Barts and The London
School of Medicine and Dentistry

ORDIT: Organ Dysfunction in Trauma

A national prospective point prevalence study of multiple organ dysfunction in critical care trauma patients

http://www.c4ts.qmul.ac.uk/national-studies-ordit/what-is-ordit

Full Title	Organ Dysfunction in Trauma: A national prospective point prevalence study
Short Title/Acronym	**ORDIT**
Sponsor	Queen Mary, University of London Contact person of the above sponsor organisation is: Dr Sally Burtles Joint Research Management Office 5 Walden Street London E1 2EF Phone: 020 7882 7260 Email: sponsorsrep@bartshealth.nhs.uk
REC Reference	England/Wales: 15/LO/1626, South East, 29.10.2015
Chief Investigator	Karim Brohi, Professor of Trauma Sciences, Queen Mary University of London
Principal Investigator	Elaine Cole, Trauma Research Fellow, Queen Mary University of London

MTC STUDY SITES: ENGLAND AND WALES

Addenbrooke's Hospital Cambridge, Cambridge University Hospitals NHS foundation trust

Aintree University Hospital Liverpool, Aintree University Hospitals NHS Foundation Trust

Derriford Hospital Plymouth, Plymouth Hospitals NHS Trust

Frenchay Hospital Bristol, North Bristol NHS Trust

Hull Royal Infirmary, Hull and East Yorkshire Hospitals NHS Trust

James Cook University Hospital Middlesbrough, South Tees Hospitals NHS foundation trust

John Radcliffe Hospital Oxford, Oxford University Hospitals NHS trust

King's College Hospital London, King's College Hospital NHS foundation trust

Leeds General Infirmary, Leeds teaching Hospitals NHS trust

Manchester Royal Infirmary, Central Manchester University Hospitals NHS Foundation Trust

Morriston Hospital Swansea, Abertawe Bro Morgannwg University Health Board

Northern General Hospital Sheffield, Sheffield Teaching Hospitals NHS Foundation Trust

Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust

Queen's Medical Centre Nottingham, Nottingham University Hospitals NHS trust

Royal Liverpool University Hospital, Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal London Hospital, Barts Health NHS Trust

Royal Preston Hospital, Lancashire Teaching Hospitals NHS Foundation Trust

Royal Sussex County Hospital Brighton, Brighton and Sussex University Hospitals NHS Trust

Royal Victoria Infirmary Newcastle, The Newcastle Upon Tyne Hospitals NHS foundation trust

Salford Royal Hospital, Salford Royal NHS Trust

St George's Hospital London, St George's Healthcare NHS Trust

St Mary's Hospital London, Imperial College Healthcare NHS Trust

University Hospital Coventry, University Hospitals Coventry and Warwickshire NHS Trust

University Hospital of North Staffordshire Stoke on Trent, University Hospitals of North Midlands NHS Trust.

University Hospital South Manchester, The University Hospital of South Manchester NHS Foundation Trust

University Hospital Southampton, University Hospital Southampton NHS Foundation Trust

University Hospital of Wales, Cardiff, Cardiff and Vale University Health Board

GLOSSARY OF TERMS AND ABBREVIATIONS

CI	Chief Investigator
CRF	Case Record Form
CRO	Contract Research Organisation
GAfREC	Governance Arrangements for NHS Research Ethics Committees
JRMO	Joint Research Management Office
MTC	Major Trauma Centre
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 or study
PCIS	Personal Consultee Information Sheet
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SMG	Study Management Group

IINTRODUCTION

Multiple organ dysfunction syndrome (MODS) is a dysfunctional systemic inflammatory response following major tissue trauma causing significant morbidity and in-hospital mortality (1, 2). Recent reports suggest that the incidence of MODS following severe injury is falling and but with significant variation in reported rates (10 - 33%) from Australia, USA and Germany (3-5). Novel therapeutic approaches in early trauma management have increased survival of many people who would previously have died from major haemorrhage (6). Similarly, contemporary trauma systems have resulted in mortality benefits for those who would not have otherwise survived the early post-injury phase (7-9). However this has resulted in greater numbers of severely injured patients admitted to critical care who are at risk of developing MODS (3, 10).

The pattern and temporal trends of contemporary MODS also appear to be changing. Historic studies observed a bimodal pattern of MODS development characterised by 'early' and 'late' organ dysfunction (1, 11). Recent registry data now suggests that the onset of MODS has a multimodal distribution with a peak incidence present within the first 48-72 hours following injury and that this early fulminant MODS has the greatest association with mortality (5, 12). Other studies describe an early onset MODS which is more transient, tending to resolve within four to five days post injury (3, 10). Further, the phenotype of persistent inflammation-immunosuppression catabolism syndrome (PICS) has been described which is characterised by a late, non-resolving MODS lasting more than seven - ten days post injury (12-14).

The definition of MODS lacks an international standard (1, 15) with a number of physiological scoring systems e.g. Sequential Organ Failure Assessment Score (SOFA), Denver Score and Marshall Score (16, 17), used to diagnose the condition following trauma. Once present, MODS has a considerable impact on the patient experience and health costs. Evidence suggests that MODS increases resource use, prolongs critical care and hospital stay, and further complicates longer term patient recovery (3, 4).

From April 2010, inclusive trauma systems were introduced in England and Wales, with Scotland to implement in 2016. An inclusive trauma system is organised to deliver optimum care at the most appropriate facility at the right time (18). Regionalised trauma care is delivered within a specified geographical location, with the most severely injured patients managed in Level 1 hospitals (19), known in the UK as Major Trauma Centres (MTCs). The national system is perfectly positioned to prospectively capture the current situation of MODS for severely injured patients admitted to UK MTC critical care units.

At present there is no specific treatment for MODS, however a greater understanding of the clinical manifestation of post-traumatic MODS in the UK will facilitate enhanced stratification of at-risk populations to improve outcomes, predict resource use, and aid the design of future clinical trials.

STUDY OBJECTIVES

Primary Objective

The primary objective is to investigate the prevalence of MODS in severely injured patients admitted to MTC critical care units in the UK.

Secondary Objectives

Secondary objectives are to:

- characterise the severity and temporal variation of MODS in critical care trauma patients
- examine the incidence and mode of mortality associated with MODS following trauma
- evaluate the relationship between MODS and other clinical outcomes, length of stay and quality of life.

Primary Outcome

The primary outcome will be the presence of MODS during the study period. This is defined as a SOFA score of >2 in two or more organ systems.

Secondary Outcomes

Secondary outcomes include in-hospital mortality, ventilator use, organ support, length of critical care stay (levels 3 and 2), total hospital stay and quality of life one year post injury.

METHODOLOGY

Study Design

A one month prospective national point prevalence cohort study of trauma patients ≥16 years admitted to an adult critical care unit within a Major Trauma Centre (MTC).

Settings

There are 26 MTCs in England, two in Wales and four (pre-designation) in Scotland. Using voluntary convenience sampling, each MTC will be invited to participate. Each site will have a nominated study lead and data collector(s) from within the critical care clinical team. Organ injury scoring training will be provided prior to study commencement. Each site will

be supported by an 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

All consecutive trauma patients (≥16 years of age) admitted to adult critical care from 08.00 on day one of the study to 07.59 on the final day of the in-hospital study period (one month in total) who subsequently provide informed consent to participate. This includes all trauma patients: 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

- Any inclusion criteria not met
- <16 years old
- Burns only injury
- Prisoner
- Decline to participate
- Decline to provide informed consent

All consecutive trauma patients (≥16 years of age) admitted to adult critical care from 08.00 on day one of the study to 07.59 on the final day of the in-hospital study period (one month in total) will be identified by clinical care staff. The local study investigator will be responsible for patient enrolment, participant consent, data collection, de-identification and data storage.

STUDY PROCEDURES

Data will be collected in individual centre critical care units using a paper case record form (CRF). The de-identified data required 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 in routine care by critical care clinical staff on a daily basis. This will be completed for every eligible trauma patient in the critical care unit during the study period. Paper CRFs will be stored within a locked office in each centre only accessible

to the centre study lead and data collectors. Each centre will be identified by a numeric code rather than name.

In hospital data collection for each patient:

A Admission variables: age, gender, time and date of traumatic injury, ED admission physiology (base deficit, lactate, systolic blood pressure and GCS), ED admission coagulation (INR), intravenous fluids, blood products and antifibrinolytics administered in first 24 hours post injury.

B Injury variables: mechanism of injury, list of injuries, surgical or interventional radiology episodes and a confirmed list of all injuries.

C Critical care data: date of admission to CCU, admission APACHE score, daily organ failure scores using Sequential Organ Failure Assessment (SOFA), days on organ support (inotropes and renal replacement therapy), ventilator free days, daily highest CRP and lowest lymphocyte counts (all blood taken as part of routine care – fields omitted if not taken by clinical care team). If more than one blood test is taken in a 24 hour period, the worst value will be recorded

D Follow up data: date of in-hospital mortality or date of discharge, critical care and hospital length of stay.

Data will be de-identified by the clinical care team. A coding log will include identifiable patient data in order to allow follow-up of outcomes and this will only be accessed by local collaborators. This will allow local collaborators to identify individual patients whilst other members of the study team cannot trace data back to an individual patient. At the end of the initial phase of the study when all patients have been discharged within each site, the anonymous CRFs will be scanned and sent to the Principal Investigator via an NHS net email account.

At ten months post study commencement, the Principal Investigator (Elaine Cole: EC) will access the contact details and preferences for each patient from the participating sites. In England and Wales, the NHS Health and Social Care Information Centre and in Scotland the unique patient identifier will be accessed by to ensure that the patient is still alive at this time point. At 12 months post injury, the EQ5D questionnaire (Five questions in total - takes

5-10 minutes to complete) will be administered to each patient who has provided informed consent, to determine their quality of life (QoL) at 12 months post injury and MODS.

End of Study Definition

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

STATISTICAL CONSIDERATIONS

Estimated sample size: 550

The rate of admission to critical care is likely to vary between MTCs nationally. Each MTC is required to submit annual trauma patient figures to the Trauma Audit and Research Network (TARN). We used the severely injured cohorts (ISS>15) from TARN as a surrogate measure of annual trauma admissions to critical care. From this we calculated monthly critical care admissions. Local critical care unit pilot data analysis (From ACIT II and POET studies) showed that there are approximately 300 severely injured patient admissions per annum, which is approximately 25 patients in a month period. This number was then multiplied by the maximum number of MTCs that may participate (32) = 800 if all units participate. We understand that not all patients will provide informed consent however local data suggests that decline-to-participate rates in ACIT II and POET are 1%. We therefore set a conservative estimate of two thirds of the potential total but hope to exceed this target to get the most representative cohort.

Statistical analysis will be performed using SPSS v21 (IBM Corporation, Armonk, NY, USA). Univariate analysis of variables between two groups 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 will be conducted using ANOVA or Kruskal Wallis tests. Percentages or proportions will be analysed using Chi square or Fisher's exact tests. A p value of <0.05 is considered statistically significant for univariate analysis. Multivariate analysis will be used to determine statistically independent relationships between MODS and other variables. Factors achieving significance of $p<0.15$ in univariate analysis will be entered into the regression models. 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.

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 **REC South East (England/Wales): 15/LO/1626**.

Each participant in the study will be approach for informed consent to allow:

1. Non-clinical care staff (QMUL Principal Investigator) to access de-identified clinical data
2. The Principal Investigator to access the status of the participant at ten months post injury via NHS Health and Social Care Information Centre/Scottish Unique identifier
3. Follow up contact via telephone, letter or email at 12 months post injury

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 ORDIT 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. If this occurs, the study can be explained by the local collaborator and a participant information sheet given to the patient for 24 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 (who has no connection with the study) 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 based on the advice provided by the personal consultee or nominated consultee.

The Principal Investigator and local collaborators have responsibility to ensure patient anonymity is protected and maintained. They will also ensure their 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.

Data will be de-identified by the clinical care team. A coding log will include identifiable patient data in order to allow follow-up of outcomes and this will only be accessed by local collaborators. This will allow local investigators to identify individual patients whilst other members of the study team cannot trace data back to an individual patient. At the end of the initial phase of the study when all patients have been discharged within each site, the anonymous CRFs will be scanned and sent to the Principal Investigator via an NHS net email account: Elaine.cole1@nhs.net

Prior to the 12 month follow up, NHS Health and Social Care Information Centre will be contacted to ensure that the patient is still alive at this time point. This will avoid erroneous follow up and exposing relatives to undue distress. In England and Wales, the NHS spine and in Scotland the unique patient identifier will be accessed.

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.

STUDY LEADERSHIP

The Chief Investigator of the study is Professor Karim Brohi, Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London (QMUL). The study will be coordinated by Elaine Cole, Principal Investigator, Centre for Trauma Sciences, Blizard Institute, QMUL. Both of these investigators hold honorary clinical positions at Barts Health NHS Trust. There will also be a local named collaborator from each participating site. These individuals will comprise the study management group (SMG) and will have the following responsibilities:

To provide leadership for the study within the individual MTC,
Nominate local data collection personnel,
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 national coordinator and Principal Investigator.

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. Study collaborators will be named as authors on any publication or report. Findings will be disseminated via the centre for trauma sciences website, and via online seminars for MTC participation.

See all study documents at:

http://www.c4ts.qmul.ac.uk/national-studies-ordit/what-is-ordit

REFERENCES

1. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009 Sep;40(9):912-8. PubMed PMID: 19541301. Epub 2009/06/23. eng.
2. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Archives of surgery (Chicago, Ill : 1960). 2005 May;140(5):432-8; discussion 8-40. PubMed PMID: 15897438. Epub 2005/05/18. eng.
3. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. The journal of trauma and acute care surgery. 2013 Mar;74(3):774-9. PubMed PMID: 23425734. Epub 2013/02/22. eng.
4. Frohlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: An analysis of 31,154 patients from the TraumaRegister DGU. The journal of trauma and acute care surgery. 2014 Apr;76(4):921-8. PubMed PMID: 24662853. Epub 2014/03/26. eng.
5. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, et al. Temporal trends of postinjury multiple-organ failure: Still resource intensive, morbid, and lethal. The journal of trauma and acute care surgery. 2014 Mar;76(3):582-93. PubMed PMID: 24553523. Epub 2014/02/21. eng.
6. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014 Oct 18;384(9952):1455-65. PubMed PMID: 25390327. Epub 2014/11/13. eng.
7. Gunst M, Ghaemmaghami V, Gruszecki A, Urban J, Frankel H, Shafi S. Changing epidemiology of trauma deaths leads to a bimodal distribution. Proceedings (Baylor University Medical Center). 2010 Oct;23(4):349-54. PubMed PMID: 20944754. Pubmed Central PMCID: PMC2943446. Epub 2010/10/15. eng.
8. Davenport RA, Tai N, West A, Bouamra O, Aylwin C, Woodford M, et al. A major trauma centre is a specialty hospital not a hospital of specialties. The British journal of surgery. 2010 Jan;97(1):109-17. PubMed PMID: 20013932. Epub 2009/12/17. eng.
9. Twijnstra MJ, Moons KG, Simmermacher RK, Leenen LP. Regional trauma system reduces mortality and changes admission rates: a before and after study. Annals of surgery. 2010 Feb;251(2):339-43. PubMed PMID: 20010086. Epub 2009/12/17. eng.
10. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Critical care medicine. 2012 Apr;40(4):1129-35. PubMed PMID: 22020243. Pubmed Central PMCID: PMC3343366. Epub 2011/10/25. eng.
11. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. The Journal of trauma. 1996 Apr;40(4):501-10; discussion 10-2. PubMed PMID: 8614027. Epub 1996/04/01. eng.
12. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. The journal of trauma and acute care surgery. 2012 Jun;72(6):1491-501. PubMed PMID: 22695412. Pubmed Central PMCID: PMC3705923. Epub 2012/06/15. eng.
13. Hu D, Ren J, Wang G, Gu G, Chen J, Zhou B, et al. Persistent inflammation-immunosuppression catabolism syndrome, a common manifestation of patients with enterocutaneous fistula in intensive care unit. The journal of trauma and acute

care surgery. 2014 Mar;76(3):725-9. PubMed PMID: 24553541. Epub 2014/02/21. eng.
14. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, et al. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. The journal of trauma and acute care surgery. 2014 Jan;76(1):21-9; discussion 9-30. PubMed PMID: 24368353. Epub 2013/12/26. eng.
15. Dewar DC, Balogh ZJ. The epidemiology of multiple-organ failure: a definition controversy. Acta anaesthesiologica Scandinavica. 2011 Feb;55(2):248-9; author reply 9-50. PubMed PMID: 21226867. Epub 2011/01/14. eng.
16. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive care medicine. 1999 Jul;25(7):686-96. PubMed PMID: 10470572. Epub 1999/09/02. eng.
17. Lansink KW, Leenen LP. Do designated trauma systems improve outcome? Current opinion in critical care. 2007 Dec;13(6):686-90. PubMed PMID: 17975391. Epub 2007/11/03. eng.
18. Lansink KW, Gunning AC, Spijkers AT, Leenen LP. Evaluation of trauma care in a mature level I trauma center in the Netherlands: outcomes in a Dutch mature level I trauma center. World journal of surgery. 2013 Oct;37(10):2353-9. PubMed PMID: 23708318. Epub 2013/05/28. eng.