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The 65 trial

Submission date 10/04/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 11/04/2017	**Overall study status** Completed	
Last Edited 03/05/2024	**Condition category** Circulatory System	

Plain English summary of protocol

Background and study aims
The best blood pressure target to guide treatment in critical care is not known. It is, however, well-known that both very low blood pressure (severe hypotension) and, side effects from medications that increase blood pressure (vasopressors), can increase the risk of death. Current guidelines recommend that clinicians aim for a mean arterial pressure (MAP) of 65 mmHg or more. These guidelines are based on low quality evidence and no guidance is given on an upper limit. Previous research shows MAP values in critical care frequently rise significantly higher than 65 mmHg, exposing patients to potentially unnecessary doses of vasopressors and associated side-effects. There is emerging evidence suggesting that using a lower MAP target (permissive hypotension) to guide treatment may increase survival in older critically ill patients. A large clinical trial is therefore needed to evaluate this idea. The aim of this study is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target of 60 - 65 mmHg during vasopressor therapy) in critically ill patients aged 65 years or over with hypotension.

Who can participate?
Older adults with low blood pressure who are to be treated with blood pressure raising medication.

What does the study involve?
Eligible participants are randomly allocated to one of two groups. Participants in the first group are treated using the 60 – 65 mmHg MAP target when they need vasopressor therapy in the in the critical care unit. Participants in the second group continue to receive usual care (as per local practices). Participants are approached to provide consent to take part once they are well enough to do so. Participants are then sent questionnaires about their wellbeing and quality of life to complete at 90 days and one year (only patients recruited during the first 14 months of the recruitment period are contacted at one year). In addition, survival rates and information about lengths of hospital stays are recorded using patient notes.

What are the possible benefits and risks of participating?
The benefits and risks of using a lower blood pressure target to guide treatment, instead of usual care, are unclear at this time, which is why this research is needed. It is not yet known whether participants will benefit directly from their participating in the 65 Trial. If the permissive hypotension strategy is found to be clinically and cost-effective, then participants in this group may benefit directly in terms of improved survival or by experiencing less side-effects associated

with vasopressors. There are no potential significant benefits of taking part for participants in the usual care group, other than the understanding that information from the trial will be used to improve the care of future critically ill patients. There are no notable risks associated with this study.

Where is the study run from?
65 adult, general, critical care units at NHS hospitals in England, Northern Ireland and Wales (UK)

When is the study starting and how long is it expected to run for?
March 2017 to October 2019

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Mr Alvin Richards-Belle
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Study website
https://www.icnarc.org/Our-Research/Studies/Sixty-Five

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CPMS 34223

Study information

Scientific Title
Evaluating the clinical and cost-effectiveness of permissive hypotension in critically ill patients aged 65 years or over with vasodilatory hypotension

Study objectives
The aim of this study is to evaluate the clinical and cost-effectiveness of permissive hypotension (MAP target of 60 - 65 mmHg during vasopressor therapy) in critically ill patients aged 65 years or over with hypotension.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford C Research Ethics Committee, 24/04/2017, ref: 17/SC/0142

Study design
Randomized; Interventional; Design type: Treatment, Process of Care, Management of Care

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Hypotension

Interventions
Current intervention as of 20/03/2019:
Patients will be randomised following a 1:1 sequence to either the intervention group (permissive hypotension) or usual care.

Permissive hypotension group: Patients will be treated using a MAP target range 60 - 65 mmHg whilst receiving vasopressor therapy. The decision to discontinue vasopressors will depend on the patients' ability to maintain the MAP target stipulated by the protocol without vasopressors. The trial treatment will apply at any point the patient requires vasopressors during their admission in the critical care unit.

Usual care group: Patients will continue to receive usual care (as per local practices).

Follow-up for survival status at 90 days and at one year will also be obtained via data-linkage with nationally held records. At each time-point, survivors will be posted a questionnaire containing the EQ-5D-5L, IQCODE (short version) and health services questionnaire. Only patients recruited during the first 14 months of the recruitment period will be contacted at one year.

Previous intervention:
Patients will be randomised following a 1:1 sequence to either the intervention group (permissive hypotension) or usual care.

Permissive hypotension group: Patients will be treated using a MAP target range 60 - 65 mmHg whilst receiving vasopressor therapy. The decision to discontinue vasopressors will depend on the patients' ability to maintain the MAP target stipulated by the protocol without vasopressors. The trial treatment will apply at any point the patient requires vasopressors during their admission in the critical care unit.

Usual care group: Patients will continue to receive usual care (as per local practices).

Follow-up for survival status at 90 days and at one year will also be obtained via data-linkage with nationally held records. At each time-point, survivors will be posted a questionnaire containing the EQ-5D-5L, IQCODE (short version) and health services questionnaire. Only patients recruited during the first nine months of the recruitment period will be contacted at one year.

Intervention Type
Other

Primary outcome measure
Clinical evaluation:
All-cause mortality is assessed through data-linkage with nationally held death registrations at 90 days.

Economic evaluation:
Incremental net monetary benefit (INB), evaluated at the NICE recommended threshold of £20,000 per quality-adjusted life year (QALY), at 90 days.

Secondary outcome measures
1. Mortality at discharge from the critical care unit and acute hospital is assessed by reviewing patient medical notes at critical care unit discharge
2. Duration of survival is assessed through data-linkage with nationally held death registrations at the longest available follow-up (e.g. patients will be followed up for a minimum of six months following randomisation, with the earliest recruited patients followed-up for survival to 24 months)
3. Duration of advanced respiratory and renal support (defined according to the Critical Care Minimum Dataset [CCMDS]) during the critical care unit stay is assessed by reviewing patient medical notes at critical care unit discharge
4. Days alive and free of advanced respiratory support and renal support is assessed by reviewing patient medical notes at critical care unit discharge
5. Duration of critical care unit and acute hospital stay is assessed by reviewing patient medical

notes at critical care unit and hospital discharge
6. Cognitive function is assessed using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE, short version) at 90 days and one year
7. Health-related quality of life is assessed using the EuroQol EQ-5D-5L questionnaire at 90 days and one year
8. Resource use and costs is assessed using a health services questionnaire at 90 days and one year
9. Estimated lifetime incremental cost-effectiveness

Overall study start date
01/03/2017

Completion date
31/10/2019

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/02/2018:
1. Age 65 years or older
2. Vasodilatory hypotension as assessed by treating clinician
3. Started infusion (for at least one hour) of vasopressors within prior 6 hours (if noradrenaline, then a minimum dose of 0.1 µg kg-1 min-1)
4. Adequate fluid resuscitation is completed or ongoing
5. Vasopressors expected to continue for 6 hours or more as assessed by treating clinician

Previous inclusion criteria:
1. Age 65 years or older
2. Vasodilatory hypotension as assessed by treating clinician
3. Decision to start vasopressors or started within prior 6 hours following/during adequate fluid resuscitation
4. Vasopressors expected to continue for 6 hours or more as assessed by treating clinician

Participant type(s)
Patient

Age group
Senior

Lower age limit
65 Years

Sex
Both

Target number of participants
Planned Sample Size: 2600; UK Sample Size: 2600

Total final enrolment
2600

Key exclusion criteria
1. Vasopressors being used solely as therapy for bleeding, acute ventricular failure (left or right) or post-cardiopulmonary bypass vasoplegia
2. Ongoing treatment for brain injury or spinal cord injury
3. Death perceived as imminent
4. Previous enrolment to the 65 Trial

Date of first enrolment
03/07/2017

Date of final enrolment
16/03/2019

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Poole Hospital
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre
Darent Valley Hospital
Darenth Wood Road
Dartford
United Kingdom
DA2 8DA

Study participating centre
Medway Maritime Hospital
Windmill Road
Gillingham
United Kingdom
ME7 5NY

Study participating centre

Bristol Royal Infirmary
Upper Maudlin Street
Bristol
United Kingdom
BS2 8HW

Study participating centre
Royal Berkshire Hospital
Craven Road
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RG1 5AN

Sponsor information

Organisation
Intensive Care National Audit & Research Centre

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Sponsor type
Hospital/treatment centre

Website
www.icnarc.org

ROR
https://ror.org/057b2ek35

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/10/2020

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		09/09/2019	13/09/2019	Yes	No
Statistical Analysis Plan	statistical and health economic analysis plan	03/07/2019	13/09/2019	Yes	No
Results article		12/02/2020	13/02/2020	Yes	No
Results article		01/02/2021	03/03/2021	Yes	No
HRA research summary			28/06/2023	No	No
Protocol article		08/12/2020	03/05/2024	Yes	No