

Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension: Statistical and health economic analysis plan for the 65 trial in article*

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Abstract

The 65 trial is a pragmatic, multicentre, parallel-group, open-label, randomised clinical trial of permissive hypotension (targeting a mean arterial pressure target of 60–65 mmHg during vasopressor therapy) versus usual care in critically ill patients aged 65 years or over with vasodilatory hypotension. The trial will recruit 2600 patients from 65 United Kingdom adult general critical care units. The primary outcome is all-cause mortality at 90 days. An economic evaluation is embedded. This paper describes the proposed statistical and health economic analysis for the 65 trial.

Keyword

Vasopressors, mean arterial pressure, critical care, intensive care, health economics, clinical trial, statistical analysis plan

Introduction

The 65 trial is a randomised clinical trial to evaluate the clinical and cost-effectiveness of permissive hypotension (a mean arterial pressure target of 60–65 mmHg during vasopressor therapy), in comparison with usual care for critically ill patients aged 65 years or over with vasodilatory hypotension. The statistical and health economic analysis plan for this trial contains a full description of the planned endpoints and analysis methods which will be used to evaluate the results of this trial. A brief outline is presented below.

2.5% for withdrawal/loss to follow-up. A single-planned interim analysis was performed in the first 500 patients, using a Peto-Haybittle stopping rule ($P < 0.001$).

Study methods

Sample size

A sample size of 2600 patients (1300 per group) provides 90% power to detect a 6% absolute risk reduction for 90 days mortality to 29%, with allowance of

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Statistical principles

All statistical tests will be for superiority and will be two-sided with significance set at $P < 0.05$. All analyses will adhere to the intention-to-treat principle.

Clinical effectiveness analysis

The primary outcome of number and percentage of deaths by 90 days following randomisation will be reported. The primary effect estimate will be the absolute risk reduction, reported with a 95% confidence interval. Deaths by 90 days following randomisation will be compared between the groups, unadjusted, using Fisher's exact test. Patients with missing survival data at 90 days will be excluded from the primary effect estimate.

An analysis of the primary and secondary outcomes, adjusted for baseline data, will also be conducted using multilevel logistic regression with a random effect of site. Outcomes will be reported in a limited set of pre-specified patient subgroups.

Cost-effectiveness analysis

The primary cost-effectiveness outcome is net monetary benefit at 90 days following randomisation. A full cost-effectiveness analysis will be undertaken to assess the relative cost-effectiveness of the intervention compared to usual care.

The cost analysis will take a health and personal health services perspective. Health-related quality of life (HRQoL) will be assessed using the EuroQol EQ-

5D-5L questionnaire, with valuation using the EQ-5D-5L value set for England.¹ HRQoL data will be combined with the survival data to report quality-adjusted life years (QALYs) at 90 days post randomisation.

Missing data in costs and EQ-5D score will be handled with multiple imputation, assuming the data are missing at random conditional on the observed data.

The cost-effectiveness analysis will follow the intention-to-treat principle and use regression methods to report the mean (95% confidence interval) incremental net benefits at a National Institute for Health and Care Excellence (NICE) recommended threshold willingness-to-pay for a QALY gain. The same statistical approach will be used to evaluate the secondary cost-effectiveness outcomes. Subgroup analysis will be performed as per the clinical effectiveness analysis.

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1. Devlin NJ, Shah KK, Feng Y, et al. Valuing health-related quality of life: an EQ-5D-5L value set for England. *Health Econ* 2018; 27: 7–22.