Full title	Multiple Organ Dysfunction in Elderly Trauma: A pan-London major trauma prospective observational study
Short Title/Acronym	MODET
Sponsor	Queen Mary University of London Contact person of the above sponsor organisations is: Dr Sally Burtles Director of Research Services and Business Development Queen Mary University of London Joint Research Management Office (JRMO) Queen Mary Innovation Centre Lower Ground Floor, 5 Walden Street London, E1 2EF Tel: 020 7882 7260 Office fax: 020 7882 7276 (Internal: 13-7276) E-mail: sponsorsrep@bartshealth.nhs.uk
IRAS reference	IRAS 209230
REC Reference	16/LO/1720
ReDA sponsors reference	011319
Chief Investigator	Dr Elaine Cole Director of Research and Innovation, Pan-London Trauma System Centre for Trauma Sciences Blizard Institute Queen Mary University of London 4 Newark Street, London, E1 2AT Tel: 07808400582 E-mail: e.cole@qmul.ac.uk
List of sites	St Mary's Hospital, Imperial NHS Trust, London Royal London Hospital, Barts Health NHS Trust, London Kings College Hospital, Kings Health Partners NHS Trust, London St Georges Hospital, St Georges NHS Trust, London

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1. GLOSSARY of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

2. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol **(Version 0.7, dated 12/08/2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Elaine Cole

Chief Investigator Site: Blizard Institute, QMUL, London

Signature and  Date: 09_05_16

Professor of Trauma Science: Karim Brohi

Site: Blizard Institute, QMUL, London

Signature  and Date: 08_08_16

Principal Investigator Agreement

The clinical study as detailed within this research protocol **(Version 0.7, dated 12/08/2016)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

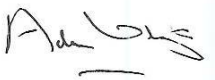
Principal Investigator Name: Dr Phil Hopkins

Principal Investigator Site: Kings College Hospital

Signature and Date:  11.07.2016

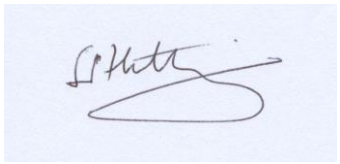
Principal Investigator Name: Dr Adam Woodgate

Principal Investigator Site: Royal London Hospital

Signature and Date:  20.07.16

Principal Investigator Name: Mr Shehan Hettiaratchy

Principal Investigator Site: St Marys Hospital

Signature and Date:  18.07.2016

Principal Investigator Name: Ms Christine Ryan

Principal Investigator Site: St Georges Hospital

Signature and Date: 19.07.16

Christine Ryan

3. SUMMARY/SYNOPSIS

Short Title	MODET
Method	Multi-site prospective observational study
Research Sites	Major Trauma Centres (MTC) within the Pan-London Major Trauma System: Royal London Hospital, Barts Health NHS Trust St Marys Hospital, Imperial College Healthcare NHS Trust Kings College Hospital, King's College Hospital NHS Foundation Trust St Georges Hospital, St George's University Hospitals NHS Foundation Trust
Objectives/Aims	This study aims to: Identify the prevalence, severity and patterns of multiple organ dysfunction syndrome (MODS) Determine predictors and risk factors of developing MODS Identify age related characteristics that contribute to MODS Examine the mode of mortality associated with MODS Analyse the relationship between MODS and longer-term recovery and quality of life
Number of Participants/Patients	1346
Main Inclusion Criteria	Inclusion criteria: Adult patients (≥16 years of age) with multiple injuries admitted to adult critical care unit within the four London MTCs.
Statistical Methods and Analysis	Analysis populations: Patients who are greater than 64 years of age will comprise the older-age cohort and younger patients (controls) are defined as ≤64 years. Primary outcome analysis: Difference in proportion will be examined with chi squared or fishers exact tests. Secondary outcome analysis: Univariate analysis of variables between the two age groups will be conducted using unpaired students t-tests or Mann Whitney U tests. Analysis of more than two groups or variables will be conducted using ANOVA or Kruskal Wallis tests.
Proposed Start Date	1st February 2017
Proposed End Date	1st May 2020
Study Duration	Three years

4. INTRODUCTION

For the first time there are 11 million people aged 65 or over in the UK[1]. The number of older people suffering traumatic injury is increasing [2-6]. In those who survive the initial period after injury a significant proportion goes onto develop adverse events such as multiple organ dysfunction (MODS) [7,8]. This occurs as a result of an exaggerated systemic inflammatory response following major tissue trauma[9], where one or more organs do not function as they did prior to the traumatic injury. Recent reports suggest that MODS affects up to 33% of trauma patients [7,10-12]. Younger injured people who develop MODS usually recover quickly[13], whereas older patients appear to suffer prolonged organ dysfunction, which is complicated by persistent immunosuppression and infectious episodes[10,14,15]. This extends hospital stay, increases resource use and delays recovery after trauma [11,12]. MODS in older people is also associated with increased mortality [16-18] characterised by late, indolent death [14,19]. International evidence suggests that older age is strongly associated with MODS after trauma [7,11,12,14], however the age-related characteristics that contribute to this burden in the UK have not been reported.

Previously, we have examined the relationship between trauma and adverse outcomes but have not specifically focused on older patients [20-22]. It is possible that the immune systems of older patients react differently to injury when compared to younger cohorts, and this may increase vulnerability to MODS [14,23,24]. Decreased skeletal muscle mass in older people is reported to impair immune system function in intensive care patients[25] and severe injury may further alter immune cell activity, causing physiological changes leading to adverse outcomes[26,27]. Altered metabolism after trauma is associated with increased inflammatory responses[28] and together with the nutritional deficits observed in critically injured older people[29] these may contribute to age-related MODS. Frailty is also known to reduce physiological function [30,31] and frailty in older people independently predicts in-hospital complications such as pneumonia or deep vein thrombosis after injury [32]. Therefore it may be that frailty rather than age increases the risk of MODS after severe injury. Previous trauma studies suggest that both older age and frailty are associated with decreased longer-term independence after injury [32,33]. However the impact of MODS on longer-term function, dependence and recovery in older people has not been investigated. The lack of UK-based evidence means that the prevalence, predictors and outcomes of MODS in our older trauma patients are unknown.

This prospective observational study will evaluate the patterns of MODS in trauma patients and determine to what extent it is related to ageing and frailty. By understanding specific age-related predictors or drivers of MODS we aim to identify treatment or prevention strategies which will enhance recovery for severely injured older people. MODS is also associated with late, indolent death, and by studying patterns of this mortality in older patients we may be able to prognosticate futility. This may enable stratification of older patients most likely to respond to intervention and those who would benefit from supportive or palliative care. Finally, evidence of how MODS impacts longer-term recovery and quality of life will support rehabilitation practice, and where appropriate, self-managed recovery for older trauma patients and their support networks.

5. STUDY OBJECTIVES

This study aims to:

- Identify the prevalence, severity and patterns of MODS in older patients
- Determine predictors and risk factors of developing MODS for older patients
- Identify age related characteristics that contribute to MODS
- Examine the mode of mortality associated with MODS
- Analyse the relationship between MODS and longer-term recovery and quality of life for older patients

The primary outcome is the presence of MODS during the critical care admission period. An individual Sequential Organ Failure Assessment (SOFA) score of 1 in any organ represents dysfunction. Multiple organ dysfunction syndrome (MODS) is defined as a total daily SOFA score of >5.

Secondary outcomes are in-hospital mortality, ventilator use, level of organ support, adverse events such as infection or stroke, critical care stay and total length of stay. Longer terms outcomes are quality of life and recovery at one year post injury.

6. METHODOLOGY

Study Design

This is a pan-London prospective observational study which aims to characterise organ dysfunction in older trauma patients ≥65 years. All adults admitted to an adult critical care unit within one the London Major Trauma Centres (MTCs) will be considered for enrolment, with younger patients (<65 years) recruited as a control group.

Settings

There are four MTCs in London. Each site will have a nominated Principal Investigator (PI). Organ injury scoring training will be provided for local research nurses or data collectors prior to study commencement. Two funded research nurses from Queen Mary University of London (QMUL) will support patient enrolment, data collection and data quality monitoring across the four MTCs. Each site will be supported by an on-line information folder with the protocol, guidance/explanatory notes and contact details of the Principal Investigator. **For this study, a critical care unit is defined as either an Intensive Care Unit (Level 3 care) or a combined unit of Intensive Care (Level 3 care) and High Dependency Unit (Level 2 care).**

Inclusion Criteria

- Adult major trauma patients (≥16 years of age) admitted to adult critical care within one of the four London Trauma System MTCs. This includes direct admissions from the Emergency Department, admissions from the operating theatre or from a ward, transfers from other facilities and readmission to critical care.

Exclusion Criteria

- Patients with a burns-only injury
- Patients who are prisoners
- Patients who decline to provide informed consent or do not have consultee consent

Study Design / Plan – Study Visits

Trauma patients (≥16 years of age) admitted to MTC critical care during the enrolment phase of the study (two years in total) will be identified by the local PI together with clinical care staff. The local PI will be responsible for ensuring patient enrolment, participant consent, data collection, patient detail de-identification, data entry and storage. Data from routine clinical care records will be recorded daily by local and QMUL research nurses whilst the patient is admitted to the critical care unit.

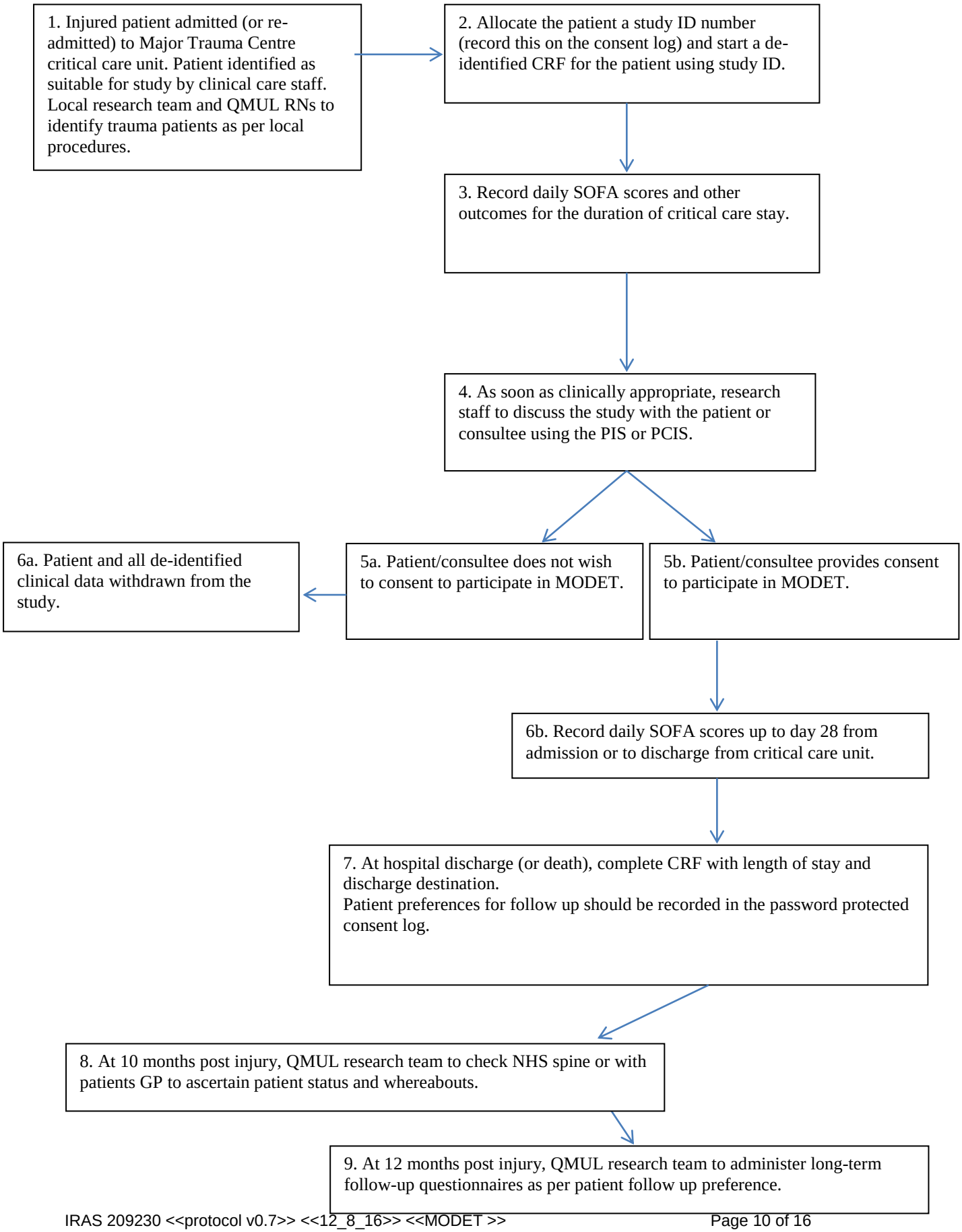
The clinical data collection will include:

- Demographics: Age within a range, gender, co-morbid disease, pre-injury medication
- Injury variables: Mechanism of injury, Injury Severity Score (ISS)
- Organ dysfunction: The frequency, pattern and severity will be measured daily using Sequential Organ Failure Assessment (SOFA) scoring
- Total number of days on organ support (CTCOFR score)
- Immune cell function: Daily clinical measures of lymphocyte and neutrophil counts
- Adverse events: Such as infection, delirium, stroke or cardiac dysfunction
- Nutrition: Nutritional requirements, nutrition intake and weight measurements
- Frailty screening using the Edmonton Frail Scale (https://www.nscphealth.co.uk/edmontonscale-pdf)
- Length of stay: In critical care and total hospital stay
- Mortality: Mode and timing

As soon as clinically appropriate (determined by the clinical care team in charge of the patient), consent will be sought for inclusion of data into the study and long term follow up. If the patient remains incapacitated due to injury or treatment, consent will be sought from a personal or nominated consultee.

At 12 months post injury patients will be approached by letter, email or telephone (according to patient wishes) and health-related quality of life and longer-term recovery data will be collected using the EuroQol-5D (EQ5D) questionnaire. This was chosen as it has been previously validated to capture outcomes in trauma patients including older people and takes approximately 15 minutes to complete.

Study Scheme Diagram



7. STUDY PROCEDURES

Each MTC will be identified by a number rather than name.

Eligible trauma patients admitted to the critical care unit during the study period will be identified by the clinical care team.

The PI and research nurses have responsibility to ensure patient anonymity is protected and maintained. They will also ensure that patient identities are protected from any unauthorised parties. Information regarding study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Although patient identifiable data will be available to research staff they will not be entering it on to the paper case record form (CRF). The de-identified data required for this study is already recorded as part of routine clinical care and as part of the Intensive Care National Audit and Research Centre (ICNARC) audit. Organ failure scoring is not usually conducted as part of routine clinical care however it uses parameters that are recorded by critical care clinical staff on a daily basis.

Paper CRFs will be stored within a locked office in each centre (only accessible to the centre PI and data collectors) and then entered onto the password protected study website by QMUL research nurses.

A password protected coding log which will include identifiable patient data (name, address and date of birth) for patients who have consented to long term outcome follow-up. This will be transferred to Elaine Cole (CI) at the end of the in-hospital data collection period. At ten months after injury the NHS Health and Social Care Information Centre (NHS Spine) or patients General Practitioner (GP) will be contacted to ensure that the patient is still alive at this time point. This will avoid erroneous long term follow up and exposing relatives to undue distress. At 12 months post injury, the EQ5D and questionnaire will be administered to each participant who has provided informed consent.

Schedule of Assessment

	In critical care	At discharge from hospital	10 month post injury NHS spine check/GP check	12 months post injury
Enrolment	x			
CRF initiation	x			
Informed consent	x			
Daily SOFA score and outcomes recorded	x			
CRF completion		x		
Long term follow up			x	x

End of Study Definition

The study will be formally completed when 12 month follow up for all patients has been obtained and data analysis is complete.

8. STATISTICAL CONSIDERATIONS

Sample size:

We are planning a study of older patients (≥65 years) and younger (<65 years) controls. Prior research data suggest that the MODS rate among younger patients is 23% and for older patients is 33%. If the true MODS rate in older people is 0.33, we will need to include 259 older subjects and 414 younger subjects per year to be able to reject the null hypothesis that the prevalence of MODS for older and younger patients is equal (power 0.80, alpha 0.05). The total sample size for the two year period is 1346 (518 older patients and 828 younger controls). Each London MTC will aim to enroll:
130 older patients (>64 years) and 207 younger patients (<65 years).

Methods of analysis:

Statistical analysis will be performed using SPSS v.23 (IBM Corporation, Armonk, NY,USA). A p value of <0.05 is considered statistically significant for univariate analysis. De-identified data will be cleaned and categorical data formatted into binary fields for analysis. Normal distribution will be assessed with the Shapiro-Wilk test.

Univariate analysis of variables between the two age groups (< 65 years and ≥65 years) will be conducted using unpaired students t-tests or Mann Whitney U tests (for parametric and non-parametric data respectively). Analysis of more than two groups (for example thresholds of immune counts or degrees of organ dysfunction) will be conducted using ANOVA or Kruskal Wallis tests. Chi-squared statistic or Fisher's exact tests will be used to compare proportions of MODS between the two cohorts.

Multivariable regression analysis will be used to determine statistically independent relationships between MODS and age plus other significant independent variables (such as the effect of injury severity, blood transfusion, on the development of MODS). Multivariate linear regression will be used to analyse continuous dependent variables and binary logistic regression for binary dependent variables. Results of linear regression will be reported as Beta co-efficient with 95% confidence intervals, and for logistic regression adjusted Odds ratios (OR) with 95% confidence intervals.

9. ETHICS

This study will be carried out in accordance with the ethical Principals in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. The study has been reviewed and approved by the London South East Research Ethics Committee on 26th October 2016.

Each participant in the study will be approach for informed consent to allow non-clinical care staff (QMUL research nurses and Chief Investigator) to:

1. access the status of the participant at ten months post injury via NHS Health and Social Care Information Centre or the patients GP
2. follow up the participant via telephone, letter or email at 12 months post injury

Incapacity:

For most of the severely injured patients admitted to a critical care unit, there will be a period of time where they require sedation and ventilation (life support) resulting in temporary incapacity. Specific injury factors such as hypoxia, haemorrhage or the presence of a traumatic brain injury may also add to the incapacity. During the in-hospital stage of the study, all of the data being collected is part of routine clinical care therefore there is time to wait to see if the patient regains capacity. Once this occurs, the study can be explained by the local collaborator and a participant information sheet given to the patient for 24-48 hours prior to seeking informed consent.

In those patients where capacity is not regained during the critical care stay every effort will be made to identify and consult with someone who knows the person who lacks capacity, such as a relative or significant other next-of-kin. The study will be explained to the personal consultee. This individual will be provided with a personal consultee written information sheet prior to seeking consent on a personal consultee consent form.

Where the person who lacks capacity has no family or friends who are willing and able to fulfil this role the local collaborator will ask the patients critical care consultant to provide consent as a nominated consultee.

Patients who die during the in-hospital study period will have their de-identified data included in the study.

10. DATA HANDLING AND RECORD KEEPING:

Routine de-identified clinical data will be collected and stored as per local Trust policies in accordance with the Data Protection Act and NHS Caldicott Guardian. When the study is complete, the Principal Investigator will ensure that records are to be stored for 20 years as per the Sponsors Research Governance Framework and Trust Policy in the approved repository for long-term storage of local records is the Trust Modern Records Centre.

11. TRIAL COMMITTEES

The Chief Investigator of the study is Elaine Cole, Centre for Trauma Sciences, Blizard Institute, QMUL. Each participating MTC will have a local PI. These individuals will participate in the study management group (SMG) together with trauma, geriatric and nutritional expert advisors. The SMG will have the following responsibilities:

To provide leadership and/or subject expertise for the study within the individual MTC,
Nominate local data collection personnel to work with QMUL research nurses,
Ensure consent procedures are followed as per REC ethics approval,
Act as guarantor for the integrity and quality of the local data,
Communicate with the Chief Investigator.

The SMG will also have a statistician (from QMUL) and a PPI representative. Funding obtained for both of these SMG members has been obtained from the Dunhill Medical Trust.

12. FINANCE AND FUNDING

This study is fully funded by the Dunhill Medical Trust (R460/0216). This funding provides two research nurses to assist with data collection across the four MTCs and perform with long term follow up. The funding also covers statistician input and PPI travel, subsistence and meeting time.

13. INDEMNITY

The sponsor is Queen Mary University of London.

14. DISSEMINATION OF RESEARCH FINDINGS

Data will be written up, presented and disseminated in a timely manner. Elaine Cole will draft the initial scientific report of this study. The main outputs will be research papers for general journals and trauma specialty journals, research abstracts for presentation to national and international meetings and a final report summarising the overall findings. Findings will be disseminated via the website: http://www.londontraumasystem.org and the public/patient-focussed trauma website: http://www.aftertrauma.org/

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