The VitamIn C, HydrocorTisone and ThiAMINe in Patients with Septic Shock Trial

The VITAMINS Trial

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Statistical analysis plan for an interim analysis
Version 3.0, 2nd November 2018

Purpose

The purpose of this statistical analysis plan is to define the details of the interim analysis of the VITAMINS trial to monitor the safety of the intervention and to re-calculate the sample size.

Synopsis of the VITAMINS trial

The VITAMINS trial aims to determine whether the intravenous administration of high dose vitamin C, thiamine and hydrocortisone in patients with septic shock leads to a more rapid resolution of shock and shortens the duration of vasopressor dependence compared to hydrocortisone alone.

The trial is designed as a pilot, feasibility, multi-centre, randomised, open-label, phase IIb clinical trial. Patient screening started on 2nd May 2018 and the first patient was randomised on May 8, 2018.

ICU patients with septic shock are enrolled as soon as possible after fulfilling the criteria. Patients are allocated in a 1:1 ratio to either the treatment group, receiving intravenous vitamin C (1.5g every 6 hours), thiamine (200mg every 12 hours) and hydrocortisone (50mg every 6 hours) or to the control group, receiving hydrocortisone (50mg every 6 hours) alone. The treatment continues until shock resolves, the patient is discharged from ICU, but for a maximum of 10 days.
The **primary outcome** is time **alive and free of vasopressors at day 7** (168 hours) post-randomisation.

Statistical analysis plan

Definition

Septic shock: Sepsis that required vasopressor therapy for >2 hours to maintain MAP >65 mmHg, and lactate >2 mmol/L despite adequate fluid resuscitation.
Shock resolution is defined as the first time point after randomisation when a patient is alive at discontinuation of all vasopressors for at least 4 continuous hours in the presence of a MAP>65 mmHg for the same 4 hour period as recorded in the ICU charts.
Time alive and free of vasopressors at day 7 (168hours): The time that a patient is alive and free of all vasoactive drugs **after shock resolution** (censored at 7 days). If a patient dies while on vasopressor therapy, in such a patient, the time alive and vasopressor free time is 0. If a patient dies after ICU discharge within 7 days after randomization, the time alive and vasopressor free time is the sum of the time observed in the ICU and the time the patient spent in the ward.

Patient population eligible to the interim analysis

Inclusion criteria: The first 60 patients enrolled in the study.
Exclusion criteria: Patients without the consent of participation to the study.

Data used in the interim analysis

Baseline data (the time of randomisation)
Shock resolution (the time point of shock resolution, the outcome [survived/died] for the index septic shock)
Consent data (date of consent, date of consent withdrawal)
All reported serious adverse event (including SUSARs)

Outcome

Time (hrs) alive and free of vasopressors at day 7 (168hrs after randomisation).
This is calculated as below

- If the patient survived and the index septic shock resolved during the first 168 hours of randomisation, it is calculated as below:

$$168 - (the\ date\ and\ time\ of\ shock\ resolultion - the\ date\ and\ time\ of\ randomisation)$$

- If the index septic shock did not resolve within the first 168 hours of randomisation, or if the patient died for the index septic shock without the shock resolution, it is zero.

Timing

The interim analysis will be conducted when all the data for the analysis of the first 60 patients are collected, and the data will be fixed.

Sample size re-calculation

The original sample size calculation was based on a conservative SD of 42 hours and a clinically relevant increase in hours alive and vasopressor free at 7 days of 22% (25 hours) (i.e. increase from 113 to 138 hours alive and vasopressor free at day 7) with a power of 90% at an alpha level of 0.05. The numbers of time alive and vasopressor free on day 7 was derived from the study by Marik et al. CHEST 2017. We accounted for an estimated drop-out rate of approximately 5%, and 126 patients are going to be enrolled in the current study (63 patients per group).

Sample size re-calculation
We will recalculate the sample size to have 90% power (2 sided p-value of 0.05) to detect a 25 hour difference in hours alive and vasopressor free at 7 days based on the pooled standard deviation of hours alive and vasopressor free of the first 60 patients included in the interim analysis.
To account for non-normality of the primary outcome (alive & vasopressor free) and for dropouts we will add 20%. (15% for non-normality (E. L. Lehmann, *Nonparametrics: Statistical methods based on ranks, revised* Prentice Hall, 1998) and 5% for dropout) to the sample size.

Feasibility of the trial

We will summarise all reports on any serious adverse event (including SUSARs) in each group with the numbers and the proportions.

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The VITAMINS Trial

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Statistical analysis plan for the final sample size calculation
Version 1.0, 15th February 2019

Purpose

The purpose of this statistical analysis plan is to define the details of the sample size calculation of the VITAMINS trial to finalise the sample size.

Synopsis of the VITAMINS trial

The VITAMINS trial aims to determine whether the intravenous administration of high dose vitamin C, thiamine and hydrocortisone in patients with septic shock leads to a more rapid resolution of shock and shortens the duration of vasopressor dependence compared to hydrocortisone alone.

The trial is designed as a pilot, feasibility, multi-centre, randomised, open-label, phase IIb clinical trial. Patient screening started on 2nd May 2018 and the first patient was randomised on May 8, 2018.

ICU patients with septic shock are enrolled as soon as possible after fulfilling the criteria. Patients are allocated in a 1:1 ratio to either the treatment group, receiving intravenous vitamin C (1.5g every 6 hours), thiamine (200mg every 12 hours) and hydrocortisone (50mg every 6 hours) or to the control group, receiving hydrocortisone (50mg every 6 hours) alone. The treatment continues until shock resolves, the patient is discharged from ICU, but for a maximum of 10 days.
The **primary outcome** is time **alive and free of vasopressors at day 7** (168 hours) post-randomisation.

Statistical analysis plan

Definition

Septic shock: Sepsis that required vasopressor therapy for >2 hours to maintain MAP >65 mmHg, and lactate >2 mmol/L despite adequate fluid resuscitation.
Shock resolution is defined as the first time point after randomisation when a patient is alive at discontinuation of all vasopressors for at least 4 continuous hours in the presence of a MAP>65 mmHg for the same 4 hour period as recorded in the ICU charts.
Time alive and free of vasopressors at day 7 (168hours): The time that a patient is alive and free of all vasoactive drugs **after shock resolution** (censored at 7 days). If a patient dies while on vasopressor therapy, in such a patient, the time alive and vasopressor free time is 0. If a patient dies after ICU discharge within 7 days after randomization, the time alive and vasopressor free time is the sum of the time observed in the ICU and the time the patient spent in the ward.

Patient population eligible to the final sample size calculation

Inclusion criteria: The first 108 patients enrolled in the study.
Exclusion criteria: Patients without the consent of participation to the study.

Data used in the sample size calculation

Baseline data (the time of randomisation)
Shock resolution (the time point of shock resolution, the outcome [survived/died] for the index septic shock)
Consent data (date of consent, date of consent withdrawal)

Outcome

Time (hrs) alive and free of vasopressors at day 7 (168hrs after randomisation).
This is calculated as below

- If the patient survived and the index septic shock resolved during the first 168 hours of randomisation, it is calculated as below:

$$168 - (the\ date\ and\ time\ of\ shock\ resolultion - the\ date\ and\ time\ of\ randomisation)$$

- If the index septic shock did not resolve within the first 168 hours of randomisation, or if the patient died for the index septic shock without the shock resolution, it is zero.

Timing

The sample size recalculation will be conducted when all the data for the analysis of the first 108 patients are collected, and the data will be fixed.

Sample size re-calculation

The original sample size calculation was based on a conservative SD of 42 hours and a clinically relevant increase in hours alive and vasopressor free at 7 days of 22% (25 hours) (i.e. increase from 113 to 138 hours alive and vasopressor free at day 7) with a power of 90% at an alpha level of 0.05. The numbers of time alive and vasopressor free on day 7 was derived from the study by Marik et al. CHEST 2017. We accounted for an estimated drop-out rate of approximately 5%, and 126 patients are going to be enrolled in the current study (63 patients per group).

The previous sample size re-calculation

We recalculated the sample size to have 90% power (2 sided p-value of 0.05) to detect a 25-hour difference in hours alive and vasopressor free at 7 days based on the pooled standard deviation of hours alive and vasopressor free of the first 60 participants (50%) included in the interim analysis. One participant was excluded from the analysis as consent was not obtained at the moment of the calculation. The pooled standard deviation of hours alive and vasopressor free at 7 days for the 59 patients was 51.6 hours which was higher than the preliminary estimation of 42.
To account for non-normality of the primary outcome (alive & vasopressor free) and dropouts, we added 20% (15% for non-normality and 5% for dropout) to the sample size.
Based on these values, the required sample size was 180 patients (90 per group). Allowing for a 20% inflation for non-normality and dropout/withdrawal, the required total sample size has been 216 (108 per group). The robustness of our sample size estimate will be further assessed after recruitment of 108 patients (50% of the sample size).

The final sample size re-calculation

To assess the robustness of our sample size estimation, we will recalculate the sample size based on the pooled standard deviation of hours alive and vasopressor free of the first 108 patients included in the interim analysis. The method will be the same as the previous sample size re-calculation.