a Phase 4, multicentre, randomised, double-blind, placebo-controlled study in participants who present to the ED at approximately 30 US sites. Approximately 300 adult participants with hyperkalaemia (K^+ ≥5.8 mEq/L) will be enrolled. Participants will be randomised 1:1 to receive glucose (25 g intravenously [IV] <15 minutes before insulin), insulin (5 units IV bolus) and aerosolised albuterol (10 mg over 30 minutes), followed by a single oral dose of either 25.2 g patiromer or placebo, with a second dose of patiromer (8.4 g) or placebo after 24 hours. The primary endpoint is net clinical benefit, defined as the mean change in the number of additional interventions less the mean change in serum K^+, at hour 6. Secondary endpoints are net clinical benefit at hour 4, proportion of participants without additional K^+-related medical interventions, number of additional K^+-related interventions, and proportion of participants with sustained K^+

reduction (K^+ ≤5.5 mEq/L). Safety endpoints are the incidence of adverse events, and severity of changes in serum K^+ and magnesium.

Ethics and dissemination: Participants will provide written consent and the local Institutional Review Board and Ethics Committee provided protocol approval. Primary results will be published in peer reviewed manuscripts promptly following study completion.

Trial registration: NCT04443608.

Strengths and limitations of this study

- PLATINUM is planned to be the largest emergency department (ED) randomised controlled hyperkalaemia trial ever performed, with the opportunity to assess a standardised approach to hyperkalaemia management, as well as establish a new evaluation parameter (i.e., net clinical benefit) for acute hyperkalaemia treatment investigations.
- Limitations include the difficulties of patient recruitment in an ED environment, and that further studies may be required to assess the benefit of patiromer as an adjunct treatment to other ED hyperkalaemia therapies (other than the protocol-specified standard of care).

Introduction

Hyperkalaemia, generally defined as serum potassium (K^+) >5.5 mEq/L, is common, can lead to life-threatening cardiac arrhythmias, and frequently effects patients in the emergency department (ED)[1-3]. In 2014, more than 1 million ED visits had an ICD-9 code related to hyperkalaemia [4], with emergent hyperkalemia likely to rise in parallel with increasing prevalence of hyperkalaemia risk factors[5] (e.g. chronic kidney disease [6 7], heart failure [8] and hypertension [9]). In addition, many patients have recurrent hyperkalaemia following discharge from the ED [10]. Expert panel recommendations and treatment algorithms for the management of hyperkalaemia [11-14] exist, however there is no standardised US protocol for ED hyperkalaemia management [15]. Common medications currently used to treat hyperkalaemia in the ED, such as nebulised albuterol and intravenous insulin, with or without glucose [11 12 14-24], often cause adverse events (AEs), such as hypoglycaemia or hyperglycaemia [15-19 2529]. Additionally, treatments that only shift K^+ into the cell, rather than remove it, frequently result in recurrence of hyperkalaemia 2–3 hours after treatment [41], particularly in patients undergoing hemodialysis[7]. Repeat treatment to counter hyperkalaemia recurrence then further increases the risk of AEs.

Alternatively, the use of K^+ binders to eliminate K^+ may be a better treatment strategy for emergent hyperkalaemia, although the current evidence lacks evaluation in a large randomised controlled trial [24]. Two small randomised studies (REDUCE and ENERGIZE) have shown promising results by adding either patiromer or sodium zirconium cyclosilicate to insulin and glucose therapy or investigator-designated standard of care, however, these studies were statistically inconclusive [26 27]. Sodium polystyrene sulfonate (SPS) is a historically established treatment for chronic hyperkalaemia, reducing serum K^+ via colonic excretion [28]. However, the onset of

action, degree of K^+ lowering, and patient tolerance of SPS are unpredictable [7 29 30]. Loop diuretics are commonly used in management of acute hyperkalemia; however, there is a lack of clinical studies to support their use in this setting [2]. Ultimately, dialysis represents a definitive treatment for hyperkalaemia, however effective management of hyperkalaemia through dialysis is complex and challenging[7] . Thus, the new oral K^+ binders with fewer adverse effects, such as patiromer, may offer a solution for the removal of excess K^+ in hyperkalaemic patients presenting to the ED. Patiromer is a non-absorbed, oral K^+ binder using sodium-free exchange [31] with efficacy in the treatment of hyperkalaemia in patients with chronic kidney disease and heart failure [21 27 32-36] and approval for use in the US [22] and EU [23] for treatment of hyperkalaemia. Given the variability of hyperkalaemia treatment in the ED [15], the challenge of emergent dialysis [7] , and the serious risks of AEs [15-19 2529], there is a need for evaluation of novel K^+ binders as additional treatments in the ED that act to remove excess K^+ [37], which have fewer AEs.

The PLATINUM trial will employ a systematic approach to investigate the use of patiromer as an adjunct treatment in hyperkalaemic patients presenting to the ED. The primary objective is to determine if patiromer, as adjunct to intravenous (IV) insulin, glucose and inhaled beta-agonist therapy, reduces the need for additional medical interventions for the management of hyperkalaemia. Secondary objectives are to determine if adjunctive treatment with patiromer results in fewer additional K^+-related medical interventions, enables a sustained reduction in K^+ without additional medical interventions, and leads to a sustained reduction in K^+ 24 hours after ED discharge.

Methods and analysis

Study design

This is a Phase 4, multicentre, randomised, double-blind, placebo-controlled, parallel-group study (NCT04443608, **Figure 1**). It is planned that PLATINUM will enrol approximately 300 participants with hyperkalaemia at about 30 sites in the US (**Figure 2**). The schedule of assessments is shown in **Table 1**.

Table 1. Assessment schedule during treatment period and follow-up.

Procedures	Baseline	Treatment Period					Follow-up	
	Assessment 1	Assessment 2	Assessment 3	Assessment 4	Assessment 5	Assessment 6/ET	Assessment 7	Assessment 8
	Hour 0 (1)	Hour 2±15 min	Hour 4±15 min	Hour 6±15 min	Hour 8±15 min	Hour 10 or EoED (2)	Hour 0 +30–48 hours	EoED +14 days +3 days
Informed consent	X							
Eligibility criteria (3)	X							
IWRS entry	X							
Demographics	X							
Medical/surgical history	X							
Weight, height	X							
Vital signs (4)	X							
Electrocardiogram	X		X					
Potassium level (5)	X	X	X	X	X	X	X	
Magnesium level	X			X			X	
Pregnancy test (for female participants)	X							

Adverse events	X	X	X	X	X	X	X	X
Prior medications [6]	X							
Concomitant medications	X	X	X	X	X	X	X	X
Randomisation	X							
Administer study drug	X					X [7]		
Administer standard combination therapy (SCT) [8]	X	Potassium-related medical intervention as needed, but prefer SCT						

1 Hour 0 is defined as the time of study drug administration (study drug needs to be administered within 60 mins of verifying eligible serum potassium and administering SCT).

2 EoED defined as discharge from Emergency Department or initiation of dialysis, whichever occurs sooner.

3 Includes verbal check of pregnancy status for female participants. Pregnancy status to be confirmed for female participants via laboratory (blood or urine samples acceptable) at Assessment 1.

4 Blood pressure, heart rate, pulse oximetry, respiratory rate, and temperature.

5 Obtained from the laboratory only, not point of care

6 Up to 72 hours prior to baseline visit.

7 A study drug packet will be given to participants to prepare and take 24 hours after the first dose is administered.

8 SCT is defined as insulin (5 U administered as a bolus), glucose (25 g administered intravenously <15 minutes before the insulin), and aerosolised albuterol (10 mg over 30 minutes) at baseline. Further potassium-related medical interventions, defined as additional administrations of insulin, glucose, or albuterol (or their combination) at any dose, or any other potassium-lowering medication can be initiated and repeated at the discretion of the Investigator at any time; however, SCT is preferred.

EoED, end of Emergency Department; ET, early termination; IWRS, Interactive Web Response System; SCT, standard combination therapy.

Participants who are admitted to the ED with hyperkalaemia, provide informed consent, and satisfy eligibility criteria, will be enrolled and undergo assessment.

The treatment period will be from the completion of the baseline assessment until discharge from the ED or initiation of dialysis, whichever occurs first. The expected duration of subject participation is 15 days; the treatment period is up to 1 day, and the follow-up period is 14 days. Participants who prematurely discontinue study drug will remain in the study to be monitored and assessed. Additional K^+-related medical interventions, defined as post-baseline administration of insulin/glucose, with or without albuterol, or any other K^+-lowering medication, can be initiated and repeated at any time during the treatment period at the discretion of the investigator or treating team. However, a standard combination therapy (SCT) is encouraged if additional K^+ related interventions are needed.

Ethics and dissemination

This study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [38], and the amended International Council for Harmonisation Good Clinical Practice guidelines [39]. The informed consent form used for the study will comply with the Declaration of Helsinki, federal regulations, and International Council for Harmonisation guidelines; and will be approved by the appropriate Institutional Review Board, Ethics Committee or Independent Ethics Committee prior to use. Participants will provide consent in writing prior to study entry. The protocol and any protocol amendments will be approved by the local Institutional Review Board, Ethics Committee or Independent Ethics Committee.

Primary results will be published in peer reviewed manuscripts promptly following study completion.

Participants

Eligible participants must be ≥18 years of age with hyperkalaemia, defined as K^+ ≥5.8 mEq/L (chosen as the value where an intervention is required in the ED), obtained via local laboratory or point-of-care testing. Exclusion criteria include clinically significant arrhythmia, hemodynamic instability (defined as mean arterial pressure ≤65 mmHg, or heart rate ≤40 or ≥125 beats per minute), hyperkalaemia solely due to overdose of K^+ supplements, known bowel obstruction, treatment with K^+ binders in the 7 days prior to enrolment, expected dialysis during the first 6 hours of study treatment, known hypersensitivity to patiromer or its ingredients, participation in any other investigational study <30 days prior to screening, life expectancy <6 months, and pregnancy or breastfeeding.

Study drug formulation

Patiromer sorbitex calcium (patiromer) or placebo (microcrystalline cellulose) will be stored between 2 and 8°C and provided to the participant blinded, as a powder for oral suspension in packets.

Randomisation and treatment

Participants will be randomised 1:1 to 25.2 g of patiromer at baseline and 8.4 g 24 hours after the initial dose, or placebo, in addition to SCT, using permuted block randomisation, stratified by baseline chronic dialysis status (on dialysis vs not on dialysis). A maximum of 50% of participants will be on chronic dialysis. Randomisation will be by a centralised list accessed electronically via an interactive web response system at baseline. Immediately following baseline procedures and randomisation, participants will be administered SCT consisting of glucose (25 g IV <15 minutes before insulin) given if the blood sugar is below 400 mg/dL, insulin (5

units administered as an IV bolus), and aerosolised albuterol (10 mg over 30 minutes). Participants then receive a single oral dose of study drug (25.2 g) at baseline (patiromer or placebo). The study drug will be prepared immediately prior to administration and given at least 3 hours before or after other orally administered medications, if possible, in the ED. Study drug will be mixed with water, apple juice, or cranberry juice only. A second dose of the same study drug will be administered 24 hours after the initial dose.

Endpoints

The primary endpoint is the net clinical benefit, as previously described in a *post hoc* analysis of the REDUCE study [40], defined as the mean change in the number of interventions less the change in serum K^+, at hour 6 between the groups (**Figure 3**). Interventions consist of additional potassium-related medical interventions, defined as post-baseline administration of insulin, glucose, or albuterol (or their combination) at any dose, or any other potassium-lowering medication provided to participants at any time during the treatment period at the discretion of the Investigator. Assessment of the efficacy of K^+ binders in the ED can be confounded owing to repeat administrations of insulin and/or albuterol. Therefore, net clinical benefit is used to simultaneously assess both the number of additional potassium-lowering medications required and the change in serum K^+. Secondary endpoints are the net clinical benefit at hour 4; the proportion of participants without post-baseline K^+-related medical interventions at hours 4, 6, and 8; the number of post-baseline K^+-related medical interventions up until hours 6 and 8, and ED discharge; the proportion of participants with sustained K^+ reduction (defined as K^+ ≤5.5 mEq/L and 4 hours without K^+-related medical intervention) at hours 6 and 8; and serum K^+ 24

hours after ED discharge. An exploratory endpoint is the time to ED discharge. Safety endpoints are the incidence and severity of AEs, and changes from baseline in serum K^+, magnesium, and electrocardiogram (ECG). AEs and concomitant medications will be assessed every 2 hours after enrolment, until hour 10 or discharge from the ED; glucose checks are performed when clinically indicated by the medical team (a glucose check is not required by the protocol) e.g., when a basic metabolic panel is drawn for K^+ value, a glucose value will also be recorded.

Statistical analysis

Based on the pilot study [27], a power calculation determined that a sample size of 60 participants per treatment arm provides 90% power to detect a difference between the placebo and patiromer groups at 2-sided α=0.05. Accounting for a potential treatment discontinuation rate of 60% by 6 hours, based on the nature of the disease and the need for emergent interventions beyond this protocol, 150 participants per treatment arm will be enrolled to reach the required sample size of 60 participants per arm for the final analysis.

The full analysis set (FAS) will consist of all participants who receive at least one dose of randomised treatment and have at least two post-baseline assessments or a 4-hour post-baseline blood draw. The FAS will be used for the evaluation of efficacy. The per-protocol set will consist of all participants who, in addition to the FAS criteria, have no major protocol deviations. The safety set will consist of all randomised participants who received at least one dose of study drug. Participants in the safety set will be analysed based on the study drug they received.

Net clinical benefit at hour 6 will be compared between groups using a Student's t-test. A modified intention-to-treat analysis will be used for the primary endpoint, with

an imputation method applied for missing data: participants who have been on placebo or patiromer for at least 4 hours will have the last observation carried forward to the hour 6 analysis. Secondary endpoints involving proportions of participants and counts of interventions will be analysed using the Cochran-Mantel-Haenszel method. Continuous variables (K^+ level at specified time points) will be analysed using analysis of covariance (ANCOVA) methods. Kaplan-Meier curves will be used to analyse the time to ED discharge. Safety variables will consist of all AEs, clinical laboratory test results (serum K^+ and magnesium), clinically significant ECG findings, and reasons for discontinuing study drug. Abnormal ECGs or other safety assessments will qualify as an AE if they meet any of the following criteria; 1) it is accompanied by clinical symptoms or leads to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE); 2) it results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation); 3) it results in a medical intervention, a change in concomitant therapy, or referral for further testing outside the protocol; 4) it is a clinically significant abnormality, as judged by the investigator.

Patient and Public Involvement

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

Discussion

Although hyperkalaemia is common and potentially life-threatening, there is no standardised ED treatment protocol [1-3 15]. The efficacy and safety of many hyperkalaemia treatments are not well established in the ED, resulting in a considerable variation in treatment, which is not only detrimental to patients but hampers the ability to perform comparative assessments of the benefit of novel therapies.

The PLATINUM study will assess the benefit of adding patiromer to an SCT regimen: glucose (25 g IV <15 minutes before insulin), insulin (5 U administered as an IV bolus), and aerosolised albuterol (10 mg over 30 minutes). As some SCT agents temporarily shift K^+ into the cells repeat administration is commonly required to prevent rebound in serum K^+ levels, increasing the risk of AEs [15-19 25 41 42]. In contrast, patiromer removes K^+ via binding in the gastrointestinal tract [37]. Of note, the PLATINUM study will use 5 U of insulin, as this has similar efficacy to 10 U [41].

Recently, a retrospective cohort study of 881 unique encounters from emergency departments, inpatient units, and intensive care units, reported that a single dose of patiromer monotherapy was associated with a significant reduction from baseline in serum K^+ in non-emergent hyperkalaemia [43]. An open-label, pilot study in participants randomised to standard of care (SOC) (according to individual practice pattern or hospital protocol) versus 25.2 g of patiromer plus SOC demonstrated a reduction in serum K^+ within 2 hours of with the addition of patiromer; however, reduction in K^+ was not statistically significant at 6 hours, likely due to the small sample size and large variability in mean change in serum K^+ [27].

In a *post hoc* analysis of the REDUCE study [40], net clinical benefit was utilised to evaluate the efficacy of patiromer plus SOC, compared to SOC alone. Net clinical benefit was defined as the mean change in the number of additional interventions, less the mean change in serum K^+. This novel method of assessing the effect of K^+ binders considers the overall benefit of both lowering serum K^+ and simultaneously reducing the number of interventions required. Hence, net clinical benefit combines two potential merits of a novel agent and will also be useful in future trials as a method to investigate the effect of K^+ binders to treat hyperkalaemia.

The secondary endpoint, serum K^+ 24 hours after ED discharge, will provide insight on the value of giving a second dose of patiromer at discharge from the ED. Importantly, this study may support a standardised care algorithm with consistent dosing, reporting efficacy and safety data from a large, randomised, multi-centre trial.

Conclusion

PLATINUM is planned to be the largest ED randomised controlled hyperkalaemia trial ever performed, with the opportunity to assess a standardised approach to hyperkalaemia management, as well as establish a new evaluation parameter (i.e., net clinical benefit) for acute hyperkalaemia treatment investigations.

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Licence Statement

Contributorship statement

ZR: Creating the protocol, Interpretation of data, Editing the manuscript

JB: Interpretation of data, Editing the manuscript

CMQ: Interpretation of data, Editing the manuscript

YD: Site investigator, Interpretation of data, Editing the manuscript

BS: Site investigator, Acquisition and interpretation of data, Editing the manuscript

SB: Site investigator, Data collection, Interpretation of data, Editing the manuscript.

JJB: Site investigator, Data collection, Interpretation of data, Editing the manuscript

BED: Site investigator, Data collection, Interpretation of data, Editing the manuscript

FP: Obtaining co-funding, Creating the protocol, Editing the manuscript

CAH: Contributed to study design, Editing the manuscript

MW: Interpretation of data, Editing the manuscript

AS: Interpretation of data, Editing the manuscript

Competing Interests

ZR: No relevant conflicts of interest to disclose

JB: Employee and shareholder of CSL Vifor

CMQ: Employee and shareholder of CSL Vifor

YD: No relevant conflicts of interest to disclose

BS: NHLBI, CDC, Comprehensive Research Associates (institutional grants)

SB: No relevant conflicts of interest to disclose

JJB: No relevant conflicts of interest to disclose

BED: No relevant conflicts of interest to disclose

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MW: Consulting fees: CSL Vifor and AstraZeneca. Honoraria: CSL Vifor.

AS: Research grants: Comprehensive Research Associates. Consulting fees: Astra Zeneca.

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Figure legends

Figure 1. PLATINUM study design.

*Local laboratory or point-of-care testing may be utilised to confirm eligibility for the study. Potassium testing can be repeated at the discretion of the Investigator at any time during the treatment period but is required at hour 4.

ED, Emergency Department; EoED, end of Emergency Department stay (defined as discharge from the ED or initiation of dialysis); SCT, standard combination therapy (defined as 5 U intravenous insulin, 25 g intravenous glucose, and 10 mg aerosolised albuterol) and potassium-related medical intervention (defined as additional administration of insulin, glucose, or albuterol [or their combination] at any dose, or any other potassium-lowering medication can be initiated and repeated at the discretion of the Investigator at any time); however, SCT is recommended.

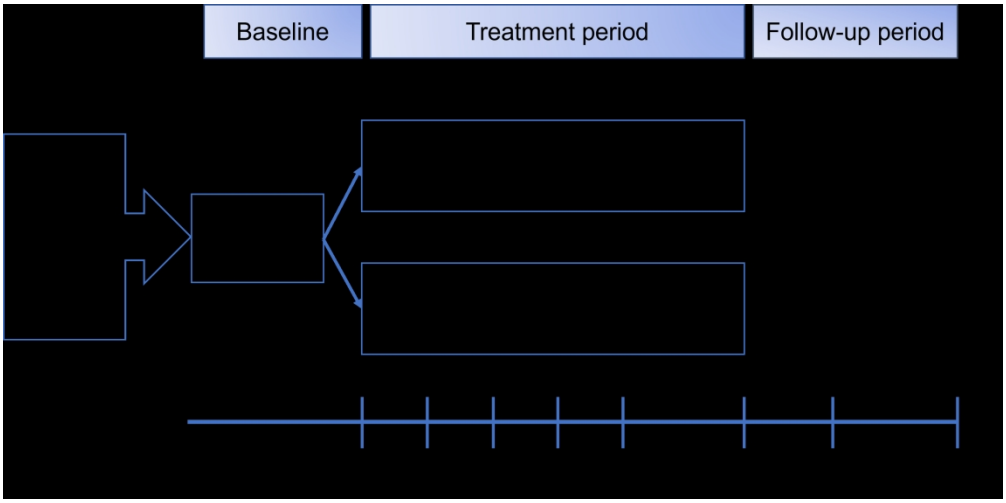
Figure 2. Proposed study centre locations.

Study centres actively enrolling participants are shown on map. 1) Stanford University School of Medicine, California; 2) Henry JN Taub Hospital/Baylor College of Medicine, Texas; 3) Hennepin County Medical Center. University of Minnesota, Minnesota; 4) Stony Brook University Hospital, Stony Brook, New York; 5) Yale University, Connecticut; 6) Henry Ford Hospital, Michigan; 7) University of Cincinnati, Ohio; 8) Wake Forest University, North Carolina; 9) The Ohio State University Wexner Medical Center, Ohio; 10) Baystate Health, Massachusetts; 11) Washington University in St. Louis, Missouri; 12) UT Memorial Hermann Hospital,Texas Medical Center, Texas; 13) Mt Sinai. Icahn School of Medicine, New York; 14) Cristiana Care, Wilmington, Delaware; 15) University of Kansas Medical Center, Kansas; 16)

Meritus Medical Center, Maryland; 17) George Washington University, Washington D.C.

Figure 3. Primary Endpoint: net clinical benefit.

‡ Number of additional potassium (K^+) lowering interventions after initial treatment. ΔK will be determined from laboratory potassium (K^+) values.



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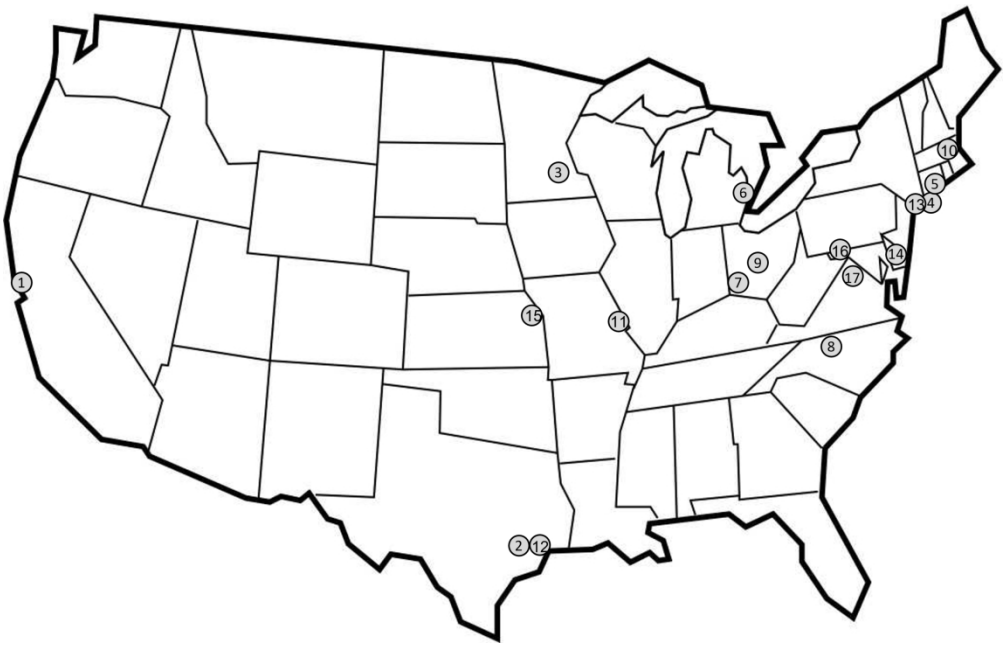
262x129mm (300 x 300 DPI)



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247x157mm (300 x 300 DPI)

Figure 3. Primary Endpoint: net clinical benefit

‡ Number of additional potassium (K+) lowering interventions after initial treatment. ΔK will be determined from laboratory potassium (K+) values.

126x21mm (300 x 300 DPI)

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	4
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7-8
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	9-10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	10
	4b	Settings and locations where the data were collected	9, 23
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	11-12
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	12
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	10-11
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	10
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	10-11
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	10-11
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	10
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	N/A
	14b	Why the trial ended or was stopped	N/A
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	N/A
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	N/A
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Patiromer utility as an adjunct treatment in patients needing urgent hyperkalaemia management (PLATINUM): design of a multicentre, randomised, double-blind, placebo-controlled, parallel group study

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Patiromer utility as an adjunct treatment in patients needing urgent hyperkalaemia management (PLATINUM): design of a multicentre, randomised, double-blind, placebo-controlled, parallel group study

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Running title (< 50 characters incl. spaces): Patiromer in hyperkalaemia (PLATINUM): protocol

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Abstract

Introduction: Hyperkalaemia is common, life-threatening, and often requires emergency department (ED) management, however no standardised ED treatment protocol exists. Common treatments transiently reducing serum potassium (K^+) (including albuterol, glucose and insulin) may cause hypoglycaemia. We outline the design and rationale of the Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalaemia Management (PLATINUM) study, which will be the largest ED randomised controlled hyperkalaemia trial ever performed, enabling assessment of a standardised approach to hyperkalaemia management, as well as establishing a new evaluation parameter (net clinical benefit) for acute hyperkalaemia treatment investigations.

Methods and analysis: Platinum is a Phase 4, multicentre, randomised, double-blind, placebo-controlled study in participants who present to the ED at approximately 30 US sites. Approximately 300 adult participants with hyperkalaemia (K^+ ≥5.8 mEq/L) will be enrolled. Participants will be randomised 1:1 to receive glucose (25 g intravenously [IV] <15 minutes before insulin), insulin (5 units IV bolus) and aerosolised albuterol (10 mg over 30 minutes), followed by a single oral dose of either 25.2 g patiromer or placebo, with a second dose of patiromer (8.4 g) or placebo after 24 hours. The primary endpoint is net clinical benefit, defined as the mean change in the number of additional interventions less the mean change in serum K^+, at hour 6. Secondary endpoints are net clinical benefit at hour 4, proportion of participants without additional K^+-related medical interventions, number of additional K^+-related interventions, and proportion of participants with sustained K^+ reduction (K^+ ≤5.5 mEq/L). Safety endpoints are the incidence of adverse events, and severity of changes in serum K^+ and magnesium.

Ethics and dissemination: A central Institutional Review Board and Ethics Committee provided protocol approval (#20201569), with subsequent approval by local IRBs at each site, and participants will provide written consent. Primary results will be published in peer reviewed manuscripts promptly following study completion.

Trial registration: ClinicalTrials.gov, NCT04443608.

Strengths and limitations of this study

- PLATINUM is planned to be the largest emergency department (ED) randomised controlled hyperkalaemia trial ever performed.
- This study will provide the opportunity to assess a standardised approach to hyperkalaemia management.
- The study will also establish a new evaluation parameter (i.e., net clinical benefit) for acute hyperkalaemia treatment investigations.
- Limitations include the difficulties of patient recruitment in an ED environment, and that further studies may be required to assess the benefit of patiromer as an adjunct treatment to other ED hyperkalaemia therapies (other than the protocol-specified standard of care).

Introduction

Hyperkalaemia, generally defined as serum potassium (K^+) >5.5 mEq/L, is common, can lead to life-threatening cardiac arrhythmias, and frequently effects patients in the emergency department (ED)[1-3]. In 2014, more than 1 million ED visits had an ICD-9 code related to hyperkalaemia [4], with emergent hyperkalemia likely to rise in parallel with increasing prevalence of hyperkalaemia risk factors[5] (e.g. chronic kidney disease [6 7], heart failure [8] and hypertension [9]). In addition, many patients have recurrent hyperkalaemia following discharge from the ED [10]. Expert panel recommendations and treatment algorithms for the management of hyperkalaemia [11-14] exist, however there is no standardised US protocol for ED hyperkalaemia management [15]. Common medications currently used to treat hyperkalaemia in the ED, such as nebulised albuterol and intravenous insulin, with or without glucose [11 12 14-24], often cause adverse events (AEs), such as hypoglycaemia or hyperglycaemia [15-19 25]. Additionally, treatments that only shift K^+ into the cell, rather than remove it, frequently result in recurrence of hyperkalaemia 2–3 hours after treatment [41], particularly in patients undergoing hemodialysis[7]. Repeat treatment to counter hyperkalaemia recurrence then further increases the risk of AEs.

Alternatively, the use of K^+ binders to eliminate K^+ may be a better treatment strategy for emergent hyperkalaemia, although the current evidence lacks evaluation in a large randomised controlled trial [24]. Two small, randomised studies (REDUCE and ENERGIZE) have shown promising results by adding either patiromer or sodium zirconium cyclosilicate to insulin and glucose therapy or investigator-designated standard of care, however, these studies were statistically inconclusive [26 27]. Sodium polystyrene sulfonate (SPS) is a historically established treatment for chronic hyperkalaemia, reducing serum K^+ via colonic excretion [28]. However, the onset of

action, degree of K^+ lowering, and patient tolerance of SPS are unpredictable [7 29 30]. Loop diuretics are commonly used in management of acute hyperkalemia; however, there is a lack of clinical studies to support their use in this setting [2]. Ultimately, dialysis represents a definitive treatment for hyperkalaemia, however effective management of hyperkalaemia through dialysis is complex and challenging[7] . Thus, the new oral K^+ binders with fewer adverse effects, such as patiromer, may offer a solution for the removal of excess K^+ in hyperkalaemic patients presenting to the ED. Patiromer is a non-absorbed, oral K^+ binder using sodium-free exchange [31] with efficacy in the treatment of hyperkalaemia in patients with chronic kidney disease and heart failure [21 27 32-36] and approval for use in the US [22] and EU [23] for treatment of hyperkalaemia. Given the variability of hyperkalaemia treatment in the ED [15], the challenge of emergent dialysis [7] , and the serious risks of AEs with insulin treatment [15-19 25], there is a need for evaluation of novel K^+ binders as additional treatments in the ED that act to remove excess K^+ [37 38], which have fewer AEs.

The PLATINUM trial will employ a systematic approach to investigate the use of patiromer as an adjunct treatment in hyperkalaemic patients presenting to the ED. The primary objective is to determine if patiromer, as adjunct to intravenous (IV) insulin, glucose and inhaled beta-agonist therapy, lowers K^+ and reduces the need for additional medical interventions for the management of hyperkalaemia. Secondary objectives are to determine if adjunctive treatment with patiromer results in fewer additional K^+-related medical interventions, enables a sustained reduction in K^+ without additional medical interventions, and leads to a sustained reduction in K^+ 24 hours after ED discharge.

Methods and analysis

Study design

This is a Phase 4, multicentre, randomised, double-blind, placebo-controlled, parallel-group study (NCT04443608, **Figure 1**). It is planned that PLATINUM will enrol approximately 300 participants with hyperkalaemia at about 30 ED sites in the US (**Figure 2**). The schedule of assessments is shown in **Table 1**.

Impact of COVID-19

To minimise the impact of staffing and institution challenges resulting from the COVID-19 pandemic on enrolment, the trial has been extended by more than two years. Additional efforts to maintain enrolment include: new and total enrolment counts being sent to each site on a weekly basis; increased communication with primary investigators at each site, as well as regular primary investigator and research staff teleconferencing; and increased reimbursement to cover unanticipated costs associated with the pandemic.

Table 1. Assessment schedule during treatment period and follow-up

Procedures	Baseline		Treatment Period				Follow-up	
	Assessment 1	Assessment 2	Assessment 3	Assessment 4	Assessment 5	Assessment 6/ET	Assessment 7	Assessment 8
	Hour 0 (1)	Hour 2±15 min	Hour 4±15 min	Hour 6±15 min	Hour 8±15 min	Hour 10 or EoED (2)	Hour 0 +30–48 hours	EoED +14 days +3 days

Informed consent	X							
Eligibility criteria [3]	X							
IWRS entry	X							
Demographics	X							
Medical/surgical history	X							
Weight, height	X							
Vital signs [4]	X							
Electrocardiogram	X		X					
Potassium level [5]	X	X	X	X	X	X	X	
Magnesium level	X			X			X	
Pregnancy test (for female participants)	X							
Adverse events	X	X	X	X	X	X	X	X
Prior medications [6]	X							
Concomitant medications	X	X	X	X	X	X	X	X
Randomisation	X							
Administer study drug	X					X [7]		
Administer standard combination therapy (SCT) [8]	X	Potassium-related medical intervention as needed, but prefer SCT						

1 Hour 0 is defined as the time of study drug administration (study drug needs to be administered within 60 mins of verifying eligible serum potassium and administering SCT).

2 EoED defined as discharge from Emergency Department or initiation of dialysis, whichever occurs sooner.

3 Includes verbal check of pregnancy status for female participants. Pregnancy status to be confirmed for female participants via laboratory (blood or urine samples acceptable) at Assessment 1.

4 Blood pressure, heart rate, pulse oximetry, respiratory rate, and temperature.

5 Obtained from the laboratory only, not point of care.

6 Up to 72 hours prior to baseline visit.

7 A study drug packet will be given to participants to prepare and take 24 hours after the first dose is administered.

8 SCT is defined as insulin (5 U administered as a bolus), glucose (25 g administered intravenously <15 minutes before the insulin), and aerosolised albuterol (10 mg over 30 minutes) at baseline. Further potassium-related medical interventions, defined as additional administrations of insulin, glucose, or albuterol (or their combination) at any dose, or any other potassium-lowering medication can be initiated and repeated at the discretion of the Investigator at any time; however, SCT is preferred.

EoED, end of Emergency Department; ET, early termination; IWRS, Interactive Web Response System; SCT, standard combination therapy.

Participants who are admitted to the ED with hyperkalaemia, provide informed consent, and satisfy eligibility criteria, will be enrolled and undergo assessment.

The treatment period will be from the completion of the baseline assessment until discharge from the ED or initiation of dialysis, whichever occurs first. The expected duration of subject participation is 15 days; the treatment period is up to 1 day, and the follow-up period is 14 days. Participants who prematurely discontinue study drug will remain in the study to be monitored and assessed for safety and efficacy. The 14-day follow-up will be conducted via a phone call. Additional K^+-related medical interventions, defined as post-baseline administration of insulin/glucose, with or without albuterol, or any other K^+-lowering medication, can be initiated and repeated at any time during the treatment period at the discretion of the investigator or treating team. However, a standard combination therapy (SCT) is encouraged if additional K^+ related interventions are needed.

The investigational drug was FDA approved before any enrolments took place. However, insurance was obtained and maintained by the grantor and the sponsor to ensure the consequences of any unanticipated complications could be mitigated.

Participants

Eligible participants must be ≥18 years of age with hyperkalaemia, defined as K^+ ≥5.8 mEq/L (chosen as the value where an intervention is required in the ED), obtained via local laboratory or point-of-care testing. Exclusion criteria include clinically significant arrhythmia, hemodynamic instability (defined as mean arterial pressure ≤65 mmHg, or heart rate ≤40 or ≥125 beats per minute), hyperkalaemia solely due to overdose of K^+ supplements, known bowel obstruction, treatment with K^+ binders in the 7 days prior to enrolment, expected dialysis during the first 6 hours of study treatment or enrolment, known hypersensitivity to patiromer or its

ingredients, participation in any other investigational study <30 days prior to screening, life expectancy <6 months, and pregnancy or breastfeeding.

Study drug formulation

Patiromer sorbitex calcium (patiromer) or placebo (microcrystalline cellulose) will be stored between 2 and 8°C and provided to the participant blinded, as a powder for oral suspension in packets.

Randomisation and treatment

Participants will be randomised 1:1 to 25.2 g of patiromer at baseline and 8.4 g 24 hours after the initial dose, or placebo, in addition to SCT, using permuted block randomisation, stratified by baseline chronic dialysis status (on dialysis vs not on dialysis). A maximum of 50% of participants will be on chronic dialysis. Randomisation will be by a centralised list accessed electronically via an interactive web response system at baseline. Immediately following baseline procedures and randomisation, participants will be administered SCT consisting of glucose (25 g IV <15 minutes before insulin) given if the blood sugar is below 400 mg/dL, insulin (5 units administered as an IV bolus), and aerosolised albuterol (10 mg over 30 minutes). Participants then receive a single oral dose of study drug (25.2 g) at baseline (patiromer or placebo). Participants, site personnel, clinical providers and the Sponsor will be blinded to the study drug. The clinical trial supply management team will provide blinded sachets of patiromer and placebo, and the site investigational pharmacists will maintain the blinding. In the case of a medical emergency, the Investigator may request that the blind be broken if it is considered important to the management of the medical emergency, or for study-specific suspected unexpected serious adverse reaction (SUSAR) and aggregate safety

reporting to Health Authorities. In such cases, the Investigator will be unblinded via the IWRS. The study drug will be prepared immediately prior to administration and given at least 3 hours before or after other orally administered medications, if possible, in the ED. Study drug will be mixed with water, apple juice, or cranberry juice only. A second dose of the same study drug will be administered 24 hours after the initial dose.

Endpoints

The primary endpoint is the net clinical benefit, as previously described in a *post hoc* analysis of the REDUCE study [39], defined as the mean change in the number of interventions less the change in serum K^+, at hour 6 between the groups (**Figure 3**). Interventions consist of additional potassium-related medical interventions, defined as post-baseline administration of insulin, glucose, or albuterol (or their combination) at any dose, or any other potassium-lowering medication provided to participants at any time during the treatment period at the discretion of the Investigator. Assessment of the efficacy of K^+ binders in the ED can be confounded owing to repeat administrations of insulin and/or albuterol. Therefore, net clinical benefit is used to simultaneously assess both the number of additional potassium-lowering medications required and the change in serum K^+. Secondary endpoints are the net clinical benefit at hour 4; the proportion of participants without post-baseline K^+-related medical interventions at hours 4, 6, and 8; the number of post-baseline K^+-related medical interventions up until hours 6 and 8, and ED discharge; the proportion of participants with sustained K^+ reduction (defined as K^+ ≤5.5 mEq/L and 4 hours without K^+-related medical intervention) at hours 6 and 8; and serum K^+ 24 hours after ED discharge. An exploratory endpoint is the time to ED discharge.

Safety endpoints are the incidence and severity of AEs, and changes from baseline in serum K^+, magnesium, and electrocardiogram (ECG). AEs and concomitant medications will be assessed every 2 hours after enrolment, until hour 10 or discharge from the ED; glucose checks are performed when clinically indicated by the medical team (a glucose check is not required by the protocol) e.g., when a basic metabolic panel is drawn for K^+ value, a glucose value will also be recorded.

Statistical analysis

Based on the pilot study [27], a power calculation determined that a sample size of 60 participants per treatment arm provides 90% power to detect a difference in NCB at 6 hours (primary outcome) between the placebo and patiromer groups at 2-sided α=0.05. Accounting for a potential treatment discontinuation rate of 60% by 6 hours, based on the nature of the disease and the need for emergent interventions beyond this protocol, 150 participants per treatment arm will be enrolled to reach the required sample size of 60 participants per arm for the final analysis.

The full analysis set (FAS) will consist of all participants who receive at least one dose of randomised treatment and have at least two post-baseline assessments or a 4-hour post-baseline blood draw. The FAS will be used for the evaluation of efficacy. The per-protocol set will consist of all participants who, in addition to the FAS criteria, have no major protocol deviations. The safety set will consist of all randomised participants who received at least one dose of study drug. Participants in the safety set will be analysed based on the study drug they received.

Net clinical benefit at hour 6 will be compared between groups using a Student's t-test. A modified intention-to-treat analysis will be used for the primary endpoint, with an imputation method applied for missing data: participants who have been on

placebo or patiromer for at least 4 hours will have the last observation carried forward to the hour 6 analysis. Secondary endpoints involving proportions of participants and counts of interventions will be analysed using the Cochran-Mantel-Haenszel method. Continuous variables (K^+ level at specified time points) will be analysed using analysis of covariance (ANCOVA) methods. Kaplan-Meier curves will be used to analyse the time to ED discharge. Safety variables will consist of all AEs, clinical laboratory test results (serum K^+ and magnesium), clinically significant ECG findings, and reasons for discontinuing study drug. Abnormal ECGs or other safety assessments will qualify as an AE if they meet any of the following criteria; 1) it is accompanied by clinical symptoms or leads to a diagnosis (in such case the symptom or diagnosis will be recorded as an AE); 2) it results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation); 3) it results in a medical intervention, a change in concomitant therapy, or referral for further testing outside the protocol; 4) it is a clinically significant abnormality, as judged by the investigator.

Data management

An independent Data and Safety Monitoring Board/Data Monitoring Committee will not be established due to the short duration of the study. The integrity and quality of subject data will be ensured by providing training and process instructions for the completion of the eCRFs, performing quality control checks, conducting ongoing clinical data review (including medical and safety reviews), and performing source data verification and data reconciliation. The sponsor may conduct site monitoring visits at regular intervals in accordance with FDA and ICH guidelines. The Investigator will permit monitors to review and inspect facilities, and all records

relevant to this study. The Investigator will arrange for the retention of all study documentation (such as eCRF files or printed forms, research files, and master files) for the duration specified in their respective site contract or as specified by the applicable Regulatory Authority, whichever is longer.

Patient and Public Involvement

None.

Ethics and dissemination

This study will be conducted according to the principles of the World Medical Association's Declaration of Helsinki [40], and the amended International Council for Harmonisation Good Clinical Practice guidelines [41]. The informed consent form for the study complies with the Declaration of Helsinki, federal regulations, and International Council for Harmonisation guidelines; and was approved by the appropriate Institutional Review Board (IRB), Ethics Committee or Independent Ethics Committee. A copy of the consent form is shown in the supplement section (Supplementary File 1). Participants will provide consent in writing to the Investigator or an authorized associate prior to study entry. The protocol (version 1.0, 20th March 2020) was approved by a central IRB (#20201569) and subsequently by the local IRB at each site. Each applicable Regulatory Authority/IRB/EC/IEC will review and approve amendments prior to their implementation. Primary results will be published in peer reviewed manuscripts promptly following study completion. All authors will meet the ICJME requirements for authorship. A communications agency may provide editing of that manuscript, as well as administrative support for journal submission.

Standard clinical trials information can be found on ClinicalTrials.gov (NCT04443608). There are no plans to grant public access to the participant-level data set or statistical code.

Discussion

Although hyperkalaemia is common and potentially life-threatening, there is no standardised ED treatment protocol [1-3 15]. The efficacy and safety of many hyperkalaemia treatments are not well established in the ED, resulting in a considerable variation in treatment, which is not only detrimental to patients but hampers the ability to perform comparative assessments of the benefit of novel therapies.

The PLATINUM study will assess the benefit of adding patiromer to an SCT regimen: glucose (25 g IV <15 minutes before insulin), insulin (5 U administered as an IV bolus), and aerosolised albuterol (10 mg over 30 minutes). As some SCT agents temporarily shift K^+ into the cells repeat administration is commonly required to prevent rebound in serum K^+ levels, increasing the risk of AEs [15-19 25 42 43]. In contrast, patiromer removes K^+ via binding in the gastrointestinal tract [37]. Of note, the PLATINUM study will use 5 U of insulin, as this has similar efficacy to 10 U [42].

Recently, a retrospective cohort study of 881 unique encounters from emergency departments, inpatient units, and intensive care units, reported that a single dose of patiromer monotherapy was associated with a significant reduction from baseline in serum K^+ in non-emergent hyperkalaemia [44]. An open-label, pilot study in participants randomised to standard of care (SOC) (according to individual practice pattern or hospital protocol) versus 25.2 g of patiromer plus SOC demonstrated a reduction in serum K^+ within 2 hours of with the addition of patiromer; however, reduction in K^+ was not statistically significant at 6 hours, likely due to the small sample size and large variability in mean change in serum K^+ [27].

In a *post hoc* analysis of the REDUCE study [39], net clinical benefit was utilised to evaluate the efficacy of patiromer plus SOC, compared to SOC alone. Net clinical benefit was defined as the mean change in the number of additional interventions, less the mean change in serum K^+. This novel method of assessing the effect of K^+ binders considers the overall benefit of both lowering serum K^+ and simultaneously reducing the number of interventions required. Hence, net clinical benefit combines two potential merits of a novel agent and will also be useful in future trials as a method to investigate the effect of K^+ binders to treat hyperkalaemia.

The secondary endpoint, serum K^+ 24 hours after ED discharge, will provide insight on the value of giving a second dose of patiromer at discharge from the ED. Importantly, this study may support a standardised care algorithm with consistent dosing, reporting efficacy and safety data from a large, randomised, multi-centre trial.

The protocol has several limitations. First, subjects with hyperkalaemia are invariably critically ill and the ED is a challenging environment for enrolment in interventional trials and so the attrition rate is expected be high. Second, standard-of care-in hyperkalaemia is not well defined and in the absence of guidelines it will be difficult to control the standard-of-care treatment regimen. Lastly, a successful enrolment requires an eligible K^+, signed consent and administration of both SOC treatment and investigational drug to occur with sixty minutes and that time window can be challenging.

The PLATINUM study started enrolment in October 2020 and is expected to end May 2023. It is the largest ED randomised controlled hyperkalaemia trial ever performed, with the opportunity to assess a standardised approach to hyperkalaemia

management, as well as establish a new evaluation parameter, the net clinical benefit, for acute hyperkalaemia treatment investigations.

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Contributors

ZR: Creating the protocol, interpretation of data, editing the manuscript.

JB: Interpretation of data, editing the manuscript.

CMQ: Interpretation of data, editing the manuscript.

YD: Site investigator, interpretation of data, editing the manuscript.

BS: Site investigator, acquisition and interpretation of data, editing the manuscript.

JJB: Site investigator, data collection, interpretation of data, editing the manuscript.

BED: Site investigator, data collection, interpretation of data, editing the manuscript.

CAH: Contributed to protocol (study design), editing the manuscript.

MRW: Contributed to protocol, interpretation of data, editing the manuscript.

AJS: Contributed to protocol, interpretation of data, editing the manuscript.

SB: Site investigator, data collection, interpretation of data, editing the manuscript.

KMS-R: Creating the protocol, data collection and management, interpretation of data, editing the manuscript.

WFP: Creating the protocol, obtaining co-funding, editing the manuscript.

All authors will have access to the final trial dataset. There are no contractual agreements limiting such access.

Competing interests

ZR: Advisory board memberships (Cardiorenal disease) for AstraZeneca and CSL Vifor.

JB: Employee and shareholder of CSL Vifor.

CMQ: Employee and shareholder of CSL Vifor.

YD: No relevant conflicts of interest to disclose.

BS: NHLBI, CDC, Comprehensive Research Associates (institutional grants).

JJB: No relevant conflicts of interest to disclose.

BED: No relevant conflicts of interest to disclose.

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Figure legends

Figure 1. PLATINUM study design

*Local laboratory or point-of-care testing may be utilised to confirm eligibility for the study. Potassium testing can be repeated at the discretion of the Investigator at any time during the treatment period but is required at hour 4.

ED, Emergency Department; EoED, end of Emergency Department stay (defined as discharge from the ED or initiation of dialysis); SCT, standard combination therapy (defined as 5 U intravenous insulin, 25 g intravenous glucose, and 10 mg aerosolised albuterol) and potassium-related medical intervention (defined as additional administration of insulin, glucose, or albuterol [or their combination] at any dose, or any other potassium-lowering medication can be initiated and repeated at the discretion of the Investigator at any time); however, SCT is recommended.

Figure 2. Proposed study centre locations

Study centres actively enrolling participants are shown on map. 1) Stanford University School of Medicine, California; 2) Henry JN Taub Hospital/Baylor College of Medicine, Texas; 3) Hennepin County Medical Center. University of Minnesota, Minnesota; 4) Stony Brook University Hospital, Stony Brook, New York; 5) Yale University, Connecticut; 6) Henry Ford Hospital, Michigan; 7) University of Cincinnati, Ohio; 8) Wake Forest University, North Carolina; 9) The Ohio State University Wexner Medical Center, Ohio; 10) Baystate Health, Massachusetts; 11) Washington University in St. Louis, Missouri; 12) UT Memorial Hermann Hospital,Texas Medical Center, Texas; 13) Mt Sinai. Icahn School of Medicine, New York; 14) Cristiana Care, Wilmington, Delaware; 15) University of Kansas Medical Center, Kansas; 16)

Meritus Medical Center, Maryland; 17) George Washington University, Washington D.C.

Figure 3. Primary endpoint: net clinical benefit

‡ Number of additional potassium (K^+) lowering interventions after initial treatment.

ΔK will be determined from laboratory potassium (K^+) values.

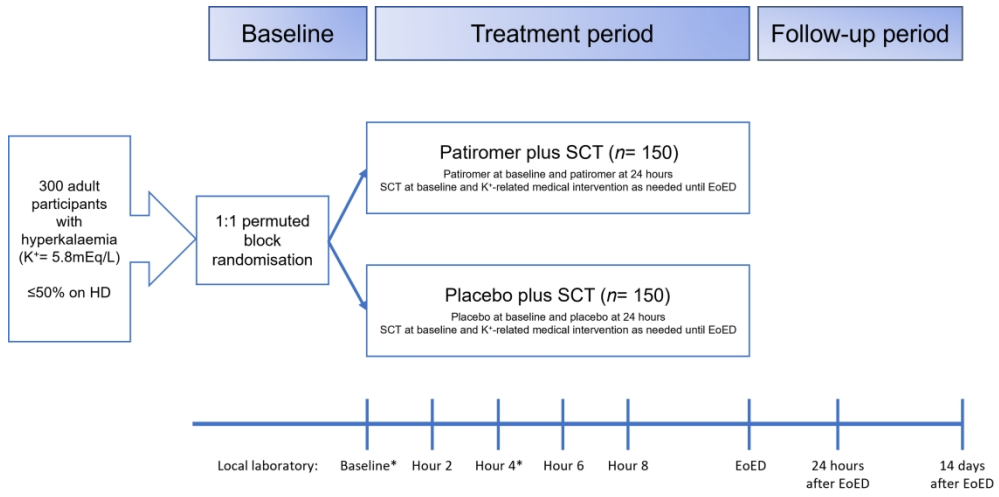

Figure 1. PLATINUM study design*Local laboratory or point-of-care testing may be utilised to confirm eligibility for the study. Potassium testing can be repeated at the discretion of the Investigator at any time during the treatment period but is required at hour 4. ED, Emergency Department; EoED, end of Emergency Department stay (defined as discharge from the ED or initiation of dialysis); SCT, standard combination therapy (defined as 5 U intravenous insulin, 25 g intravenous glucose, and 10 mg aerosolised albuterol) and potassium-related medical intervention (defined as additional administration of insulin, glucose, or albuterol [or their combination] at any dose, or any other potassium-lowering medication can be initiated and repeated at the discretion of the Investigator at any time); however, SCT is recommended.

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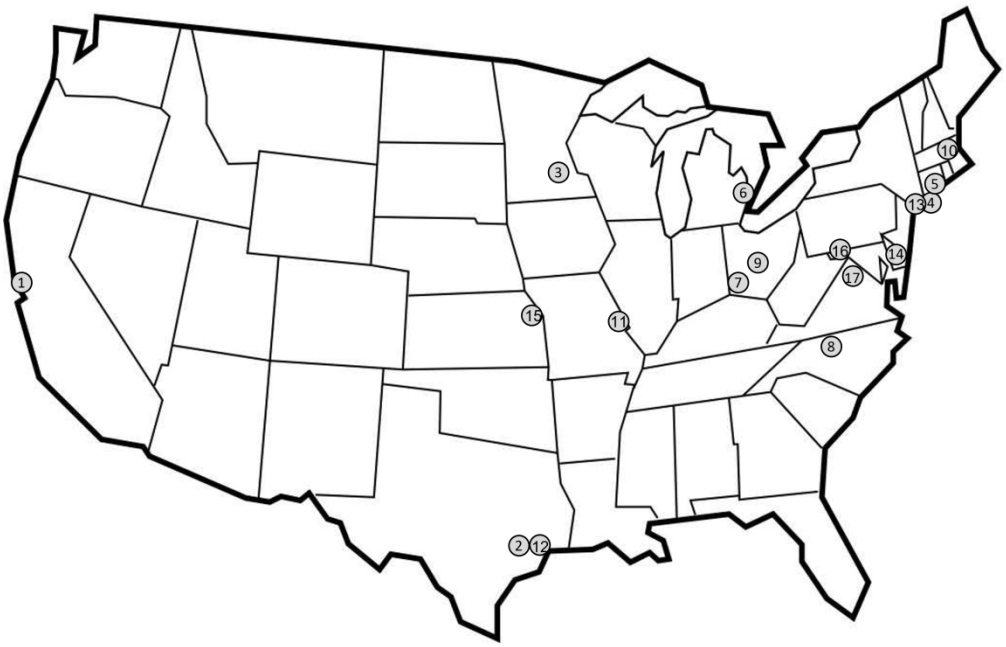

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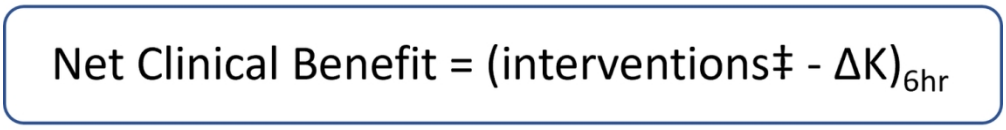

Figure 3. Primary Endpoint: net clinical benefit‡ Number of additional potassium (K+) lowering interventions after initial treatment. ΔK will be determined from laboratory potassium (K+) values.

126x21mm (300 x 300 DPI)

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Jun 18, 2020

RESEARCH SUBJECT CONSENT FORM
AND
AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

TITLE:	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Phase 4 Study of the Efficacy and Safety of Patiromer for Oral Suspension in Combination with Standard of Care Treatment in Emergency Department Patients with Hyperkalemia
SHORT TITLE:	Patiromer Utility as an Adjunct Treatment in Patients Needing Urgent Hyperkalemia Management (PLATINUM)
PROTOCOL NO.:	CRA-US-001 WIRB® Protocol #20201569
SPONSOR:	Comprehensive Research Associates
INVESTIGATOR:	Name Address City, State, Zip Country
STUDY-RELATED PHONE NUMBER(S):	Phone Number Phone Number (24 hours) [24 hour number is required]

You are being asked for your consent to take part in a research study. This document provides a summary of this research. It describes the key information that we believe most people need in order to decide whether to take part in this research.

Please read this form carefully. Take time to ask as many questions about the study (also called, 'trial') as you would like. The study staff can explain words or information that you do not understand. Reading this form and talking to the study staff may help you decide whether to take part or not. If you decide to take part in this study, you must sign your name at the end of this form. You cannot take part in this research study if you do not sign this form.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled if you decide to not participate.

- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled if you decide to withdraw your participation, even if you have already started participation.
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

Why is this research being done?

You are being asked to take part in a clinical research trial because you have been found to have an elevated potassium level in your blood, also known as hyperkalemia. The reason for the study is to find more effective treatments for elevated blood potassium. Clinical trials are a type of research to help doctors find ways to improve health and medical care.

This research study is being conducted by Comprehensive Research Associates. (CRA), also known as the study Sponsor. [Institution] is being paid by CRA to conduct this study.

The purpose of this research is to see if a drug, called patiromer, already approved by the U.S Food and Drug Administration (FDA), can help lower potassium while patients are in the emergency department.

Before you decide whether to take part, you should understand the possible benefits and risks associated with this study. You will be able to ask the staff any questions you may have. This consent form is designed to explain that information to you. Taking part in this study is entirely voluntary.

About 300 patients with hyperkalemia, across the US will take part in this research.

How long will I be in this research?

If you decide to take part in the study, you will not be asked to spend time in the hospital that you would not be spending anyway due to your diagnosis of hyperkalemia (high potassium).

The treatment period, i.e., expected duration of the ED stay, is up to 1 day and the follow-up period is 14 days (+3 days). The total duration of your participation in the study is anticipated to be 15 days (about 2 weeks).

What happens to me if I agree to take part in this research?

If you agree to take part, study staff will look at your records, ask you questions and may do a blood test to see if this study is right for you.

If this study is right for you, you will start the study. It will be decided by chance, using a computer, if you will receive active study drug (patiromer) plus standard of care treatment for your condition or placebo (not active) study drug plus standard of care of care treatment. You have an equal chance of receiving placebo or patiromer with standard of care treatment. During

the research, you and your study doctor will not know which group you are in, but your doctor can find out in case of an emergency.

Baseline:

- The study drug will be given to you to take by mouth.
- The study staff will assess your overall health, review your medical history, signs and symptoms you had at check-in to the emergency room, including any medications you may be taking or have taken in the past 3 days.
- The study staff will record your blood pressure, breathing rate, pulse, temperature, the level of oxygen in your blood, height, and weight.
- Blood may be taken for testing if it was not already done as part of your routine care to check your general health
- If you are female and able to have children, a pregnancy test will be done.
- A 12-lead electrocardiogram will be done, if not already done as part of your care, this procedure records the electric signals in your heart. It is done by placing sticky pads on your chest and limbs and produces a paper tracing.

Treatment

The treatment phase will last until you leave the emergency department, receive dialysis (if needed) or have been in the emergency department for 10 hours.

- Your doctor will periodically check your electrolytes (like potassium) blood levels, every 2 hours (up to 5 times)
- A 12-lead electrocardiogram will be repeated 4 hours after taking study drug if you are still in the emergency department

Day 1 (24 hours after taking study drug)

When you depart the emergency department you will be given a packet of study drug powder to take with you. You will dissolve this powder in liquid and drink it 24 hours after you took the first dose of study drug, staff will explain what to do and they will give you the instructions in writing as well.

Day 2 follow up (48 hours after taking study drug)

You will be asked to return for a follow up visit. You will be asked at what time you took the second dose of study drug, and blood will be collected to check your electrolytes levels.

Day 14 follow up

Your study doctor will contact you or your family member by phone or may contact your regular doctor to check your health and discuss any health problems you may have had.

HOW MUCH BLOOD IS TAKEN DURING THE STUDY?
Blood samples will be collected during your stay in hospital as part of routine care, to allow your doctors to assess your medical status and make treatment decisions. In addition, blood samples will be taken for study-specific testing. The amount taken will not be more than 5 teaspoons.

What are my responsibilities if I take part in this research?

If you agree to take part in this study, you must take the study treatment as instructed and do all study test and assessments. It is important that you follow the instructions from your study doctor. It is also important that you tell study staff about any other medicines, vitamins or herbal supplements you are taking before and during the study.

We do not know the effect of study drug on babies before they are born, or on nursing children. If you are female, you must not be pregnant or breast-feeding. Tell your study doctor if you are pregnant, are attempting to become pregnant or are breastfeeding. The randomization may take place before the result of the pregnancy test performed in this study is available. If the pregnancy test is positive you will discontinue treatment with study medication in the study. If you become pregnant during the study you should notify the study doctor right away.

You are not allowed to take part in any other research study while you are in this research study. If you have any health care contact such as with a doctor or a dentist, tell them that you re in this research study.

You should inform your study doctor or the study staff of any concerns you may have or any new health issues you may experience

Could being in this research hurt me?

The study medication may cause side effects that we do not already know about. In previous studies people have had the side effects listed below. You may get none, some or all of these.

The most common side effects seen in clinical studies are:

- Constipation
- Hypomagnesemia (low magnesium level in blood)
- Diarrhea
- Nausea
- Abdominal discomfort
- Flatulence (passing gas)

It is also not possible to rule-out the chance of an allergic reaction to the study drug. Some symptoms of allergic reactions are mild (hives, itching) while others can be life-threatening (difficulty breathing, swelling of the throat), your study doctor will be closely watching your medical status for any side effects and will provide treatment as necessary.

In addition, there are risks associated with some of the tests performed for the study, however, many of these tests are routine and would be performed anyway as standard care for patients who have abnormal electrolyte levels.

Risks associated with drawing blood samples:

- Fainting, or feeling light-headed
- Pain at the site where the needle is placed
- Swelling and bruising at the site where the needle is placed
- Rarely, there may be a small blood clot or infection at the site of the needle puncture.

While taking vital signs, the blood pressure cuff may also cause discomfort or bruising to the upper arm.

It is very important that you tell the study doctor and the study staff about any side effects that you might experience. You may experience side effects or discomforts that are not listed on this form.

Another non-medical risk is loss of confidentiality of your health information. Confidentiality of your health information is described the section titled "What happens to the information collected for this research?"

Your study doctor will tell you of any information learned during the study, including changes that might cause you to change your mind about taking part in the study.

Will it cost me money to take part in this research?

You will not be charged to take part in the study. The study drug and all study-specific test and medical checks required by the study are provided at no cost to you.

Will being in this research benefit me?

You may not receive direct medical benefit from receiving the study drug. It is possible if you are assigned to receive the study drug, it may help your hyperkalemia, but this is not guaranteed.

Just by taking part in this research study, you may be helping future patients by providing important information about the study drug and by contributing to medical knowledge.

What other choices do I have besides taking part in this research?

Your participation in this study is voluntary. Your alternative to taking part is not to participate. If you choose not to participate, you will still be able to receive standard care for your disease, your usual medical care will not change. You can speak with your doctor or other healthcare professional regarding options and alternatives for treatment.

What happens to the information collected for this research?

Unless required by law, your name will not be disclosed outside the research institution. Your name will be available only to the following people or agencies: the study staff, Institutional Review Boards (IRBs; groups that ensure the study is run properly), health authority inspectors such as the U.S. Food & Drug Administration, and CRA (study monitors; people that review the study data and documents). The above-mentioned individuals will use the personal information collected as part of this study, including your medical records ("Study Information") to check that the study is conducted correctly and to ensure the accuracy of the study information. These people are all obligated to maintain confidentiality by the nature of their work, and are bound by confidentiality laws. If required, the study doctor may contact your personal doctor to collect additional medical information and your past medical history.

The study doctor may only share your study information with people whom you have permitted to see it.

While participating in this study, the study doctor will replace your name with a special code to be associated with your information and that will be used for all the entities working to complete, monitor, and manage this study. All Study Information will be kept confidential within the limits of the law. If the results of this study are published or presented, you will not be named, and nobody will be able to tell that you were in the study from the publication or presentation.

Your participation in this study is voluntary and you may cancel this consent at any time and without any reason. If you do withdraw from the study, your participation will end and study staff will stop collecting information from you. However, CRA will continue to retain and use any research results that have already been collected. If you have withdrawn from the study, for safety reasons you may be asked to complete a final study assessment visit.

If you have any questions about the collection and/or use of your information or would like to exercise rights that you may have regarding this information, you should ask the study staff. If you wish to leave the study, please inform the study staff.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data or specimens collected in this research will be de-identified and might be used for future research or distributed to another investigator for future research without your consent.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (800) 562-4789, help@wirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?

If you are injured or get sick because of being in this research, call the study team immediately. The study team will arrange for you to receive emergency medical treatment. Your insurance may be billed for this treatment. The sponsor will pay any charges that are not covered by insurance policy or the government, provided the injury was not due to your underlying illness or condition and was not caused by you or some other third party. No other payment is routinely available from the study staff or sponsor.

Can I be removed from this research without my approval?

The study staff, CRA, FDA, or the IRB may also decide to remove you from the study at any time without your consent. The study staff may choose to take you out of the study because of unexpected or serious side effects, or for other scientific, technical, logistical, or safety considerations.

Examples of why you may be taken out of the study are:

- Staying in the study would be harmful to you
- You need treatment that is not allowed in this study
- You failed to follow study instructions
- You become pregnant
- The study is cancelled

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

Your participation in this study is strictly voluntary. You may refuse to take part in it, or you may stop participating at any time, even after signing this informed consent. There will be no penalty or loss of benefits to which you are otherwise entitled. However, if you decide to leave the study before it ends, the study staff will ask to see you before you are released from the study.

If you decide to leave the study, you should tell the study staff as soon as possible. They will make sure that proper procedures are followed, and a final visit is made for your safety.

Will I be paid for taking part in this research?

CRA will refund reasonable expenses including travel or parking that you incur because of this study.

DO I HAVE TO SIGN THIS HEALTH INFORMATION AUTHORIZATION?

Yes, in order to participate in this study, you must authorize the release of your health information. If you do not agree, you cannot participate in this study.

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Jun 18, 2020

Statement of Consent:

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____ ___:___
Signature of Research Subject able to consent Date Time

_____
Printed Name of Research Subject

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject the nature and purpose of the above study. There has been an opportunity for the subject to ask questions about this research study. I have been and will be available to answer any questions the subject (or their family member) has about this study.

_____ ____/____/____ ___:___
Signature and Name of Person Explaining Consent Date Time

IMPARTIAL WITNESS

If the person signing this consent form (Research Subject or their family member) is illiterate, an impartial witness must sign below. (Ideally, the witness should be selected by the subject or family member and should have no connection to the research team).

I have witnessed the accurate reading of the consent form to the research subject/ their family member, and the individual has had the opportunity to ask questions. I confirm the consent has been given freely.

_____ ____/____/____ ___:___
Signature of Impartial Witness Date Time

_____
Printed Name of Impartial Witness

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Jun 18, 2020

HIPAA Authorization Agreement
Permission to Review, Use and Release Information about You

If you decide to be in this study, the study doctor and research team will use and share health data about you to conduct the study. Health data may include:

- Your name
- Address
- Phone number
- Date of birth
- Medical history
- Information from your study visits, including all test results

Health data may come from your study records or from existing records kept by your doctor or other health care workers.

For this study, the research team may share health data about you with authorized users. Authorized users may include:

- Representatives of Comprehensive Research Associates, including their affiliates and other vendors
- The Food and Drug Administration (FDA) and other US governmental agencies
- Governmental agencies of other countries
- The Institutional Review Board (IRB)
- Other authorized users

The Sponsor and those working for the Sponsor may use the health data sent to them:

- To see if the study drug works and is safe
- To compare the study drug to other drugs
- For other research activities related to the study drug

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy laws and could be further shared without your permission.

This permission will be good until December 31, 2070.

You may take back your permission to use and share health data about you at any time by writing to the study staff. If you do this, you will not be able to stay in this study. No new health data that identifies you will be gathered after your written request is received. However, health data about you that has already been gathered may still be used and given to others as described in this form.

Your right to access your health data in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

If you decide not to sign this form, you will not be able to take part in the study.

IRB Approved Template
MUST BE APPROVED
FOR SITES BEFORE USE
Jun 18, 2020

STATEMENT OF AUTHORIZATION

I have read this form and its contents were explained. My questions have been answered. I voluntarily agree to allow study staff to collect, use and share my health data as specified in this form. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ___/___/___ ___:___
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

STATEMENT OF PERSON EXPLAINING AUTHORIZATION

I have carefully explained to the subject the nature and purpose of this form. I have been and will be available to answer any questions the subject has about this form.

_____
Printed Name of Person Explaining Authorization

_____ ___/___/___ ___:___
Signature of Person Explaining Authorization Date Time

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	ItemNo	Description	Page(s)
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Pg. 1, Lines 1–3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Pg. 4, Lines 61
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	Pg. 15, Lines 292
Funding	4	Sources and types of financial, material, and other support	Pg. 20, Lines 353–364
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Pg. 1, Lines 4–20 Pg. 21, Lines 376–389
	5b	Name and contact information for the trial sponsor	Pg. 20, Lines 358–360
	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	Pg. 20, Lines 362–365
	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	Pg. 14–15, Lines 269–281

		applicable (see Item 21a for data monitoring committee)	
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	Pg. 5–6
	6b	Explanation for choice of comparators	Pg. 5, Lines 87–115 Pg. 6, Lines 118–120
Objectives	7	Specific objectives or hypotheses	Pg. 6, Lines 116–124
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)	Pg. 7, Lines 127–130 and Figure 1
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	Pg. 7, Lines 129 and Figure 2
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)	Pg. 10, Lines 169–178
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pg. 11–12, Lines 186–208
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial	Pg. 10, Lines 157–164

		participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A interventions administered in emergency department setting
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Pg. 10, Lines 157–164
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	Pg. 12–13, Lines 211–233
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)	Table 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	Pg. 13, Lines 235–242
Recruitment	15	Strategies for achieving adequate participant	Pg. 7, Lines 131–136

		enrolment to reach target sample size	
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	Pg. 10, Lines 190–191
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	Pg. 11, Lines 196–199
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Pg. 11, Lines 190–191
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Pg. 11, Lines 196–199
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Pg. 11–12, Lines 199–204
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial	Pg. 13–14, Lines 243–267

		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	
	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	Pg. 10, Lines 154–158
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	Pg. 14–15, Lines 269–281
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	Pg. 13–14, Lines 235–267
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Pg. 13, Lines 243–249
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	Pg. 14, Lines 270–271
	21b	Description of any interim analyses and stopping guideLines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Pg. 14, Lines 258–267
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Pg. 14, Lines 275–278
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Pg. 15, Lines 284–298
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	Pg. 15, Lines 294–295

		registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Pg. 15, Lines 291–292
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Pg. 14, Lines 271–281
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Pg. 21–22, Lines 391–417
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	Pg. 22, Lines 419–421
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	Pg. 10, Lines 165–167
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	Pg. 15, Lines 295–300

	31b	Authorship eligibility guideLines and any intended use of professional writers	Pg. 15, Lines 296–298
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Pg. 15, Lines 299–300
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form provided in supplementary appendix
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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