SPOT-Light Protocol

(Sepsis: Pathophysiological & Organisational Timing)

Protocol Version 1.1

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11 Pages

Project Summary

It is useful to consider time in critical illness from two perspectives. The first of these begins logically with onset of the pathology. With the exception of conditions such as myocardial infarction or trauma where this moment is marked by a classic symptom or an external event, then defining time zero is difficult. For this reason, an organisational frame of reference, such as hospital admission or time of referral to specialist team, is more commonly used. Delay following this organisational time is important because it is often a modifiable factor with regard to the delivery of health care. However, pathophysiological timing remains relevant because if the disease process is dynamic (and this is part of the hypothesis of this study) then it determines the phenotype of disease at any particular moment.

This project proposes to measure delay to admission to Intensive Care (ICU) using both organisational and pathophysiological timing. Delays in the United Kingdom NHS are widely reported (1) possibly because there are fewer ICU beds than in many other developed health care systems. (2) We intend to measure the chronological time between the moment when a patient is 'referred and assessed as requiring Critical Care', and their actual time of admission. We will determine how often delays occur, and whether they affect outcome. Requirements for critical care are not, however, absolute. Importantly, the assessment of a prospective patient is not made in isolation. If ICU beds are already fully occupied, then decision makers must organise a transfer to another unit (with risks to the patient), organise a premature discharge of another patient, or defer admission. We will also therefore consider such deferments alongside delays, and their impact on survival.

In addition, the project will consider pathophysiological timing. This is of particular importance in sepsis where current biological models suggest that there is a phased response to infection. (3) In this case, it is possible that patients are admitted to critical care at different phases of disease; moreover, these phases may be clinically relevant and affect response to treatment. pathophysiological delay will be estimated using the concept of illness trajectories (which also may have a biological correlate) (4). This means that a patient who is slowly deteriorating is likely to have been ill for longer. In other words, their pathophysiological time zero will be earlier than another patient who is is rapidly deteriorating. This illness trajectory will be estimated by measuring the change in severity of illness between ward assessment and ICU admission. The effect of these illness trajectories, and therefore of the pathophysiological timing of ICU admission, will be evaluated with particular attention to severe sepsis.

Research Objectives

This study aims to describe the impact of delay to critical care on patient survival (90 day) and resource utilisation (organ support free days). Delay will be considered from both a chronological perspective, and placed in the context of resource availability, and from a pathophysiological perspective.

This produces the following specific objectives.

1. To measure the proportion of patients not immediately admitted to critical care, the duration of the interval between assessment and admission, and to understand the circumstances surrounding this.
2. To use this detailed description to validate the Delayed Admission Field in the much larger Case Mix Programme (ICNARC CMP Version 3.1), and from this evaluate the impact of delay in a larger population.
3. To measure the effect on 90 day survival of the interval between the moment when a patient is referred and assessed as requiring critical care, and the actual time of admission.
4. To use the rate of deterioration in acute physiology prior to ICU admission to estimate the duration of the pathological process, and to measure the effect of this trajectory (as a proxy for pathological delay) on 90 day survival with specific attention to those patients with severe sepsis.

Background

The National Patient Safety Agency analysed 425 acute hospital deaths, and reported that 15% involved delay in recognition and response to physiological deterioration. (5) Delay has traditionally been considered to simply lead to a greater severity of illness. With regard to sepsis however, delay may have a more complex effect.

Sepsis commences with an uncontrolled and overwhelming pro-inflammatory response. Among survivors of this insult, there is a transition to an anti-inflammatory cytokine milieu and at varying times development of multi-organ failure. (6) There are accompanying changes in endocrine (7), and metabolic (8) phenotypes. Similar severities of illness may therefore conceal different pathophysiological clinical syndromes. An important corollary is that a therapy modulating any of these pathways may be less effective or even harmful in these late phenotypes. (9, 10). This is the basis of considering delay (or duration of illness) with regard to pathophysiological timing.

Now, in addition, critical care is an expensive and scarce resource. The UK in particular has seven fold fewer critical care beds than Germany. (2) Intensive Care Units must run at maximum occupancy, and there is a continual process of triage. Evaluation of ward patients and early recognition of severe illness has become a national priority. (5) There is a paradox here, however. To merit admission to ICU, a patient has to reach a certain severity threshold. Now sometimes severe physiological disturbance may arrive suddenly as with, for example, a heart attack (myocardial infarction). In other cases, and the paradigm here is sepsis, then a patient progresses at varying speed from early and mild disease to late and severe disease. In such cases, the process of triage, by selecting only the severest cases, may delay access to the benefits of critical care.

While there have been great efforts to predict which ward patients are likely to require critical care (11), there has not as yet been a systematic evaluation of how this delay affects outcome.

There is biological (12) and clinical (12) evidence that delay in antibiotics and in fluid resuscitation (13) reduces survival. But these are treatments which may be administered on the ward. With regard to organ support, which may only be provided in critical care areas, the picture is less clear. On the one hand there is weak evidence that early renal replacement therapy is of benefit. (14) whilst with mechanical ventilation the issue is more subtle - some patient groups showing benefit (15) and others appear to be safe to 'watch and wait'. (16)

This means there is a lack of knowledge as to which patients might benefit most from early admission. With a fixed number of beds, admitting one patient who gains less benefit from an early therapy, simultaneously delays the admission of another patient who may respond better. Even when there is evidence that delay to admission is harmful (17), it is not known whether there is a linear relationship between the timeliness of therapy and benefit. If after an early window of opportunity the response to prompt intervention flattens out then it may in fact be best to triage those with early mild disease than those with late severe disease. These are unanswered questions.

This study will distinguish itself from previous work by asking not just whether delay causes harm, but how the magnitude of delay modifies its effect, and repeat this using two metrics: organisational and pathophysiological timing.

Study Design

Patient Flow

Sites may participate in the study by collecting patient data in one of two ways.

1. Patient data will where possible be collected prospectively. This means that patients assessed on the ward by critical care decision makers (outreach teams or medical staff) will have their severity of illness documented at the time of assessment on a standardised case report form. It is obviously not possible to predict which patients will be admitted to critical care at this stage. Those patients who go on to be admitted to critical care will then be linked to the data abstracted for the Case Mix Programme.
2. Where prospective data collection is not feasible (because of local constraints) then sites may choose to collect data retrospectively. In this case, when a patient is admitted to critical care their medical record will be reviewed and details of their severity of illness at the time of first contact with a critical care decision maker will be abstracted onto the case report form.

Patients from sites collecting data prospectively who are not admitted to critical care will act as the comparator group for the secondary analysis of reasons for delayed or deferred admission.

Data Collection

A data collection form, data collection manual (with rules/definitions), field specification and flows will be produced.

Data collection for the study will be piggybacked onto routine data collection for the Case Mix Programme (CMP), the national comparative audit of patient outcomes from adult general critical care units in England, Wales and Northern Ireland. Specifically, Critical Care Outreach Teams (CCOT) and medical staff will be will be invited to submit data for evaluations of patients assessed outside the ICU.

The amount of additional data required for each patient, over and above those routinely collected for the CMP, will be relatively small. Additional data will include:

- Time and Date of evaluation of the patient on the ward
- Severity of illness at the time of evaluation
- Outcome of the evaluation in terms of recommendation for the location of ongoing care
- Bed status or workload of the critical care unit at the time of the evaluation
- Severity of illness (Sepsis-Related Organ Failure Assessment - SOFA score) on the second and the final day of the critical care admission.
- Timing of initiation of organ support (already collected but not abstracted as part of the Department of Health's Critical Care Minimum Data Set)

Depending on local infrastructure for CMP data collection, one of three possible modes for data collection will be identified:

- Modification of existing Version 3.1 CMP-compatible software applications to include the additional fields,
- Web-based data entry of additional fields and CMP Admission Number for linkage to CMP data,
- Simple, one-page, paper form to include the additional fields.

As for CMP data, all the additional data will undergo extensive validation, both locally and centrally, for completeness, illogicalities and inconsistencies. Data collection is anticipated to be completed in twelve months, assuming 50 participating critical care units with around 500 admissions per year of which 160 spend time on the ward prior to admission (numbers derived from CMP database 2007).

Inclusion & Exclusion Criteria

The following patients will be eligible:

Ward patients who are referred for formal assessment by a critical care decision maker (e.g. the CCOT or any member of the medical staff) for consideration of admission to ICU.

Exclusions include

Paediatric patients (Age < 18 years)

Elective or planned admissions to critical care

Sample Size

Power for sample sizes is tabulated below for mortality increases arising from delay to admission. Based on 2007 CMP data, ≈160 patients are seen per CCOT per year prior to ICU admission with an eventual mortality of ≈29%. Ward delays are estimated to occur in between 10-40% of admissions. (1) Collaborative arrangements already exist with 30 Outreach teams, and similar projects have successfully recruited >80 units.

If we hypothesise that delay increases mortality by 5, 7.5 or 10% then the following sample sizes would be required:

Sample Size	Number of Centres	5%	7.5%	10%
4,830	30	61-95%	91-100%	99-100%
6,440	40	73-95%	97-100%	100%
8,050	50	82-99%	99-100%	100%

In other words, 40 CCOTs participating (6440 patients) gives a power to detect a 5% mortality increase ranging from 73% (if 10% of admissions are delayed) to 95% (if 40% are delayed)).

We have set a target sample size of 9,000 patients which includes a 10% adjustment for missing data and then rounds up. We further estimate on the basis of site recruitment to date that around one half of sites will be able to collect data prospectively and the ratio of patients assessed to patients admitted at these sites will be around 1:5. This means that 12,075 to 20,125 patients who referred for, but assessed as not requiring, critical care will be available for analysis.

Interventions

None

Outcome Measures

The Medical Research Information Service will be used to trace the current status of patients to determine survival to 90 days. Organ-support free survival will be calculated by subtracting days of basic and advanced organ support (derived from the existing Critical Care Minimum Dataset) from the survival period.

Missing Data

Extensive data validation will be employed to ensure the data are as complete as possible. Patients missing large amounts of routine data (for example, patients dying at or around the time of evaluation) will

be excluded from the modelling. Other missing data will be handled with multiple imputation techniques. (18)

Analysis

A hierarchical (multilevel) cox proportional hazards regression model will be used to assess the effect of the interval between the time of initial evaluation on the ward and subsequent ICU admission. Using a hierarchical model, with patients nested within critical care units, will enable us to include both fixed and random effects at the unit level, taking appropriate account of the covariance structure. Adjustment will be made for the diagnosis, the severity of illness (at the time of the evaluation), and for the clinical decision resulting from that evaluation. Survival among patients who are referred and assessed as not requiring critical care will provide the baseline against which this comparison will be made. The duration of organ support free survival will be a secondary endpoint. This will form the basis for the evaluation of organisational delays to critical care.

Reasons for deferred or delayed admission to critical care will be evaluated. Risk factors (in terms of patient demographics and severity of illness at time of ward assessment) will be identified which distinguish those patients who are referred to critical care from those who are not.

Secondly a trajectory of illness will be estimated for each patient based on the rate of deterioration preceding ICU admission (calculated as the ratio of the difference between acute physiology scores at ward assessment and ICU admission, and the time interval between assessment and admission). This trajectory will be used as a marker of the likely pathological delay between ICU admission and illness onset. A similar model to that for organisational delays will be constructed, but replacing delay with this estimate of pathophysiological time-zero.

Finally, since the underlying hypothesis of this project focuses on the time dependence of sepsis, then such patients will form the principle a priori sub-group analysis. In addition, the time dependence of specific critical care therapies (ventilation, renal replacement etc.) will be separately modelled.

Organisation

Service User Involvement

We will promote and support active public involvement in this research with a view to ensuring any recommendations regarding future research and policy are relevant to future patients' needs and concerns. We will circulate recommendations for future research and policy, arising from this work, to a wide range of users for comment, feedback, and where appropriate, direct inclusion.

All involvement of service users in this study will follow the guidelines and recommendations for good practice from INVOLVE (http://www.invo.org.uk).

Funding

Research costs for this study have been met by a grant from the Wellcome Trust (Wellcome Research Training Fellowship 088613). There are no NHS support costs or excess treatment costs associated with this research as there is no deviation from usual care. We will nonetheless seek for this study to be adopted by the National Institute of Health Research (NIHR) so that support may be provided via the Comprehensive Local Research Network (CLRN).

Research Governance

This study will be managed according to the Department of Health Research Governance Framework (http://www.dh.gov.uk/en/Researchanddevelopment/A-Z/Researchgovernance /index.htm) and the Medical Research Council Guidelines for Good Research Practice (http://www.mrc.ac.uk/pdf-good_research_practice.pdf), Guidelines for Good Clinical Practice in Clinical Trials (http://www.mrc.ac.uk/pdf-ctg.pdf) and Procedure for Inquiring into Allegations of Scientific Misconduct (http://www.mrc.ac.uk/pdf-mis_con.pdf). The study will be co-ordinated at the Intensive Care National Audit & Research Centre (ICNARC). ICNARC has developed its own policies and procedures based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

Ethical arrangements

Ethical approval will be sought from the National Health Service Research Ethics Service. Because a very large proportion of patients will be deemed incapable of consent as a consequence of the severity of their illness, a request to extract data from patients without their consent will be made. This will be justified on similar grounds to the Intensive Care National Audit & Research Centre Case Mix Programme (ICNARC-CMP), and the (SPOT)light study (REC approval 10/H0306/19). A separate application will be made to the National Information Governance Board for Section 251 approval to use patient identifiable information (name, date of birth, postcode and NHS number) to link study records to the Medical Research Information Service (MRIS) to determine 90 day survival - again this will be similar to the successful applications for the ICNARC CMP and (SPOT)light.

Indemnity

ICNARC holds professional liability insurance (certificate number A05305/0808, Markel International Insurance Co Ltd) to meet the potential legal liability of the sponsor for harm to participants arising from the management of the research. Indemnity to meet the potential legal liability of the sponsor and employers for harm to participants arising from the design of the research is provided by the NHS indemnity scheme. Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

Study Management Group

The day-to-day running of the trial will be overseen by a Study Management Group consisting of the Chief Investigator and Co-investigators.

Data monitoring

As the study does not involve any change to usual care for patients, an independent Data Monitoring Committee (DMC) will not be required. The SSG will oversee those responsibilities usually delegated to a DMC and these have been incorporated into the terms of reference.

Appendix

Study Steering Group

The role of the Study Steering Group (SSG) is to provide overall supervision for this study on behalf of the funder (Wellcome) and sponsor (ICNARC) and to ensure that the study is conducted to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice. The day-to-day management of the study is the responsibility of the Investigators, and the Chief Investigator will set up a separate Study Management Group (SMG) to assist with this function.

The SSG should approve the protocol and study documentation in a timely manner.

In particular, the SSG should concentrate on progress of the study, adherence to the protocol, patient safety and consideration of new information of relevance to the research question.

In the absence of a Data Monitoring Committee, the SSG should monitor the study data, and data emerging from other related studies, and consider whether there are any ethical or safety reasons why the study should not continue.

The safety, rights and well being of the study participants are the most important consideration and should prevail over the interests of science and society.

The SSG should provide advice, through its chair, to the Chief Investigator, the sponsor, and the funder, on all appropriate aspects of the study. Specifically, the SSG will:

- Monitor recruitment rates and encourage the SMG to develop strategies to deal with any recruitment problems.
- Monitor data completeness and comment on strategies from SMG to encourage satisfactory completion in the future.
- Monitor follow-up rates and review strategies from SMG to deal with problems including sites that deviate from the protocol.
- Approve any amendments to the protocol, where appropriate.
- Approve any proposals by the SMG concerning any change to the design of the study.
- Oversee the timely reporting of study results.
- Approve and comment on the statistical analysis plan.
- Approve and comment on the publication policy.
- Approve and comment on the main study manuscript.
- Approve and comment on any abstracts and presentations of results during the running of the study
- Approve external or early internal requests for release of data or subsets of data.

Membership of the SSG should be limited and include an independent Chair and at least two other independent members. The Investigators and the study staff are ex-officio.

Responsibility for calling and organising the SSG meetings lies with the Chief Investigator. The SSG should meet at least annually, although there may be periods when more frequent meetings are necessary.

There may be occasions when the sponsor or another stakeholder will wish to organise and administer these meetings in exceptional circumstances.

The SSG will provide evidence to support any requests for extensions, including that all practicable steps have been taken to achieve targets.

The SSG will maintain confidentiality of all study information that is not already in the public domain.

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