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Effects of low-dose hydrocortisone and hydrocortisone plus fludrocortisone in adults with septic shock: a protocol for a systematic review and meta-analysis of individual participant data

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ABSTRACT

Introduction The benefits and risks of low-dose hydrocortisone in patients with septic shock have been investigated in numerous randomised controlled trials and trial-level meta-analyses. Yet, the routine use of this treatment remains controversial. To overcome the limitations of previous meta-analyses inherent to the use of aggregate data, we will perform an individual patient data meta-analysis (IPDMA) on the effect of hydrocortisone with or without fludrocortisone compared with placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Methods and analysis To assess the benefits and risks of hydrocortisone, with or without fludrocortisone for adults with septic shock, we will search major electronic databases from inception to September 2020 (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature), complimented by a search for unpublished trials. The primary analysis will compare hydrocortisone with or without fludrocortisone to placebo or no treatment in adult patients with septic shock. Secondary analyses will compare hydrocortisone to placebo (or usual care), hydrocortisone plus fludrocortisone to placebo (or usual care), and hydrocortisone versus hydrocortisone plus fludrocortisone. The primary outcome will be all cause mortality at 90 days. We will conduct both one-stage IPDMA using mixed-effect models and machine learning with targeted maximum likelihood analyses. We will assess the risk of bias related to unshared data and related to the quality of individual trial.

Ethics and dissemination This IPDMA will use existing data from completed randomised clinical trials and will comply with the ethical and regulatory requirements regarding data sharing for each of the component trials. The findings of this study will be submitted for publication in a peer-review journal with straightforward policy for open access.

PROSPERO registration number CRD42017062198.

Strengths and limitations of this study

- This will be to the best of our knowledge the first individual-patient data meta-analysis on the use of hydrocortisone with or without fludrocortisone for septic shock.
- The use of individual patient data will allow estimation of subgroup effects based on patient-level covariates.
- The analysis will provide the best assessment with currently available data on whether hydrocortisone with or without fludrocortisone confers benefits to patients with septic shock and to assess whether there is an optimal regimen for administration.
- The main limitations are regulatory barriers in accessing individual data from original trials, and technical barriers to combining individual patient data from the component trials.

INTRODUCTION

Rationale

Septic shock is a global health priority.[1] In 2017, there were about 49 million incident cases of sepsis worldwide and 11 million sepsis-related deaths, representing roughly one out of five of all global deaths.[2] There is a need for improved treatments for this unacceptably high mortality rate. The Surviving Sepsis Campaign[3] recommend that, in the first hour of sepsis recognition, physicians obtain blood cultures, administer broad-spectrum antibiotics, start appropriate fluid resuscitation and begin vasopressors whenever needed. Beyond these core measures, there has been little change in the management of sepsis.

What has changed in recent years, has been the understanding that dysregulation of the host response to infection is key to

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understanding the pathophysiology of septic shock.[4] This dysregulated host response may be a therapeutic target to improve mortality in patients with septic shock. As early as the 1950s, physicians have used corticosteroids with clinical success in patients with severe infection not responding to antibiotic treatment.[5] Seventy years later, their use in the management of sepsis remains controversial. The fourth revision of the Surviving Sepsis Campaign guidelines suggested against the use of hydrocortisone except in patients poorly responsive to fluids and vasopressors.[3] Since this revision of the guidelines, two major trials have substantially contributed to the understanding of the benefits and risks of corticosteroids for adults with septic shock.[6 7] Both trials used a daily intravenous dose of 200 mg hydrocortisone for 7 days without taper-off. The main differences in the trials' design included continuous infusion of hydrocortisone[7] versus intravenous bolus every 6 hours,[6] hydrocortisone alone[7] versus with fludrocortisone,[6] unspecified vasopressor dependency[7] versus requirement for a minimal dose of ≥0.25 µg/kg/min or ≥1 mg/hour norepinephrine/epinephrine[6] and unspecified ventilator dependency[7] versus need for mechanical ventilation.[6] These trials found similar benefits in terms of resolution of shock and organs dysfunction, of accelerating weaning off mechanical ventilation and reducing length of stay in the intensive care unit (ICU). They also found no evidence for serious adverse complications with corticosteroids. A mortality benefit with corticosteroids was only reported in Activated Protein C and Corticosteroids for Human Septic Shock (APROCCHSS) trial[7] but not in Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock (ADRENAL).[6]

Since 2018, eight trial-level meta-analyses have addressed the effects of corticosteroids in sepsis.[8–15] They have different designs including differences in trials eligibility criteria, search strategies and in statistical models. The number of included trials ranged from 14 to 61 and the number of participants ranged from 6935 to 12 192. The relative risk (RR) of death in the short-term varied from 0.90 to 0.98, and the upper limit of the 95% CI varied from 0.98 to 1.08. The magnitude and direction of the pooled RR of dying in the short term were consistent across these meta-analyses in favouring corticosteroids but differed mainly by the presence of some imprecision in the point estimate. More recent meta-analyses found substantial heterogeneity in the results possibly explained by differences in type of participants (eg, all ages vs adults only, all sepsis severity vs only septic shock or community-acquired pneumonia or sepsis and ARDS, and in treatments administration (hydrocortisone vs synthetic glucocorticoids, low vs high dose, short vs long course). Intravenous administration of hydrocortisone may be the most frequent prescribed regimen and people may use this drug in sepsis with or without shock.[16] A noteworthy limitation of these meta-analyses is the use of aggregate data, limiting the opportunity to harmonise outcome definitions across trials, adjust the estimated treatment effect on potential confounders and investigate different subgroups.

To address this significant drawback of earlier meta-analyses, we will perform a systematic review and individual patient data meta-analysis (IPDMA) from trials to assess the effect of intravenous hydrocortisone with or without fludrocortisone, compared with placebo or usual care on 90-day mortality and other outcomes in patients with septic shock.

Objectives

The primary objective of this IPDMA is to assess the effect on 90-day mortality of intravenous hydrocortisone therapy, with or without fludrocortisone, compared with placebo or usual care, in adults with septic shock.

Other objectives of this IPDMA include:

- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone, for differing modes of hydrocortisone therapy:
  - Bolus compared with continuous infusion.
  - Tapered dosing compared with abrupt discontinuation.
  - Duration of treatment at full dose: fixed duration versus based on vasopressor dependency.
- To compare the effects of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock on secondary outcomes including 28-day and 180-day mortality, requirement for, and duration of organ support, resources utilisation as measured by ICU and hospital length of stay, and serious adverse events.
- To compare the effect on 90-day mortality of intravenous hydrocortisone therapy with or without fludrocortisone in adults with septic shock in clinically important subgroups defined by:
  - Age.
  - Sex.
  - Vasopressor dependency.
  - Vasopressin administration.
  - Predicted mortality.
  - Sepsis-related Organ Failure Assessment (SOFA) score.
  - Arterial lactate concentrations and
  - Etomidate exposure.

METHODS AND ANALYSIS

This protocol follows the recommendations from the EQUATOR network statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[17] and will allow the report of the completed study to comply with reporting items recommended in the PRISMA of Individual Participant Data.[18]

Eligibility criteria

Types of studies

We will consider only randomised trials. We will exclude quasi-randomised trials, trials with a crossover design

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or those for which the unit of randomisation is not the patient. We will only include trials, which received an appropriate approval from a research ethics committee and where there was an appropriate method of obtaining consent.

Types of participants

We will consider trials that have included adults with sepsis or septic shock as defined in original studies. Trials of mixed population will be eligible whenever separate information will be available for the subset of patients with septic shock as defined in original studies. We will exclude trials in children or those performed in patients without sepsis.

Types of interventions and controls

We will consider trials in which the experimental intervention was intravenous hydrocortisone at a maximal daily dose of 400 mg for at least 72 hours at full dose, whether given as intermittent bolus or as a continuous infusion, and whether tapered off or not. We will also consider trials that have investigated the combination of intravenous hydrocortisone and oral (or enteral) fludrocortisone. We will consider trials in which the comparator was a placebo, no treatment or hydrocortisone alone when the experimental intervention was the combination of hydrocortisone to fludrocortisone. We will also consider trials that compared two doses of hydrocortisone or bolus versus continuous administration.

We will exclude trials that have investigated

1. Corticosteroids other than hydrocortisone or fludrocortisone.
2. Dosage of hydrocortisone higher than 400 mg per day.
3. Duration of hydrocortisone of less than 72 hours at full dose.
4. Oral route of hydrocortisone.

We will also exclude trials for when we are unable to contact the primary author and/or sponsor or they refuse to share data. Nevertheless, in case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis, as described in the statistical plan.

Types of outcome measures

We will only consider trials for inclusion in this review that have information on crude mortality rates at any time point postrandomisation.

Information sources

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, in progress). We will use the strategy of the recently completed Cochrane systematic review on the use of corticosteroids in sepsis.[9]

We will search the Cochrane Central Register of Controlled Trials (2020 Issue 9) using the search terms 'sepsis', 'septic shock', 'steroids' and 'corticosteroids'. We will also search (up to September 2020) MEDLINE, EMBASE and Latin American Caribbean Health Sciences Literature using the topic search terms in combination with the search strategy for identifying trials developed by The Cochrane Collaboration (see online supplemental appendix 1).[19]

We will check the reference lists of all trials identified by these methods, and we will contact study authors to request individual published or unpublished data. We also will search the proceedings of annual meetings of major critical care medicine symposia, that is, Society of Critical Care Medicine (1998–2020), American Thoracic Society (1998–2020), International Symposium on Intensive Care and Emergency Medicine (1998–2020), American College of Chest Physicians and European Society of Intensive Care Medicine (1998–2020).

Search strategy

The full search strategy is available in online supplemental appendix 1.

Study records

Selection processes and data management

We will perform all screening in duplicate with disagreements resolved by consensus and third-party adjudication when consensus could not be reached. After implementation of the search strategy, reviewers will work in pairs to screen all potentially relevant citations and references. Screening will be performed in two stages, initially reviewing titles and abstracts, and then full text for possibly relevant manuscripts. We will capture reasons for exclusion.

Obtaining individual patient data

One reviewer (DA) will contact the primary author and/or sponsor of all selected trials for potential agreement to share deidentified individual patient data from their trial for the purpose of this patient-level meta-analysis. They will define whether data will be freely available or only after application to and approval by a learnt intermediary and whether we will require a data use agreement. In case of non-response or refusal, we will use published aggregated data and combine them to the IPDMA results in a sensitivity analysis. Data will be stored on a secure server hosted by University of Versailles SQY.

Data extraction and management

Two reviewers (RP and DA) will independently check data supplied for included trials for missing data, internal data consistency, randomisation integrity (balance of patient characteristics at randomisation, pattern of randomisation), follow-up and censoring pattern. We will check summary tables with the trial protocol and latest trial report or publication. We will solve any discrepancies or unusual patterns with the study investigator. We will return a final copy of the form from each trial to the appropriate trial investigator for verification.

Data items

Specifically, with regard to the population of patients for the primary analysis, these will be adult patients with

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septic shock. Adults will be those 18 years or older at time of randomisation. Septic shock will be defined according to the definition used in each clinical trial. Each included patient will meet at least one of the following criteria

1. Systolic blood pressure <100 mm Hg or mean arterial pressure <65 mm Hg after fluid resuscitation.
2. Lactate >2 mmol/L.
3. Requirement for vasopressors to maintain an adequate blood pressure.

The intervention of interest is hydrocortisone, administered intravenously at a dose of less than 400 mg per day, either in divided bolus doses, or as a continuous infusion. We will record the dose, the mode of administration, the duration of administration, and the mode of cessation, either tapered or abruptly ceased. We will record whether fludrocortisone was administered, the dose and duration of administration. The details of the comparison group, either placebo or standard care will be recorded.

Outcomes and prioritisation

The primary outcome measure for this meta-analysis will be 90-day all-cause mortality.

Secondary outcomes will include:

- All-cause mortality at ICU and hospital discharge, at 28 days and at 180 days.
- Time to resolution of organ failure (defined as an SOFA <4), time to vasopressor withdrawal and time to cessation of mechanical ventilation. We will also calculate organ-failure/vasopressor/mechanical ventilation free days (up to 28 days). Event-free days will be calculated as the number of days alive from randomisation to day 28 and having an SOFA score <4, being off vasopressors, off mechanical ventilation. When death occurred before reaching an SOFA <4 or before being off vasopressor or mechanical ventilation, the number of event-free days will be 0. For these outcomes, we will consider only the first episode. Recovery from organ failure will be defined by an SOFA score <4 for at least 24 hours. Weaning from vasopressor will be defined by being off any dose of vasopressor/inotrope for at least 24 consecutive hours. Weaning from mechanical ventilation will be defined by being off any mode of respiratory support for at least 24 hours.
- Length of stay in the ICU and in the hospital.
- Superinfection, as defined by any new infection occurring >48 hours after randomisation.
- Number of days with hyperglycaemia defined as, at least one episode of blood glucose levels >180 mg/dL in the corresponding 24 hours.
- Number of days with hypernatraemia, defined as at least one episode of serum sodium concentration >150 mmol/L in the corresponding 24 hours.
- Bleeding complications: gastroduodenal defined as any episode of gastroduodenal bleeding reported by the investigators of original studies, regardless the need for transfusion or haemostatic intervention.
- Critical illness associated muscle weakness at the longest follow-up as defined in individual trials.

Risk of bias in individual studies

Risk of bias will be assessed, independently and in duplicate, for each of the individual studies using a modified Cochrane risk of bias tool[20] that classifies risk of bias as 'low', 'probably low', 'probably high' or 'high' for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting and other bias. We will rate the overall risk of bias as the highest risk attributed to any criterion. Reviewers will not contribute to risk of bias assessment for trials in which they have participated.

Data synthesis

Baseline patient characteristics will be presented by study and treatment group. For continuous variables, mean and SD or median and IQR will be reported, as appropriate. For categorical variables, the number of observations in each category and corresponding proportions will be reported. Patient characteristics across groups will be contrasted using non-parametric Kruskal-Wallis tests for continuous variables and χ^2 test or Fisher's exact tests for categorical variables. Since earlier and later deaths may stem from qualitatively different processes, to provide a more comprehensive depiction of mortality, length of stay in the ICU or in the hospital will be reported in the overall population as well as in the subpopulation of survivors at day 90. All tests will be two sided and conducted at significance level 0.05. No formal adjustment for multiple testing will be undertaken. Given the number of secondary outcomes and subgroup analyses to be performed, interpretation of p values, beyond the primary outcome, will be undertaken very cautiously.

Data analysis

We will consider as the primary analysis, the comparison between hydrocortisone (with or without fludrocortisone) and placebo (or no treatment) on 90-day mortality for patients with septic shock.

Prespecified secondary analyses will include all possible pairwise comparisons, namely, hydrocortisone versus placebo, hydrocortisone plus fludrocortisone versus placebo, hydrocortisone plus fludrocortisone versus hydrocortisone.

In order to increase the robustness of the results, we will perform two different statistical approaches, that is, a one stage conventional meta-analysis and machine-learning targeted maximum likelihood analysis.

As suggested by different studies comparing one-stage to two-stage approaches,[21 22] the conventional will be performed using a one-stage meta-analysis. In one-stage meta-analysis, all data from all studies are aggregated and the primary outcome is analysed simultaneously by adopting a single statistical model that accounts for potential heterogeneity across studies.[23] Analyses will rely on generalised linear mixed effect models (GLMM) where both the intercept and the treatment effect will be treated as random variables with the study as the subject (ie, a random study intercept and a random study-by-treatment

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interaction). For the primary outcome and for binary secondary outcomes, we will use a GLMM with a logit link function. Continuous secondary outcomes will be analysed using a GLMM with an identity link function. Our estimates of the average treatment effect will be adjusted for study (random effect), age, predicted mortality from SAPS2 or APACHE 2, SOFA, admission type (medical, elective surgery or emergent surgery), infection site infection type (hospital vs community-acquired infection) and type of pathogen, baseline and increment in cortisol levels post corticotrophin, lactate levels and need for mechanical ventilation (fixed effects). A study-by-treatment interaction term will be also be included in the model. For withdrawal of vasopressor therapy, withdrawal of mechanical ventilation, and recovery from organ failure (defined by an SOFA score <4 for at least 24 hours, we will use only cases with complete data for SOFA score), cumulative event incidences will be estimated using a non-parametric estimator and will be compared using Gray's test, with death treated as a competing risk[24] and study used as random effect.[25] We will not adjust for multiple testing and consider findings from analyses other than the primary analysis of the primary outcome, as of exploratory nature.[26–28]

We will also estimate the average treatment effect via a more flexible estimator, namely the targeted maximum likelihood estimator (TMLE).[29] In this analysis, different portions of the likelihood will be modelled using super learner (SL) and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear. We will use a SL with a large library including logistic regression models, stepwise regression models based on the Akaike information criterion, mixed logistic models with random effect to account for study-level and patient-level heterogeneity, multivariate adaptive regression splines, random forests, Bayesian generalised linear models, elastic net regularised generalised linear models and gradient boosting, to estimate flexibly the relationship between mean outcome and covariates. For the pairwise comparisons between combinations of hydrocortisone, fludrocortisone and placebo, we will use network meta-analysis techniques[30] to assess the robustness of the results.

For binary outcomes, we will describe the average treatment effect using risk ratio (RR) or OR estimate along with corresponding 95% CI and p value. For continuous outcomes, we will describe the average treatment effect using mean difference (MD) estimate along with a corresponding 95% CI and p value. We will test for qualitative interaction between treatment effect and subgroup of interest using the Gail and Simon interaction test.[31]

Subgroup analysis

We will perform, if data permit, the following subgroup analyses:

- We will examine treatment effect in the subgroup of patients meeting sepsis or septic shock criteria according to Sepsis 3 definition.[4]
- We will also examine any variation in response to treatment according to baseline prognosis factors including:
  - Age (by quartiles).
  - Sex.
  - Vasopressor dependency (yes vs no, and by quartiles of baseline dose).
  - Vasopressin administration (yes or no).
  - Predicted mortality from SAPSII or APACAHEII (by quartiles).
  - SOFA score and each of its component (by quartiles).
  - Aarterial lactate levels (by quartiles).
  - Etomidate-free versus etomidate-exposed patients.
  - Appropriate antibiotic treatment.
- We will examine any variation in treatment response according to patient's adrenal status, that is, responders to standard corticotrophin test (those whom stimulated cortisol levels increased by >9 µg/dL from baseline value) versus non-responders to corticotrophin test.
- We will examine any variation in treatment response according to pre-existing conditions other than sepsis that are likely to be associated with altered hypothalamic–pituitary adrenal axis, the renin–angiotensin–aldosterone axis or both. We will examine any variation in treatment response according to timing of hydrocortisone initiation, that is, within 24 hours vs >24 hours of meeting trial's criteria of shock.
- We will examine any variation in response to treatment according to infection characteristics, that is,
  - Community versus hospital acquired.
  - Medical versus surgical, lung versus other sources of infection.
  - Gram negative versus gram positive versus polymicrobial.

Methods to assess bias

We will assess for the potential for publication bias or small study bias by inspection of funnel plots and the use of Egger's test. The potential bias introduced by the studies that could not be included in the analyses will be evaluated[32] by performing a two-stage meta-analysis aggregating the results obtained on shared data and treatment effect estimates published for unshared data, if data permit. Specifically, the available IPD will first be reduced to aggregated data using the modelling methods described above. Then, these aggregated data will be pooled with published aggregated data into a weighted average.[33 34] Heterogeneity will be assessed by using an estimate of τ^2 generated from the one stage and two-stage models.

Confidence in cumulative evidence

We will present a summary of results and recommendations in accordance with the Grading of Recommendations Assessment, Development and Evaluation approach to assess the overall quality of the evidence.[35 36]

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Patient and public involvement

This protocol is under review by sepsis survivors and stakeholders from the Australian Sepsis Network.[37]

ETHICS AND DISSEMINATION

Ethics

This planned IPDMA will use existing data from completed randomised controlled trials, reporting explicitly ethical approval of the original protocol and the process for obtaining patients consent.

Publications plan

We will report the findings according to the PRISMA-IPD statement.[18] We will share the findings from this IPDMA with primary authors and sponsors of included trials prior to submitting the results of this primary analysis for publication.

1. The study protocol including the statistical analysis plan will be published prior to publishing the results of the primary analysis.
2. On completion of the primary analysis, the main manuscript will be submitted to one of the major clinical journals regardless of the results.
3. Substudies, as approved by the executive committee, can be published after the publication of the primary analysis. The executive committee will grant authorship depending on personal input but shall include appropriate acknowledgement of the included trials, site Investigators and the Clinical Trials Groups where appropriate.

Authorship guidance

In keeping with the ICMJE guidance (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html), authors shall meet the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content.
- Final approval of the version to be published.
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorships specifics

For the principal publication, the study will be conducted in the name of the Utility of Steroids in Septic Shock IPDMA investigators and acknowledge the included studies, and where appropriate, the Clinical Trials Groups. Where individuals' name is required for publication (eg, publication mast) the listing of authors will be as follows: RP will be the first author, DA will be the second (listed as cofirst) and corresponding author, followed by members of the writing committee, with AD as the senior author. The writing committee shall comprise the included trials' chief investigators and members of the executive committee who have contributed substantially to one or more of: trial design or management, or data analysis and meet the ICMJE criteria for authorship.[38]

DISCUSSION

This IPDMA will provide the highest level of evidence about the benefit and risk of hydrocortisone therapy for adults with septic shock .[39 40] This collaborative group includes most of the principal investigators of trials on hydrocortisone for sepsis/septic shock, reducing the risk of sharing refusal. In contrast to trial-level meta-analyses, this IPDMA will permit clarifying the role of fludrocortisone and identifying the optimal modalities for corticosteroids administration in septic shock. In addition, it will help identifying subgroups of patients more likely to benefit from corticosteroids and those at high risk of harm. Finally, we will use the one-stage analysis and a machine learning with targeted maximum likelihood analysis (TMLE).[29] TMLE may reduce bias and increase efficiency and power when applied to treatment effect estimation in trials.[41] TMLE requires to model separately different parts of the likelihood. A wide variety of flexible regression algorithms including mixed-effect models may help mitigating the risk of model misspecification associated with standard regression approaches. The SL[42] is an ensemble machine-learning algorithm that automatically constructs an optimal weighted combination estimator based on a collection of supplied candidate estimators. The SL yields an estimator that is mathematically guaranteed to perform essentially as well as or better than the best candidate among the ones it is built on—this is significant since in practice which of the candidate estimators behaves best in a given problem and dataset is not known to the analyst.[42] In the context of IPDMA, as compared with GLMM, this approach may avoid any strong assumption about the functional form of the relationship between outcome and explanatory variables. It may help leverage the advantages of all candidate learners such as GLMM. Finally, it may allow accounting for potential high-order interactions by including in the library highly flexible algorithms such as random forests. In this analysis, different portions of the likelihood will be modelled using SL and combined to produce a plug-in estimator of the average treatment effect that is consistent, double robust and asymptotically linear.

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Contributors DA is the guarantor of the study. DA and RP were responsible for the conception of the study. DA and AD made substantial contributions to the conception and design of the study, drafting of the study protocol, substantial contributions to the analysis plan, revising the work critically for important intellectual content and providing approval for the final version to be published. LB and RP made substantial contributions to the trial design and analytical plan, revising the work critically for important intellectual content and provided approval for the final version to be published. SC, AW, JC, SF, AG, NH, JM and BV made substantial contributions to the drafting of the study protocol, revised the work critically for important intellectual content and provided approval for the final version to be published.

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