

**FULL TITLE OF THE PROJECT:**

**The mortality effect of
relative hypotension in
people with emergency care needs**

**SHORT PROJECT TITLE / ACRONYM:**

Relative hypotension in emergency care / RHEC

**REGULATORY APPROVALS REFERENCE:**

IRAS: 313451 University ethics: 33749

**PROTOCOL VERSION NUMBER AND DATE:**

1.0, 10 March 2022

**CHIEF INVESTIGATOR:**

Dr James van Oppen

**SPONSOR:**

University of Leicester

**FUNDER:**

No specific funding

Confidentiality Statement

All information contained within this protocol is regarded as, and must be kept confidential.  No part of it may be disclosed by any Receiving Party to any Third Party, at any time, or in any form without the express written permission from the Chief Author/Investigator and / or Sponsor.

*This protocol has regard to the Office for Data Release guidance on protocol content*

*This protocol has regard for the HRA guidance on protocol content*

## SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the project in compliance with the approved protocol and will adhere to the principles outlined in GCP guidelines, the Sponsor’s (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the project publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the project will be given; and that any discrepancies and serious breaches of GCP from the project as planned in this protocol will be explained.

|  |
| --- |
| **For and on behalf of the Project Sponsor:** |
| Signature: *[original signed]* |  | Date: 08/03/2022 |
| Name (please print): Yasmin Godhania |  |  |
| Position: Research Governance Officer |  |  |
| **Chief Investigator:** |
| Signature: *[original signed]* |  | Date: 21/03/2022 |
| Name: (please print): Dr James van Oppen  |  |  |
| **Statistician:** |  |  |
| Signature: *[original signed]* |  | Date: 22/03/2022 |
| Name: (please print): Dr Rhiannon Owen |  |  |
| Position: Associate Professor of Statistics  |  |  |

## KEY TRIAL CONTACTS

|  |  |
| --- | --- |
| Chief Investigator | Dr James van OppenDepartment of Health Sciences, University of Leicester(Honorary: Emergency & Specialist Medicine, UHL)*[address removed]* |
| Sponsor | University of Leicester*[address removed]* |
| Funder(s) | This project does not require specific funding. An application is being made to Royal College of Emergency Medicine for statistician support.Salaries for Dr van Oppen & Dr Beishon are funded by NIHR Fellowships |
| Protocol Contributors | Prof Timothy Coats*[address removed]*Dr Lucy Beishon*[address removed]*Mr Will Jones*[address removed]* |
| Statistician | Dr Rhiannon Owen*[address removed]* |

CONTENTS

[i. SIGNATURE PAGE 2](#_Toc96945543)

[ii. KEY TRIAL CONTACTS 3](#_Toc96945544)

[iii. LIST OF ABBREVIATIONS 5](#_Toc96945545)

[iv. Project SUMMARY 6](#_Toc96945546)

[v. FUNDING AND SUPPORT IN KIND 6](#_Toc96945547)

[vi. ROLE OF project SPONSOR 6](#_Toc96945548)

[vii. DATA FLOW 6](#_Toc96945549)

[1. BACKGROUND 8](#_Toc96945550)

[2. RATIONALE 8](#_Toc96945551)

[3. OBJECTIVE 9](#_Toc96945552)

[4. STUDY DESIGN AND DATA ANALYSIS 9](#_Toc96945553)

[5. ELIGIBILITY CRITERIA 9](#_Toc96945554)

[6. STUDY PROCEDURES 10](#_Toc96945555)

[6.1. Informed consent 10](#_Toc96945556)

[6.2. Definition of End of Study 10](#_Toc96945557)

[6.3. Source data 10](#_Toc96945558)

[7. Statistics and data analysis 10](#_Toc96945559)

[8. DATA HANDLING AND RECORD KEEPING 12](#_Toc96945560)

[8.1. Dataset Creation 12](#_Toc96945561)

[8.2. Data Transfer 12](#_Toc96945562)

[8.3. Data Storage 12](#_Toc96945563)

[8.4. Data Processing 12](#_Toc96945564)

[8.5. Data Archiving and Destruction 12](#_Toc96945565)

[8.6. Access to Data 12](#_Toc96945566)

[9. MONITORING, AUDIT & INSPECTION 13](#_Toc96945567)

[10. ETHICAL AND REGULATORY CONSIDERATIONS 13](#_Toc96945568)

[10.1. Research Ethics Committee (REC) review & reports 13](#_Toc96945569)

[10.2. Peer review 13](#_Toc96945570)

[10.3. Public and Patient Involvement 13](#_Toc96945571)

[10.4. Data protection and patient confidentiality 13](#_Toc96945572)

[10.5. Indemnity 13](#_Toc96945573)

[11. DISSEMINATION POLICY 14](#_Toc96945574)

[12. REFERENCES 14](#_Toc96945575)

## LIST OF ABBREVIATIONS

Define all unusual or ‘technical’ terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

CI Chief Investigator

GCP Good Clinical Practice

NHS R&D National Health Service Research & Development

PI Principal Investigator

REC Research Ethics Committee

SOP Standard Operating Procedure

## Project SUMMARY

|  |  |
| --- | --- |
| Project Title | The mortality effect of relative hypotension in people with emergency care needs |
| Project Design | Retrospective cohort study |
| Planned Sample Size | Estimated 10,000 individuals |
| Follow up duration | Anonymised dataset pertaining to adults who attended emergency care at University Hospitals Leicester NHS Trust between 01/01/2019 and 31/12/2019 |
| Planned Project Period | Data analysis will take approximately three months and will commence immediately on receipt of regulatory approvals |
|  | Objectives | Outcome Measures |
| Primary | Evaluation of the impact of Emergency Department hypotension relative to an individual’s baseline blood pressure, considering the effects of factors including age, frailty, ethnicity, and coded clinical comorbidities. | 30-day mortality |

## FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER(S)**(Names and contact details of ALL organisations providing funding and/or support in kind for this trial) | **FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN** |
| National Institute for Health Research | Salaries for Dr van Oppen & Dr Beishon are funded by NIHR Fellowships |

## ROLE OF project SPONSOR

The sponsor of this research is the University of Leicester. The University of Leicester is registered as a research sponsor with the Department of Health and routinely takes responsibility as sponsor for research activities within the NHS.

## DATA FLOW

The dataset will be generated at University Hospitals of Leicester NHS Trust (UHL), by Mr W Jones exporting from the NerveCentre system. The data will be anonymised at UHL by Mr W Jones at the point of generation, using a mask on the ID number field (data flow diagram, Figure 1). The mask link will not be retained. Row headers and the analysis code will be shared with the supervising statistician Dr R Owen. Dr Owen will be able to view the data (using Microsoft Teams screen-sharing facility) but not to handle the data.



Figure 1: Data flow diagram

## **BACKGROUND**

Hypotension is well-recognised as a predictor of deterioration and mortality and appears prominently in the National Early Warning Score (NEWS). For this reason, blood pressure is regularly and frequently measured for people attending emergency departments.

The NEWS has limitations when applied to older people. As humans age, they develop altered physiological responses to health events such as infection and trauma. Older people are more likely to be living with hypertension, and so may have significantly reduced blood pressure unrecognised by the NEWS, as the figures may still be within the ‘normal’ range (Figure 2). Similarly, they more often use medications such as beta blockers which blunt adaptive responses. The NEWS has recently been demonstrated to underestimate mortality risk for older people (Nissen et al., 2021).

Figure 2: 'Relative hypotension' with normal Early Warning Score. This study will examine the prevalence of relative hypotension and its association with 30-day mortality.



A recent Dutch study quantified ‘baseline’ blood pressure for older patients in Emergency Departments by reviewing primary care records and outpatient letters (Candel et al., 2021). 20% had hypotension relative to their baseline, which was associated with a 1-in-5 risk of death.

## RATIONALE

This study builds on the work by Candel, et al. (2021) to investigate whether 30-day mortality is predicted by relative hypotension observed in routinely available UK hospital data. While UK Emergency Departments often have poorer access to vital signs data from primary care electronic health records, there is often ready access to vital signs recorded during previous episodes at that department. In Leicester, the NerveCentre electronic record system displays not only current and previous ED vital signs records, but also observations recorded for individuals during continuing inpatient admissions. NerveCentre has been used for all adult observations (except Intensive Care) since 2016.

There is no established definition for ‘baseline’ blood pressure. Blood pressure readings taken during the acute phase of hospital admission (often defined as the first 72 hours (Conroy et al., 2021)) are likely to be unreliable approximations of ‘baseline’ as people are still unwell and anxious. In this study, as people are usually only discharged from inpatient admissions when they have reached more stable health, the average blood pressure readings during the last 48 hours of admission will be considered as a reference ‘baseline’ for the person’s subsequent ED attendance.

## OBJECTIVE

Evaluation of the prevalence and distribution of relative hypotension in a typical Emergency Department and its association with 30-day mortality, considering the effects of factors including age, frailty, ethnicity, and coded clinical comorbidities. Furthermore, this study will provide evidence for the adequacy or inadequacy of NEWS2 to predict 30-day mortality in the sub-groups of older people and people living with frailty.

This is a pragmatic initial exploratory analysis of data available in real-world emergency care decision-making. If a general effect is observed in certain groups (such as older people), then future work will seek funding to examine subgroups (such as those living with atrial fibrillation or hypertension) to ensure that they would not be potentially disadvantaged by any change in scoring system.

## STUDY DESIGN AND DATA ANALYSIS

This is a retrospective cohort study using secondary collection of effectively anonymised data. The dataset contains people’s vital signs and outcomes from their index ED attendance and previous (‘reference’) hospital admissions in the period 2016-2019. This observation period was selected to mitigate for a plausible effect on mortality data observed during the Covid-19 pandemic.

The dataset will be generated at University Hospitals of Leicester NHS Trust. Their Emergency Department (LRI ED) uses NerveCentre as a software dashboard and electronic patient care record. Electronic records routinely collected in the ED include data for patients’ demographics, vital signs, and clinical diagnoses. ICD-10 co-morbidity coding is routinely recorded on hospital discharge. These data are routinely reported and analysed for audit and service improvement work, and regularly used for research. The investigators include Honorary Emergency Physicians and Geriatricians in the clinical teams.

The dataset will be prepared by the Emergency Department’s Transformation Lead, Mr W Jones. People will be identified as unique patients by hospital record numbers. Mr Jones will apply a mask algorithm to pseudonymise these hospital numbers and will then discard the algorithm to effectively anonymise the data. Individuals will therefore not be identifiable to the investigators as it will not be possible to reverse the mask. In addition, the limited number of variables and large number of observations in the dataset creates an extremely low risk of re-identification of a particular person. In the unlikely event that any summary counts are less than 5, summary statistics will be reported as n<5 to avoid the potential risk of disclosure.

The dataset will be passed to Dr van Oppen through secure UHL to UHL email. Dr van Oppen will use the University ‘MyFiles’ portal to transfer the dataset to University of Leicester’s R: Drive, where a network folder will be accessible to only the research team investigators. Dr Owen will be able to view but not handle the data, using screen-sharing through University-assured software (Microsoft Teams).

## ELIGIBILITY CRITERIA

The dataset will be generated from all adult (aged at least 18) emergency care attendances at University Hospitals Leicester NHS Trust during the observation period, excluding Eye Casualty. Only those patients for whom there is an eligible reference hospital admission will be included:

* UHL emergency care attendances (excluding Eye Casualty) between 01 January 2019 and 31 December 2019 by adults whose previous vital signs were entered during a previous (‘reference’) UHL admission:
	+ Within the previous 3 years
	+ Lasting more than 72 hours
	+ With discharge more than 14 days before the index emergency care attendance

## STUDY PROCEDURES

### Informed consent

This study will use anonymised data from UHL in line with their Privacy Notice. Therefore, participant consent is not required. The investigators will not receive any patient identifiable data and therefore there will be no breach of the common law duty of confidence.

### Definition of End of Study

The study will be complete when all analyses described in section 7 have been conducted, no later than the End Date approved by the Ethics Committee.

### Source data

The dataset will be produced by exporting a date-range report using business analytics applications. Where individuals have attended emergency care on multiple occasions, only the first attendance in the dataset will be included in analyses. The dataset is anticipated to contain rows for approximately 10,000 individuals.

Variables will include:

* Record number, pseudonymised using mask
* Date of index emergency care attendance (first attendance in year 2019)
* Immediate prior (‘reference’) hospital discharge date and duration of admission (for episodes meeting the above eligibility criteria)
* Age, clinical frailty score (CFS), sex, ethnicity
* Co-morbidities (e.g. hypertension, cardiovascular disease) – from ICD-10 codes recorded for the immediate prior (‘reference’) hospital discharge. The hospital frailty risk score (HFRS) will be calculated from coded co-morbidities.
* Vital signs in final 48 hours of reference admission
* First vital signs observation in index emergency care attendance
* Disposition from index emergency care attendance (discharge, admission, death)
* Date of index emergency care or subsequent hospital discharge
* Date of death
* Cause of death

## Statistics and data analysis

#### Summary and descriptive statistics

Summary statistics will be presented for the age, frailty scores (CFS and HFRS), co-morbidities, length of stay, emergency care disposition, and mortality outcome for people with emergency care attendances and eligible reference hospital admissions. Charlson comorbidity indices will be calculated from ICD-10 codes. ICD-10 data will have been coded for reference admissions by the hospital. ICD-10 codes are acknowledged to have limitations, but are used pragmatically in this study as a valid representation of the data available for real-world emergency care decision-making.

‘Baseline’ systolic, diastolic, and mean arterial (MAP) blood pressures will each be calculated as the average of the last two observations made during the final 48 hours of the immediate prior reference admission. Early Warning Scores will be calculated from component scores using the NEWS2 (Royal College of Physicians, 2017). Normotension, hypertension, and hypotension will be defined using NEWS2 thresholds for systolic blood pressure, respectively 111-219, <111, >219. Relative (Δ) systolic, diastolic, and MAP values will each be calculated by subtracting the baseline inpatient pressures from the first index emergency care observation. ‘Relative hypotension’ will initially be indicated as negative relative systolic values exceeding 7mmHg; the tertile above this value had increased mortality in the study by Candel (2021). ‘Relative hypotension’ will be redefined later following elicitation of thresholds.

The frequencies of 30-day mortality vs survival will be sub-classified by the presence of relative hypotension and variables of interest, including age, frailty, Charlson comorbidity index, and index systolic pressure (Table 1). Values for relative systolic pressure will be plotted as the dependent variable against index relative systolic pressure and against age.

Table 1: Sub-classification of 30-day mortality and relative hypotension by variables of interest.

|  |  |  |
| --- | --- | --- |
|  | Died within 30 days | Alive after 30 days |
| Indicated relative hypotension(ΔsBP > 7mmHg) | Indicated relative normotension(ΔsBP < 7mmHg) | Indicated relative hypotension(ΔsBP > 7mmHg) | Indicated relative normotension(ΔsBP < 7mmHg) |
| Age | <65 | n, % |  |  |  |
|  | 65-85 |  |  |  |  |
|  | >85 |  |  |  |  |
| Frailty (CFS) | <5 |  |  |  |  |
|  | 5-6 |  |  |  |  |
|  | >6 |  |  |  |  |
| Charlson index | 0-2 |  |  |  |  |
|  | 3-4 |  |  |  |  |
|  | >4 |  |  |  |  |
| Index sBP | <111 |  |  |  |  |
|  | 111-219 |  |  |  |  |
|  | >219 |  |  |  |  |
| Index pulse | <51 |  |  |  |  |
|  | 51-90 |  |  |  |  |
|  | >90 |  |  |  |  |
| Index NEWS2 | 0 |  |  |  |  |
|  | 1-4 |  |  |  |  |
|  | 5+ *or* 3 in any component |  |  |  |  |

#### Tests for association

Age, frailty, and relative hypotension values will each be assessed for normality using visual and statistical (Shapiro Wilk) methods, and then examined for interaction using ANOVA or the Kruskal Wallis test or appropriately transformed. Analyses will include categories for data which is missing, to examine for trends in missingness. Cox regression analysis will be performed to assess associations between relative hypotension, initial index blood pressures, and 30-day mortality (adjusted for age, gender, frailty, Charlson index, and ethnicity).

The relationship between relative hypotension and 30-day mortality will be further examined using logistic regression models. The effect of plausible explanatory variables (age, frailty, comorbidities including hypertension, diabetes, and chronic kidney disease) will be adjusted for in the models.

##### Model 1

To determine the accuracy of relative hypotension as a predictor of 30-day mortality, we will conduct receiver operating characteristic (ROC) curve analysis. We will determine the area under curve, sensitivity, specificity, positive, and negative predictive values for relative hypotension to predict 30-day mortality. The optimal threshold for sensitivity and specificity will be determined using the Youden Index ([sensitivity + specificity]/100).

##### Models 2 and 3

Model 1 will be repeated, this time with frailty and then initial (index) blood pressure as covariates.

##### Model 4

Next, to determine whether relative hypotension is a more accurate predictor than frailty or index blood pressure of 30-day mortality, we will conduct the same analysis using these covariates combined.

##### Model 5

A final comprehensive model will determine a relative hypotension threshold in order to develop a risk tool. The model will repeat the earlier analysis, this time adjusting for other clinically relevant factors (age, gender, ethnicity, coded comorbidities including cardiovascular disease and diabetes). If the sample size is calculated to provide adequate power, we will derive and validate this final model splitting the dataset randomly into two cohorts. If the sample size is too small then we will build on our existing collaborations towards external validation, subject to the necessary approvals at that time.

## DATA HANDLING AND RECORD KEEPING

### Dataset Creation

These analyses use anonymised routine clinical data. These will be handled in line with University of Leicester’s and University Hospitals of Leicester NHS Trust’s Privacy Notices. The legal basis for this is that is a ‘Task in the Public Interest’. The dataset will be exported and processed using routine methods by the Department’s Transformation Lead, Mr W Jones. The report will include hospital record numbers. A mask (an electronic algorithm) will be applied to transform these to random numbers. The mask will then be discarded, resulting in an anonymised dataset. Anonymisation will be carried out in line with UHL Standard Operating Procedures.

Individuals will not be identifiable to the investigators as they will not be able to reverse the mask. In addition, there are limited variables in the dataset which means the risk of re-identification of a particular person is extremely low.

### Data Transfer

Dr van Oppen will receive the dataset through the secure UHL to UHL email system. Dr van Oppen will use the University ‘MyFiles’ portal to transfer the dataset to University of Leicester’s R: Drive, where a network folder will be accessible to only the research team investigators.

Analyses will be conducted by Dr van Oppen, Dr Beishon, and UHL clinical academic trainees under their supervision. Variable headers and mock data entries (containing no data pertaining to any real individual) may be shared with the statistician Dr Owen when seeking advice. If required, Dr Owen will be able to view but not handle the data, using screen-sharing through University-assured software (Microsoft Teams).

### Data Storage

The dataset will be stored on the University R: Drive in a folder accessible only to the investigators. All investigators with access will be recorded on the Delegation of Authority log for the project, which will be stored in the Trial Master File.

### Data Processing

Analyses will be conducted in Stata and R using a bitlocker-secured, University of Leicester-assured laptop issued to Dr van Oppen.

### Data Archiving and Destruction

At the end of the project, the anonymised dataset will be archived on the R: Drive for five years. No further analyses will be conducted without an amendment to regulatory permissions being submitted and approved. After five years, the dataset will be securely deleted. This will be recorded in the Trial Master File. The Trial Master file will be stored for six years to allow auditing.

### Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

## MONITORING, AUDIT & INSPECTION

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures.

The University of Leicester operate a risk-based audit programme to which this study will be subject to.

## ETHICAL AND REGULATORY CONSIDERATIONS

### Research Ethics Committee (REC) review & reports

**Sponsor Standard Operating Procedures**

All relevant Sponsor SOPs will be followed to ensure that this study complies with all relevant legislation and guidelines

**Declaration of Helsinki**

The Chief Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

**ICH Guidelines for Good Clinical Practice**

The Chief Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

**Approvals**

No analyses will take place before the required regulatory approvals are in place. All amendments will be submitted to the sponsor for review.

**Participant Confidentiality**

The Chief Investigator will ensure that the participants’ anonymity is maintained. No personal identifiable data will be transferred to the University of Leicester. The participants will be identified only by their anonymous ID number in the de-identified dataset. All documents will be stored securely and will only be accessible by the study team and authorised personnel. The study will comply with the Data Protection Act/GDPR. Data will be completely anonymised.

**End of Study Notification**
An end of study form will be completed and submitted to the Sponsor, REC and NHS organisations. Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications or abstracts, to the Sponsor and REC. If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

### Peer review

This protocol has been reviewed by Dr Jatinder Minhas (Geriatrician and Clinical Lecturer, University of Leicester) and Prof Simon Conroy (Professor of Geriatric Medicine, University College London).

### Public and Patient Involvement

The research proposal has not been formally discussed with a patient and public involvement group.

### Data protection and patient confidentiality

All investigators will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

### Indemnity

University of Leicester’s insurance applies

## DISSEMINATION POLICY

The approved protocol will be deposited in a publicly accessible database. The final dataset will remain the property of University of Leicester and will not be made publicly available. On completion of data analysis, a final report will be prepared and submitted for journal publication. The research team (Dr van Oppen, Dr Beishon, Mr Jones, Prof Coats) and statistician (Dr Owen), and any eligible trainees under their supervision will have publication authorship.

## REFERENCES

CANDEL, B. G. J., VAN INGEN, I. B., VAN DOORMALEN, I. P. H., RAVEN, W., MIGNOT-EVERS, L. A. A., DE JONGE, E. & DE GROOT, B. 2021. The difference between the patients' initial and previously measured systolic blood pressure as predictor of mortality in older emergency department patients. *European Geriatric Medicine***,** 1-7.

CONROY, S., CARPENTER, C. & BANERJEE, J. 2021. *Silver Book II,* London, UK, British Geriatrics Society.

NISSEN, S. K., CANDEL, B. G. J., NICKEL, C. H., DE JONGE, E., RYG, J., BOGH, S. B., DE GROOT, B. & BRABRAND, M. 2021. The Impact of Age on Predictive Performance of National Early Warning Score at Arrival to Emergency Departments: Development and External Validation. *Annals of Emergency Medicine*.

ROYAL COLLEGE OF PHYSICIANS. 2017. *National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS* [Online]. Available: <https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2> [Accessed 10 February 2022].