# Measuring Morbidity following Major Surgery

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I, Michael Patrick William GROCOTT, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis (below).

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**Abstract**

A systematic review of the efficacy of a specific perioperative haemodynamic management strategy was performed to explore the balance between therapeutic benefit and adverse effects. Whilst mortality and length of hospital stay were reduced in the intervention group, pooling of morbidity data for between-group comparisons was limited by the heterogeneity of morbidity reporting between different studies. Classification, criteria and summation of morbidity outcome variables were inconsistent between studies, precluding analyses of pooled data for many types of morbidity. A similar pattern was observed in a second systematic review of randomised controlled trials of perioperative interventions published in high impact surgical journals.

The Post-operative Morbidity Survey (POMS), a previously published method of describing short-term postoperative morbidity, lacked validation. The POMS was prospectively collected in 439 patients undergoing elective major surgery in a UK teaching hospital. The prevalence and pattern of morbidity was described and compared with data from a similar study using the POMS in a US institution.

The type and severity of surgery was reflected in the frequency and pattern of POMS defined postoperative morbidity. In the UK institution, many patients remained in hospital without morbidity as defined by the POMS, in contrast to the US institution, where very few patients remained in hospital in the absence of POMS defined morbidity. The POMS may have utility as a tool for recording bed occupancy and for modelling bed utilization.

Inter-rater reliability was adequate and a priori hypotheses that the POMS would discriminate between patients with known measures of morbidity risk, and predict length of stay were generally supported through observation of data trends. The POMS was a valid descriptor of short-term post-operative morbidity in major surgical patients.

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The patients.

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# Abbreviations

| | |
|---|---|
| ACS | American College of Surgeons |
| APACHE | Acute Physiology and Chronic Health Evaluation |
| ARDS | Acute Respiratory Distress Syndrome |
| ASA-PS | American Society of Anesthesiologists (ASA) Physical Status Classification |
| ASN | Association of Surgery of the Netherlands |
| BUPA | British United Provident Association |
| BHOM | Biochemistry and Haematology Outcomes Model |
| CONSORT | Consolidated Standards of Reporting Trials |
| CO | Cardiac Output |
| CI | Cardiac Index |
| $DO_2$ | Oxygen Delivery Index |
| DUMC | Duke University Medical Centre |
| GDP | Gross Domestic Product |
| HDU | High Dependency Unit |
| HLOS | Hospital Length of Stay |
| HMO | Health Management Organisation |
| HRQoL | Health Related Quality of Life Instrument |
| HQCFA | High Quality Care for all |
| HTA | Health Technology Assessment |
| ICC | Interclass correlation |
| ICU | Intensive Care Unit |
| KR20 | Kuder-Richardson formula 20 |
| MD | Mean Differences |
| MODS | Multiple Organ Dysfunction Syndrome |
| NCEPOD | National Confidential Enquiry into Perioperative Death |
| NSQUIP | National Surgical Quality Improvement Program |
| NVASRS | National Veterans Affairs Surgical Risk Study |
| NYHA | New York Heart Association |
| OE ratio | Observed to expected ratio |
| OR | Odds Ratio |

| | |
|---|---|
| P4P | Payment for Performance |
| POD | Post Operative Day |
| POMS | Postoperative Morbidity Survey |
| POSSUM | Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity |
| P-POSSUM | Portsmouth version of the POSSUM |
| PROMS | Patient Reported Outcome Measures |
| QALYs | Quality-adjusted life years |
| QoR | Quality of Recovery Score |
| RCRI | Revised Cardiac Risk Index or Lee Cardiac Risk Index |
| RCT | Randomized controlled trials |
| RC | Reliable Change |
| ROC | Receiver Operator Curve |
| SOFA | Sepsis Related Organ Failure Assessment Score |
| SIRS | Systemic Inflammatory Response Syndrome |
| SF-36 | Short Form (36) Health Survey |
| SRS | Surgical Risk Score |
| SSI | Surgical Site Infection |
| SV | Stroke Volume |
| $SVO_2$ | Mixed Venous Oxygen Saturation |
| TRACS | Trauma Registry of the American College of Surgeons |
| USATS | United States Association of Thoracic Surgeons |
| VA | US Department of Veterans Affairs |
| $VO_2$ | Oxygen consumption |
| WHO | World Health Organisation |

# Chapter 1: Background

## *1.1 Introduction*

This chapter will discuss the potential value of high quality reporting of outcomes following major surgery, review the currently available metrics for achieving this aim, and discuss some of the methodological issues surrounding validation of these clinical measurement tools.

I will start by discussing the value and utility of being able to describe quantitatively the elements of the surgical journey and their impact on the patient, and by briefly placing this area in the current political context.

I will then review the available metrics for describing risk in relation to surgery and outcome following surgery; interpretation of outcome is profoundly limited in the absence of a contextual description of risk. The lack of an adequate validated tool for describing clinically significant, short-term non-fatal postoperative harm will be highlighted.

Finally I will discuss the technical issues surrounding the development and validation of outcome metrics in general, and in the perioperative environment in particular. Specifically I will explore the contrasting conceptual models, and consequent statistical differences, of the psychometric and clinimetric approaches to survey and score development.

## *1.2 Why measure outcomes relating to surgery?*

Outcome following surgery is a significant public health issue. Data published in a recent study sponsored by the World Health Organisation (WHO) suggest that more than 234·2 (95% CI 187·2—281·2) million major surgical procedures are undertaken every year worldwide [1]. In this study major surgery was defined as "any intervention occurring in a hospital operating theatre involving the incision, excision, manipulation, or suturing of tissue, usually requiring regional or general anaesthesia or sedation." The authors concluded, "In view of the high death and complication rates of major surgical procedures, surgical safety should now be a

substantial global public-health concern." and that "Public-health efforts and surveillance in surgery should be established."

Surgical procedures have major physical, psychological and social impacts on patients and consume significant resources. The goals of surgical intervention are to increase length (e.g. cancer surgery) or quality of life (e.g. joint replacement surgery). However the tissue trauma related to surgical procedures and the associated physiological disturbance of anaesthesia and other perioperative interventions may cause significant harm to some patients: surgery (and particularly major surgery) is associated with a significant risk of death or other adverse outcome.

The United States has the highest per capita and total healthcare expenditure in the world [2] and might therefore be expected to produce surgical outcomes that are amongst the best possible. The US National Veterans Affairs Surgical Risk Study reported an overall mortality of 1.2-5.4% for major non-cardiac surgery [3] and a morbidity rate between 7.4 and 28.4% [4]. A larger US epidemiological study (1994-1999) including more than 2.5 million patients reported mortality rates between 2.0% and 23.1% for major surgical procedures including cardiac and thoracic surgery [5]. More recent US data from the 20,000 patients in the National Surgical Quality Improvement Program (NSQIP) reported a mortality rate of 1.7-2.2% for major surgery and corresponding morbidity rates of 13.1-14.3% [6].

In a UK dataset of more than 4 million surgical admissions to hospital (1999-2004), mortality was 0.44% following elective surgery and 5.4% following emergency surgery [7]. In this cohort the authors identified a high-risk group, comprising 0.5 million patients (12.5%) with a mortality of 12.3% [7]. Accepting the WHO estimate of total global surgical volume and assuming a global mortality rate relating to surgery between 0.44 [7] and 2.2% [6] (probably conservative as developed world outcomes are likely to be better than developing world outcomes) then death following surgery occurs between 1 and 5 million times per year and significant complications at approximately 5-10 times this rate. Furthermore, long-term outcome following major surgery is becoming recognised as a significant public health problem. A recent follow-up study (16-19 years later) of a

prospective cohort (1985-1988) of more than 6000 civil servants in the UK, sickness absence of > 7 days for any surgical operation was associated with a hazard ratio for mortality of 1.9 (95% CI 1.2 to 3.1) after adjustment for age, gender and employment grade, and this was the second largest category effect after circulatory diseases (adjusted hazard ratio 2.2, 95% confidence intervals 1.3 to 2.1) [8]. This effect may be modulated by immediate (in-hospital) postoperative outcome. In a US study of more than 100,000 patients who underwent major surgery between 1991 and 1999 and were followed up for an average of 8 years, the most important determinant of decreased postoperative survival was the occurrence of one of 22 predetermined complications within 30 days of surgery [9]. Median survival was reduced by 69% in patients meeting this criterion and this was a more important determinant than preoperative risk or intraoperative events [9].

There is a moral and political imperative to improve quality of care and cost-effectiveness with respect to healthcare in general, and surgery in particular. Maximising the benefit gained from the scarce resources available within health systems and minimising the harm of surgery should be self-evident and accepted goals of those involved with healthcare systems, be they consumers, providers, managers, policy makers or community members. However it is unclear how these goals can be achieved if we are unable to describe the quality, or cost-effectiveness, of care.

In this context, meaningful description and reporting of outcomes following major surgery has a number of potential merits. First, it allows monitoring and comparison of the process and delivery of care between peers (people, teams or institutions) [3]. Thus it is possible to spread best practice, highlight and remediate situations where practice may be less good, and thereby improve the overall standard of healthcare delivery [10]. Second it allows informed choice for the consumers of healthcare: patients [11] and purchasers [12]. Interestingly, although there is data to suggest that some patients may be both ambivalent and poorly informed about choosing providers based on performance indicators [13,14], more recent data suggest that performance data and information on other patients experiences are valued [15]. Third it permits more effective evaluation of innovations

in healthcare [16]. Fourth it facilitates rational decisions about resource distribution within a health care system [17]. Finally reporting outcomes may have direct value in engaging healthcare professionals (clinicians and managers) more closely with the consequences of their actions, and thereby drive improvements in care at a local level [18].

### 1.3.1 UK Perspective

The 1942 Beveridge Report identified the 'Five Giants' (want, disease, ignorance, squalor and idleness) that a civilised society should seek to collectively address. Following legislation by the Labour government of 1946, the National Health Service (NHS) was formally established on 5 July 1948. The underlying principals, universal provision of healthcare, free at the point of contact and paid for out of general taxation are for the most part intact at the beginning of the 21st century. However, by the beginning of the 21st century a chronic funding deficit relative to comparable developed nations (proportion of Gross Domestic Product) had resulted in a perception, in some cases supported by data [19], that clinical outcomes were worse than comparator nations.

In addition high-profile "scandals", including the case of Manchester general practitioner Harold Shipman and the enquiry into excess deaths following children's cardiac surgery at the Bristol Royal Infirmary [20], had undermined government and public confidence in the idea of professional self-regulation. The resulting changes aimed to introduce openness and accountability into monitoring of health care in the UK. In the surgical arena, the publication of outcome data for cardiac surgery on a named surgeon basis is a direct result of the Bristol enquiry and similar changes will follow in other surgical specialties [21].

In response to press comments about the quality of UK healthcare in the winter of 2001, the government announced a major new NHS funding initiative with the specific aim of bringing UK funding levels up to equivalence with the European Union average over 5 years. An important element of the proposed plan was that additional accountability within the NHS was essential to demonstrate that the additional funding was resulting in improved outcomes. However, the majority of indicators reported by the Health Care Commission were measures of process not outcome (see below, 1.4.2), and none were risk adjusted (see below, 1.4.4).

Explicit performance targets are now an integral part of how hospitals are assessed and rewarded financially. In an effort to performance manage the NHS, the UK government introduced "Payment by Results" in 2002, with money supposedly following improved performance [22]. However the current financial flows almost universally relate to activity measures rather than measures of clinical quality, and have been labelled "payment for activity" to reflect that "money flows irrespective of outcomes." [23].

Most recently the "NHS Next Stage Review" chaired by Lord Darzi, and the publication of the final report of this process "High Quality Care For All" [24] have changed the context of outcome reporting within the UK healthcare economy. This document places "quality" at the centre of the national healthcare agenda. The key aims of the report are to give patients and the public more information and choice, "work in partnership" and to have quality of care at the heart of the NHS (quality defined as clinically effective, personal and safe) [24]. Three key domains of metrics are identified: safety, clinical effectiveness (including patient reported outcomes) and personal experience (see below, 1.4.1 Performance and quality indicators in healthcare). The need for reliable and valid measures of outcome is now at the centre of the UK health agenda.

### 1.3.2 USA Perspective

An alternative model for healthcare exists in the US with the majority of richer individuals and families receiving private healthcare paid for by employer provided or private insurance schemes. Some older and poorer individuals and families have access to health care provision by government-funded schemes paid for out of general taxation: Medicare provides for patients aged over 65 (or meeting other special criteria) and Medicaid provides for families with low incomes or limited resources. Although both these systems are perceived to offer a lower standard of care than the private system, the published data suggests that risk adjusted mortality is similar for public and for-profit hospitals but lower for not-for-profit hospitals [25]. Interestingly cost per patient for delivered care is similar for public, for-profit and not-for-profit hospitals [26], and in comparison with the NHS [27] but the scope of delivered care differs. The Veterans Affairs program is a separate government funded health system supervised by the Department of

Veterans Affairs and caring for veterans of the American military services and their close family.

Escalating costs, particularly in the private sector, have resulted in a position where healthcare costs are close to 15% of Gross Domestic Product [2] and cost containment has become high priority for both the government funded and private systems. In the private sector, market driven changes have led to the aggregation of purchaser power in Health Management Organisations (HMOs) with aggressive cost-containment programs and this is driving cost-containment across the healthcare spectrum [28]. Political pressure for cost containment within the public sector has led to several cost containment programs and quality/cost-effectiveness initiatives. In relation to surgery the United States Association of Thoracic Surgeons (USATS) has a track record of reporting named surgeon and institutional cardiac surgery outcomes [29].

For patients undergoing other types of surgery the National Surgical Quality Improvement Program (NSQIP) has been developed and validated within the Veterans Administration hospitals and is embedded within their process of care for surgical patients (see below, 1.5.7) [30]. More recently the NSQIP has been validated within a number of private hospitals [10] and it is now being extended nationwide in a process being driven by the American College of Surgeons under a congressional mandate (July 2005). In the US "Payment for performance" (P4P) has been introduced and in the surgical specialties it is anticipated that P4P will be linked directly to outcomes as defined by the ACS-NSQIP [31].

## *1.4 Evaluating Outcome following Surgery*

### 1.4.1 Performance and quality indicators in healthcare

Performance targets can be used to guide progress towards defined objectives in healthcare [32]. Measurement of performance for organisations developed from the work of Peters and Waterman in the early 1980s [33]. A variety of performance measurement systems are now in use in the healthcare environment, for example the "balanced scorecard" [34-36]. Performance targets should be defined by stated organisational objectives and should reflect critical success factors. Critical success factors are elements (processes or events) that are essential for the

successful achievement of defined objectives [37,38]. They should be simple to understand, focus attention on major concerns, be easy to communicate and easy to monitor [37]. Organisational objectives or targets (within or without healthcare) are believed to be most effective when they fulfil the following "SMART" conditions: specific, measurable, achievable, realistic and time-bound [39,40]. Organisational objectives of healthcare institutions are commonly published in the public domain. For example, the mission statement of the University College London Hospitals (a UK teaching hospital) states: "UCLH is committed to delivering top quality patients care, excellent education and world class research." [41]. Interestingly, and consistent with national targets, of the ten stated UCLH objectives (2008-2009), only three relate directly to patient quality, perhaps reflecting a tension between desired objectives and measurable outcomes.

Quality indicators are a subgroup of performance indicators. Quality is defined as "the degree of excellence" of the object of concern [42]. Within the context of healthcare in the UK, "High Quality Care for all" (HQCFA) has categorised quality into three domains [24]: safety, clinical effectiveness and personal experience. Safety is not explicitly defined in HQCFA but the implicit meaning in the document centres around the injunction to "do no harm," to reduce avoidable harm (e.g. healthcare associated infections and drug errors) and to eradicate "never events" (events that should never happen, e.g. wrong-side surgery). Clinical effectiveness is defined as success rates from treatments measured by clinicians and/or patients (Patient Reported Outcome Measures (PROMs)). These are clinical outcomes (see below, 1.4.2) and include mortality, complication rates (e.g. morbidity), subjective function (e.g. pain-free movement of a joint: a PROM) as well as well-being and quality of life measures. Personal experience is defined by the analysis and understanding of patient satisfaction including satisfaction with quality of caring (compassion, dignity and respect).

The use of quality measures can be divided into three areas: internal quality improvement, external accountability (performance management) and external "data for judgement" [43]. The two external uses of data can be distinguished by whether the data is used in a non-perjorative manner to prompt further investigation and remedial measures, or whether the data is used for sanction or

reward (e.g. suspension for poor performance, financial benefit for good performance) [43].

### 1.4.2 Dimensions of quality in relation to surgery

The dimensions by which quality of healthcare can be assessed are commonly divided into structure, process and outcomes [44]. Structure consists of the components of the environment in which health care is delivered (institution, equipment, personnel etc). Process comprises actions of the healthcare providers in relation to the patient (preoperative preparation, intraoperative management including choice of procedure, and postoperative care). Outcome refers to the patient's subsequent heath status (including mortality, morbidity and quality of life).

There is debate about which element of the quality dimension triad is the most suitable for assessing quality of care. Although clearly fundamental to the quality of delivered care, structural measures are relatively stable over time and therefore not amenable to performance measurement and management. Whilst a structural measure may be a critical success factor for a clinical objective (e.g. commencing an ambulatory surgery service requires a day-theatre and staff), structure is generally considered to be a component of the environment that permits quality rather than an element or quality itself. Process measures reflecting structural factors (hospital size), including the number of procedures of a particular type performed each year by an individual surgeon (surgical volume) [45] or hospital (hospital volume) [5], are associated with outcome (surgical mortality). On a smaller scale, process measures such as the correct (evidence based) administration of perioperative antibiotics (correct antibiotic, within one hour of incision, discontinued within 24 hours), have also been associated with better outcomes [15]. However, although structural and process measures may be associated (and in some cases causally related) with outcomes, and thereby merit monitoring and improvement initiatives, their validity rests on their relationship with, and influence on, patient outcomes (as demonstrated in the studies cited above).

Lilford and others have argued persuasively that process measures are more suitable than outcome measures for judging and rewarding quality [43]. They cite a low signal to noise ratio and "risk-adjustment" fallacy as reasons why outcome

measurement has limited utility. Correlation between quality of care and mortality is low in some studies [46,47] whereas others are able to detect small differences in hospital risk adjusted mortality in association with differences in hospital performance [48]. Low correlation between these two measures indicates that a limited amount of variance in the measured outcome (mortality) can be attributed to variance in quality (low signal to noise ratio) suggesting that factors other than quality of care may be affecting mortality. Alternatively, these data might be interpreted as indicating limitations in the quality metrics (many of which were process based) [46,47] or in the assumption that process measures accurately reflect outcome measures (which is central to the validity of process measures) or in the risk adjustment metrics. Limitations in risk adjustment complicate the interpretation of outcome data. Residual confounding from unmeasured (perhaps unknown) determinant variables, variation in outcome definitions, and flawed modelling assumptions may all limit the precision of risk estimates [43,49]. Finally, when patients are the reporters of outcomes, reporting of outcomes can be confounded by patient expectations [50].

Process measures have some advantages including reduced stigma (or fault attribution), reduced risk of "case-mix bias", reduced focus on "sick" outliers, and ease of recording, but these benefits are relative, not absolute. Theoretically, empirically, and in practice, the validity of process measures of clinical care rests on their relationship with outcome. World-class outcomes in association with imperfect processes are self-evidently preferable to perfect processes with poor outcomes. However process measures have significant limitations. When quality or performance is defined by process measures (e.g. volume of procedures completed, compliance with care bundle) there is a risk that perverse incentives may arise as an unintended consequence of well-intended measurement initiatives. For example, managers may be compelled to meet imposed process targets (with financial consequences if they fail) despite the fact that this may result in overall worse outcomes. A specific example occurs in relation to so-called extreme-value targets such as the four-hour-wait in emergency departments: overall costs have risen as clinicians have admitted patients to hospital who previously were safely discharged home, in order to meet the

imposed target [51]. In relation to such targets, it is recognised that "typically avoiding extremes consumes disproportionate resources." [52]

Lilford's critique highlights potential limitations of outcome measurement that must be overcome if outcome measures are to be valid. However, rather than making a convincing case for process as superior to outcome measurement, his comments highlight the importance of outcome measures. Comprehensive quality reporting is likely to involve the complementary use of process and outcome measures, particularly where outcomes verification (and therefore assessment) is delayed. Comprehensive quality reporting will require ongoing validation of outcome measures (in relation to changes in populations and patterns of care) as well as validation of process measures to ensure that the underlying assumption of relationship with outcome remains valid.

Public reporting of outcomes and outcomes-funding linkage will increase the incentives for those involved in the system to subvert results in order to improve the reputational or financial position of individuals and institution. This subversion may take the form of fraud, whereby results are deliberately inaccurately recorded to misrepresent outcomes, or may be more subtle whereby results are accurately recorded but patterns of behaviour/referral/patient selection/coding are altered to improve results: so-called "gaming". Gaming is clearly different to fraud, but may result in unintended consequences. If methods of assessment are seen to favour either low- or high-risk procedures the result may be that patterns of clinical decision-making are distorted. The hazard inherent in gaming is that deliberate patient selection to optimize measured outcomes results in worse care on a population level but improved reported outcomes (perverse incentives). For example high-risk patients who might have the greatest relative gain from a procedure may be denied access to surgery because they have significant potential to adversely affect reported outcomes. This occurred in New York State when cardiac surgery outcomes were first published and referral patterns changed [53].

In conclusion, from the perspective of monitoring of quality, structure elements are both easy to monitor, and slow to change, and therefore not suitable for

monitoring quality and performance in relation to delivery of care. Process and outcome measures may both be used to evaluate quality following surgery and understanding the strengths and limitations of each category of measure is important.

The subject of this thesis is outcome measurement. I will therefore confine subsequent discussion of process measures to situations where process is used as a surrogate of outcome (e.g. duration of hospital stay following surgery).

A classification matrix of quality metrics (with examples) can be defined using the domains and dimensions of quality discussed above (Table 1).

**Table 1** Classification Matrix of Quality in Healthcare (with examples)

| | **Structure** | **Process** | **Outcome** |
|---|---|---|---|
| **Safety** | • Spacing of beds<br>• Ventilation | • Frequency of ward cleaning | • Hospital associated infection |
| **Effectiveness** | • Number of operating theatres | • Surgical volume | • Mortality<br>• Post Operative Morbidity Survey (POMS) |
| **Expectation** | • Number of places in car park | • Duration of wait for appointment | • Pain (PROM)<br>• Courtesy of staff |

### 1.4.2 Perspectives on outcome following surgery

Outcome following surgery may be viewed from a variety of perspectives: patient, relative or friend, clinician, payer, administrator, politician. The relative importance of different outcomes, and elements of the quality of care, is likely to differ depending on which perspective is adopted. It is notable that whilst clinicians believe quality of care to be the highest priority, patients sometimes rate other factors (e.g. convenience of access to the healthcare institution) as more important [54].

Patient Related Outcome Measures (PROMs) report perceived health outcomes from the perspective of the patient. A recent report from the US Food and Drugs

Administration defines PROMs as: ‘‘a measurement of any aspect of a patient’s health status that comes directly from the patient (i.e., without the interpretation of the patient’s responses by a physician or anyone else)” [55,56]. Examples of PROMs include the Short From (36) Health Survey (SF36) [57], a Health-related Quality of Life Instrument (HRQoL) and the Oxford Hip Score [58]. PROMs have been used particularly in the monitoring of postoperative outcome in conditions where improvement of symptoms is the aim of surgery (e.g. joint replacement surgery) [59,60]. In clinical trials, PROMs may be better discriminators of treatment response (in comparison with placebo) than physician reported outcomes or biomarkers [61]. However in clinical practice, PROMs (and in particular HRQoLs) may have substantial [62], or little or no impact on clinical decision making [63], and do not seem to impact patient health status [62]. Concerns have been expressed about combining different PROMs within meta-analyses because bias maybe introduced due to heterogeneity of responsiveness [64]. PROMs may also be susceptible to confounding due to variation in patient expectations [50].

### 1.4.3 A conceptual model for outcome following surgery

A surgical episode can be conceptualised as having a number of inputs to a defined process that has a defined output (or outcome). The inputs are the patient’s state prior to surgery and the structural elements of the quality of care model discussed above. The process comprises what the healthcare providers do to the patient (preoperative preparation, intraoperative management including choice of procedure, and postoperative care): the process dimension of the quality of care model described above. The output is the patient’s state following surgery (the outcomes), the dimensions of which will be discussed further in Section 1.6.

Iezzoni has proposed the following model [65]:

**Patient Factors + Effectiveness of Care + Random Variation = Outcome**

Effectiveness of care encompasses both structure and process. Risk adjustment (or case-mix adjustment) allows separation of the effects of patient factors and effectiveness of care.

### 1.4.4 The importance of risk (case-mix) adjustment

Theoretically risk adjustment compensates for inter-individual differences (patient factors) in order to remove any confounding in the assessment of effectiveness of care and thereby maximize the signal to noise ratio, recognizing that residual noise from random variation will always be present. In practice residual confounding remains due to the effect of unmeasured and/or unanticipated but influential patient factors [66].

Adequate risk adjustment allows the separation of patient related factors from the structure and process elements of effectiveness of care in the perioperative setting, which in turn permits the identification of variation, and thereby drives improvement in delivered care. By this means, high quality care will be identified and promoted whereas lower quality care can be replaced with more effective approaches.

Risk adjustment scores are commonly developed from cohort studies. A large group of candidate independent variables believed to be associated with adverse outcome (e.g. age, comorbidities) and dependent variables (outcome, e.g. mortality) are collected in an observational cohort study (derivation cohort). Subsequently regression analysis is used to define the relationship between the independent and dependent variables in order to derive a model that underpins the risk adjustment scoring scheme. Scoring may incorporate weighting of variables, or more complex manipulation of data involving entering derived variables into regression equations with coefficients derived from the derivation cohort. Subsequent prospective validation of the developed system in a separate cohort (validation cohort) should include evaluation of calibration (goodness of fit) of the observed outcomes when compared to those predicted by the model, discrimination between patients with and without the condition under test (e.g. area under receiver operator curve (ROC)) and reliability (see 1.7.3 Reliability) [67]. Importantly, risk-adjustment models are only validated for the conditions under which they are tested: the validation is outcome, timeframe, population and purpose specific [66]. For example, the original Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity (POSSUM) equation developed by Copeland is specific to in-hospital mortality and morbidity (two

separate equations) in adults undergoing major surgery in the UK [68].
Extrapolation of validity to other populations may be possible but should never be assumed; rather it should be formally tested to establish validity in the new context.

In some systems of risk adjustment, the expected outcome for an observed cohort is obtained by summing the individual risks of a specific event for all the members of that cohort. This value is then compared with the observed frequency of the event under consideration and an observed to expected ratio (OE ratio) calculated [68] in a manner analogous to the calculation of standardized mortality rates (e.g. Acute Physiology and Chronic Health Evaluation in intensive care patients) [69,70]. An OE ratio of greater than one signifies worse outcomes in the study cohort than expected, less than one indicates better expected outcomes in the study cohort, and a ratio of 1 indicates that the study cohort's results are consistent with our expectations (based on data from the derivation and validation cohorts). This approach emphasizes the importance of considering validity relative to the outcome, timeframe, population and purpose characteristics of the original derivation and validation cohorts.

### 1.4.6 Terminology: Perioperative or Surgical Outcomes?

Although the terms "Surgical Outcomes" and "Perioperative Outcomes" are commonly used interchangeably, strictly they refer to distinct but overlapping patient groups. Perioperative refers to events occurring in temporal relation to an operation (procedure). Surgical may be used with the same meaning, but may also be used to refer to the group of patients who are cared for by surgeons, and/or have conditions that are potentially amenable to surgical treatment. Clearly the definition of surgical is both inconsistent and context dependent (e.g. the same patient might be cared for by physicians or surgeons depending on the arrangements within a particular institution). The term perioperative is therefore preferred for reasons of consistency and clarity.

Perioperative encompasses the pre- intra- and post-operative phases. Within this thesis, preoperative is defined as before surgery (prior to entering the anaesthetic room), intraoperative is defined as during and around the time of surgery (from arrival in the anaesthetic room to leaving operating room) and postoperative is

defined as everything occurring thereafter. Outcome following Surgery is therefore synonymous with postoperative outcome. Alternative definitions of start and end of surgery may alter the attribution of events to the pre- intra- and post-operative phases. For example, if the criterion for "before surgery" is "knife to skin", then events relating to the induction of anaesthesia will be defined as preoperative, whereas if "entering the anaesthetic room" is the criterion, of such an event would be classified as intraoperative.

## *1.5 Risk (case-mix) adjustment of outcomes and surgery*

### 1.5.1 Introduction

A variety of methods have been used to identify patients at increased risk of adverse outcome (mortality and morbidity) following major surgery and to quantity the level of this risk. There is a balance between ease of use in the clinical setting and precision in distinguishing between different levels of risk: simple systems which are easy to use tend to have fewer variables which are readily accessible and a simple method of deriving the score (e.g. simple sum). More complicated systems incorporating multiple variables from a variety of sources, and utilizing more complicated methods (e.g. regression analysis) to derive the score achieve greater precision but with the cost that they may be cumbersome to use in clinical practice. The advent of clinical information systems integrating multiple inputs and available at the bedside may overcome some of the problems associated with more complicated scoring systems. This section describes a variety of approaches to describing risk in relation to major surgery. The scope of this review is limited to major surgery and scores developed specifically for cardiac surgery or neurosurgery are not included.

### 1.5.2 American Society of Anesthesiologists Physical Status Classification

The simplest and oldest recognised classification of risk in patients undergoing surgery is the American Society of Anesthesiologists (ASA) physical status classification (ASA-PS). The classification was originally published in 1941 [71] and revised to close to its current form in 1963 [72,73]. The current reference description of the ASA-PS is presented in Table 2 [74]. The 1963 version of this classification [73], (probably the most commonly used and referenced version), includes reference to

differences in "functional limitation" in the criteria for classes II and II (see footnotes to Table 2). Several authors have however developed scores based on the ASA-PS score to produce models that more effectively predict outcome following non-cardiac surgery (see below).

**Table 2** American Society of Anesthesiologists Physical Status Score (ASA 2008)

| ASA Grade | Criterion |
|---|---|
| I | A normal healthy patient |
| II | A patient with mild systemic disease* |
| III | A patient with severe systemic disease** |
| IV | A patient with severe systemic disease that is a constant threat to life |
| V | A moribund patient who is not expected to survive without the operation*** |
| VI | A declared brain-dead patient whose organs are being removed for donor purposes |

***Notes to table 2:*** ** qualified in 1963 version with '(no functional limitation)', ** qualified in 1963 version with '(definite functional limitation)', *** alternate 1963 version 'Moribund patient unlikely to survive 24 h with or without operation'.*

The ASA score subjectively categorizes patients into five subgroups by preoperative physical fitness (with one additional category for patients prior to organ donation who have been diagnosed brain dead). The system has been repeatedly shown to divide patients up into categories of relative risk with preoperative ASA-PS score being predictive of adverse outcome (one or more of increased length of stay, mortality or morbidity) following surgery in patients as diverse as those with cirrhosis [75], congenital heart disease [76], abdominal surgery [77], renal artery surgery [78], cranial meningioma surgery [79], pancreatoduodenectomy [80], oesophagogastrectomy [81,82], thoracic surgery [83], head and neck surgery [84], hip-fracture surgery [85] over 80 being operated for colorectal or gastric cancer [86] and following major trauma in the elderly [87]. Of note, in 1996 Woltes et al examined the association between ASA-PS, other perioperative risk factors and postoperative outcome in over 6000 patients [88]. In univariate anlaysis, there was a significant association between ASA-PS status and both mortality and postoperative complications. In multivariate analysis the strongest predictors of postoperative complications were ASA IV > ASA III > class of operation (operative severity) > ASA II > emergency operation [88]. However a follow-on paper highlighted the limitations of this approach in clinical practice: whilst an

uncomplicated course was correctly predicted with a frequency of 96%, complications were correctly predicted in only 16% of patients (positive predictive value = 57%, negative predictive value = 80%). The ASA-PS was originally envisaged as a descriptor of "anaesthetic" risk for epidemiological purposes. Even at the time of its introduction it was recognised that the properties of the ASA-PS (sensitivity, specificity, positive and negative predictive values) would not be adequate to predict outcome with confidence on an individual patient basis. The ASA-PS score is not commonly used to derive observed-expected ratios for postoperative outcomes.

Several authors have however developed scores based on the ASA-PS score to produce models that more effectively predict outcome following non-cardiac surgery (see below).

### 1.5.3 Surgical Risk Score and other ASA derivatives

The Surgical Risk Score (SRS)(Table 3) combines the CEPOD/NCEPOD categories for surgical urgency, with British United Provident Association operative severity categories and the ASA-PS [89]. The resulting score is produced by a simple sum of the numerical categories. In patients undergoing low-risk surgery the SRS was significantly predictive of mortality following surgery and did not over-predict at low-levels of risk [89]. In high-risk surgical patients there was no significant difference in predictive accuracy (area under ROC for mortality) between the SRS, POSSUM and P-POSSUM [90]. Using a similar approach Donati developed a model incorporating the ASA-PS, age, type of surgery (elective, urgent, emergency), and degree of surgery (minor, moderate, major) [91]. For mortality prediction, the Donati model had superior discrimination in comparison with the ASA-PS, whereas in comparison with POSSUM and P-POSSUM the new model exhibited better calibration, but less good discrimination [91].

**Table 3** The Surgical Risk Score (Sutton et al 2002)

| | Criterion | Score |
|---|---|---|
| **CEPOD** | | |
| Elective | Routine booked non-urgent case, e.g. varicose veins or hernia | 1 |
| Scheduled | Booked admission, e.g. cancer of the colon or AAA | 2 |
| Urgent | Cases requiring treatment within 24±48 h of admission, e.g. obstructed colon | 3 |
| Emergency | Cases requiring immediate treatment, e.g. ruptured AAA | 4 |
| **BUPA** | | |
| Minor | Removal of sebaceous cyst, skin lesions, oesophagogastric duodenoscopy | 1 |
| Intermediate | Unilateral varicose veins, unilateral hernia repair, colonoscopy | 2 |
| Major | Appendicectomy, open cholecystectomy | 3 |
| Major plus | Gastrectomy, any colectomy, laparoscopic cholecystectomy | 4 |
| Complex major | Carotid endarterectomy, AAA repair, limb salvage, anterior resection, oesophagectomy | 5 |
| **ASA-PS** | | |
| I | No systemic disease | 1 |
| II | Mild systemic disease | 2 |
| III | Systemic disease affecting activity | 3 |
| IV | Serious disease but not moribund | 4 |
| V | Moribund, not expected to survive | 5 |

***Notes to Table 3:*** *NCPOD = National Confidential Enquiry into Perioperative Deaths, ASA = American Society of Anesthesiologists – Physical Status Score, BUPA = British United Provident Association (BUPA) operative severity scores, AAA = Abdominal Aortic Aneurysm.*

### 1.5.4 Criteria for "High-risk major surgery"

The concept behind "high-risk major surgery" is that there is a subset of patients undergoing major surgery who, by virtue of a combination of their pre-morbid condition (chronic diseases and acute physiology) and the type of operation they undergo, can be categorised into a group where the risk of death following surgery is high (5-10% +). The concept derives from Shoemaker and colleagues who reported a list of characteristics that could be used to define patients undergoing "high-risk major surgery" [92] (Table 4). Shoemaker used these categories as inclusion criteria for randomized controlled trials (RCTs) testing the strategy of "optimizing" these patients: aiming in all patients for the physiological goals

(oxygen delivery in particular) exhibited by survivors in order to improve overall survival.

**Table 4** Criteria for "high-risk general surgical patients" (Shoemaker et al 1988)

| Criteria for "High Risk" |
|---|
| **Previous severe cardiorespiratory illness**: (acute MI, COPD, stroke etc) |
| **Extensive ablative surgery planned for carcinoma**: e.g. oesophagectomy and total gastrectomy, prolonged surgery (>8 hr) |
| **Severe multiple trauma**: e.g. > 3 organs or > 2 systems, or opening 2 body cavities. |
| **Massive acute blood loss:** (>8 units), Blood Volume <1.5 L/$m^2$, Hct <20% |
| **Age over 70 years and evidence of limited physiologic reserve of one or more vital organs** |
| **Shock**: Mean Arterial Pressure<60mmHg; Central Venous Pressure <15cm$H_2O$ and Urine output<20ml/hr |
| **Septicemia**: positive blood cultures or septic focus, WBC>13,000, spiking fever to 101°F for 48 hour, and hemodynamic instability |
| **Respiratory failure**: e.g. $PaO_2$<60 on $FiO_2$>0.4; Qs/Qt>30%; mechanical ventilation needed>48 h |
| **Acute abdominal catastrophe with hemodynamic instability**: e.g. pancreatitis, gangrenous bowel, peritonitis, perforated viscus, Gastrointestinal bleeding |
| **Acute renal failure:** (Blood Urea Nitrogen>50mg/dl; creatinine>3mg/dl) |
| **Late stage vascular disease involving aortic disease** |

***Notes to Table 4:*** *MI: myocardial infarction; COPD = Chronic Obstructive Pulmonary Disease; Hct = Haematocrit; $PaO_2$=Arterial partial pressure of oxygen $FiO_2$ = Inspired fractional concentration of oxygen; Qs/Qt = shunt fraction*

Subsequent authors have modified these criteria whilst maintaining their primary aim [93,94]. Outside of RCTs these descriptive categories have not been widely adopted for several reasons. Firstly the list approach can be cumbersome to use. Secondly, this approach provides only a dichotomous classification of the presence of absence of risk, rather than a graded or continuous measure of risk. Finally this approach has been superseded by more structured and sophisticated alternatives.

### 1.5.5 Charlson Score

The Charlson score was originally developed to classify comorbidity in longitudinal studies in medical and surgical patients (Table 5) [95]. It was subsequently shown to be a valid predictor of death in patients undergoing elective surgery [96].

**Table 5** Charlson Score (Charlson et al 1987)

| 1 | 2 | 3 | 6 |
|---|---|---|---|
| Myocardial infarction | Hemiplegia | Moderate or severe liver disease (e.g. cirrhosis with ascites) | Metastatic solid tumor |
| Congestive heart failure | Moderate or severe renal disease | | AIDS |
| Peripheral vascular disease | Diabetes with end organ damage | | |
| Cerebrovascular disease | Any malignancy | | |
| Dementia | | | |
| Chronic pulmonary disease | | | |
| Connective Tissue disease | | | |
| Ulcer disease | | | |
| Mild liver disease | | | |
| Diabetes | | | |

***Notes to Table 5:*** *AIDS = Acquired Immune Deficiency Syndrome*

The Charlson score was found to predict mortality and duration of hospital stay following colorectal surgery [97] and mortality following cardiac surgery [98]. When compared with ASA-PS, the Charlson score showed equivalent [99] predictive ability after laparoscopic urological surgery, head and neck surgery [84] and radical prostatectomy [100] however the ASA-PS was superior to the Charlson score in the prediction of mortality and morbidity in patients undergoing liver resection [101]. Interestingly, no consistent relationship was found between hospital costs in relation to elective surgery and either ASA-PS or the Charlson score [102].

### 1.5.6 Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity

In 1992 Graham Copeland, a urology surgeon from Warrington (UK) described a "scoring system for surgical audit" [68]. Copeland called his system the Physiological and Operative Severity Score for the Enumeration of Mortality and Morbidity and took some liberties with spelling in his adoption of the acronym POSSUM for the score. He used a process of multivariate discriminant analysis to assess 48

physiological variables and 12 operative and postoperative variables to develop a system to predict 30-day mortality and morbidity rates following surgery. Analysis of the predictive performance of variables in the development cohort was used to develop the score. Those variables with the highest predictive ability were selected to be elements of the score. The resultant 18 component score comprises 12 variables forming the physiological assessment and 6 variables forming the operative severity assessment [68]. The physiological variables are recorded prior to surgery and include clinical symptoms and signs, results of biochemical and haematological test and an electrocardiographic assessment (Table 6). The operative severity variables are recorded following completion of surgery and in some cases are not available for a considerable time after the operation (e.g. number of subsequent operations within 30 days, presence of malignancy) (Table 7). The values for the variables are categorised on an exponential scale, summed to produce the two component scores, and then entered into logistic regression equations to derive the percentage risk of a defined outcome. Two separate equations (with different coefficients) are used for calculating the risk for mortality and morbidity. The logistic regression predictor equations derived from the development cohort were tested for goodness of fit on a separate validation cohort. Observed rates of mortality and morbidity are compared with expected values obtained from the POSSUM predictor equations and observed:expected ratios calculated. Confidence intervals can be obtained for cohort estimates of expected risk and OE ratios and their magnitude will be dependant on the size of the cohort and the frequency of adverse outcomes under consideration.

**Table 6** POSSUM physiological variables (Copeland et al 1992)

| Score | 1 | 2 | 4 | 8 |
|---|---|---|---|---|
| Age (years) | ≤60 | 61-70 | ≥71 | - |
| Cardiac signs | Normal | Cardiac drugs or steroids | Oedema, Warfarin | Elevated JVP |
| Chest radiograph | Normal | - | Borderline cardiomegaly | Cardiomegaly |
| Respiratory signs | Normal | SOB exertion | SOB stairs | SOB rest |
| Chest radiograph | Normal | Mild Chronic Obstructive Airways Disease | Moderate Chronic Obstructive Airways Disease | Any other change |
| Systolic BP (mmHg) | 110-130 | 131-170<br>100-109 | ≥171<br>90-99 | ≤89 |
| Pulse (bpm) | 50-80 | 81-100<br>40-49 | 101-120 | ≥121<br>≤39 |
| Coma Score | 15 | 12-14 | 9-11 | ≤8 |
| Urea (mmol $L^{-1}$) | ≤7.5 | 7.6-10 | 10.1-15 | ≥15.1 |
| $Na^+$ (mEq $L^{-1}$) | ≥136 | 131-135 | 126-130 | ≤125 |
| $K^+$ (mEq $L^{-1}$) | 3.5-5 | 3.2-3.4<br>5.1-5.3 | 2.9-3.1<br>5.4-5.9 | ≤2.8<br>≥6.0 |
| Hb (g $dL^{-1}$) | 13-16 | 11.5-12.9<br>16.1-17 | 10.0-11.4<br>17.1-18 | ≤9.9<br>≥18.1 |
| WCC ($\times 10^{12}$ $L^{-1}$) | 4-10 | 10.1-20<br>3.1-3.9 | ≥20.1<br>≤3 | - |
| ECG | Normal | - | Atrial Fibrillation (60-90) | Any other change |

***Notes to Table 6:*** *JVP = jugular venous pressure, SOB = shortness of breath, BP = blood pressure, WCC = white cell count, ECG = electrocardiogram.*

**Table 7** POSSUM Operative Severity Variables (Copeland et al 1992)

| **Score** | **1** | **2** | **4** | **8** |
|---|---|---|---|---|
| Operative magnitude | Minor | Intermediate | Major | Major + |
| Number of operations within 30 days | 1 | - | 2 | >2 |
| Blood loss per operation (mls) | ≤100 | 101-500 | 501-999 | ≥1000 |
| Peritoneal contamination | No | Serous | Local Pus | Free bowel content, pus or blood |
| Presence of malignancy | No | Primary cancer only | Node metastases | Distant metastases |
| Timing of operation | Elective | - | Emergency, resuscitation possible, operation <24 hours | Emergency, Immediate operation < 2 hours |

The original development and validation cohorts were from within Copeland's own institution, a district general hospital in the North of England. Both cohorts included elective and emergency patients and several surgical specialties: gastrointestinal, vascular, hepatobiliary, urology, and orthopaedic [68]. Although subsequent populations from different hospitals have been shown to produce similar results, it is intrinsic to the POSSUM system that all current cohort data is compared with these specific historical cohorts, and knowledge of the nature of these cohorts is important when interpreting derived OE ratios.

Although POSSUM can be used to predict risk for an individual patient great care should be used when interpreting such data. Highlighting high-risk cases by this means may be useful. However suggesting futility, based on these estimates, is fraught with ethical and statistical risk and this data should be used only as part of a much broader assessment. Furthermore, as some of the variables are not available until after surgery is completed, this information cannot be used alone to decide on the appropriateness of a procedure (if the predicted risk is close to 100%, for example, it could be argued that an operation would be futile).

The POSSUM system has been used in clinical effectiveness studies [94], in comparisons of outcomes between different countries [19], in comparisons of individual surgeons [103], and in comparison of types of care (e.g. preoperative intensive care admission) [104].

The original POSSUM methodology used logistic regression equations to predict event risk. This has been criticized for theoretical and empirical reasons. Theoretically the use of logistic models produces some problems: the lowest possible mortality risk using POSSUM (which occurs when all components of the score are normal producing a physiological score of 12 and an operative severity score of 6) is 1.08% [105]. Empirical evidence suggests that in some cases POSSUM over-predicts risk of death by up to six-fold (for those with a predicted risk of mortality under 10%) [105].

An alternative method using the same variables but alternative risk equations was suggested by David Prytherch working at Portsmouth Hospital in the UK. He

developed a new risk model (Portsmouth POSSUM, P-POSSUM) validated on a large local dataset. Overall P-POSSUM seems to reflect mortality risk (hospital) better than POSSUM [106]. However this group did not develop a morbidity prediction model. Interestingly this is because of the Portsmouth's group lack of confidence in reliable postoperative morbidity recording [106].

Variants of POSSUM for use in specific surgical populations have been validated on large cohorts of patients. These include orthopaedic [107], colorectal [108], oesophageal [109], and vascular surgical populations [110]. The advantage of speciality –specific scores is that for individual specialty datasets, improved goodness of fit is obtained and the model is better calibrated. The disadvantage is that this limits generalisability and cross-speciality inter-institutional comparisons.

### 1.5.7 National Surgical Quality Improvement Program: a US approach

The US Department of Veterans Affairs (VA) (NSQIP) is a nationally validated, outcome based, risk adjusted, peer-controlled program for the measurement and enhancement of the quality of surgical care in major surgical specialties [30]. In 1986 the US Congress passed a law mandating the VA to report it's surgical outcomes annually "compared with the national average." In addition it added the stipulation that the outcomes should be adjusted for the severity of patient's illnesses. Between October 1991 and December 1993 the VA prospectively collected data on 117000 major surgical procedures in 44 VA medical centres (Phase 1) as part of the National VA Surgical Risk Study (NVASRS) [111]. Predictive risk adjustment models for 30-days mortality and morbidity for 9 surgical specialties (including cardiac) were developed from this data. Data from the eight non-cardiac major surgical specialties are now subjected to annual logistic regression analysis to create models for all operations and for the eight specialties [112]. Risk adjusted outcomes for each assessed population are expressed as OE ratios (see above) with 90% confidence intervals (CI) and data from all the 133 participating institutions are compared to identify outliers. The pooled data obtained is fed back to chiefs of surgery annually. Consistent outlier institutions are informed of concerns about this. The program also provides self-assessment tools to providers and managers, organizes structured site visits to assess data quality and performance and assists in the identification and dissemination of best practice within the program hospitals [112].

The NVARS validated the concept that NSQIP hospitals where the lower limit of the OE ratio 90% CI is greater than one (high outliers) are more likely to have inferior processes and structures of care [113]. Conversely those hospitals where the upper limit of the OE ration 90% CI is less than one (low outliers) are more likely to have superior structures and processes [113]. NSQIP has now been successfully implemented at non-veterans academic hospitals [114] and in the private sector [10].

NSQIP is a model for what can be achieved in terms of structured validated reporting of outcome following surgery. Similar data are not available in the UK. Of note, from the perspective of recording the short-term harms following surgery (acute morbidity), the approach uses a traditional classification of defined complications (e.g. deep venous thrombosis) collected retrospectively (30 days after surgery) [4]. However the levels of morbidity recorded are broadly similar to those obtained using other systems [4].

### 1.5.8 Cardiac risk scores for non-cardiac major surgery

A number of scoring systems have been devised to describe the specific risk of developing cardiac complications in non-cardiac surgery. In 1977 Goldman described a "Multifactorial index of cardiac risk in non-cardiac surgical procedures" (Table 8) [115]. Patients with a score >25 had a 56% incidence of death (22% incidence of cardiovascular complications) whereas patients with a score <26 had a 4% incidence of death (17% incidence of severe cardiovascular complications) [115]. The Goldman index was widely adopted and subsequent studies showed that it is superior to the ASA_PS for predicting cardiac complications of non-cardiac surgery [116]. The Goldman index has also been shown to be predictive of all-cause mortality but in this respect is inferior to the ASA-PS score [117].

**Table 8** Goldman cardiac risk index (Goldman et al 1977)

| Criterion | Score |
|---|---|
| Third heart sound (S3) | 11 |
| Elevated jugular venous pressure | 11 |
| Myocardial infarction in past 6 months | 10 |
| ECG: premature atrial contractions or any rhythm other than sinus | 7 |
| ECG shows > 5 premature ventricular contractions per minute | 7 |
| Age > 70 years | 5 |
| Emergency procedure | 4 |
| Intra-thoracic, intra-abdominal or aortic surgery | 3 |
| Poor general status, metabolic or bedridden | 3 |

***Notes to Table 8:*** *ECG = electrocardiogram*

In 1978 Cooperman et al identified five risk factors associated with cardiovascular complications following major vascular surgery (congestive heart failure, prior myocardial infarction, prior stroke, abnormal electrocardiogram) [118]. Using multivariate analysis an equation (Cooperman Equation) was developed that predicted the risk of postoperative cardiovascular complications. However this approach has remained relatively obscure in comparison with the Goldman index. The Detsky index [119] is a modification of the original Goldman index using the same collected variables but an alternative Bayesian statistical approach. When tested in parallel on the same cohort there was no significant difference between the Goldman and Detsky indices, or the ASA-PS for the prediction of perioperative cardiovascular complications [120]. Eagle's clinical markers of low risk (no evidence of congestive heart failure, angina, prior myocardial infarction or diabetes) have also been used for comparative risk evaluation in non-cardiac surgery [121] and have contributed to the development of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) [122,123].

The Revised Cardiac Risk Index (RCRI) developed by Lee et al [124] is a more recent approach to quantifying cardiac risk in relation to non-cardiac surgery using a small list of criteria (similar to Eagle's clinical markers) (Table 9) and has been widely adopted.

**Table 9** Lee Cardiac Risk Index (Lee et al 1999)

| Risk Factors |
|---|
| High-risk type of surgery |
| Ischaemic heart disease |
| History of congestive heart failure |
| History of cerebrovascular disease |
| Insulin therapy for diabetes |
| Preoperative serum creatinine >2.0 mg/dL |

***Notes to Table 9:*** *Class I = 0 risk factors, Class II = 1 risk factor, Class III = 2 risk factors, Class IV = ≥ 3 risk factors.*

Finally an adaptation of the RCRI by Boersma et al (adapted Lee Index) increased the number of surgical risk categories from 2 to 4, added variables for laparoscopic (vs. open) surgery and emergency (vs. elective) surgery and included 6 age categories [125]. In a large (108,593 non cardiac surgical procedures) retrospective analysis of data from a clinical database the adapted Lee Index was predictive of cardiovascular mortality and performed better than Lee's original RCRI [125]. Importantly, the performance of these indices in predicting postoperative cardiac/cardiovascular complications does not seem to be matched by their prediction of all-cause postoperative mortality and morbidity. In a comparison of ASA-PS, SRS, P-POSSUM, and the Goldman index, the Goldman index was less good at discriminating between risk groups for mortality than the other three scores [126].

### 1.5.9 Miscellaneous approaches to describing surgical risk

The Acute Physiology and Chronic Health Evaluation (APACHE) developed by Knaus and colleagues is a validated model for predicting outcome in patients in a critical care environment based on variables measured during the first twenty four hours of stay on the critical care unit [70]. APACHE is not validated for this purpose outside of the critical care unit. Additionally several of the components of the score require special techniques, for example blood gas measurement, which are often not available outside of critical care units, and the absence of which further limits the utility of the score in this context. However, APACHE scores were predictive of mortality and morbidity in post-surgical patients inpatients [127] and in patients with cirrhosis undergoing major surgery [75]. Similarly, Preoperative

APACHE scores were superior to ASA-PS scores in the prediction of postoperative mortality and morbidity in patients undergoing general surgical procedures [128].

Prytherch has developed a risk-scoring system based on laboratory tests results, age, gender and British United Provident Association (BUPA) operative severity scores (the Biochemistry and Haematology Outcomes Model, BHOM) [129] which demonstrated equivalent discrimination to P-POSSUM and SRS for mortality following urgent or emergency surgery [126].

A variety of speciality specific scores have been shown to predict mortality effectively in sporadic studies. For example, a simple score incorporating age, neurological comorbidity, weight loss and emergency surgery (the AFC score) showed better goodness of fit than the ASA-PS in a large cohort of patients undergoing colorectal surgery [99]. Intriguingly, a simple clinician visual–analogue risk measure had equivalent predictive value for complications as POSSUM and the Charlson Score in a study of patients undergoing hip fracture surgery [130].

## *1.6 Postoperative Outcome Measures*

### 1.6.1 Introduction and definition of scope

The measures currently available, or proposed, to describe patient outcomes following surgery include physiological, pathological, psychological and social descriptors.

Physiological outcomes include level of fitness (peak physical work, maximum sustainable physical work) and cognitive function. Pathological outcomes include pain, persistent organ dysfunction and scarring or deformity. Psychological outcomes include depression and anxiety associated with preceding surgery. Social outcomes include return to work, income, relationship difficulties or social engagement (e.g. religious or cultural activities). Quality of life measures may encompass some or all of these dimensions. For example the Short Form (36) Health Survey (SF36) comprises an eight scaled score relating to vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning and mental health [57]. The SF36 is used in health economics as a variable unit in the Quality-adjusted life years

(QALYs) to determine the overall cost-effectiveness of health treatment [131,132]. Of note, there is evidence that non-pathological outcomes may significantly impact overall health. For example maintenance of physical fitness is associated with improved survival, irrespective of whether surgery has taken place [133-136] and there may be a similar effect in relation to psychological well being [137-139]. The impact of surgery may spread beyond the patient having the operation. There is evidence that hospitalization can increase the risk of death in patients' spouses, although the interaction of this effect with surgery is unclear. There was increased mortality in spouses of patients admitted with hip fractures but no increased risk in spouses of patients admitted for colon cancer [140].

Within this thesis I will limit the scope of postoperative outcomes to those that are "clinically significant". In doing this I recognize that the concept of clinical significance is limited as a criterion, being traditionally based on the subjective view of "expert" clinicians. Furthermore, for patients non-clinically significant morbidity may have a greater importance (e.g. financial concerns, sexual dysfunction) in their life. However defining clinical significance as those outcomes requiring, or benefiting by, medical intervention has the dual benefit of clearly defining the scope of this thesis and confining it to the realm of clinical medicine. Although there is a substantial literature on postoperative cognitive dysfunction [141,142], I will further limit the scope of this thesis to the physical manifestations of pathophysiology following surgery.

Standardising the temporal frame of measurement of postoperative outcome measures is important. Where the frame of measurement is based on an element of process (e.g. discharge from hospital in the case of "hospital mortality") confounding due to heterogeneity of discharge criteria and systems efficiency is likely. Timeframe based measurements are more likely to be reliable but are harder to collect than hospital based measures [112].

Outcomes following surgery may be short term or long-term. There is no accepted classification for what constitutes medium or long term following surgery. For the purposes of this MD short-term outcomes are here defined as including the duration of hospital stay.

Hospital based outcome reporting systems will, by definition, only record outcomes occurring in hospital. One means of overcoming this problem would be to give patients self-report cards to go home with or to conduct telephone follow-up a specified period after operation or discharge. Report cards have been used to monitor outcomes following surgery [68] (Copeland in early POSSUM study) and characteristics of a model report card following surgery have been proposed in the USA [143]. Report cards may also be used to validate assumptions implicit in hospital-based measures, that discharged patients are uniformly well. The occurrence of readmissions due to post-surgical morbidity suggests that this assumption is not fully valid.

### 1.6.2 Death

Death following surgery (surgical mortality) has strengths and limitations as an outcome measure. Death is easy to diagnose, apparently easy to define, commonly recorded and self-evidently clinically significant. However the length of time over which data is collected affects the measured rate within a particular population and the impact of competing causes of death. For example, in a study in cardiac surgical patients, mortality in the control group at 28 days was 3.0%, at 6 months was 3.6% and at 1 year was 4.6% (protocol group: 1.0%, 1.5%, 2.0% respectively)[144]. Studies of surgical patients commonly report hospital morality and sometimes report 28-day or 30-day mortality as an alternative (see Chapter 2). The relationship between these variables is, in part, dependent on the range of lengths of stay observed in the patient group being studied. Although mortality at a specific time-point (e.g. 28-day, 30-day) has the advantage of more precise attribution (due to absence of confounding due to variation in length of stay), hospital data are substantially easier to collect and therefore more commonly reported. Loss of patients to follow-up after hospital discharge may decrease the precision of mortality data collected over longer timeframes. Furthermore, when considering mortality levels over longer periods of time it is important to know the background rate of attrition for the population under consideration; so-called competing causes of death such as the ongoing death-rate associated with comorbidities such as heart disease or cancer may be significant in older populations and may dilute the effect of studied variables such as different individual surgeons [9,145]. Cause-specific survival rates may be more appropriate

for long-term follow-up [145]. Recent data suggests that adverse outcome during the perioperative period may have a significant impact on long-term mortality [9] and that interventions administered for a short period of time during the perioperative period may modify the pattern of recovery from surgery and subsequent mortality over both the short and longer term [144].

Notwithstanding these issues mortality has a significant drawback as a comparative tool in a number of surgical settings for another reason. The overall mortality rate associated with a variety of types of surgery has decreased with time [146,147]. This is probably due to a combination of improvements in the standard of surgical, anaesthetic and general hospital care of surgical patients as well as overall improvement in the health of the population. The consequence of this is that for many types of surgery the event rate (for death) has become very low. This means that to compare institutions or surgeons in a valid manner (to detect statistically significant differences) the denominator number (the number of patients from whom information has to be collected in the study populations) needs to be very large, and therefore timeframe of collection is increased. The timeframe of comparisons may then start to become meaningless if the purpose is to attempt to improve quality of care.

For example, with a background mortality rate of 10%, a 50% relative risk reduction (5% absolute risk reduction) can be detected with two samples of 343 patients; with a background mortality rate of 1%, a 50% relative risk reduction (0.5% absolute risk reduction) would require two samples of 3681 (power = 0.8, $p \leq 0.05$, 1 sided test). For hospitals undertaking 500-1000 surgeries per year the former is a practical timeframe for comparison, the latter implied comparisons over multi-year timeframes.

However recording of mortality is important for two reasons. The face and content validity of outcomes datasets is important, and a dataset not containing mortality data would be missing a meaningful outcome. Secondly, although comparisons of small sample-size groups will have limited utility, pooled data across hospitals or regions may provide useful information.

### 1.6.3 Duration of Hospital (and Critical Care) Stay

Length of hospital stay (HLOS) is a resource utilisation (process) measure often used as a summary measure of clinical outcome. It has significant practical advantages in that it is easy to define and measure and routinely recorded in most hospital systems. However HLOS has significant shortcomings as a marker of clinical outcome. At least two assumptions are inherent in the use of HLOS as a surrogate for clinical outcome. First, the assumption that patients are discharged at a standard level of well-being and therefore discharge from hospital is a marker of that level of wellbeing (or lack of morbidity). If patients are discharged from one institution sicker than those in another institution this assumption does not hold and inter-institutional bias may exist. Second, the assumption that all patients who have achieved this level of wellness will then be discharged from hospital: if patients remain in hospital when "well" for non-clinical reasons, for example waiting for a social services package at home, then this will reduce the validity of HLOS as an index of patient clinical outcome. This may result in both intra- and inter-institutional bias. HLOS is a measure of resource utilisation, although even in this respect it has limitations: different levels of intensity of care are associated with different costs. Strictly, HLOS tells us about bed utilisation and any additional inferences are based on often-flawed assumptions and with limited validity. Comparisons between healthcare systems may be confounded where discharge arrangements are different (e.g. use of convalescent facilities).

Similar considerations apply when considering length of Critical Care stay as a marker of acute serious adverse outcome. The threshold for admission to, and discharge from, critical care environments will vary between institutions depending on the acuity of patients, the availability of critical care beds, and any blocks to discharge from critical care facilities. The rate of readmission of patients to hospital (and critical care) following surgery is also used as a surrogate measure of outcome [148] and as a process measure is subject to similar confounding by variation in discharge and admission thresholds.

### 1.6.4 Postoperative morbidity

The World Health Organisation (WHO) classification of the "consequence of disease" has been suggested as a framework for the classification of outcomes used

to evaluate surgical treatments [149]. The WHO classification defines *impairments* as restrictions of physiological or anatomic structure or function, *disabilities* as restrictions in the ability to perform activities within the range considered normal and *handicaps* as those disadvantages that limit the fulfilment of a usual role, such as going to work. Outcome following surgery may be classified into disease-specific and generic measures [149]. Disease specific measures have in general been shown to be more responsive but less generalisable when compared to generic measures [149]. Disease specific measures tend to focus on impairments (e.g. unable to tolerate enteral diet) whereas generic measures tend to focus on handicaps (e.g. not going to work). Short-term harm or morbidity following surgery is principally manifest as disease specific impairment measure and would be expected to be responsive to change (1.7.3 Reliability) but not generalisable to other populations e.g. medical patients with rheumatoid arthritis or patients with mental health problems. The "disease" in this case is the context of undergoing major surgery.

Clinically significant short-term postoperative harm may be classified into morbidity and mortality. Morbidity has traditionally been defined by the presence or absence of specific postoperative complications, but alternative approaches are possible. For the purposes of this thesis morbidity will be used as a generic term for clinically significant, non-fatal, adverse outcome. Surgical complications are one means of describing morbidity following surgery using traditional medical diagnoses (e.g. deep venous thrombosis) rather than alternative classification models.

Traditional classification of morbidity associated with surgery commonly presented in basic surgical manuals divides complications into local (involving the operation site) and general (affecting other systems of the body) or specific (relating to an individual operation) and general (complications of any operation) [150,151]. Complications may be further subdivided into categories, based on the timing of their occurrence in relation to the index operation (e.g. immediate, early, late and long-term based on arbitrary time thresholds). No consistent system of definition is extant [150,151].

Within these categories, complications have been categorised based on medical diagnoses (e.g. deep venous thrombosis, wound infection). Whilst many types of morbidity can be attributed to general (e.g. acute renal failure) or specific categories (e.g. wound dehiscence), some provide dilemmas of attribution (e.g. postoperative ileus) suggesting that these groups are not mutually exclusive. Furthermore, they are closely interlinked. For example a leaking bowel anastamosis (local and procedure specific) may result in a number of general (procedure independent) outcomes such as fever, malaise, inability to tolerate enteral diet, and cardiovascular failure. At present it is unclear whether general postoperative morbidity has an effect on procedure specific long-term outcome (e.g. joint function) or quality of life, although an influence on mortality has been described [9]. There is also limited data to support the idea that procedure related adverse outcomes (e.g. failure of joint replacement) will influence more general outcome (e.g. quality of life) [152,153].

#### *1.6.4.1 Postoperative morbidity: syndrome, construct or non-entity?*

A fundamental question in relation to postoperative morbidity is whether the cluster of pathophysiological findings that tends to occur together following major surgery constitutes a true syndrome. In other words, is the aim of investigating postoperative morbidity simply to be able to describe the prevalence and pattern of a variety of unrelated but clinically relevant phenomena, or is there an underpinning common pathology to be measured?

The process of defining an operational definition and a diagnostic syndrome or disease is an important step in epidemiological description and subsequent management of the problem with any as-yet-undefined cluster of clinical findings. The definition of a syndrome is a pathological condition associated with a cluster of co-occurring symptoms, usually three or more [154]. It is often used provisionally with the expectation that once the nature of the condition is clarified, a more precise designation will take its place [154]. It is also often used synonymously with "disease" [154].

It can be argued that the cluster of symptoms or clinical findings which occur after different types of surgery meet this criteria. First, morbid events (morbidity) following surgery are associated by temporal and contextual factors. It is clear

that many clinical findings cluster together in the sickest patients, but not all patients have all findings. It is suspected, but not verified, that where clinical findings are not evident, more patients may exhibit sub-clinical organ dysfunction. Unfortunately, inconsistency of reporting of postoperative morbidity limits the confidence with which this case can be made.

Importantly, the existence of a common underlying pathological condition is central to the definition of a syndrome [154]. In critically ill patients Multiple Organ Dysfunction Syndrome (MODS) is an accepted syndrome with over 900 PubMed entries. Scoring systems to quantify MODS have been developed (e.g. Multiple Organ Dysfunction Score, MODS) [155] and the importance of a coherent conceptual framework for MODS and its relationship with other clinical entities such as sepsis and the Systemic Inflammatory Response Syndrome (SIRS) [156,157] has been emphasised [158]. MODS is considered to be a response to SIRS which is in turn a massive inflammatory reaction resulting from systemic mediator release secondary to a variety of precipitating factors [159]. Major surgery is recognised to be one cause of SIRS and MODS [160]. A case can be made that Postoperative Morbidity is a mild version of MODS, consequent on a less massive inflammatory reaction than occurs in SIRS. Susceptibility in different organ systems in MODS is recognised to be heterogeneous [161] and the same is likely to be true of organ dysfunction occurring after surgery that is of insufficient severity to meet the MODS criteria. Finally there is evidence that surgery leads to the release of systemic mediators (cytokines) and that this response is related to surgical outcome. The magnitude of cytokine release is related to survival following major surgery [162]; patients with a lesser inflammatory response have improved short-term outcomes [163] and interventions which reduce cytokine release are associated with improved outcomes [164]. Furthermore, when levels of tissue trauma differ for otherwise similar operations, such as laparoscopic procedures in comparison with open procedures, the inflammatory response is of a lesser magnitude [165]. However, the finding that although convalescence may be shorter following laparoscopic surgery, other short and long-term outcomes are similar to those occurring after open procedures is inconsistent with this view [162,166,167].

In summary it seems likely, but is not proven, that Postoperative Morbidity represents a mild variant of MODS, consequent on a mild version of SIRS precipitated by the tissue trauma and physiological disturbance of surgery, anaesthesia and other perioperative perturbations. The case for Postoperative Morbidity to be considered a true syndrome will be strengthened if systematically collected epidemiological data from the postoperative period demonstrates reliable clustering of symptoms/clinical findings.

#### *1.6.4.3 Previous approaches to describing short-term postoperative harm*

The only systematic review addressing this question highlights the heterogeneity in recording of postoperative morbidity and emphasizes the requirement for an objective standardized tool [168]. The Health Technology Assessment Report on the measurement and monitoring of surgical adverse events (2001) concluded: "The use of standardised, valid and reliable definitions is fundamental to the accurate measurement and monitoring of surgical adverse events. This review found inconsistency in the quality of reporting of postoperative adverse events, limiting accurate comparison of rates over time and between institutions." [168]. The same review found 41 different definitions and 13 grading scales for surgical wound infection in 82 studies and 40 definitions of anastamotic leak from 107 studies [168].

The family of studies of the development of perioperative risk prediction scores and scales is one place to explore the different ways in which morbidity is reported. Morbidity reporting in these studies has been inconsistent. In-hospital mortality was the outcome variable used in the studies investigating the performance of the SRS [89,90]. The morbidity reporting (type and criteria) used in the studies of Donati [91], Woltes [88] and Copeland [68] is inconsistent between studies and is summarised in Table 10. The developers of P-POSSUM cited the difficulties of defining postoperative morbidity and the lack of reliability of recording of complications data as a justification for not developing a morbidity prediction equation [105].

**Table 10** Morbidity reporting in a sample of perioperative epidemiological studies

| **Copeland et al 1991** [68] | | |
|---|---|---|
| **Type** | **Complication** | **Criteria** |
| Haematological | Wound haemorrhage | Local haematoma requiring evacuation |
| | Deep haemorrhage | Postoperative bleeding requiring re-exploration |
| | Other | - |
| Infection | Chest | Production of purulent sputum with positive bacteriological cultures, with or without chest radiography changes or pyrexia, or consolidation seen on a chest radiograph. |
| | Wound | Wound cellulitis or the discharge of purulent exudate |
| | Urinary | The presence > $10^5$ bacteria/ml with the presence of white cells in the urine, in previously clear urine |
| | Deep infection | The presence of an intra-abdominal collection confirmed clinically or radiologically |
| | Septicaemia | Positive blood culture |
| | Pyrexia of unknown origin | Any temperature above 37°C for more than 24h occurring after the original pyrexia following surgery (if present) had settled, for which no obvious cause could be found |
| | Other | - |
| Wound dehiscence | Superficial | Wound breakdown |
| | Deep | Wound breakdown |
| Thrombosis | Deep Vein Thrombosis | When suspected, confirmed radiologically by venography or ventilation/perfusion scanning, or diagnosed at post mortem |
| | Pulmonary Embolus | |
| | Cerebrovascular accident | |
| | Myocardial Infarction | |
| | Other | |
| Renal | Impaired renal function | Arbitrarily defined as an increase in blood urea of > 5 mmol/l from preoperative levels |
| Pulmonary | Respiratory failure | Respiratory difficulty requiring emergency ventilation |

| Type | Complication | Criteria |
|---|---|---|
| Cardiovascular | Cardiac failure | Symptoms or signs of left ventricular or congestive cardiac failure which required an alteration from preoperative therapeutic measures |
| | Hypotension | A fall in systolic blood pressure below 90 mmHg for more than 2 hours as determined by sphygmomanometry or arterial pressure transducer measurement |
| Gastrointestinal | Anastamotic leak | Discharge of bowel content via the drain, wound or abnormal orifice. |
| | Other | Any other complication |
| **Woltes et al 1996** [88] | | |
| **Type** | **Complication** | **Criteria** |
| Pulmonary | Bronchopulmonary infection | Positive sputum culture and/or positive chest radiograph |
| | Atelectasis | Chest radiograph |
| | Pleural effusion | Chest radiograph |
| Cardiac | Significant arrhythmias | E.g. Atrial fibrillation |
| | Acute myocardial infarction | ECG changes AND increased CPK-MB enzyme levels |
| Wound | Wound inflammation | Clinical |
| | Wound infection | Clinical, including purulent discharge |
| Gastrointestinal | Anastomotic Leak | Clinical |
| Renal | Urinary Tract Infection | Positive urine culture |
| **Donati et al 2004** [91] | | |
| **Type** | **Complication** | **Criteria** |
| Haematological | Anaemia | - |
| Cardiovascular | Heart failure | NYHA 3-4 |
| | Previous myocardial infarction | - |
| | Arterial hypertension | - |
| Metabolic | Diabetes mellitus | - |
| Renal | Renal failure | - |
| | Hepatic failure | - |
| | Previous stroke | - |
| Pulmonary | Severe bronchopulmonary disease | - |

***Notes to Table 10:*** *ECG = electrocardiogram, CPK-MB = Creatine phosphokinase – myocardial band, NYHA = New York Heart Association.*

Similarly, morbidity reporting was inconsistent in studies using the "High-risk major surgery" criteria suggested by Shoemaker et al [92]. This is discussed in more detail in Chapter 2. The NSQIP morbidity definitions are not publicly available [4].

Recent attempts to formalise the classification of complications following surgery have taken diverse approaches. The Association of Surgery of the Netherlands (ASN) uses a classification system based on the nature, localization specification and any additional description of the complication [169]. The Trauma Registry of the American College of Surgeons (TRACS) uses traditional diagnoses (e.g. deep venous thrombosis) classified using 4 digit codes [169]. An alternative classification of surgical complications is based on three categories (complications, failure to cure, sequelae) qualified by the subsequent result (treatment or outcome), ranging from simple symptomatic treatment to death, in 8 sub-categories [170]. A different approach was adopted by Myles who developed a patient-rated nine-point quality of recovery index score (QoR Score) derived from a 61-item questionnaire with questions ranging from "able to breathe easily?" to "interest in work?" (Table 11) [171]. The QoR score has been shown to be valid and reliable and suggested a useful measure of recovery for anaesthesia and surgery.

**Table 11** Quality of recovery score (QoR score) (Miles et al 1999)

| | Not at all | Some of the time | Most of the time |
|---|---|---|---|
| 1. Had a feeling of general well-being. | 0 | 1 | 2 |
| 2. Had support form others (especially doctor and nurses). | 0 | 1 | 2 |
| 3. Been able to understand instructions and advice. Not being confused. | 0 | 1 | 2 |
| 4. Been able to look after personal toilet and hygiene unaided. | 0 | 1 | 2 |
| 5. Been able to pass urine ("waterworks") and having no trouble with bowel function. | 0 | 1 | 2 |
| 6. Been able to breathe easily. | 0 | 1 | 2 |
| 7. Been free from headache, backache or muscle pains. | 0 | 1 | 2 |
| 8. Been free from nausea, dry-retching or vomiting. | 0 | 1 | 2 |
| 9. Been free from experiencing severe pain, or constant moderate pain. | 0 | 1 | 2 |

In summary, morbidity description in the published literature is inconsistent in scope, method and criteria of data collection and no established method is consistently used.

#### *1.6.4.3 The Postoperative Morbidity Survey (POMS)*

The POMS was developed within the Department of Anesthesiology at Duke University Medical Centre (DUMC), by Dr Elliot Bennett-Guerrero working with Professor Michael (Monty) Mythen. The need was identified for a measure of clinically significant postoperative short-term harm. This measure was anticipated to have potential utility in clinical decision making, in clinical governance activities and in quality of care, prognostic, and effectiveness research. The previously discussed limitations of mortality and length of stay as outcome measures following surgery, and the lack of a validated measure of morbidity were identified. However this perceived gap in the literature was not formally investigated (e.g. with a systematic review).

The POMS (Table 12) is an 18-item tool that addresses nine domains of morbidity relevant to the post-surgical patient: pulmonary, infection, renal, gastrointestinal,

cardiovascular, neurological, wound complications, haematological and pain. For each domain either presence or absence of morbidity is recorded on the basis of precisely defined clinical criteria [172]. The original publication describing the POMS was an epidemiological description of 438 patients undergoing elective major surgery at Duke University Medical Centre [172].

The POMS was designed with two guiding principles. First, it should only identify morbidity of a type and severity that could delay discharge from hospital. Second, the data collection process should be as simple as possible so that large numbers of patients can be routinely screened. Following on from these principles, a measure was produced that focused on easily collectable indicators of clinically important dysfunction in key organ systems. The indicators are obtainable from routinely available sources and do not require special investigations. These sources include observation charts, medication charts, patient notes, routine blood test results, and direct questioning and observation of the patient. Crucially, the indicators define morbidity in terms of clinically important consequences, rather than traditional diagnostic categories [172]. For example, a patient with a clinically significant chest infection would register POMS defined morbidity in the pulmonary (requirement for supplemental oxygen or other respiratory support) and infection (currently on antibiotics or temperature >38°C in the last 24 hours) domains, rather than meeting specific diagnostic criteria for a chest infection. The relative dependence of some of the domain definitions on administered care is discussed further in chapter 4 (Validation of the POMS).

**Table 12** The Postoperative Morbidity Survey (POMS)

| | Criterion | Source |
|---|---|---|
| **Pulmonary** | *De novo* requirement for supplemental oxygen or other respiratory support (e.g. mechanical ventilation or CPAP) | Patient observation<br>Treatment chart |
| **Infectious** | Currently on antibiotics or temperature >38°C in the last 24 hours | Treatment chart<br>Observation chart |
| **Renal** | Presence of oliguria (<500 ml/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for non-surgical reason. | Fluid balance chart<br>Biochemistry result<br>Patient observation |
| **Gastrointestinal** | Unable to tolerate enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting or abdominal distension | Patient questioning<br>Fluid balance chart<br>Treatment chart |
| **Cardiovascular** | Diagnostic tests or therapy within the last 24 hours for any of the following: *de novo* myocardial infarction or ischemia, hypotension (requiring pharmacological therapy or fluid therapy >200 ml/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary oedema | Treatment chart<br>Note review |
| **Neurological** | Presence of *de novo* focal deficit, coma or confusion/delirium | Note review<br>Patient questioning |
| **Wound** | Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms | Note review<br>Pathology result |
| **Haematological** | Requirement for any of the following within the last 24 hours: packed erythrocytes, platelets, fresh-frozen plasma or cryoprecipitate | Treatment chart<br>Fluid balance chart |
| **Pain** | Surgical wound pain significant enough to require parenteral opiods or regional analgesia | Treatment chart<br>Patient questioning |

***Notes to Table 12:*** *CPAP = Continuous Positive Airways Pressure*

Item generation was achieved through a three-stage process [172]. First, investigators collected information directly from patients, nurses, and doctors using open questions to identify reasons why the patients remained in hospital after surgery. Second, expert clinicians categorised the responses into domains of morbidity type. Thresholds were set for individual domains to achieve the primary goal of identifying morbidity of a type and severity that could delay discharge from hospital. Finally, the derived survey was reviewed and amended

by a consensus panel of anesthesiologists and surgeons. The POMS (Table 1) contains 18 items that address nine domains of postoperative morbidity. For each domain, either presence or absence of morbidity is recorded on the basis of objective criteria. The POMS is starting to be used in outcomes research [173] and in effectiveness research [174].

A secondary objective of the original publication was to test the hypothesis that intraoperative indices of tissue hypoperfusion were good predictors of postoperative morbidity. Intraoperative variables believed to be associated with tissue hypoperfusion (gastric pHi measured using gastric tonometry and arterial base excess) were the strongest predictors of postoperative morbidity [172]. These findings are supportive of the model of postoperative organ dysfunction as a mild variant of MOF. Abnormal tissue perfusion in general [175], and abnormal splanchnic perfusion (pHi) in particular [176], are believed to be an aetiological factor in the development of SIRS.

## *1.7 Clinical Measurement Scales*

### 1.7.1 Introduction

Clinical phenomena may be directly observable, indirectly observable or unobservable. For example, height and weight are observable phenomena that can be directly measured using physical tools, and cardiac output can be indirectly observed and measured in the intact human. However, intelligence and anxiety cannot be directly observed, but may only be inferred by observing manifestations of the latent (underlying) construct. Clinical measurement of unobservable phenomena presents different challenges than those that occur with directly or indirectly observable phenomena.

#### *1.7.1.1 Levels of measurement*

An important concept, which dictates which statistical tests are appropriate for particular data, is the level of measurement. Four levels of variable can be described within a hierarchical system of increasing order of mathematical structure: nominal, ordinal, interval and ratio [177]. Nominal (categorical, discrete) data are unordered (e.g. apples, oranges). Ordinal (ordered categorical) data can be ranked or ordered, but cannot be manipulated arithmetically (e.g. small,

medium, large). Interval measurement can be added or subtracted because the differences between arbitrary pairs of adjacent measurements are identical; therefore equal differences between measurements represent equal intervals (e.g. temperature in degrees Celsius). Ratio measurements have the same qualities as interval data, and in addition may be multiplied or divided because a ratio between measurements is meaningful as the data includes a non-arbitrary zero value (e.g. temperature in degrees Kelvin) [177]. Interval and ratio data may be grouped together as continuous data.

#### *1.7.1.2 Observable and unobservable phenomena*

Many observable phenomena in clinical measurement may be described using ratio data (e.g. height, weight). Although some unobservable phenomena (e.g. IQ) have been described using continuous (interval) data, in most cases psychometric measurement is presented as nominal or ordinal data, which may on occasions be treated as interval data where this is empirically justified. This is a logical consequence of the imprecision inherent in measurements where observed manifestations of unobservable phenomena are used to quantify a latent construct.

Important methodological differences exist between clinical measures where continuous variables (e.g. haemoglobin, cardiac output) describe observable phenomena and ordinal clinical measurement scales of unobservable phenomena. Laboratory measurement and clinical monitoring involve predominantly technical challenges relating to device performance and choice of an appropriate "gold standard". In this context, validity of continuous variables is tested in relation to an accepted (albeit often flawed) gold standard (E.g. Dye dilution cardiac output measurement using the Fick principle): so-called "criterion validity" [178]. Reproducibility (consistency, agreement) is intrinsic to this comparison and consequently reliability becomes subsumed within validity. The concepts of calibration, drift, precision, bias and accuracy are used to describe the output of this testing. Statistical treatments such as those proposed by Bland Altmann (bias, precision, limits of agreement) are favoured [179].

In the case of clinical measurement scales for unobservable phenomena where measurements reflect manifestations of the latent construct, it is rare for a "gold standard" to exist. As a consequence, criterion validity cannot be determined for

such concepts as health status [180]. Where a criterion standard does exist, the requirement for the development of a new measure should be questioned - improved speed or ease of use might be legitimate justifications. Alternative methods of validation, such as hypothesis testing to establish construct validity, are therefore usually required (see below, 1.7.5 Validity).

#### *1.7.1.3 Composite Outcome Measures*

Composite outcomes such as the POMS have more diverse content than simpler tools and are believed to have a better chance of detecting unexpected adverse outcomes as well as improving the power of studies [181]. Composite outcomes, which combine several different but clinically relevant endpoints, can reduce the sample size necessary to have an adequately powered study: the higher the event rate, the smaller the number of patients required to detect any given treatment effect. Furthermore, composite endpoints that provide comprehensive coverage across organ systems have the additional advantage that they are more likely to detect unexpected adverse effects than more narrowly focused outcome measures [181]. Composite outcome measures are consistent with the clinimetric approach to measurement but sit less comfortably within the psychometric tradition (see below, 1.7.3 Clinimetrics and Psychometrics).

#### *1.7.1.4 Development of Clinical Measurement Scales*

The development of clinical measurement scales is divided into two stages. The first relates to the items within the scale and the second relates to the performance of the integrated scale. Initial development involves developing the items, selection of items and exploration of scaling properties. Subsequent development involves testing the scale for reliability and validity.

### 1.7.3 Clinimetrics and Psychometrics

Two contrasting but related approaches to test development and validation exist: Psychometrics and Clinimetrics. Psychometrics is the field of study concerned with the theory and technique of measurement in education and psychology. During the late 1800s, Francis Galton developed tests (e.g. questionnaires and surveys) and statistical approaches (including correlation and regression) for the study of biological differences, effectively inventing the field of biometrics, and contributed, with others, to the origins of psychometrics. Central to the psychometric approach is the measurement of unobservable phenomena such as

intelligence or depression. Whilst manifestations of the trait or state can be observed, the underlying or latent construct can only be inferred from these manifestations and cannot be measured directly. One consequence of this, is that the construct is assumed, if valid, to be one-dimensional [182]. Measurement requires identification of items that are manifestations of the latent construct (e.g. anhedonia in depression) [182]. These items should therefore be homogeneous in performance in order to reflect the uni-dimensional nature of the latent construct. This pattern of item performance in turn mandates an approach where allocating different weights to different items is neither required nor appropriate [183]. Finally this approach points to a hidden conceptual model within psychometrics: that the number and not the intensity of symptoms determine severity of illness [183].

The term "Clinimetrics" was coined by Dr Alvan R Feinstein in 1982 [184] to describe the "domain (area of study) concerned with indexes, rating scales and other expressions that are used to describe or measure physical symptoms, physical signs and other distinctly clinical phenomena in clinical medicine." He subsequently used it as the title of a book published in 1987 [185]. Feinstein is also notable as the individual who coined the term "comorbidity," which refers to the condition of having a disease unrelated to the one of primary interest (in the surgical context a disease other than the condition for which the operation is being carried out), and as the "father" of clinical epidemiology [186]. However, Virginia Apgar working some 20 years earlier in 1953 is considered by some the spiritual parent of clinimetrics [187]. In 1953 she implicitly introduced the concept that an intangible clinical phenomenon (a newborn child's overall condition) could be converted into a formally specified measurement (the APGAR score) [188]. Other examples of clinimetric indices with similar implicit conceptual models include the Jones Criteria for Rheumatic Fever [184], New York Heart Association functional classification [189], Glasgow Coma Sale [190] and the American Society of Anesthesiologists physical status scale [74].

Feinstein described six core principles of the clinimetric approach [185]:

1. Selection of items based on clinical expertise rather than statistical technique
2. Weighting of items based on clinicians or patients experience or preferences (not unit weights)

3. Heterogeneity of items, so as to capture all symptoms or processes that contribute to the construct (rather than homogeneity)
4. Ease of use (pen and paper or mental arithmetic not computer analysis),
5. Face validity based on inclusion of all relevant clinical phenomena (rather than exclusion of items that correlate poorly with others)
6. Using the patient's report of what is troublesome or bothersome as the source of information for subjective data.

Fayers et al [191] contrasted effect indicators with causal indicators: psychometrics being interested in effect indicators of the latent trait (e.g. IQ) whereas causal indicators create the construct of interest (e.g. quality of life). They use the example of quality of life (QoL) metrics where a physical symptom of a disease may have a causal association with low QoL whereas anxiety may be considered to have an effect relationship, being a consequence of the low QoL [191]. Some factors may fall into both categories: for example depression may be both cause and consequence of low QoL [191]. Clearly, causal indicators fit more comfortably within a clinimetric perspective of measurement.

Whilst many of the approaches of psychometrics are central to clinimetrics (e.g. reliability and validity testing), there are key conceptual elements that are different. Homogeneity of component items reflecting a latent construct is central to psychometrics. However the level of correlation inherent in homogeneity tends to reduce the responsiveness of a measure: redundancy increases item correlation but decreases sensitivity. Psychometric instruments do not usually utilize weighting of variables. This is in part because weights will not contribute significantly to the total variance of the scale if items are homogeneous. Conversely, if item correlation is close to zero or even negative, which is possible in a clinimetric scale including an item with clinical face validity and weighting, it can have a significant effect on overall variance. Use of the available evidence reflecting salience or patient significance to allot weights to items is acceptable within the clinimetric approach. The issue of scaling properties complicates the discussion of item heterogeneity. Heterogeneous items suggest that devising a scale based on a sum of item scores is unlikely to be valid. Different combinations of items may sum to the same score whilst at the same time having inconsistent

clinical and prognostic implications. In practice scaling properties may be tested empirically. Some controversy exists in the literature as to whether the distinction between psychometrics and clinimetrics is valid [192][193]. However the clinimetric literature thrives with calls for research to distinguish the relative advantages of each approach [194]. A study comparing the two approaches in the parallel development of a single measure (of upper extremity disability) concluded that the two approaches were complimentary [195].

With respect to this dichotomy of measurement approaches, the POMS (multidimensional nominal data) is clearly within the clinimetric tradition. POMS items include effect indicators (e.g. temperature) and causal indicators (e.g. wound infection) as well as indicators that are dependent on administered care (prescription of antibiotics): a pragmatic approach is taken in item selection. However, there is reason to believe that postoperative morbidity reflects a latent (underlying) construct (see 1.6.4.1). Heterogeneity of domain responses may reflect heterogeneity of individual susceptibility to different categories of morbidity in the context of an underlying postoperative inflammatory state.

### 1.7.3 Reliability

Reliability testing is based on the concept that error is inherent in all measurements, that this error can be separated into random and systematic components, and that each component can be quantified.

The literature on reliability is complicated by the inconsistent use of a variety of synonyms including objectivity, reproducibility, stability, agreement, association, sensitivity, precision [182]. The relationship between these terms and their specific use in this thesis will be explained below.

#### *1.7.3.1 Reproducibility: correlation, association, consistency and agreement*

The concept of reproducibility of a measurement has several facets: agreement, consistency, and reliability are all aspects of reproducibility. **Reproducibility** concerns the degree to which repeated measurements of the same quantity provide similar results.

**Consistency** is the tendency to record the same measurement given the same unit of observation [196]. Consistency is necessary but not sufficient for agreement. For example, one observer may record black every time another observer records white: agreement would be zero but consistency would be 100%.

**Agreement** describes how close the scores of repeated measures (under the same conditions) are to each other [197]. Consistency is necessary for agreement. Reliability and agreement have a more complex relationship. Measures of agreement include: mean +/- standard deviation, standard error of the mean, percentages of agreement (limitation does not account for chance agreement), intra-class correlation coefficient, and limits of agreement (Bland and Altmann) [197]. Consistency does not imply absence of bias: consistency may occur with a fixed bias (offset or multiple) that can be corrected for to achieve agreement.

Reliability is often viewed as a facet of reproducibility but additionally takes into account the object of measurement. However, this relationship is probably more complicated. Whilst, in general, reproducibility (agreement) is a requirement for reliability, under certain conditions (counter intuitively) reliability can be inversely related to reproducibility. For example all raters agree on the value of a particular characteristic (100% consistency, agreement, reproducibility and correlation), but all the values are equal. There is therefore no discrimination possible between levels of the measured variables, and therefore no reliability [182].

**Reliability** therefore describes the degree to which subjects (or patients) can be distinguished from each other. This is dependent on the relationship between the measurement error and the variability between subjects [197]. Formal calculation of a reliability coefficient (separating out the different components of error) uses variations of the intra-class correlation coefficient [197] discussion of which is beyond the scope of this thesis.

#### *1.7.3.2 Stability: inter-rater, intra-rater and test-retest reliability*

These terms describe how a measure performs under different conditions, commonly of time and person. Measures of stability include inter-rater reliability (inter-scorer/inter-observer reliability), intra-rater reliability (intra-scorer/intra-observer) and test-retest reliability [198]. Their differences can be summarised:

**Inter-rater reliability** different observer, same sample, same/similar time
**Intra-rater reliability** same observer, same sample, same/similar time
**Test-retest reliability** same observer, same sample, different time: for self administered tests

Statistically all three of these measures are usually approached similarly. For categorical variables Cohen's Kappa (two raters) [199] or Fleise's Kappa (> two raters) [200] are used to assess reliability and for continuous variables product moment correlation (interclass, Pearson, Spearman) is used [198]. Some authorities argue that for inter-rater reliability and intra-rater reliability, it is more appropriate to use intra-class correlation (which takes account of systematic error) whereas for test-retest reliability, product moment correlation may be more appropriate [198].

### *1.7.3 Reliability and internal consistency*

In psychometric tests, where the measurement of a uni-dimensional underlying trait is the aim of test development, the internal consistency of the test is also considered an element of reliability. The implicit assumption being that any test item reflecting the underlying trait should correlate with other tests items. If this holds true, then any test item, or group of items, should also correlate with clusters of other test elements. Consequently, if this assumption is held to be true then the internal consistency of items within a measure is an element of reliability. This can be tested by examining the relationships of individual items with the pooled other items (item-rest correlation), by dividing the test and comparing the different halves (split-half reliability) or by comparing with alternate forms of the same test (e.g. historical version of the same test or an alternative second version of the test derived from similar items) [182]. Item-rest correlation is used in the calculation of Cronbach's alpha [201] (internal consistency for polychotomous variables) and Kuder Richarson 20 [202] (internal consistency for dichotomous variables).

In summary, reliability incorporates a relationship with the underlying data (context sensitive) because the ability to distinguish between individuals reliably depends on the characteristics of the population being studied. Measurement error is related to the overall expected variation of the population being measured. Thus reliability can be stated as the ratio of variance between patients to the total

variance (patient variability plus measurement error). A zero therefore indicates a wholly unreliable measure whilst one indicates perfect reliability.

### 1.7.4 Deriving a score from multiple items

Surveys and scores (multi-item measures) are usually composed of multiple categorical (dichotomous or polychotomous variables) items. Categorical items may be derived by categorising continuous data. An ordinal score may be attributed to appropriate polychotomous items. The summary results from these types of measures may be expressed in a variety of formats. A single numerical (ordinal) result may be obtained from the sum, or weighted sum, of the item scores: a score or index. For example the Apgar score used in the assessment of neonatal well-being [188]. Alternatively a threshold value can be specified to define a single dichotomous result (e.g. presence or absence of morbidity in the POMS). An additional approach is to report individual results from more than one domain to provide a composite descriptive outcome (for example the TNM staging system for malignancy) [203].

Reporting of simple or composite dichotomous or polychotomous variables does not require additional arithmetic to obtain the outcome metric. Data used to derive scores from sums, or weighted sums, of constituent variables should meet certain criteria in order to be treated in this way. Demonstration of scaling properties is essential if a score is to be derived from a test. Scaling properties require that the arithmetic relationship between score results is consistently reflected in the underlying variable [182]. For example a morbidity score of 4 should be twice as bad as a morbidity score of two. Although this can be individually validated against independent criteria, or using hypothesis testing, a *sine qua non* of this relationship should be that there is correlation between items within a test [182]. With tests that include a heterogeneous set of items it is important to assess whether there is conceptual validity in trying to develop a single score irrespective of the statistical picture. Where statistical correlation is problematic, items in a score can be differentially weighted to improve performance of a score. However, whilst weighting items is consistent with the clinimetric approach to test development it is counter to the psychometric approach, where all items are believed to reflect underlying construct and the number of items is related to the degree of the trait.

### 1.7.5 Validity

Validity refers to the degree to which a test is measuring what it is intended to measure. Essential elements of validity are face and content validity, reliability and empirical validity. Terminology can be confused in this area and the definitions below are based on the approach of Steiner and Norman in "Health Measurement Scales" [182].

**Face validity** is the extent to which the measure "on the face of it" appears to be measuring the desired qualities. **Content validity** is a closely related concept and describes whether the items of the measure sample all the relevant domains that reflect the desired quality being measured. The assessment of face and content validity relies on subjective evaluation of appropriateness or "believability" by experts. In the case of clinical measurement tool development, believability assessment is normally undertaken by a panel of "clinical experts". In the case of PROMs it can be argued that face validity should also be apparent to the users of the measurement tools: the patients. Face and content validity have been termed "Validation by assumption" [182]. In some cases a score may be both reliable and valid (based on criterion or construct validity) but lack face validity due to the obscurity of the items. This can be an advantage in the measurement of qualities that may have stigma attached (e.g. a survey to identify alcoholism).

**Empirical validity** encompasses criterion validity and construct validity

**Criterion validity** (convergent validity, concurrent validity) describes the comparison of a new test, scale or index with a recognised criterion or "gold standard". For example, the comparison of data obtained from a novel method of cardiac output measurement with criterion results obtained using bolus thermodilution using a pulmonary artery flotation catheter (the accepted "gold standard"). In the context of test development, the existence of an established gold standard should lead to critical appraisal of the need for a new test. The new test may be justified in terms of minimising cost, duration of administration or patient disturbance. However the field of test development is littered with areas where multiple tests measure the same or similar phenomena with no obvious relative benefit e.g. clinical scores of depressive illness. The methodology for establishing

criterion validity between a new test and the gold standard is well described [182] and may include assessment of sensitivity and specificity and the methods of Bland and Altman [179]. Criterion validity may be divided into concurrent and predictive validity. **Concurrent validity** explores correlation of the new measure with the criterion measure. **Predictive validity** explores correlation of the new measure against information that will be available (e.g. correlation between intelligence tests and subsequent exam scores). However where no criterion test exists, alternative methods of assessment must be used.

**Construct Validity**: In the absence of a comparator criterion test an alternative approach is adopted. Classical hypothesis testing is utilised to explore the behaviour of the test in a variety of contexts. Ideally, these hypotheses should be consistent with an explicitly defined underling construct. For example with intelligence testing it might be hypothesized that individuals with high intelligence tests would achieve greater academic success or earn more money during their lifetime. These hypotheses can then be tested empirically and if supported by the results of the test then construct validity is supported. Construct validity is therefore limited or absent if these hypotheses are poorly supported empirically. The hypothesis testing approach asks the question: "Do the results of this study allow us to draw the inferences which we wish to?" The burden of proof arises not from a single powerful experiment but from a series of converging experiments [182].

Testing of construct validity in relation to postoperative morbidity might involve exploring hypotheses such as:

- Patients exhibiting more morbidity would be expected to stay in hospital for a longer period of time.
- Patients at higher risk of adverse outcome (based on preoperative risk adjustment scores) would be expected to have a higher prevalence of morbidity.

The population and environment in which the validation of a new measurement tool was performed define the validity of the tool. Thus, reliability and validity are not absolutes qualities, rather they are relative to the context of development and

testing: in other contexts validity may be limited or absent, and cannot be assumed. Therefore, when considering the development of a metric to describe postoperative morbidity, the type of surgery (orthopaedic, cardiac, gastrointestinal) and the type of patients (children, adults) in the validation cohort will dictate the spectrum of validity [182].

## *1.8 Summary*

1. Outcome following surgery is a significant public health issue.
2. Quality of surgical care can be defined in a variety of ways. The distinction between structure, process and outcome is important, as is the perspective of the measurer. In the UK quality has been subdivided into safety, experience and effectiveness.
3. Risk adjustment of outcome data is essential to minimise confounding by patient and surgical characteristics if effectiveness of care is to be evaluated.
4. Clinically important short-term outcomes following surgery include mortality and morbidity. Duration of hospital stay is commonly used as a surrogate measure of outcome.
5. Description and measurement of morbidity following surgery are inconsistent limiting comparisons of effectiveness of care.
6. Measurement of unobservable phenomena, such as postoperative morbidity, is dependent on measurement of hypothesised manifestation of the phenomena.
7. Reliability and validity are essential requirements in a clinical measure and are critically dependent on the context of testing. In the case of an unobservable phenomenon such as postoperative morbidity, a criterion measure may not be available and testing of construct validity is required.

# Chapter 2: "Perioperative increase in global blood flow to explicit defined goals and outcomes following surgery": a systematic review

## *2.1 Introduction*

This chapter presents a systematic review of studies assessing the efficacy of a style of haemodynamic management (perioperative administration of fluids and/or vasoactive drugs targeted to increase global blood flow to explicit defined goals) in patients undergoing major surgery. The chapter describes the effect of this complex intervention on mortality, morbidity and resource utilization as well as using stratified meta-analysis to explore the impact of components of the intervention on pooled outcomes. Heterogeneity of outcomes reporting between studies is highlighted as a limitation of this systematic review.

### 2.1.1 Context

The association between limited physiological reserve and risk of death following surgery has long been recognized [204,205]. Post hoc analysis of patients undergoing major surgery revealed that survivors had a higher cardiac index and lower systemic vascular resistance than non-survivors [206,207]. Conversely, commonly monitored vital signs (heart rate, arterial blood pressure, central venous pressure, temperature, haemoglobin concentration) were found to be poor predictors of mortality when compared with variables reflecting blood flow or oxygen flux (cardiac output, total body oxygen delivery ($DO_2$)) [208,209]. In particular survivors of major surgical procedures were found to have higher values for cardiac output or $DO_2$ compared with non-survivors. More recent studies undertaken to assess the relationship between oxygen transport variables and postoperative morbidity and mortality have shown mixed results [210-212].

New therapeutic options and monitoring techniques that became available in the 1970s, particularly the introduction of the pulmonary artery flow directed catheter (PAC) [213,214], opened up the possibility of measuring, and then manipulating, an individual's cardiovascular system. It was hypothesized that targeting goals for

cardiac output and $DO_2$ in all patients to the values manifested by the survivors of surgery would improve outcome [215]. An important principle of this manipulation was that augmentation of cardiac output and $DO_2$ would result in improved tissue perfusion and oxygenation.

Since the 1970s, a number of randomised trials have been undertaken in patients in the perioperative period that have investigated the efficacy of this approach. However, these trials differ in the case mix of the patients recruited (different operation severity and comorbidities and, therefore, expected mortality), the techniques used to measure cardiac output (PAC - thermodilution, Doppler velocimetry, arterial waveform analysis), the specific goals targeted (cardiac output, $DO_2$, maximum stroke volume), the techniques used to achieve the goals (fluids, fluids plus vasoactive drugs) and the management of the control arm. In addition some of the studies were not blinded and many had small sample sizes leading to limited statistical power. Despite this a number of non-systematic reviews have attempted to group together identified studies in order to draw general conclusions from them [216-220]. However, these reviews have identified varying numbers of trials and have not been undertaken systematically, using scientifically rigorous techniques for literature searching, or for abstraction and analysis of data. Three previous systematic reviews have addressed this question [221-223] and reported improved outcomes, but do not include recently published studies and did not focus exclusively on perioperative data.

The intervention being evaluated in this review is a complex intervention [224]. The MRC(UK) defined complex interventions as interventions built up from a number of components, which may act both independently and inter-dependently [224]. The components usually include behaviours, parameters of behaviours (e.g. frequency, timing), and methods of organising and delivering those behaviours (e.g. type(s) of practitioner, setting and location). Stratified meta-analysis may be used to investigate which components of a complex intervention contribute to the observed response [225].

### 2.1.2 Aims

The aim of this systematic review of the literature was to address the question: does perioperative administration of fluids and/or vasoactive drugs targeted to increase global blood flow, in adults undergoing surgery, reduce mortality and morbidity and resource utilisation?

A secondary aim of this review was to investigate the influence of timing of intervention, type of intervention, type of goals, mode (urgency) of surgery and type of surgery on outcome, in order to identify possible determinants of response to the intervention.

## *2.2 Methods*

### 2.2.1 Summary

A systematic review of manuscripts published in peer-reviewed journals was conducted using the Cochrane Collaboration methodology. All analyses were pre-specified in a published protocol [226] that was peer-reviewed and approved (via the Cochrane Collaboration) prior to commencement of the literature searches. Protocol development was guided by the "Optimisation Systematic Review Steering Group" (Appendix 1).

### 2.2.2 Search Strategy

MEDLINE, EMBASE, and the Cochrane Controlled Trials Register (CCTR) databases were searched between 1966 and end-October 2006 using a filter for RCTs (Appendix 2 and Appendix 3) and 54 selected key words (Appendix 4). The original filter (Appendix 2) was used to search the databases up to end December 2000. The modified filter (Appendix 3) was used to search from January 2000 to October 2006.

Reference lists of potentially eligible studies and previously published systematic reviews were also searched. Personal reference databases of the authors and Steering Group were searched. Experts in the field and relevant pharmaceutical companies were contacted and asked for published and unpublished reports.

RCTs with or without blinding were considered for inclusion. "Perioperative" was defined as initiated within 24 hours pre-surgery and up to 6 hours post-surgery. "Targeted to increase global blood flow" was defined as interventions aimed to achieve explicit measured goals, specifically: CO, cardiac index (CI), $DO_2$, oxygen delivery index, oxygen consumption ($VO_2$), oxygen consumption index, stroke volume (SV), stroke volume index, mixed venous oxygen saturation ($SVO_2$) and lactate. "Adult" was defined as aged 16 years or older. "Undergoing surgery" was defined as patients having a procedure in an operating room. "Outcome" was defined as mortality (for longest reported period), morbidity (rate of overall complications, rates of renal impairment, arrythmia, respiratory failure/ARDS (Acute Respiratory Distress Syndrome), infection, myocardial infarction, congestive heart failure/pulmonary oedema and venous thrombosis), resource use (hospital stay post-surgery, intensive care stay post-surgery) health status (six month functional health status, quality of life scores), and cost. All definitions were agreed a priori. No language restrictions were applied.

### 2.2.3 Data extraction

All definitions were agreed a priori. Two independent reviewers (the author [MG], Dr Mark Hamilton [MH]) screened the titles and abstracts of studies identified by the searches to identify potentially eligible studies. Full texts of potentially eligible studies were obtained. Study characteristics of included studies were abstracted including: study design; patient population; interventions; and outcomes. At least three attempts were made to contact authors of eligible studies to obtain any required data not available in the published report. Methodological quality of included studies was assessed using the criteria described in the component checklist of Gardner et al (Appendix 5) [227]. In addition allocation concealment and blinding were separately assessed. Differences were resolved by consensus between the author (MG) and a co-investigator (MH) after consultation with a third investigator (Dr Kathy Rowan [KR]). Abstracted data were entered and checked by MG and MH. Study authors were contacted for additional data where necessary.

### 2.2.4 Analysis plan

Abstracted data describing the eligible studies were tabulated. Inter-rater reliability for methodological assessment was assessed using Kappa statistics. Analyses of outcomes were based on intention-to-treat. A weighted treatment effect was calculated across all RCTs using Review Manager (RevMan)(Review Manager [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008).

Results are expressed as Peto odds ratios (OR) for dichotomous outcomes and mean differences (MD) for continuous outcomes. The robustness of these estimates was explored by comparing both fixed- and random-effects models and by including larger (n>=100) and higher-quality (allocation concealment grade A) studies only. An analysis of risk differences was used to estimate the number needed to treat.

Stratified meta-analyses, using mortality data only, were undertaken to investigate the influence of timing of intervention, type of intervention, type of goals, mode (urgency) of surgery and type of surgery. Subgroups were defined, a priori: (a) timing of commencement of the intervention - preoperative (before arrival in anaesthetic room/operating room), intraoperative (arrival in anaesthetic room/operating room to leaving theatre), postoperative (after leaving operating room); (b) type of intervention - fluids alone and fluids with vasoactive drugs; (c) type of goals - cardiac output and oxygen transport goals (direct flow measurement), mixed venous oxygen saturations or lactate (surrogate flow measurement) stroke volume (flow component measurement); (d) urgency of surgery - elective, emergency; (e) type of surgery - cardiac, vascular, general.

## *2.3 Results*

### 2.3.1 Description of studies

We identified 124,728 potential studies in the initial electronic search. No additional studies were identified by contacting experts in the field or relevant pharmaceutical companies or by searching personal reference databases of the authors or Steering Group. No additional studies were identified following

screening of reference lists of potentially eligible studies and previously published systematic reviews (snowballing).

Fifty potentially eligible studies were identified following screening of abstracts of potential studies (MG, HM). Twenty-eight potentially eligible studies that did not meet the study inclusion criteria are summarized in Table 13. Reasons for exclusion included: outside timing criteria (9 studies, established critical illness, severe sepsis, septic shock), not all patients underwent surgery (9 studies, trauma), ineligible flow goals (3 studies, pHi guided, intra-thoracic blood volume guided), same flow goal in both groups (4 studies), unclear flow goals (2 studies) and design (2 studies, not RCTs).

Twenty-two fully published studies (including 4546 patients) met the study inclusion criteria. Characteristics of included studies are summarized in Table 14.

Outcome reporting in these included studies was inconsistent (e.g. different criteria for classifying mortality) and many studies did not report outcomes sought by this review. Mortality, resource utilization and cost outcomes are reported in Table 15. Morbidity outcomes are reported in Table 16.

### 2.3.2 Risk of bias in included studies

Allocation concealment was adequate (Grade A) in 10/22 studies but inadequate or unclear in the remainder (Table 17). Thirteen of twenty-two studies were classified as large (>=100 patients)(Table 17). There was considerable variation in methodological quality between studies (Table 18). The degree of concordance between reviewers (MG, MH) was >90%.

**Table 13** Excluded studies and reason for exclusion

| Study | Reason for exclusion |
|---|---|
| **Alia 1999**[228] | Severe sepsis, septic shock |
| **Balogh 2003** [229] | Trauma |
| **Bishop 1995** [230] | Trauma |
| **Blow 1999** [231] | Trauma |
| **Chang 2000** [232] | Trauma, not RCT |
| **Durham 1996** [233] | Established critical illness |
| **Flancbaum 1998** [234] | Retrospective, not RCT |
| **Fleming 1992** [235] | Trauma |
| **Gattinoni 1995** [236] | Established critical illness |
| **Gutierrez 1992** [237] | pHi guided |
| **Hayes 1994** [238] | Established critical illness |
| **Ivatury 1996** [239] | Trauma |
| **Lobo 2006** [240] | Same flow goal in each group |
| **Miller 1998** [241] | Trauma |
| **Muller 1999** [242] | No explicit flow goal |
| **Pargger 1998** [243] | pHi guided |
| **Rivers 2001** [244] | Severe sepsis and septic shock |
| **Scalea 1990** [245] | Trauma |
| **Schilling 2004** [246] | Same flow goal in each group |
| **Schultz 1985** [247] | No explicit flow goal |
| **Stone 2003** [248] | No explicit flow goal |
| **Szakmany 2005** [249] | Intrathoracic blood volume goal |
| **Takala 2000** [250] | No explicit flow goal |
| **Tuchschmidt 1992** [251] | Septic shock |
| **Velmahos 2000** [252] | Trauma |
| **Yu 1993** [253] | Established critical illness |
| **Yu 1995** [254] | Established critical illness |
| **Yu 1998** [255] | Established critical illness |

**Table 14** Characteristics of included studies

| | Study population | | | Intervention | | | |
|---|---|---|---|---|---|---|---|
| **Study** | **N** | **Mode** | **Surgery** | **Timing** | **Device** | **Goals** | **F/F+V** |
| **Bender 1997** [256] | 104 | Elec | Vascular | Pre | PAFC | CI | F + V |
| **Berlauk 1991** [257] | 89 | Elec | Vascular | Pre Intra | PAFC | CI | F + V |
| **Bonazzi 2002** [258] | 100 | Elec | Vascular | Pre | PAFC | CI, $DO_2I$ | F + V |
| **Boyd 1993** [93] | 107 | Elec Emerg | General Vascular | Pre Post | PAFC | $DO_2I$ | F + V |
| **Conway 2002** [259] | 57 | Elec | General | Intra | OD | SV, FTc | F |
| **Gan 2002** [260] | 100 | Elec | General | Intra | OD | SV, FTc | F |
| **Jerez 2001** [261] | 390 | Elec | Cardiac | Post | PAFC | $SvO_2$, CI | F + V |
| **Lobo 2000** [262] | 37 | Elec | General Vascular | Intra Post | PAFC | $DO_2I$ | F +V |
| **McKendry 2004** [263] | 174 | Elec | Cardiac | Post | OD | SVI | F + V |
| **Mythen 1995** [264] | 60 | Elec | Cardiac | Intra | OD | SV | F + V |
| **Noblett 2006** [164] | 103 | Elec | General | Intra | OD | SV, FTc | F |
| **Pearse 2005** [265] | 122 | Elec Emerg | General Vascular | Post | LidCO | $DO_2I$ | F +V |
| **Polonen 2000** [144] | 393 | Elec | Cardiac | Post | PAFC | $SvO_2$, Lac | F + V |
| **Sandham 2003** [266] | 1994 | Elec Emerg | General Vascular | Pre | PAFC | $DO_2I$, CI | F + V |
| **Shoemaker 1988** [92] | 88 | Elec Emerg | General Vascular | Pre | PAFC | CI, $DO_2I$ | F + V |
| **Sinclair 1997** [267] | 40 | Emerg | General | Intra | OD | SV | F |
| **Ueno 1998** [268] | 34 | Elec | General | Post | PAFC | CI, $DO_2I$ | F + V |
| **Valentine 1998** [269] | 120 | Elec | Vascular | Pre | PAFC | CI | F + V |
| **Venn 2002** [270] | 90 | Emerg | General | Intra | OD | SV | F |
| **Wakeling 2005** [174] | 134 | Elec | General | Intra | OD | SV | F |
| **Wilson 1999** [94] | 138 | Elec | General Vascular | Pre | PAFC | $DO_2I$ | F + V |
| **Zeigler 1997** [271] | 72 | Elec | Vascular | Pre | PAFC | $SvO_2$ | F + V |

***Notes to Table 14:*** *Elec = Elective, Emerg = Emergency, Timing = start of intervention, Pre = Pre-operative, Intra = Intraoperative, Post = Postoperative, PAFC = Pulmonary Artery Flotation Catheter, OD = Oesophageal Doppler, CO = Cardiac Output, CI = Cardiac Index, DO2I = Oxygen Delivery Index, SV = Stroke Volume, SVI = Stroke Volume Index, FTc = Flow-Time Corrected, SvO2 = Flow-Time Corrected, Lac = Lactate, F = Fluids alone, F + V = Fluids and Vasoactive Drugs.*

**Table 15** Outcomes reported (excluding morbidity)

| Study | Mortality | Length of stay | Cost Analysis |
|---|---|---|---|
| **Bender 1997** | Hospital | HLOS, ICULOS | Cost |
| **Berlauk 1991** | Hospital | HLOS, ICULOS | Cost |
| **Bonazzi 2002** | Hospital | HLOS | None |
| **Boyd 1993** | 28-day | HLOS, ICULOS | Reported separately |
| **Conway 2002** | Hospital | HLOS, ICULOS | None |
| **Gan 2002** | Hospital | HLOS | None |
| **Jerez 2001** | Hospital | ICULOS | None |
| **Lobo 2000** | 28-day, 60-day | HLOS, ICULOS | None |
| **McKendry 2004** | Hospital | HLOS, ICULOS | None |
| **Mythen 1995** | Hospital | HLOS, ICULOS | Reported separately |
| **Noblett 2006** | Hospital | HLOS, ICULOS | None |
| **Pearse 2006** | Hospital, 28 day, 60 day | HLOS, ICUOS | None |
| **Polonen 2000** | 28-day, 6 month, 12 month | HLOS, ICULOS | None |
| **Sandham 2003** | Hospital, 6 month, 12 month | HLOS | None |
| **Shoemaker 1988** | Hospital | HLOS, ICULOS | Cost |
| **Sinclair 1997** | Hospital | HLOS | None |
| **Ueno 1998** | Hospital | None | None |
| **Valentine 1998** | Hospital | HLOS, ICULOS | None |
| **Venn 2002** | Hospital | HLOS | None |
| **Wakeling 2005** | Hospital, 6 month | HLOS | None |
| **Wilson 1999** | Hospital | HLOS, ICULOS | Reported separately |
| **Ziegler 1997** | Hospital | ICULOS | None |

**Table 16** Morbidity outcomes reported

| Study | Morbidity outcomes reported |
|---|---|
| **Bender 1997** | Pulmonary edema, acute myocardial infarction, arrhythmia, acute renal failure, wound infection, hemorrhage, sepsis, graft thrombosis or infection, groin hematoma. |
| **Berlauk 1991** | Acute renal failure, congestive cardiac failure, graft thrombosis, acute myocardial infarction, arrhythmia. |
| **Bonazzi 2002** | Arrythmias, myocardial infarction, congestive heart failure, renal failure. |
| **Boyd 1993** | Respiratory failure, acute renal failure, sepsis, cardiorespiratory arrest, pulmonary edema, pleural fluid, wound infection, disseminated intravascular coagulation, acute myocardial infarction, abdominal abscess, hemorrhage, gastric outlet obstruction, cerebrovascular accident, pulmonary embolism, chest infection, psychosis, distal ischaemia. |
| **Conway 2002** | Tolerating oral diet. |
| **Gan 2002** | Acute renal dysfunction (urine output <500mls), respiratory support for > 24 hours, cardiovascular (hypotension, pulmonary oedema, arrhythmia), chest infection (clinical diagnosis), severe postoperative nausea and vomiting requiring rescue antiemetic, coagulopathy, wound infection, toleration of oral solid diet. |
| **Jerez 2001** | Organ failures. |
| **Lobo 2000** | Sepsis, shock, septic shock, cardiogenic shock, nosocomial infection, acute pancreatitis, postoperative fistula, arrhythmia, cerebrovascular accident, deep vein thrombosis, gastrointestinal bleeding, hypothermia, sepsis-related organ failure assessment (SOFA) score, bronchopneumonia, urinary tract infection, wound infection, ventilator days, organ dysfunction. |
| **McKendry 2004** | Atrial fibrillation requiring treatment, pneumothorax, cerebral vascular accident, chest infection or sternal wound infection, GI bleed, acute renal failure, pleural effusion, infected leg wound, aortic regurgitation. |
| **Mythen 1995** | Knaus organ failure criteria, chest infection, pleural effusion, disorientation, respiratory failure, nausea and vomiting, cerebrovascular accident, paralytic ileus, pericardial effusion. |
| **Noblett 2006** | Surgical fitness for discharge, return of gastrointestinal function, flatus, bowel movement, toleration of oral diet, readmission rate, cytokine markers of the systemic inflammatory response. |

| Study | Morbidity outcomes reported |
|---|---|
| **Pearse 2006** | Number of patients with complications, infection (pneumonia, abdominal, urinary tract, central venous catheter, wound), respiratory (pleural effusion, pneumothorax, pulmonary embolism, adult respiratory distress syndrome (ARDS)), cardiovascular (arrhythmia, pulmonary oedema, myocardial infarction, stroke), abdominal (Clostridium Difficile, diarrhoea, acute bowl obstruction, upper gastrointestinal bleed, paralytic ileus, anasomotic leak, Intra-abdominal hypertension), post-operative massive haemorrhage. |
| **Polonen 2000** | Organ dysfunctions: central nervous system (hemiplegia, stroke, Glasgow coma scale (GCS <10)), circulatory (vasoactive medication or intraaortic counterpulsation to treat hypotension or low cardiac output), respiratory (need for mechanical or assisted ventilation), renal (low urine output or increased creatinine), hepatic increased liver enzymes or bilirubin), gastrointestinal (macroscopic bleeding or paralytic ileus), haematological (low white cell or platelet count), ICU readmission. |
| **Sandham 2003** | Myocardial infarction, congestive heart failure, supraventricular tachycardia, pulmonary embolism, renal insufficiency, hepatic insufficiency, sepsis from central venous catheter (CVC) or pulmonary-artery catheter (PAC), wound infection, pneumonia, adverse events related to PAC or CVC: pulmonary infarction, haemothorax, pulmonary haemorrhage, pneumothorax, arterial puncture. |
| **Shoemaker 1988** | Respiratory failure, renal failure, sepsis and septic shock, hepatic failure, cardiac arrest, pulmonary edema, pleural effusion, wound infection, disseminated intravascular coagulation (DIC), acute myocardial infarction, evisceration, abdominal abscess, hemorrhage, pancreatitis, gastric outlet obstruction, urinary tract infection, cerebral infarct, pulmonary embolism, ventilator days. |
| **Sinclair 1997** | None, "time declared fit for medical discharge". |
| **Ueno 1998** | Bleeding, peritoneal infection, adult respiratory distress syndrome, hyperbilirubinaemia, liver failure. |
| **Valentine 1998** | Myocardial infarction, arrhythmia, congestive heart failure, pneumonia, non-cardiogenic pulmonary insufficiency, acute renal insufficiency, catheter sepsis, ventilator days. |
| **Venn 2002** | "Time to medical fitness for discharge", deep haemorrhage requiring >2 unit blood transfusion, haematemesis, chest infection, wound infection, cellulitis, pancreatitis, pulmonary embolus, cerebrovascular accident, myocardial infarction, cardiac failure, rapid atrial fibrillation, hypotension, impaired renal function, pseudo-obstruction. |

| Study | Morbidity outcomes reported |
|---|---|
| **Wakeling 2005** | Time until fit for discharge, Bowel recovery (Flatus, bowels opening, full diet), quality of recovery score, Post operative morbidity survey (POMS), Quality of life questionnaires (European organisation for the research and treatment of cancer (EORTC) - QLQ-C30 and QLQ-CR38). |
| **Wilson 1999** | Respiratory (prolonged weaning, adult respiratory distress syndrome (ARDS), pleural effusion, secondary ventilation, sputum retention), cardiovascular (myocardial infarction, arrhythmia, cardiac arrest, pulmonary embolus, cerebrovascular accident, transient ischaemic attack, cardiac failure), gastrointestinal (infarction, hemorrhage), acute renal failure, coagulopathy, infection (bacteremia, sepsis syndrome, septic shock, respiratory sepsis, urinary sepsis, abdominal sepsis, wound sepsis, line sepsis, other sepsis), surgical (anastomotic breakdown, deep hemorrhage, wound hemorrhage). |
| **Ziegler 1997** | Hypotension, congestive heart failure, myocardial infarction, arrhythmia, oliguria, graft thrombosis, cerebrovascular accident. |

**Table 17** Risk of bias: allocation concealment and study size category

| Study | Allocation concealment | Study size | |
|---|---|---|---|
| | | Large (>=100) | Small (<100) |
| **Bender 1997** | D | Y | |
| **Berlauk 1991** | B | | Y |
| **Bonazzi 2002** | A | Y | |
| **Boyd 1993** | D | Y | |
| **Conway 2002** | D | | Y |
| **Gan 2002** | B | Y | |
| **Jerez 2001** | D | Y | |
| **Lobo 2000** | A | | Y |
| **McKendry 2004** | A | Y | |
| **Mythen 1995** | B | | Y |
| **Noblett 2006** | D | Y | |
| **Pearse 2006** | A | Y | |
| **Polonen 2000** | A | Y | |
| **Sandham 2003** | A | Y | |
| **Shoemaker 1988** | A | | Y |
| **Sinclair 1997** | B | | Y |
| **Ueno 1998** | B | | Y |
| **Valentine 1998** | B | Y | |
| **Venn 2002** | A | | Y |
| **Wakeling 2005** | A | Y | |
| **Wilson 1999** | A | Y | |
| **Ziegler 1997** | D | | Y |

**Table 18** Methodological quality of included studies for each of the 24 questions of the "Gardner" checklist (Appendix 5)

| | Bender 1997 | Berlauk 1991 | Bonazzi 2002 | Boyd 1993 | Conway 2002 | Gan 2002 | Jerez 2001 | Lobo 2000 | McKendry 2004 | Mythen 1995 | Noblett 2006 | Pearse 2006 | Polonen 2000 | Sandham 2003 | Shoemaker 1988 | Sinclair 1997 | Ueno 1998 | Valentine 1998 | Venn 2002 | Wakeling 2005 | Wilson 1999 | Ziegler 1997 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y |
| **2** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **3** | Y | Y | Y | Y | U | N | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y |
| **4** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **5** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y |
| **6** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **7** | N | Y | Y | N | N | Y | N | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N |
| **8** | U | U | Y | U | U | Y | U | U | Y | U | U | U | U | U | U | U | Y | Y | U | Y | U | U |
| **9** | N | N | N | U | N | U | N | N | N | N | N | N | N | N | N | U | Y | N | U | N | N | N |
| **10** | Y | N | Y | Y | N | Y | U | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | N | Y | Y | Y |
| **11** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **12** | N | N | N | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | N | Y | Y | Y | N |
| **13** | U | N | N | Y | N | Y | Y | N | Y | N | N | Y | Y | Y | N | N | Y | N | Y | Y | U | N |
| **14** | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **15** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **16** | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **17** | Y | U | Y | Y | Y | Y | N | N | Y | N | Y | Y | N | Y | N | N | N | N | Y | Y | N | N |
| **18** | N | U | U | U | Y | N | N | U | Y | U | U | Y | U | Y | Y | U | U | U | Y | Y | U | U |
| **19** | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **20** | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **21** | U | U | N | Y | U | U | Y | U | Y | N | Y | Y | U | U | N | N | N | N | N | Y | Y | N |
| **22** | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| **23** | N | N | N | N | N | Y | N | Y | Y | N | N | Y | N | Y | N | N | N | N | Y | N | N | N |
| **24** | N | N | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | N | Y | Y | Y | N |

## 2.3.4 Data Synthesis

### *2.3.4.1 Mortality*

All studies reported mortality data. A number of different mortality definitions were used: hospital mortality (19/22), 28 day (4/22), 60 day (2/22), 6 month (3/22), 12 month (2/22) (Table 15). Five studies reported more than one definition.

Using data from the longest reported follow-up, the overall mortality was 265/2275 (11.6%) in the control group and 216/2271 (9.5%) in the treatment group (Peto OR 0.82, 95% CI 0.67-0.99, p = 0.04, NNT 47) (Figure 1).

Post-hoc analysis of pooled hospital and 28-day data mortality was 178/2275 (7.8%) in the control group and 128/2271 (5.6%) in the treatment group (Peto OR, 0.74, 95% CI 0.58,0.93, p = 0.04, NNT 46) (Figure 2).

Sensitivity analyses for the primary outcome variable are reported in Table 19. The primary outcome was consistent when analysed using random-effects models (Mantel-Haensel and Inverse Variance) but this outcome difference was not statistically significant when fixed-effects models were used (Mantel-Haensel and Inverse Variance). Excluding smaller studies (n>100 versus n<100) or studies of lower quality (allocation concealment A versus B to D) resulted in loss of statistical significance for the primary outcome (mortality longest reported follow-up, Peto OR).

### *2.3.4.2 Morbidity*

The seven categories of morbidity reported were analysed using the definitions used by the investigators in the primary studies. No two papers used the same list of morbidities/complications following surgery (Table 16). In many cases no specific criteria were listed for definition of named morbidities. Only five studies reported using systematic criteria for classifying postoperative morbidity. One study reported sepsis-related organ failure assessment (SOFA) scores [272], one study reported Knaus organ failure criteria [273], and one study reported using a validated quality of recovery score [171] along with the POMS [172] and quality of life questionnaires (European organisation for the research and treatment of cancer

(EORTC) - QLQ-C30 and QLQ-CR38) [274-276]. One other study used a modified version of the POMS using different diagnostic criteria for each domain.

When studies reported specific diagnoses (e.g. myocardial infarction, respiratory failure), diagnostic criteria were infrequently reported. Where criteria were reported they were seldom consistent between studies. For example, diagnostic criteria for renal failure/impairment are reported in Table 20 (SOFA renal failure criteria are reported in Table 21). Twelve out of twenty-two studies used specific criteria, five of which were referenced. However one of the studies that provided a reference used a single criterion modified from the criteria described in the reference. Therefore no two studies used the same criteria for renal failure/impairment.

Data on renal impairment (sixteen studies, 3800 patients), arrhythmia (ten studies, 3728 patients), respiratory failure/ARDS (adult respiratory distress syndrome)(eight studies, 759 patients), infections (thirteen studies, 3628 patients) myocardial infarction (10 studies, 2936 patients), congestive heart failure/pulmonary oedema (11 studies, 2989 patients), and venous thrombosis (5 studies, 2385 patients) were available either in the published reports or after contacting authors.

For those studies where data were available, there was a reduction, in the treatment group, in the incidence of renal impairment (Peto OR 0.65, 95% CI 0.49-0.85, P=0.002, NNT 37)(Figure 3) respiratory failure/ARDS (Peto OR 0.39, 95% CI 0.22-0.72, P=0.002, NNT 15)(Figure 4), and infection (Peto OR 0.66, 95% CI 0.54-0.78, P<0.0001, NNT 21)(Figure 5). Arrhythmia, myocardial infarction, congestive heart failure/pulmonary oedema and venous thrombosis rates were similar for the two groups.

Pooling of morbidities was not consistent between studies and some studies summarized morbidity/complications using more than one method: number of patients with complications (14 studies, 1360 patients), number of complications per patient (3 studies, 497 patients) and total number of complications (19 studies, 2122 patients) were reported. For those studies where data were available, the

number of patients with complications was reduced in the treatment group (Peto OR 0.59, 95% CI 0.45-0.76, P<0.0001, NNT 12)(**Figure 6**). There was no difference in the number of complications per patient between groups. Data for total complications could not be pooled.

#### *2.3.4.3 Health Status*

Only one study reported health status [174]. This study used quality of life questionnaires EORTC QLQ-C30 and QLQ-CR38 completed 4–6 weeks after surgery and showed no differences between groups.

#### *2.3.4.4 Resource use*

Length of hospital stay post-surgery was significantly reduced in the treatment group (WMD -1.79 days, 95%CI -2.51 to -01.07, P<0.00001, 16 studies, n=1916)(Figure 7), but there was no difference in length of critical care stay (WMD -0.22 days, 95%CI -0.03 to 0.20, P=0.30, 8 studies, n=1382)(Figure 8). Three studies reported cost data (US dollars) in the original report. Two of these showed a non-significant increase on cost in the treatment group and one showed a reduction in cost in the treatment group but did not conduct a statistical analysis of this result. Three other studies (two reported UK pounds, one reported Euros) reported cost data in separate publications from the original report. Two of these reported significant reductions in cost in the treatment groups. The third reported cost data only on a subgroup of patients included in the trial and these data were not analysed by treatment groups. Only one study reported means and standard deviations for cost data. In view of the variety of currencies and statistical descriptors no attempt was made to pool this data.

**Figure 1** Mortality at longest follow-up

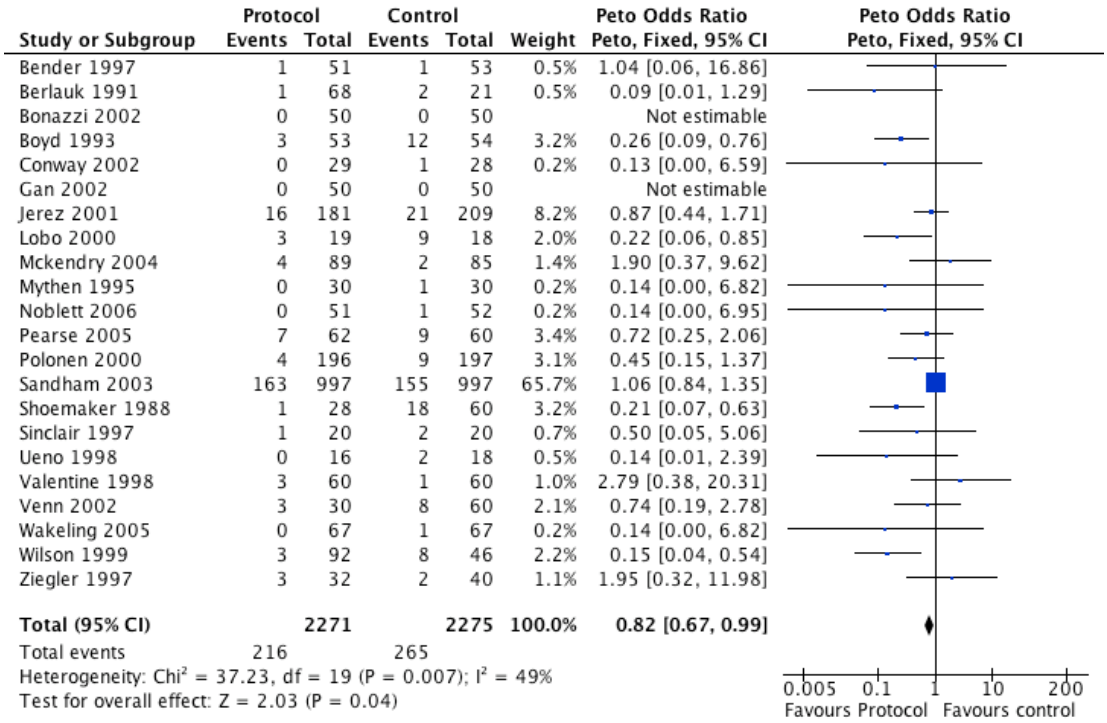



**Figure 2** Post-hoc analysis of pooled hospital and 28-day data mortality

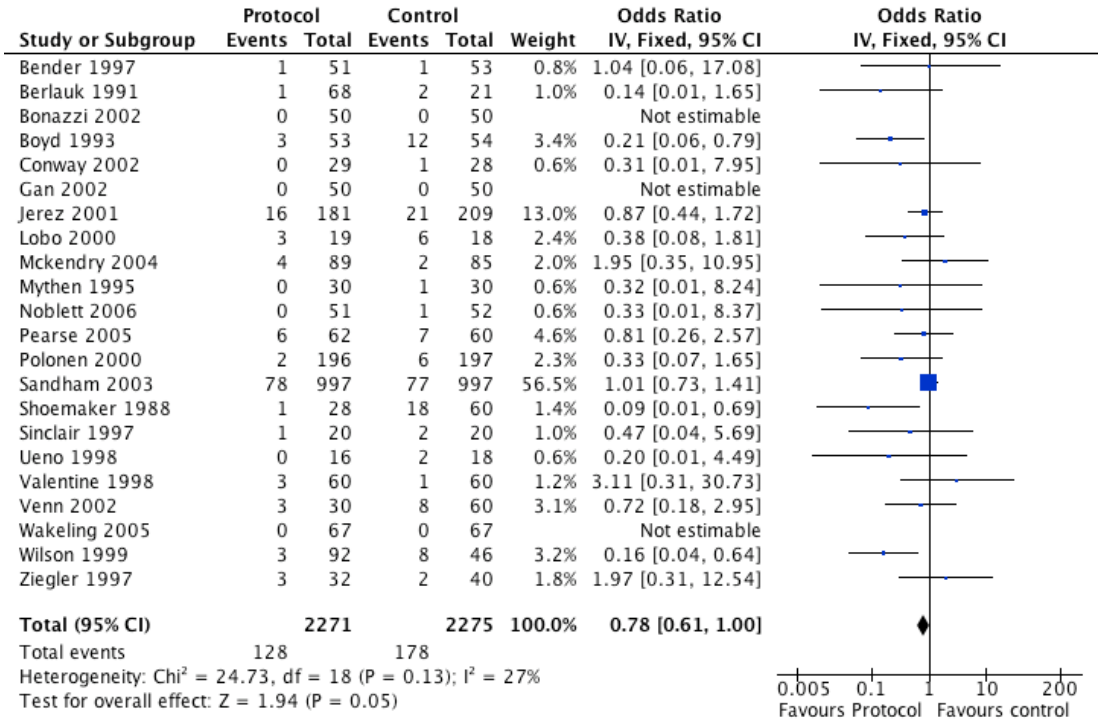


**Table 19** Sensitivity analyses for mortality at longest follow-up

| Outcome or Subgroup | Statistical Method | Studies | Effect estimate (95% CI) | P |
|---|---|---|---|---|
| All studies | Peto (FE) | 22 | 0.82 (0.67,0.99 | 0.04 |
| All studies | Mantel-Haensel RE | 22 | 0.56 (0.37,0.85) | 0.007 |
| All studies | Mantel-Haensel FE | 22 | 0.82 (0.68, 1.00) | 0.05 |
| All studies | Inverse Variance RE | 22 | 0.56 (0.37, 0.85) | 0.007 |
| All studies | Inverse Variance FE | 22 | 0.86 (0.70, 1.05) | 0.13 |
| N>=100 | Peto (FE) | 13 | 0.91 (0.74,1.12) | 0.37 |
| N<100 | Peto (FE) | 9 | 0.34 (0.19,0.61) | 0.0003 |
| Allocation concealment A | Peto (FE) | 9 | 0.91 (0.73, 1.13) | 0.38 |
| Allocation concealment B-D | Peto (FE) | 13 | 0.52 (0.33,0.82) | 0.004 |

***Notes to Table 19:*** *FE = fixed effects, RE = random-effects*

**Table 20** Criteria for renal impairment/failure

| Study | Description | Criteria |
|---|---|---|
| **Bender 1997** | Acute renal failure | Increase in baseline creatinine by more than 1 gm% |
| **Berlauk 1991** | Acute renal failure | Urine output < 0.5 mL/Kg/hr for 5 hours and/or a change in baseline serum creatinine more than 0.5 mg% |
| **Bonazzi 2002** | Acute renal failure | Worsening of preoperative renal failure with accompanying oliguria requiring high doses of furosemide (>250 mg/die) and/or continuous or intermittent replacement renal failure |
| **Boyd 1993** | Acute renal failure | Urine output <500 ml/24h despite adequate pulmonary artery occlusion pressure |
| **Conway 2002** | None | - |
| **Gan 2002** | Acute renal dysfunction | Urine output <500 ml/d) (modified from POMS criteria) [172] |
| **Jerez 2001** | None | |
| **Lobo 2000** | Renal failure | SOFA criteria*** (score 1-4)[272] |
| **McKendry 2004** | Acute renal failure | None |
| **Mythen 1995** | Renal failure | Urine output ≤ 479 ml/24 h or ≤ 159 ml/8 h, serum BUN ≥ 100mg/100ml, serum creatinine ≥ 3.5 mg/100ml. [273] |
| **Noblett 2006** | None* | - |
| **Pearse 2006** | Impaired renal function | Increase in blood urea of > 5 mmol/L from preoperative levels [68] |
| **Polonen 2000** | Renal dysfunction | Urine output <750 ml/24 h or increase in serum creatinine concentration > 150 umol/L from preoperatively normal levels |
| **Sandham 2003** | Renal insufficiency | 50% increase in creatinine concentration OR the need for dialysis in a patient with preexisting non-dialysis dependent renal failure |
| **Shoemaker 1988** | Renal failure | None |
| **Sinclair 1997** | None | - |
| **Ueno 1998** | None | - |
| **Valentine 1998** | Acute renal failure | None |
| **Venn 2002** | Impaired renal function*** | None |
| **Wakeling 2005** | POMS (renal domain) | Presence of oliguria (<500 ml/d), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for non-surgical reason. [172] |
| **Wilson 1999** | Acute renal failure | None |
| **Ziegler 1997** | Oliguria | < 0.5 ml/Kg per hour |

***Notes to Table 20:*** ** = used criteria for classification of overall complications REF, but not of organ specific complications. ** "predefined criteria" for complications not reported or referenced. ***SOFA criteria* (see table below)

**Table 21** SOFA criteria for renal failure

| ***SOFA score*** | ***1*** | ***2*** | ***3*** | ***4*** |
|---|---|---|---|---|
| ***Creatinine mg/dl (umol/L)*** | *1.2-1.9 (110-170)* | *2.0-3.4 (171-299)* | *3.5-4.9 (300-440)* | *>5.0 (>440)* |
| ***Urine output (mL/day)*** | | | *<500* | *< 200* |

**Figure 3** Renal impairment (study authors criteria)

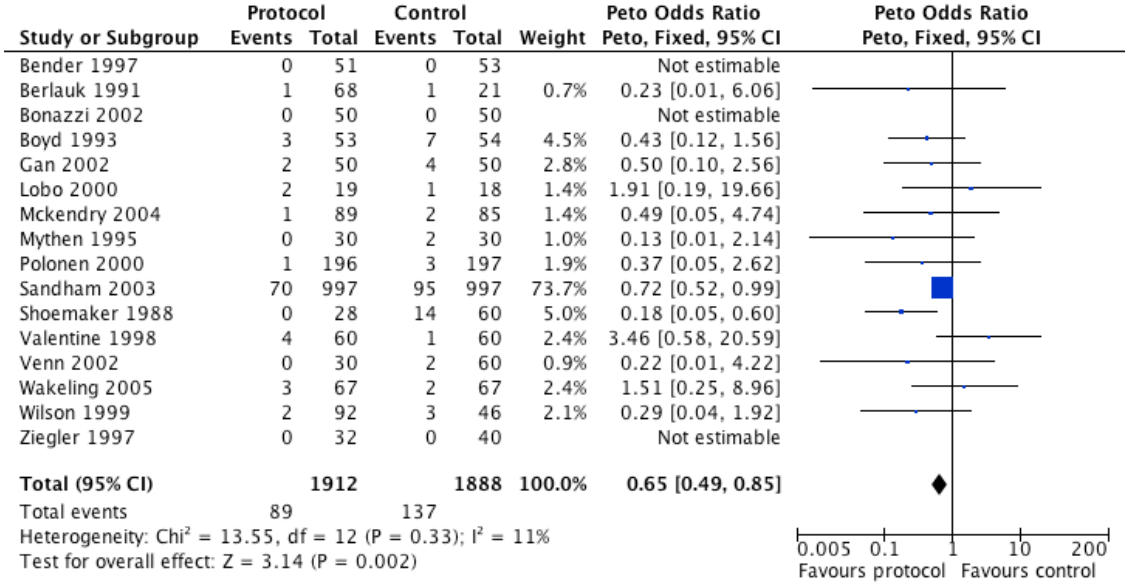


**Figure 4** Respiratory failure/ARDS (study authors criteria)

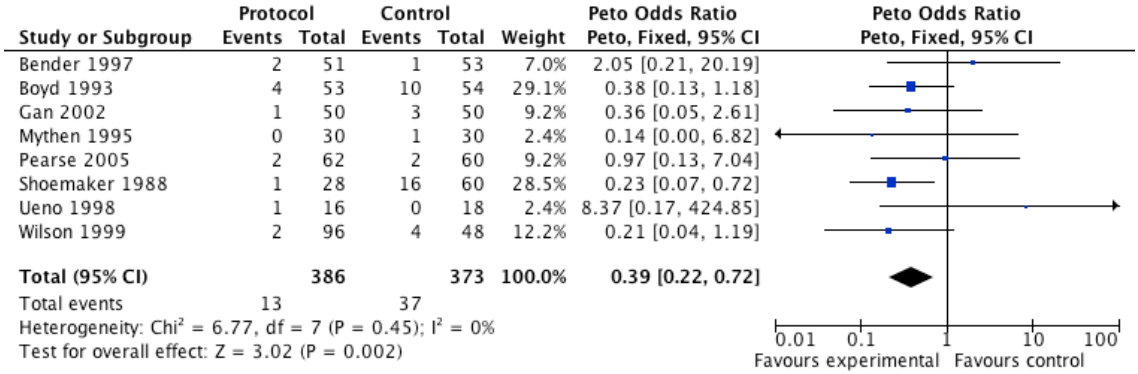



**Figure 5** Infection (study authors criteria)

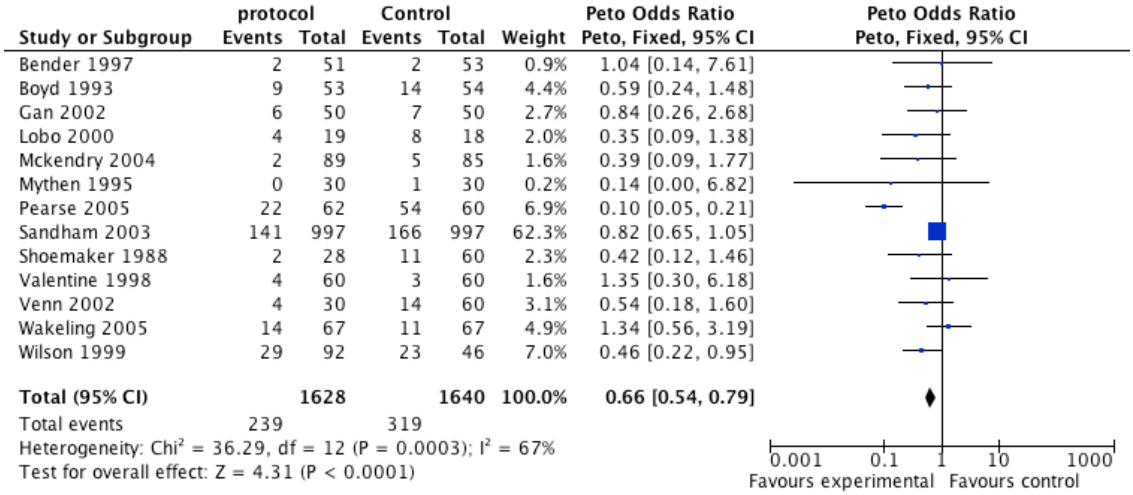


**Figure 6** Number of patients with complications

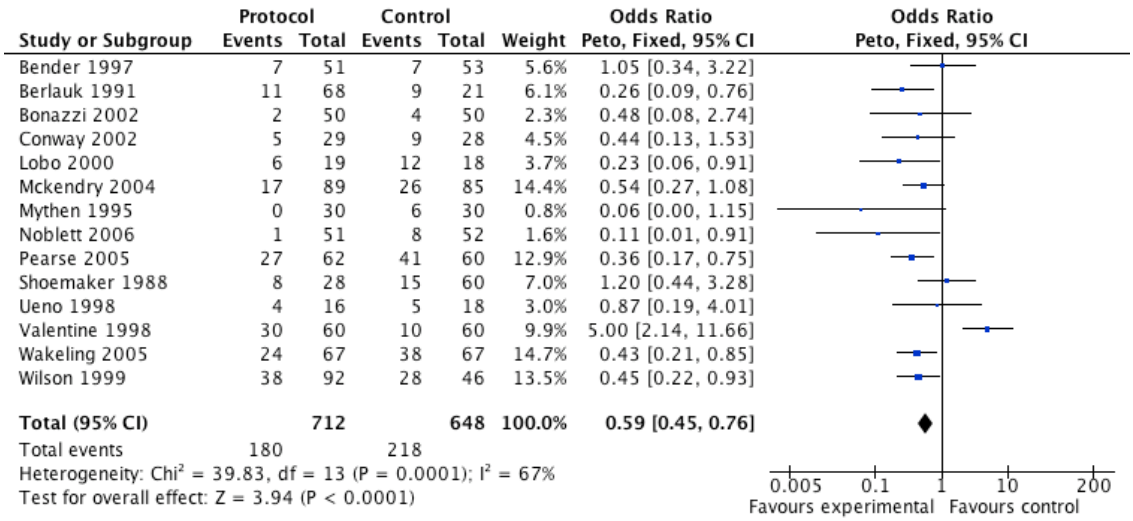



**Figure 7** Length of hospital stay

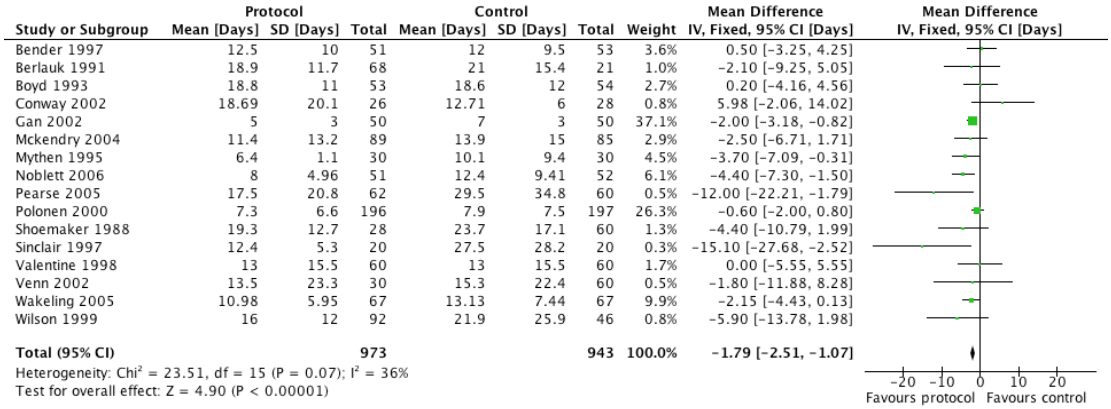
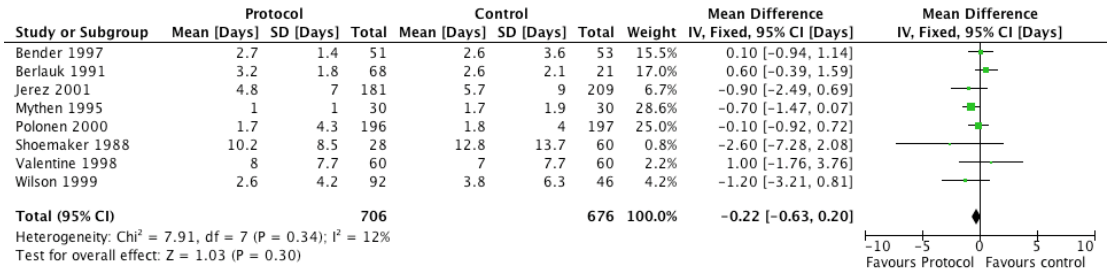



**Figure 8** Length of critical care stay



#### *2.3.4.5 Stratified meta-analysis*

The intervention was commenced in the preoperative period in nine studies, in the intraoperative period in nine studies and in the postoperative period in six studies. In one study [257] patients were randomized to two intervention groups (a preoperative and an intraoperative group) with a shared control group. In another study [93] the intervention was initiated either preoperatively or postoperatively depending on when the patients came to the attention of the investigators and were randomized. There was no evidence that this had any effect on the chances of being recruited into the study and therefore we did not consider that this had potential to confound the randomization process.

Mortality was reduced in the intraoperative group (Peto OR 0.32, 95%CI 0.15 to 0.69, P=0.004, 9 studies, n=665). Mortality was not reduced in the preoperative (Peto OR 0.97, 95%CI 0.72 to 1.13, P=0.37, 9 studies, n=2763) or postoperative (Peto OR 0.71, 95%CI 0.45 to 1.14, P=0.16, 6 studies, n=1139)(Figure 9) groups.

The intervention involved fluids alone in seven studies and fluids in combination with vasoactive drugs in 15 studies. Mortality was not reduced for fluids alone (Peto OR 0.44, 95%CI 0.16 to 1.19, P=0.11, 7 studies, n=584) or fluids in combination with vasoactive drugs (Peto OR 0.84, 95%CI 0.69 to 1.02, p=0.08, 15 studies, n=3962)(Figure 10).

**Figure 9** Mortality by timing of intervention (pre- vs. intra- vs. postoperative)

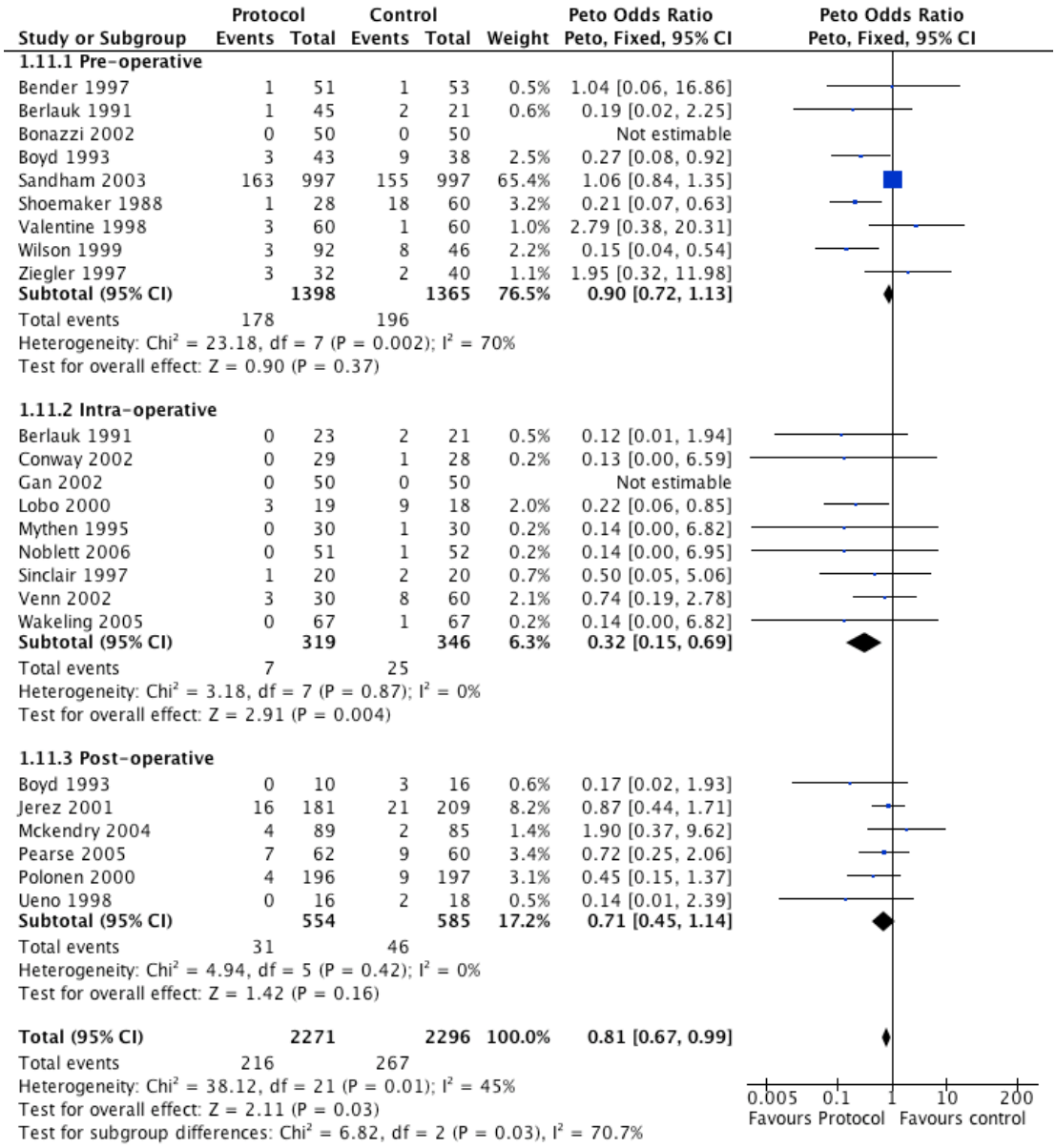
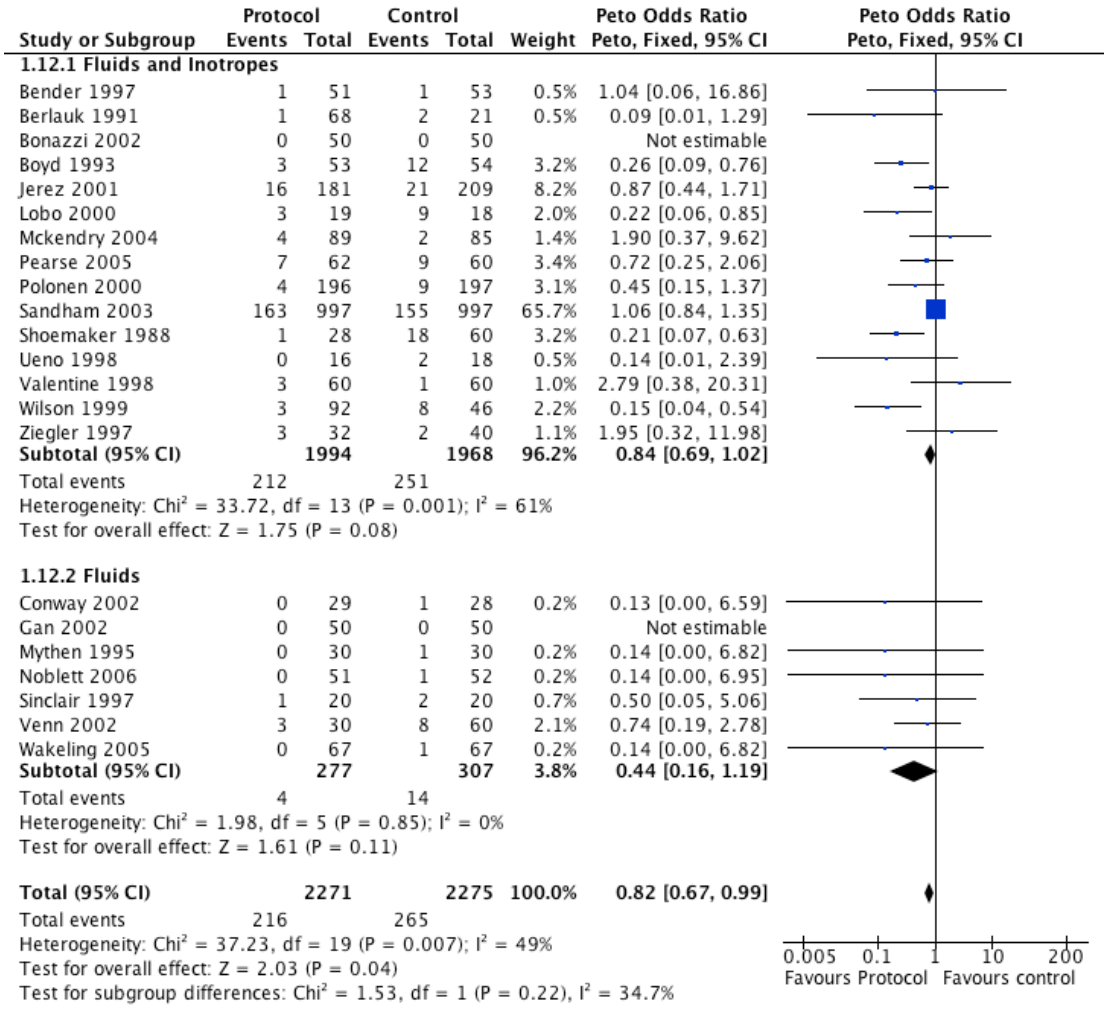


**Figure 10** Mortality by type of intervention (fluids and inotropes vs. fluids alone)



Eleven studies used cardiac output and oxygen transport goals, three studies used mixed venous oxygen saturation and lactate, and eight studies used stroke volume goals. Mortality was not reduced for any of the three groups of choice of goals; cardiac output and oxygen transport (Peto OR 0.83, 95%CI 0.67 to 1.03, p=0.09, n=2933), mixed venous oxygen saturations and lactate (Peto OR 0.80, 95%CI 0.46 to 1.38, p=0.42, n=855) stroke volume (Peto OR 0.66, 95% CI 0.28 to 1.54, p=0.33, n=758)(Figure 11).

Fifteen studies recruited patients having only elective procedures, two studies were exclusively of urgent/emergency patients and five had a mix of urgent/emergency and elective operations. None of the studies in this later group were able to provide separate data to allow comparison between elective and urgent/emergency groups. For patients having elective procedures mortality was significantly reduced in the intervention groups when compared with the control patients (Peto OR 0.52, 95%CI 0.33-0.79), P=0.003, n=1931) whereas for emergency/urgent operations there was no difference in mortality (Peto OR 0.67, 95%CI 0.21 to 2.12, P=0.49, n=130)(Figure 12).

Five studies were exclusively of patients undergoing vascular surgery. Six additional studies included patients undergoing vascular surgery but in only one of these was group-specific mortality data available. Four studies were of patients undergoing cardiac surgery. Seven studies were exclusively of patients undergoing general (non-vascular, non-cardiac) surgery. Six additional studies included patients undergoing general surgery but in only one of these was group-specific mortality data available. Mortality was significantly reduced in the intervention group for general surgery patients (Peto OR 0.31, 95%CI 0.13 to 0.71, P=0.006, n=607) but was not reduced for cardiac surgery (Peto OR 0.78, 95%CI 0.46 to 1.34, P=0.37, n=1017) or vascular surgery (Peto OR 0.80, 95%CI 0.33 to 1.90, P=0.61, n=543)(Figure 13).

**Figure 11** Mortality by goals of intervention (CO, DO2 vs. Lactate, SvO2 vs. SV)

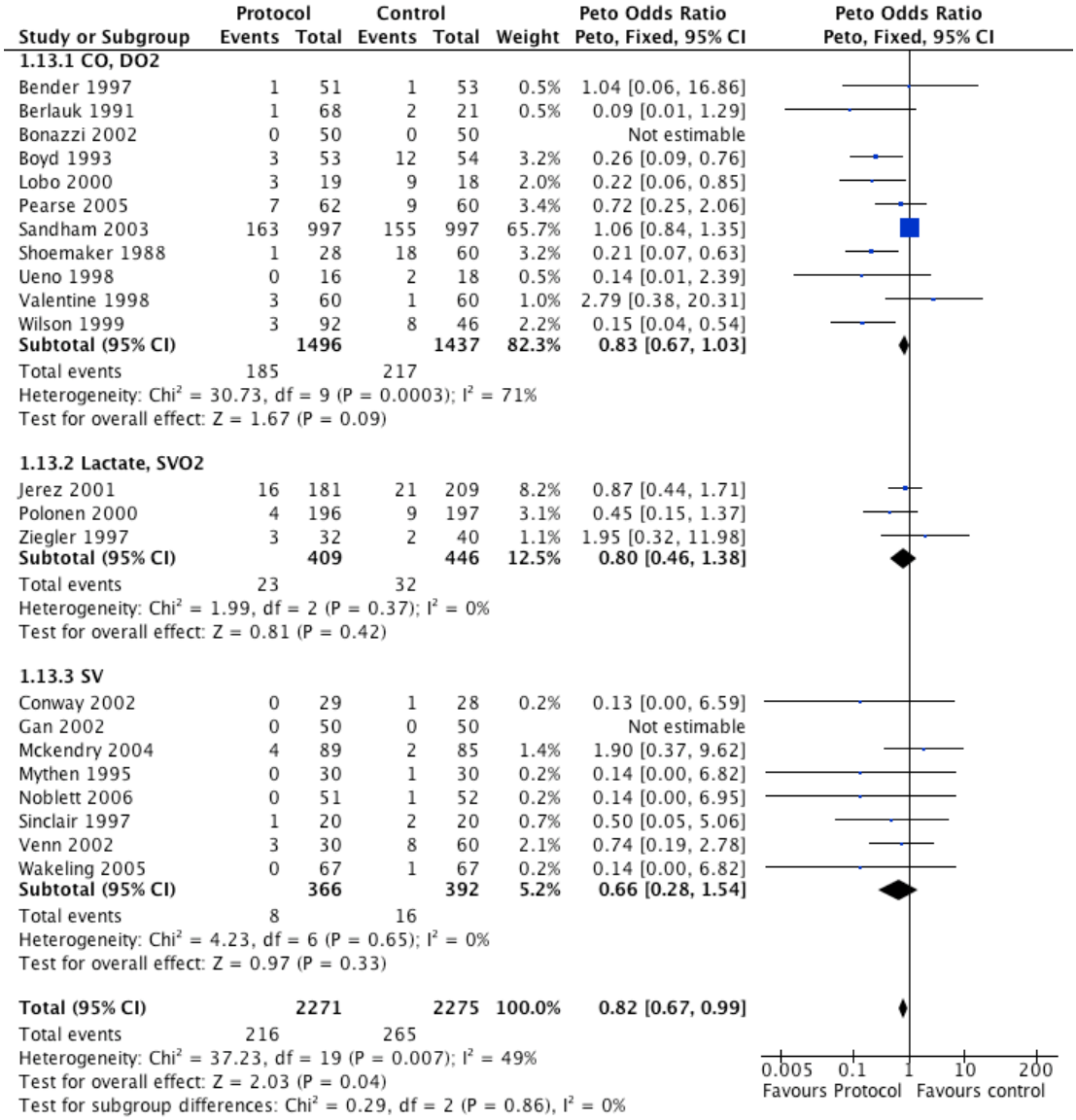


**Figure 12** Mortality by mode of surgery (elective vs. emergency)

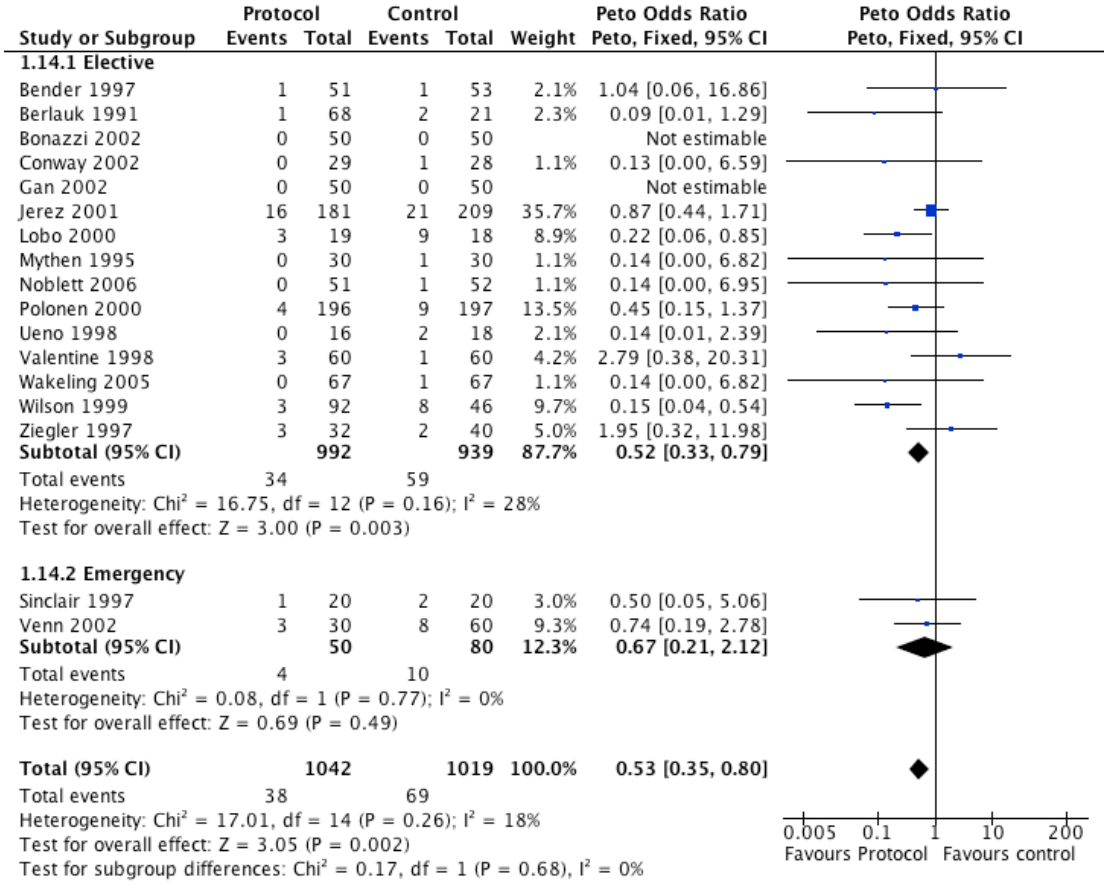
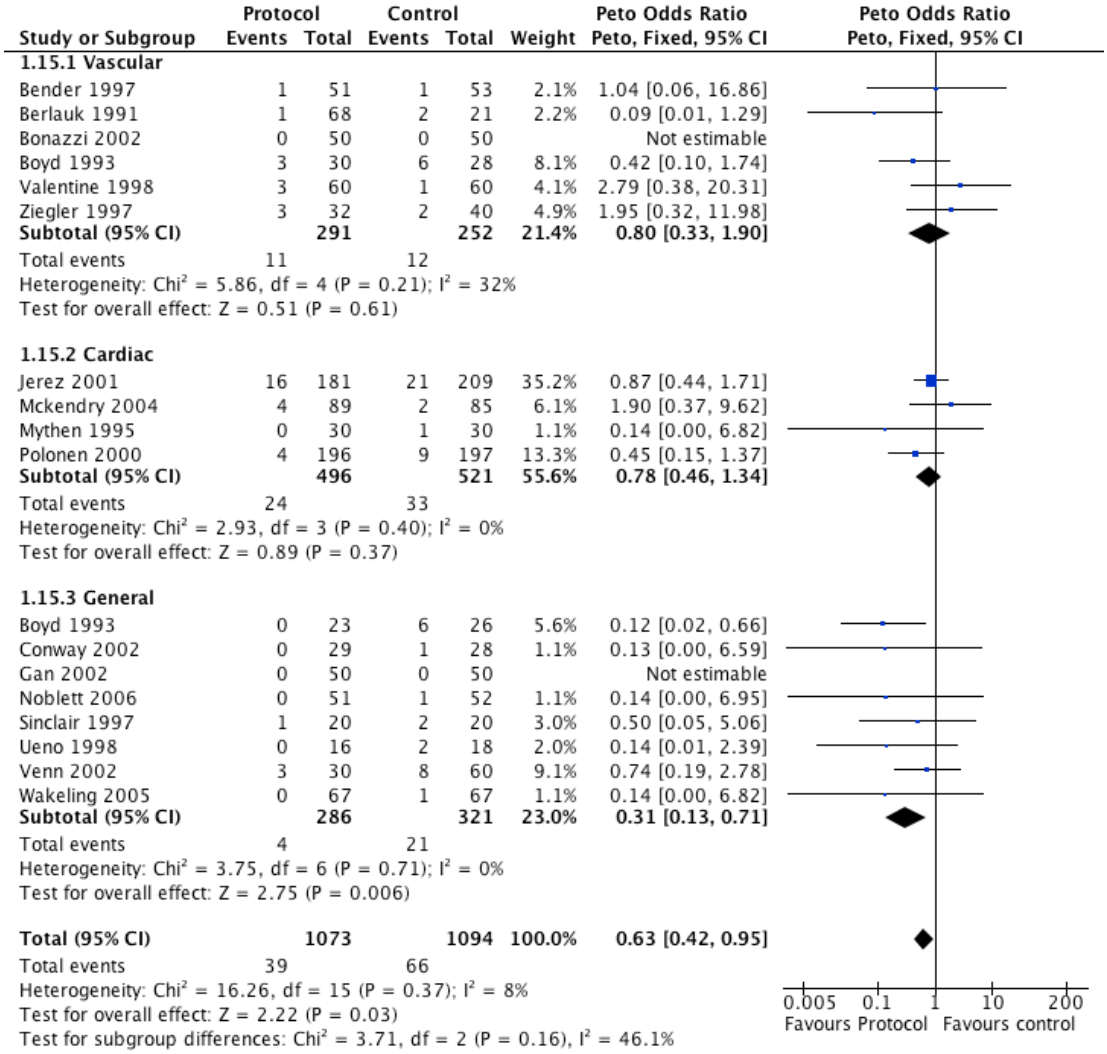


**Figure 13** Mortality by type of surgery (vascular vs. cardiac vs. general)



## *2.4 Discussion*

### 2.4.1 Summary of findings

The key finding of this study is that perioperative administration of fluids and/or vasoactive drugs targeted to increase global blood flow defined by explicit measured goals significantly reduces surgical mortality (using mortality data from longest available follow-up, Peto OR). This result is sensitive to withdrawal of smaller studies or studies of poorer methodological quality, where significance is lost. When this result was tested for robustness using alternative analyses, the result was statistically significant when random-effects models (Mantel-Haensel and Inverse Variance) were used but not when fixed-effect models (Mantel-Haensel and Inverse Variance) were used. Analyses using hospital and/or 28-day mortality (fixed- and random- effects models - post-hoc analyses) showed a statistically significant reduction in mortality.

Morbidity recording was highly variable but the limited available data showed a reduction in the number of patients with complications as well as a reduction in renal impairment, respiratory failure and infective complications, with no effect on other types of morbidity.

The available data showed a significant reduction in hospital length of stay but no difference in critical care stay in the intervention group. There was insufficient data to conduct a meta-analysis of quality of life or cost.

A stratified meta-analysis to address secondary hypotheses, determined a priori, suggested that mortality was reduced in the intervention group when the intervention was commenced intra-operatively, for elective patients and for patients undergoing general (major abdominal, urology, gynaecology, orthopaedic) surgery.

### 2.4.2 Strengths and weaknesses of this study

This study pools data from 22 studies (4546 patients) identified following a detailed systematic search of the literature. Study inclusion criteria were tightly defined and the meta-analysis was rigorously conducted according to a predefined analysis plan addressing specific hypotheses. The meta-analysis combined data

from a group of predominantly underpowered single center studies. However the included studies reflect international practice (North America n=7, Europe n=13, Japan n=1, South America n=1) although the majority of included studies are from major teaching centers. The pooled studies include adult (>16 years) patients from several specialties including abdominal, urology, gynaecology and orthopaedic, cardiac, thoracic and vascular surgery.

The predefined analysis plan, using mortality from the longest available follow-up, increased the weight attributed to the two largest studies that both reported one-year follow-up. Only one other study reported follow-up beyond 60 days. In this group of studies a proportion of the operations were for cancer resection, therefore introducing a possible competing cause of mortality.

Reporting of outcome data in the included studies was variable. Mortality was reported over a variety of timeframes (see below) and non-mortality outcomes were either limited, or inconsistent between studies, precluding meaningful analyses in many cases. Diverse criteria and description of reporting morbidity, along with infrequent use of validated metrics, limit the precision of treatment effect estimates and the confidence that can be attached to them. Furthermore, pooling of different types of morbidity was not consistent between studies limiting assessment of the overall "morbidity load".

These studies tested the effect of a complex package of care (e.g. fluids, inotropes, monitor, goals, critical care environment) rather than of a single clearly defined intervention. Heterogeneity in the components of such a complex intervention may contribute to study heterogeneity within a systematic review. Study heterogeneity may reduce the precision of treatment effect estimates and reduce the generalisability of results of meta-analyses [225]. By definition, it is not easy precisely to define the "active ingredients" of a complex intervention [224]. However, hypothesis generating stratified meta-analysis of the included studies permits exploration of the contribution of the components of a complex intervention and consequent identification of possible determinants of response to the intervention [225]. The results of the stratified meta-analysis indicated that there were insufficient data to distinguish statistically between many of the pre-

specified subgroups, and highlighted the limited quantity of data in some areas e.g. emergency surgery.

Several possible sources of bias arise in this meta-analysis. Statistical significance of the primary analysis is sensitive to withdrawal of lower quality (inadequate allocation concealment) and smaller studies, although in all cases the point estimate of effect is ≤ 0.91. Studies with adequate allocation concealment [277] and larger studies are less likely to be affected by bias [278] and inclusion of lower quality studies can alter the interpretation of the benefit of interventions in meta-analysis [279]. The primary analysis is also sensitive to method of analysis: the result is statistically significant when the Peto odds ratio is used (a priori analysis) and with random effects models, but not with the two non-Peto fixed effects models. Statistical heterogeneity is indicated by formal testing (Chi squared, p = 0.007), and by the sensitivity of the result to different methods of analysis, suggesting that a random effects analysis, which assumes statistical heterogeneity, is more appropriate that one using fixed effects. In all cases the point estimate of effect is ≤ 0.86.

The possibility of publication bias cannot be excluded. No evidence of this was found in relation to contacts with experts and industry but some of the published abstracts identified have yet to be published as full peer-reviewed papers. Language bias is also a possibility due to the electronic databases and conferences searched but there were no language exclusions in the searches. Flaws in the original study designs are a significant potential source of bias. The meta-analysis includes 4546 patients but the unit of analysis is the study (or study subgroup) and the sample size (22 studies) is relatively small. Although defined a priori, the stratified analysis (sub-group analysis) should be seen as hypothesis generating only.

This review represents the best up-to-date summary of the literature. A tightly defined question was framed and explicit inclusion criteria for studies and a pre-defined analysis plan were used. The primary result agrees with previous reviews in this area [217,219,221-223] which have been uniformly supportive of this intervention. The results of this systematic review do not however, agree with the results of the

largest study in this area [266].

The studies included in this review are typical of studies in critical care research in general in that the vast majority of studies are underpowered and single centre [280]. Future studies in this area should test an explicitly framed hypothesis, be adequately powered, methodologically rigorously and blinded (where possible). Reporting of outcomes should be standardized (to allow comparison between studies and to facilitate the conduct of future meta-analyses) and inclusive (morbidity, health status, resource usage). In particular, cost/economic analysis is fundamental.

The sensitivity of the results to method of analysis indicates that the results of this study are far from clear-cut. Further research in this area both to address the overall objective of this review and to focus on specific questions is essential. Sandham et al have shown that large multicentre studies can be conducted in this area. Future research will hopefully contribute to disentangling the complex package of care that forms the intervention (e.g. fluids, inotropes, monitor, goals, critical care environment) in order to identify effective components.

## *2.5 Summary*

1. Perioperative administration of fluids and/or vasoactive drugs targeted to increase global blood flow defined by explicit measured goals reduces mortality following surgery.
2. This intervention also reduces hospital length of stay following surgery but does not alter critical care length of stay.
3. The intervention also reduces the total number of patients with complications and the incidence of renal impairment/failure, respiratory failure/ARDS and infection.
4. Heterogeneity in the criteria, description, and pooling of reporting morbidity, along with infrequent use of validated metrics, limit the precision of treatment effect estimates and the confidence that can be attached to them.
5 Stratified meta-analysis generated hypotheses about which components of this complex intervention might be determinants of response, as highlighting areas

where additional research is required (e.g. inadequate data in relation emergency surgery).

## *Appendix 1: "Optimization Systematic Review Steering Group"*

Dr Richard Beale, Professor David Bennett, Dr Owen Boyd, Mr Mark Emberton, Ms Caroline Goldfrad, Dr Michael Grocott, Dr Mark Hamilton, Ms Julia Langham, Professor Monty Mythen, Professor Ian Roberts, Dr Kathy Rowan, Dr Jonathan Thompson.

## *Appendix 2: Search filter for randomized controlled trials with and without blinding*

1. exp research desig
2. exp clinical trials/need s
3. comparative study/ or placebos/
4. multicenter study.pt.
5. clinical trial.pt.
6. random$.ti,ab.
7. placebo$1.ti,ab.
8. (clinical adj trial$1).ti,ab.
9. (controlled clinical trial or randomized controlled trial).pt.
10. practice guideline.pt.
11. feasibility studies/
12. clinical protocols/
13. (single blind$ or double blind$ or triple blind$3).ti,ab.
14. exp treatment outcome/
15. exp epidemiologic research design/
16. double blind method/
17. 6 or 9 or 16
18. or/1-16
19.18
20. limit 19 to human

## *Appendix 3: Modified search filter for randomized controlled trials with and without blinding*

1. RANDOMIZED-CONTROLLED-TRIAL

2. RANDOMIZATION

3 .CONTROLLED-STUDY

4 . MULTICENTER-STUDY

5 . PHASE-3-CLINICAL-TRIAL

6 . PHASE-4-CLINICAL-TRIAL

7 . DOUBLE-BLIND-PROCEDURE

8 . SINGLE-BLIND-PROCEDURE

9 . 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8

10 . (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI,AB

11 . (SINGL* or DOUBL* or TREBL* or TRIPL*) near ((BLIND* or MASK*) in TI,AB)

12 . 9 or 10 or 11

13 . HUMAN in DER

14. (ANIMAL or NONHUMAN) in DER

15. 13 and 14

16. 14 not 15

17. 12 not 16

## *Appendix 4: List of Key Words used in electronic searches*

high-risk surgery, peri-operative, pre-operative, post-operative, intra-operative, optimisation, optimization, goal-directed, supra-normal, fluids, oxygen delivery, starch, gelatin, blood product, crystalloid, colloid, splanchnic, renal perfusion, tissue perfusion, blood flow, lactate, acid base, oxygen consumption, base excess, base deficit, blood volume, fluid loading, fluid administration, central venous pressure, CVP, aneurysm, vascular surgery, cardiac surgery, cancer surgery, trauma surgery, emergency surgery, orthopaedic surgery, cardiac output, cardiac index, pulmonary artery flotation catheter, PAFC, right-heart catheter, Swan Ganz, Doppler, pHi, tonometry, $PCO_2$ gap, echocardiography, fluid therapy, stroke volume, $SvO_2$, mixed venous oxygen saturation.

## *Appendix 5: Component checklist for methodological quality of clinical trials (Gardner 2000)*

**Design Features**

1 Is the objective of the trial sufficiently described?

2 Is there a satisfactory statement given of diagnostic criteria for entry to trial?

3 Is there a satisfactory statement given of source of subjects?

4 Were concurrent controls used (as opposed to historical controls)?

5 Are the treatments well defined?

6 Was random allocation to treatment used?

7 Is the method of randomization described?

8 Was there an acceptably short delay from allocation to commencement of treatment?

9 Was the potential degree of blindness used?

10 Is there a satisfactory statement of criteria for outcome measures?

11 Were the outcome measures appropriate?

12 Is a pre-study calculation of required sample size reported?

13 Is the duration of post-treatment follow-up stated?

**Conduct of trial**

14 Are the treatment and control groups comparable in relevant measures?

15 Were a high proportion of the subjects followed-up?

16 Did a high proportion of subjects complete treatment?

17 Are the dropout rates described by treatment/control groups?

18 Are the side effects of treatment reported?

**Analysis and presentation**

19 Is there a statement adequately describing or referencing all statistical procedures used?

20 Are the statistical analyses used appropriate?

21 Are the prognostic factors adequately considered?

22 Is the presentation of statistical material satisfactory?

23 Are confidence intervals given for the main results?

24 Is the conclusion drawn from the statistical analysis justified?

# Chapter 3 Morbidity reporting in surgical RCTs

## *3.1 Introduction*

In this chapter I explore further the reporting of morbidity in clinical trials by describing the standard of outcomes reporting from a sample of RCTs (of surgical interventions) published in high-impact surgical journals.

In the previous chapter marked inconsistency of morbidity reporting was observed in a homogeneous population of studies of similar interventions. In order to establish whether this observation can be generalised to other studies, a separate sample of perioperative RCTs were selected and morbidity reporting assessed. Quality of reporting of trial methodology was also evaluated.

The criteria against which these RCTs are judged are based on the CONSORT (Consolidated Standards of Reporting Trials) statement [281]. The CONSORT statement provides a standardised framework to guide reporting of RCTs. It was developed by an international group of clinicians, statisticians and biomedical editors in the mid-1990s with the aim of remedying persistent deficiencies in reporting of trial methodology [281]. The revised CONSORT statement [282] (2001) is supported by a growing number of biomedical journals and health care groups [282,283]. However, despite evidence suggesting that adherence to CONSORT guidelines improves the quality of trial reporting, enforcement remains low amongst surgical journals [284].

To derive objective criteria for evaluating the reporting of postoperative morbidity in surgical RCTs, I used the recent extension to the CONSORT statement relating to reporting of adverse events in RCTs [285]. The data obtained in this study are consistent with previous studies of standards of reporting of methodology in RCTs in surgery [284,286] and provide the first systematic description of reporting of harms (morbidity) in this category of study.

## *3.2 Methods*

### 3.2.1 Summary

A retrospective systematic review of RCTs published in four high-impact surgical journals over a single calendar year was conducted. Quality of reporting of adverse events and trial methodology were assessed using the criteria derived from the extended CONSORT statement.

### 3.2.1 Selection of journals and identification of RCTs

The four highest-ranking "surgery" journals (as defined by impact factor) were identified using the ISI Web of Knowledge's Journal Citation Report (2004) [156]. For each journal, a MEDLINE search was conducted using the terms "random" and "trial" and limited to the 2005 calendar year (January to December 2005 inclusive). The electronic search was complemented by a hand search of each journal to ensure that all eligible studies were captured. Studies were only included if they were true randomised trials involving human subjects. The "instructions to authors" section of all four journals was accessed to determine whether the journals endorsed the CONSORT statement.

### 3.2.2 Data extraction

For each included study, the following characteristics were recorded: number of authors, number of centres involved, page length, involvement of a statistician/epidemiologist, source of funding (if declared), and country of study. For each included study, two investigators independently extracted data items relating to eight methodological criteria and five aspects of harms reporting, as well as calculating Jadad scores to summarise study quality [287]. The following data items relating to harms reporting were extracted: provision of standardized or validated definitions of harms, identification of outcomes assessors, mode of data collection (active or passive), timing of data collection (prospective or retrospective) and time frame of surveillance for harms. Adequacy of reporting of items was reported as clear or unclear, or by category (e.g. prospective vs. retrospective). The following data items relating to methodology were extracted: mode of random sequence generation, allocation concealment, implementation of randomization, blinding status of outcomes assessors and data analysts, justification of sample size, intention-to-treat analysis and participant flow-

diagram. A third investigator adjudicated any disagreements until consensus was reached.

### 3.2.3 Data analysis

Item frequencies were reported as number (%). The Κ statistic was used to measure chance-adjusted inter-rater reliability. Study quality was categorised as low quality (Jadad score <3) and high quality (Jadad score ≥3). Fisher's exact tests were used to compare categories of studies. All p values are 2-sided and p values lower than 0.05 were considered statistically significant. Stata/IC software (Release 10.0) [StataCorp, College Station, TX, USA] was used for all calculations.

## *3.3 Results*

The top 4 surgical journals, as defined by 2004 impact factor, were *Annals of Surgery*, *American Journal of Transplantation*, *American Journal of Surgical Pathology* and *Annals of Surgical Oncology*. MEDLINE searching of these journals (calendar year 2005) yielded 93 articles of which 42 were eligible for inclusion in this study. Hand searching did not identify any further studies for inclusion. Reasons for study exclusion included: cohort studies (15), retrospective analysis (8), editorial/special article (6), non-randomised prospective comparisons (5), studies nested within a previously reported RCT (4), analysis of subgroup in an RCT (3), systematic review/meta-analysis (3), questionnaire (2), case-control study (1), cost-benefit analysis (1), long-term follow-up of previously reported RCT (1), letter to the editor (1) and animal study (1). The 42 included studies included 8673 subjects.

The included journals, endorsement of CONSORT statement in "instructions to authors", number of included RCTs, median RCT page length, consensus median Jadad scores and Jadad sub-group scores (<3 or $\underline{\geq}$ 3) are reported in Table 22.

**Table 22** Characteristics of studies reported in four high impact surgical journals in 2005

| Journal | 2004 Impact Factor | CONSORT endorsed | Included RCTs | Median Number of pages (Range) | Median Jadad Score (Range) | Jadad score category | |
|---|---|---|---|---|---|---|---|
| | | | | | | <3 | ≥3 |
| Annals of Surgery | 5.907 | Yes | 27 | 8 (5 – 12) | 2 (1 – 5) | 14/27 | 13/27 |
| American Journal of Transplantation | 5.306 | No | 14 | 8 (6 – 13) | 2 (2 – 5) | 10/14 | 4/14 |
| American Journal of Surgical Pathology | 4.690 | No | 0 | - | - | - | - |
| Annals of Surgical Oncology | 4.035 | Yes | 1 | 8 (8 – 8) | 2 (2 – 2) | 1/1 | 0/1 |

The agreement between the pair of observers who independently assessed the RCTs was good (median $\kappa = 0.795$, range 0.4 to 1). Of the 28 RCTs published in the two journals which did endorse the CONSORT statement, 46% (13/28) were of "high" quality (Jadad score $\geq 3$) compared with 29% (4/14) of RCTs in the journal which did not endorse CONSORT ($p = 0.30$).

Table 23 shows the study characteristics of all the RCTs included in the analysis. 10 out of 42 RCTs were multicentre with the number of centres ranging from 1 to 54. The median number of authors was 8 (range 1 – 15).

**Table 23** Characteristics of 42 surgical RCTs meeting the inclusion criteria for this study

| Characteristic | Subgroup | Number of RCTs |
|---|---|---|
| **Authors** | <6 | 10 (23.8%) |
| | 6-10 | 22 (52.4%) |
| | >10 | 10 (23.8%) |
| **Statistician/epidemiologist involvement** | No mention | 31 (73.8%) |
| | Involvement acknowledged | 5 (11.9%) |
| | Involved as co-author | 6 (14.3%) |
| **Number of centres** | Single centre | 32 (76.2%) |
| | Multicentre | 10 (23.8%) |
| **Funding source** | No mention | 14 (33.3%) |
| | Commercial | 9 (21.4%) |
| | Public sector | 11 (26.2%) |
| | Mixed | 8 (19.0%) |
| **Country** | United States | 11 (26.2%) |
| | Europe | 23 (54.8%) |
| | Others | 6 (14.3%) |
| | > 1 continent | 2 (4.8%) |

The standard of reporting of adverse events (morbidity) was poor (median number of studies with adequate reporting for each harms-related criterion 17%, range 0 – 68%). The proportion of studies meeting the extended CONSORT criteria relating to adverse events exceeded 50% for only one of the five criteria (stated time frame of surveillance, 28/41 [68%], unclear 13/41 [32%]). Reporting of adverse events assessed against the modified CONSORT criteria is presented in Table 24.

**Table 24** Reporting of adverse events in 42 surgical RCTs assessed against the modified CONSORT criteria.

| Adverse event/harms reporting criteria | All RCTs (n=42)* |
|---|---|
| Provision of standardised/validated definitions of harms | 11/41 (27%)* |
| Identification of outcomes assessors | 4/42 (9.5%) |
| Mode of data collection | |
| Active | 7/41 (17%)* |
| Passive | 0/41 (0%)* |
| Unclear | 34/41 (83%)* |
| Timing of data collection | |
| Prospective | 12/41 (29%)* |
| Retrospective | 1/41 (2%)* |
| Unclear | 28/41 (68%)* |
| Time frame of surveillance | |
| Stated | 28/41 (68%)* |
| Unclear | 13/41 (32%)* |

***Notes to Table 24:*** *Number of trials reporting criteria relating to adverse events/harms (* = adverse event/harms reporting was not relevant to one non-pharmacological non-invasive intervention RCT and so the scoring for some criteria is out of 41)*

No two studies used the same criteria for evaluating morbidity. Seven of forty-two studies reported a specific classification for adverse events. One study used the Dindo system of classifying morbidity collection [170]. Six others used a single adverse event classification: National Cancer Institute Common Terminology Criteria for Adverse Events v3.0, Centre for Disease Control definition for nosocomial infection, World Health Organisation standard criteria for toxicity, Vancouver Scar Scale Cleveland Clinical Continence Scoring System, and Centre for Disease Control definition for bloodstream infection.

Reporting of methodological criteria was poor (median number of studies adequately reporting any methodological criteria = 32.5%, range 5 – 64%). The proportion of studies meeting CONSORT criteria for adequate reporting of methodology exceeded 50% for only one of eight criteria (justification of sample size, 27/42 [64%]). Adequate reporting of information relating to the other criteria occurred in 12/42 (29%) for random sequence generation, 17/42 (40% for allocation concealment, 8/42 (19%) for implementation of randomisation, 8/42 (19%) for blinding status of outcome assessor and 2/42 (5%) for blinding

status of data analysts. Intention to treat analysis was reported in 18/42 (43%) of studies and a participant flow diagram was provided in 15/42 (36%) of studies. Jadad score category was low (<3) in 24/42 (57%) of studies and high (≥3) in 18/42 (43%) of studies. We found that page length of the manuscript (p = 0.45), author number (p = 0.50), number of centres (p = 0.47), declaration of funding source (p = 0.30) and involvement of a statistician (p = 0.087) were not associated with better reporting quality as measured by the Jadad score.

## *3.4 Discussion*

### 3.4.1 Summary

The reporting of methodological factors recommended in the CONSORT statement was poor for RCTs published in high quality surgical journals. This study is unique in systematically describing adverse event reporting in surgical RCTs, as recommended by the extended CONSORT statement. Adverse event reporting in surgical RCTs was poor, with researchers frequently failing to provide definitions of adverse events, to identify those assessing outcomes and to provide information relating to the mode, timing and duration of adverse event data collection.

### 3.4.2 Reporting of morbidity in surgical RCTs

The inconsistency and poor quality of morbidity reporting is consistent with the findings of a systematic review of perioperative haemodynamic management presented in Chapter 2 of this thesis. Using a different method of assessment on a distinct sample of studies, I have identified comparable inconsistency of reporting and infrequent use of defined measures of morbidity. Adequate definition of adverse events is essential not only for critical appraisal and interpretation of trial results but also to facilitate comparison between RCTs, systematic review and meta-analysis [285]. None of the RCTs in this study used the same methodology for reporting adverse events (morbidity) and no study used a systematic approach, incorporating a validated metric, for describing postoperative morbidity. The identity of outcomes assessors may be related to the attribution of adverse events (the process of deciding whether an adverse event is due to an intervention): blinded independent outcomes assessors are less likely to be biased by knowledge or expectation of study group allocation. It is not possible to exclude the possibility of bias in the reporting process in studies that do not identify outcome

assessors. Active surveillance (where participants are either asked about the occurrence of events in structured questionnaires or interviews, or pre-defined diagnostic tests are performed at pre-specified time intervals) for adverse events has a greater yield than passive disclosure (where participants spontaneously report on their own initiative) and prospective collection of data is less susceptible to bias and confounding than retrospectively collected data [285,288]. Furthermore the duration of surveillance for adverse events should be specified (and justified) as important events with long latency periods may otherwise be missed [285]. Failure to adequately report such information limits assessment of both internal and external validity. Of note, none of these studies used a systematic or validated system or metric (such as the POMS) for collecting morbidity data. Although this study was not designed as a systematic review to identify metrics for the description of postoperative morbidity, this finding (in a year of studies from the 4 top surgical journals by impact factor) suggests that no metric is currently in common use. This observation is supported by the description of morbidity reporting described in Chapter 2, where the POMS was the only systematic method designed specifically to record postoperative morbidity that was identified. Use of the POMS by an identified outcomes assessor would meet all of the criteria used to assess adverse event recording in this group of studies.

### 3.4.3 Reporting of methodological characteristics of surgical RCTs

The findings of this study in relation to reporting of methodological criteria are consistent with previous reports surveying surgical RCTs [284]. However, the majority of studies on quality of surgical trial reporting were published before release of the CONSORT extension [284,286,289]. The methodological criterion that was most frequently reported was justification of pre-study sample size and this was the only criterion to be reported in more than 50% of studies. In recognition of the difficulties associated with blinding patients and surgeons in surgical RCTs we limited our assessment of blinding status to outcome assessors and data analysts but nonetheless found that blinding status is inadequately reported in the majority of trials. The finding of deficient reporting of randomisation is in keeping with published studies or RCTs published in surgical and medical journals [284,290]. Adequate reporting of randomization requires description of sequence generation, allocation concealment (how randomization was concealed from those enrolling participants) and implementation (identification of the personnel who generated

the randomization sequence and who enrolled and assigned participants) [291,292]. Deficiencies in reporting of randomization procedures limit detection of selection bias and may be associated with exaggeration of treatment effect. Adequate description of "intention-to-treat" analysis (defined as analysis according to randomization) was present in only 18 of 42 RCTs (43%). Although it is known that reporting of "intention-to-treat" is associated with other aspects of good study design, this finding may be a reflection of the debate amongst the scientific community about the validity of including all randomized cases (even those not receiving treatment) in data analysis [293]. Use of participant flow diagrams was poor: not only were absolute numbers low (15/42 studies [36%] used flow diagrams), but also the proportion of diagrams that met the standard recommended by CONSORT was lower still. The purpose of the flow diagram is to explicitly report the numbers of participants being randomised, receiving treatment, completing the study and being analysed [282]. Of the 15 RCTs using flow diagrams, only 7 reached this standard, suggesting a lack of understanding of the importance of this feature.

### 3.4.4 "Quality" of surgical RCTs

The Jadad score is a validated scale for evaluating trial quality and comprises 3 questions relating to randomization, blinding and the reporting of withdrawals and dropouts [287]. A "high" score (≥3) is achievable even in non-blinded studies provided the other factors are adequately reported. We found that 46% (13/28) of RCTs from CONSORT-endorsing journals were of "high" quality (Jadad score ≥3) compared with 29% (4/14) of RCTs from the journal which did not endorse CONSORT but this did not reach statistical significance (p=0.3). Other researchers have also found that journals that endorse CONSORT do not enforce reporting issues [294]. As only three journals were included in this analysis, our sample may not be representative of the whole population of surgical journals. It has been reported that lack of available print space may be a contributing factor in sub-standard reporting and one study (of medical journals) found a weak association between RCT page length and reporting quality [290]. Our study found no association between page length and quality of reporting as measured by Jadad score. Similarly, in contrast to a previous report, we found no association between study quality and author number, number of study centres or declaration of funding source [284]. That none of these comparisons identified significant differences may

be due to lack of statistical power, due to the small sample of RCTs in this study, or maybe because no real difference exists.

### 3.4.5 Limitations of this study

Strengths of this study include good internal validity due to use of pre-defined methodology, systematic data collection from studies published within a defined time frame and double data extraction by independent reviewers. In addition this study provides new information on the reporting of harms from surgical RCTs. Limitations of this study include the sole use of impact factor to determine the study cohort and the lack of a comparator cohort. The use of an objective criterion (impact factor) to select eligible journals removed subjective bias from this process but limited the number of RCTs eligible for inclusion because the *American Journal of Surgical Pathology* (primarily a histopathology journal) did not provide any eligible studies and *Annals of Surgical Oncology* provided only one. In retrospect it may have been more appropriate to consider the scope of the journal in addition to impact factor and to give preference to journals publishing a substantial number of clinical studies. In comparison with previous studies of a similar type, this study lacks a direct comparator cohort (such as a group of RCTs from high quality medical journals or an older cohort of RCTs from the same surgical journals) and this reduces the applicability of our findings. Our study is also limited by the recognised difficulty in assessing trial methodology indirectly through the standard of reporting [284]. Although failure to report a criterion does not prove lack of implementation, adequate reporting is central to the credibility of an RCT's findings [284]. Notably, for many of the listed methodological and harms related criteria on which data are reported in this study, the largest category was unclear, rather than clearly not meeting the criterion. Reporting of surgical RCTs may not do credit to the quality of conducted studies: credibility might be improved significantly simply by better quality reporting. A larger study would have had greater statistical power to compare high and low quality studies and to distinguish between sub-groups RCTs (e.g. low and high quality).

RCTs provide high quality evidence on efficacy of health care interventions only if they are well designed and appropriately executed [292]. Interpretation of the strengths and limitations of an RCT relies on clear reporting of trial methodology [282]. Inadequate reporting can mask deficient methodology and lend false credence

to biased results. Increased attention to the quality of reporting of RCTs by investigators, reviewers and journal editors is required if studies are to meet published criteria.

## *3.5 Summary*

1. This chapter highlights the poor quality of reporting of RCTs in the surgical literature and is consistent with previous studies of reporting quality in the surgical literature. There does not appear to have been any improvement in reporting quality in this more recent cohort.
2. This study has additionally, uniquely, demonstrated deficiencies in adverse event reporting. Postoperative harms (morbidity) are inconsistently reported and this reporting does not meet criteria based on the extended CONSORT statement recommendations for the reporting of adverse events in relation to RCTs.
3. This finding is consistent with the results of Chapter 2 in this thesis (inconsistent and poorly defined reporting of morbidity outcomes) and emphasizes the importance of consistent reporting of postoperative morbidity using a reliable and valid metric. No evidence that such a metric exists (with the exception of POMS) was identified in this study.

# CHAPTER 4: The POMS in a UK teaching hospital

## *4.1 Introduction*

This chapter reports a prospective observational cohort study describing morbidity following major elective surgery in a single UK teaching hospital (Middlesex Hospital, London). The data collection described in this chapter also provides the data that is used for the POMS validation analysis presented in Chapter 5.

Within this chapter I will first present the characteristics of the study population along with the prevalence and pattern of postoperative morbidity (as defined by the POMS) within this cohort. Next, I will present the reasons for non-discharge from hospital in patients with no POMS defined morbidity with an estimate of the total subsequent morbidity-free bed days. I will then compare the POMS data from this cohort with published summary POMS data from a similar cohort in a US institution (Duke University Medical Centre, NC) [172] (see above, 1.6.4.3). Finally the relationship between morbidity and length of hospital stay in the UK and US cohorts will be compared.

## *4.2 Methods*

### 4.2.1 General

A longitudinal cohort study of adults undergoing major surgery was conducted using the POMS to describe the incidence and pattern of postoperative morbidity. Data were collected with the aim of describing quantitatively preoperative risk and intraoperative course as well as postoperative outcome, in order to evaluate the validity of the POMS as a measure of postoperative morbidity (see Chapter 5). Ethical approval was obtained from the Joint UCLH/UCL Committee on the Ethics of Human Research (reference number 01/0116). The collected data obtained were compared with published data from a similar sized cohort from a comparable US institution.

### 4.2.2 Setting

At the time of this study the Middlesex Hospital was one of the University College London Hospitals, London, UK. The data presented in this chapter were collected between July 1st 2001 and September 30th 2003. The Middlesex Hospital closed in December 2005.

### 4.2.3 Patients

All adult patients (aged 18 years or above) undergoing major elective surgery were eligible for inclusion in this prospective cohort study. Eligible in-patients were asked to provide informed consent to participate in the study. Consenting patients were recruited into the study.

Major elective surgery was defined as procedures expected to last more than two hours or with an anticipated blood loss greater than 500 milliliters. For the purposes of this study the following procedures were accepted as meeting the criteria within this definition: orthopaedic surgery (revision hip arthroplasty, total hip replacement, total knee replacement, fusion/instrumentation of multiple lumbar or thoracic vertebrae), general surgery (laparotomy including partial hepatectomy, pancreatic surgery, re-operative colon surgery, abdominoperineal resections, anterior resections, panproctocolectomies, hepatobiliary bypass procedures), urological surgery (radical prostatectomy, radical cystectomy, radical nephrectomy).

### 4.2.4 Sample size calculation

Statistical significance was set at alpha=0.05. Given an estimated prevalence of 25% for the most frequent morbidity domains from pilot data, obtained from the original single-centre descriptive study [172] conducted at Duke University Medical Centre University Medical Centre (North Caroline, USA)(Duke Cohort), a sample size of at least 400 patients was estimated to generate enough events (100) to allow for relatively narrow (approximately 10%) 95% CIs for the most common morbidity domains. In addition, a sample size of 440 patients allowed direct comparison of morbidity levels with the Duke Cohort.

### 4.2.5 Data collection

Data collection was by one of two study nurses. Consecutive patients were approached for recruitment into the study, except where recruitment was interrupted during periods of study nurse annual leave. Study data were collected onto paper forms at the bedside and then later entered into a Microsoft Access database (Microsoft Corp., Redmond, WA, USA) in the Surgical Outcomes Research Centre within the Middlesex Hospital.

Patient age, sex, surgical procedure, measures of preoperative risk (ASA-PS Score, POSSUM variables), length of postoperative stay, mortality and admission to Intensive Care Unit (ICU) were recorded.

The POMS was administered on postoperative days (POD) three, five, eight, and fifteen. POMS criteria were evaluated through direct patient questioning and examination, review of clinical notes and charts, retrieval of data from the hospital clinical information system and/or consulting with the patient's caregivers. Patients were cared for by the normal attending clinicians who were blinded to the survey results.

Where patients remained in hospital without identifiable morbidity (as defined by the POMS), we recorded reasons for delay in hospital discharge including non-medical reasons as a free text entry (last 200 recruited patients only). Reasons for delayed discharge were ascertained by detailed review of the patients' charts (medication, observation and fluid balance) and clinical note review. Where no clear answer was identified from these sources direct questioning of patients, nurses and doctors was undertaken to define the reason for remaining in hospital.

### 4.2.6 Analysis plan

#### *4.2.6.1 Description of patient characteristics and prevalence and pattern of POMS defined morbidity*

Continuous variables were expressed as mean, standard deviation (SD) and range. For continuous variables with a known skewed distribution, medians were also reported. The relationship between operative risk and mortality was expressed as a proportion of patients in each category for ASA-PS score and using the calculated

OE ratio for POSSUM mortality risk. The relationship between operative risk and postoperative length of stay was explored using univariate linear regression analysis for POSSUM morbidity risk and ordered logistic regression analysis for ASA-PS score.

#### *4.2.6.2 Relationship between postoperative morbidity and stay in hospital*

Proportions of categorical variables were compared using Chi squared tests. An estimate of the total number of bed days on which patients remained in hospital without POMS defined morbidity was calculated by summing the product of the number of patients remaining in hospital without morbidity and the mean subsequent length of hospital stay for each POD. Patients who were identified to have morbidity, that had previously been morbidity free, were counted by cross-tabulation.

#### *4.2.6.3 Comparison with published POMS data from a USA institution*

Data collected from patients in this study (Middlesex Cohort) were compared with published summary data from the Duke Cohort [172]. Proportions of categorical variables were compared using Chi-squared tests. Continuous variables were compared using t-tests. Association of morbidity (POMS defined) with ASA-PS score was tested using univariate logistic regression analysis.

### 4.2.7 Statistical approach

All p values are 2-sided and p values lower than 0.05 were considered statistically significant. Stata/IC software (Release 10.0) [StataCorp, College Station, TX, USA] was used for all calculations.

## *4.3 Results*

### 4.3.1 Characteristics of study population

Four hundred and fifty (63.7%) of the 706 patients who were candidates for inclusion were enrolled into the study. The main reasons for non-enrolment were lack of preoperative consent (139 patients), communication problems (47 patients) and enrolment in other studies (37 patients). One of the enrolled patients withdrew following provision of consent, one was found to be participating in an interventional study, one was withdrawn by the attending consultant, and eight did not have surgery.

Patient and perioperative characteristics of the 439 evaluated patients are summarised in Table 25. Mean age was 62.9 years (range 19 to 90 years) and 260 patients were female (59.2%). In the 434 patients where ASA score was recorded 79 (18.2%) were rated grade I, 253 (58.3%) were grade II, 100 (23.0%) were grade III, and two (0.5%) were grade IV. The range of postoperative event risk predicted by POSSUM was high for both morbidity (mean risk 31.9%, SD 21.3%; range 7.6% to 98.0%) and mortality (mean risk 7.9%, SD10.3%, range 1.4% to 75.6%). Six patients (1.4%) died during their hospital stay. No deaths occurred in patients with ASA-PS scores ≤II. Five of 100 patients with ASA-PS score III and one of two patients with ASA-PS score IV died. The POSSUM OR ratio for mortality was 0.17.

The median post-operative length of hospital stay for all patients was 10 days (mean 13.4 days, SD 12.8, range 1-136 days). Patients in ASA grades I or II had a shorter post-operative length of stay (mean 12.6 days, median 10 days) than those in grades III or IV (mean 16.4 days, median 12 days). Similarly, patients with ≥ 50% risk of post-operative morbidity as defined by POSSUM had a longer post-operative length of stay (mean 21.0 days, median 18 days) than those with a lower risk (mean 11.8 days, median 9 days). Seventy patients (16.0%) were directly admitted to ICU following surgery and a further 35 (8.0%) required admission to ICU following a period of ward care. In univariate analyses, POSSUM morbidity risk was linearly associated with postoperative length of stay ($p < 0.001$, $r^2$ 0.10)(Figure 14), and ASA-PS score was associated with postoperative length of stay ($p = 0.004$)(Figure 15) by ordered logistic regression. Duration of surgery was associated with postoperative length of stay ($P < 0.001$, $r^2 = 0.1488$)() using univariate linear regression analysis, but there was no significant association with estimated intraoperative blood loss.

**Table 25:** The Middlesex Hospital postoperative morbidity study (n=439), patient and perioperative characteristics. (LOS=hospital length of stay)

| **Group (% of study population)** | | **Total 439 (100%)** | **Orthopaedic 289 (65.8%)** | **General 101 (23.0%)** | **Urology 49 (11.2%)** |
|---|---|---|---|---|---|
| **Characteristic** | | | | | |
| Mean Age (+/- SD) [Range] | *(Years ) | 62.9 (+/-15.7) [19-90] | 65.2 (+/- 16.1) [19-90] | 60.2 (+/- 13.9) [24-88] | 55.2 (+/- 13.1) [27-80] |
| Sex | Female | 59.2 | 63.7 | 53.5 | 44.9 |
| ASA-PS score | ASA I | 18.0 | 22.2 | 7.9 | 14.3 |
| | ASA II | 57.6 | 55.0 | 66.3 | 55.1 |
| | ASA III | 22.8 | 21.1 | 24.8 | 28.6 |
| | ASA IV | 0.5 | 0 | 1.0 | 2.0 |
| | Missing | 1.1 | 1.7 | 0 | 0 |
| Mean POSSUM risk (range) | Morbidity | 31.9 (7.6–98.0) | 24.4 (7.6-97.4) | 48.5 (9.3-98.0) | 42.0 (9.3-97.5) |
| | Mortality | 7.9 (1.4-75.6) | 4.9 (1.4-69.2) | 13.9 (1.7-75.6) | 12.9 (1.7-69.8) |
| Post-op environment | ICU/HDU | 16.0 | 10.1 | 25.7 | 30.6 |
| | > 1 day ICU | 2.5 | 0 | 8.9 | 4.1 |
| | Ward | 84.0 | 89.9 | 74.3 | 69.4 |
| Median ICU/HDU LOS (Range) | *(Days) | 0 (0-11) | 0 (0-1) | 0 (0-11) | 0 (0-4) |
| Median Post-op LOS (Range) | *(Days) | 10 (1-136) | 10 (2-136) | 13 (4-75) | 8 (1-40) |
| Returned to Theatre | | 4.3 | 3.5 | 5.0 | 8.2 |
| Readmitted to ICU/HDU | | 2.0 | 1.3 | 3.0 | 4.1 |
| Died in hospital | | 1.4 | 1.0 | 2.0 | 2.0 |
| Discharge destination | Home | 96.8 | 97.6 | 95.0 | 95.9 |
| | Rehabilitation | 0.9 | 1.0 | 1.0 | 0 |
| | Other Hospital | 0.7 | 0.3 | 1.0 | 2.0 |

***Notes to Table 25:*** **All data expressed as % of total patients for each column unless otherwise stated*

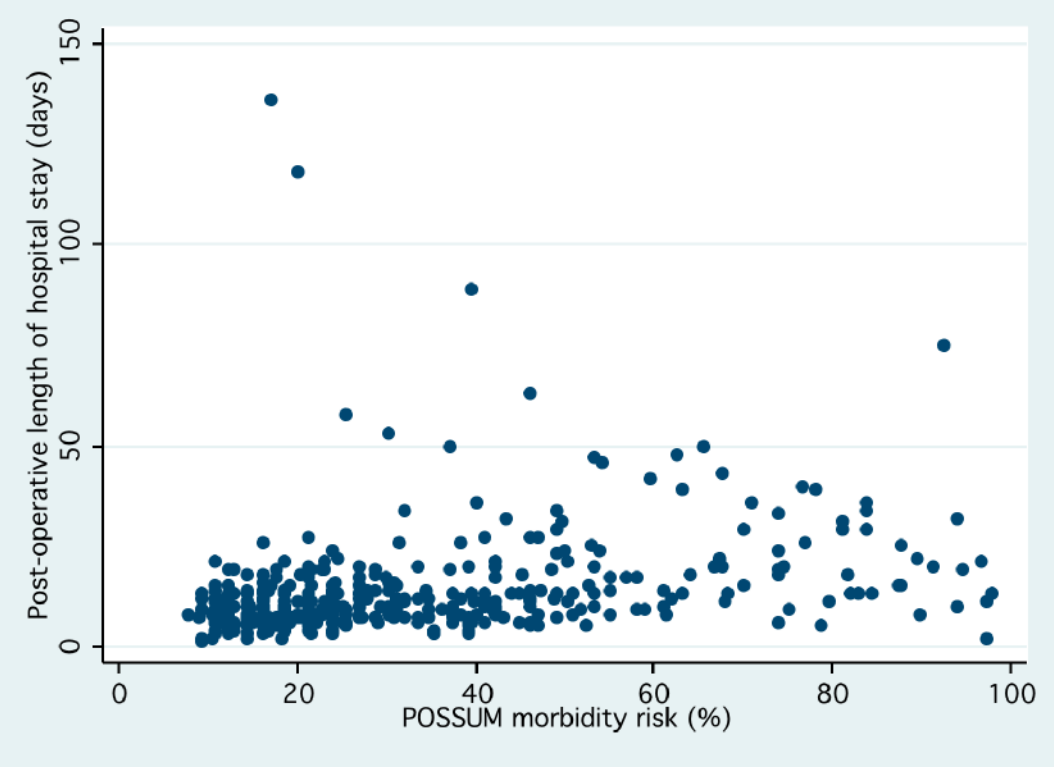



**Figure 14** Scatter plot of POSSUM morbidity risk (%) against postoperative length of hospital stay (days)

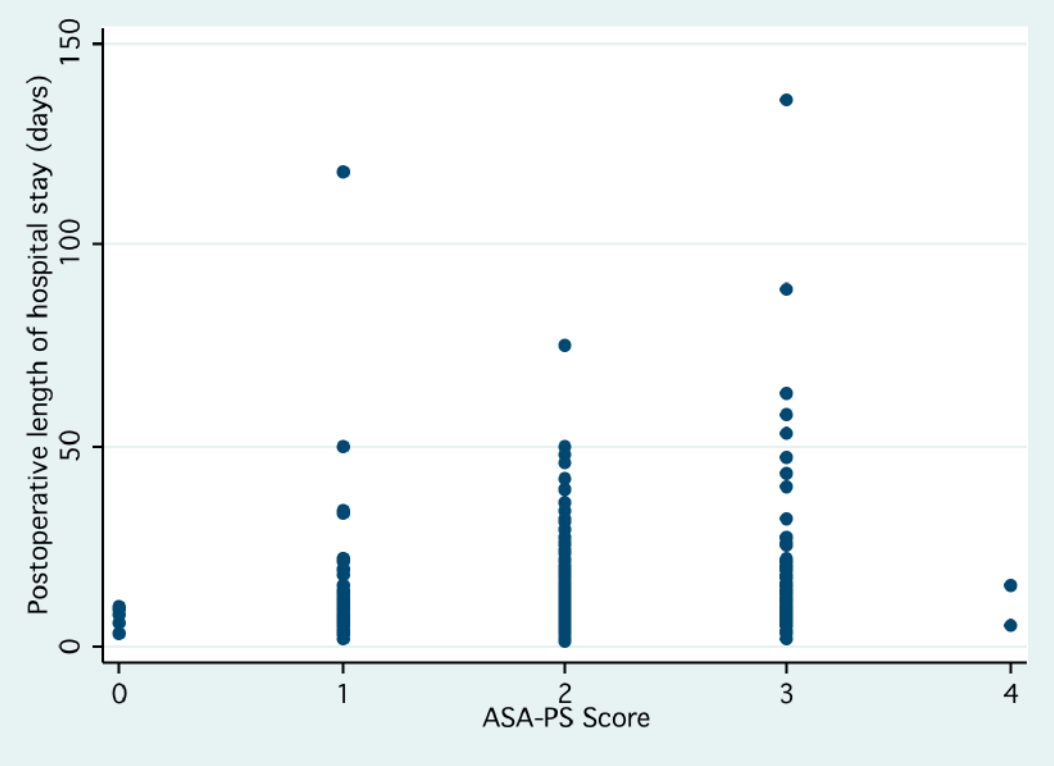



**Figure 15** Scatter plot of ASA-PS Score against postoperative length of hospital stay (days)

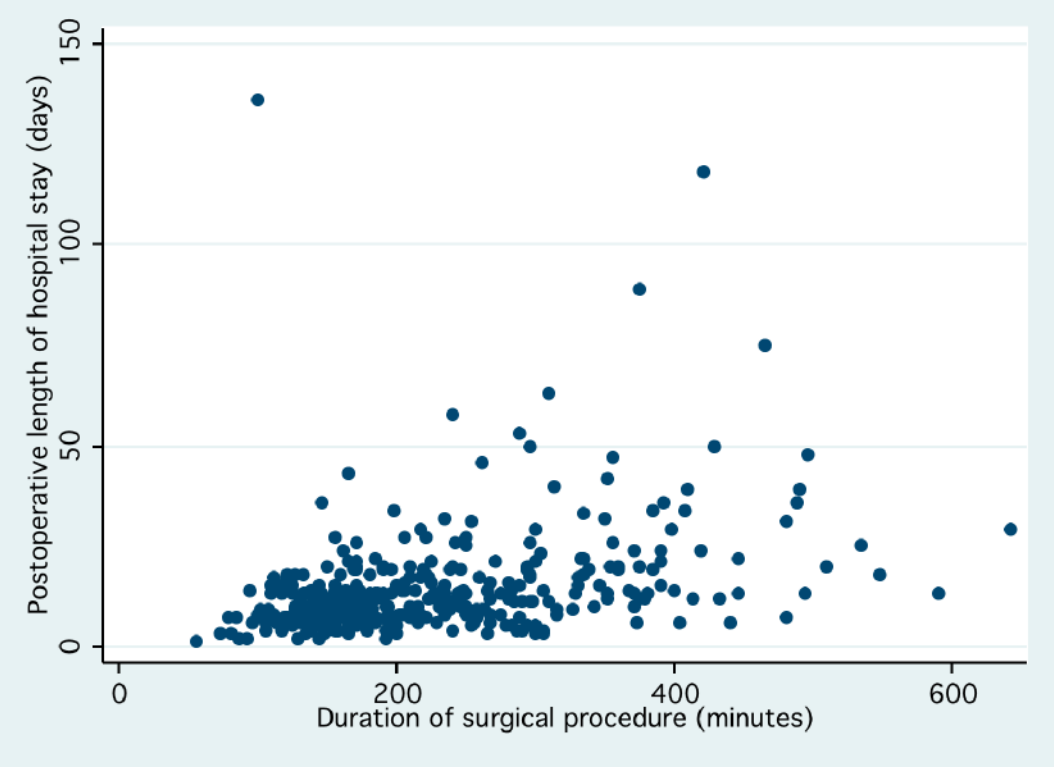



**Figure 16** Scatter plot of duration of surgical procedure (minutes) against postoperative length of hospital stay (days)

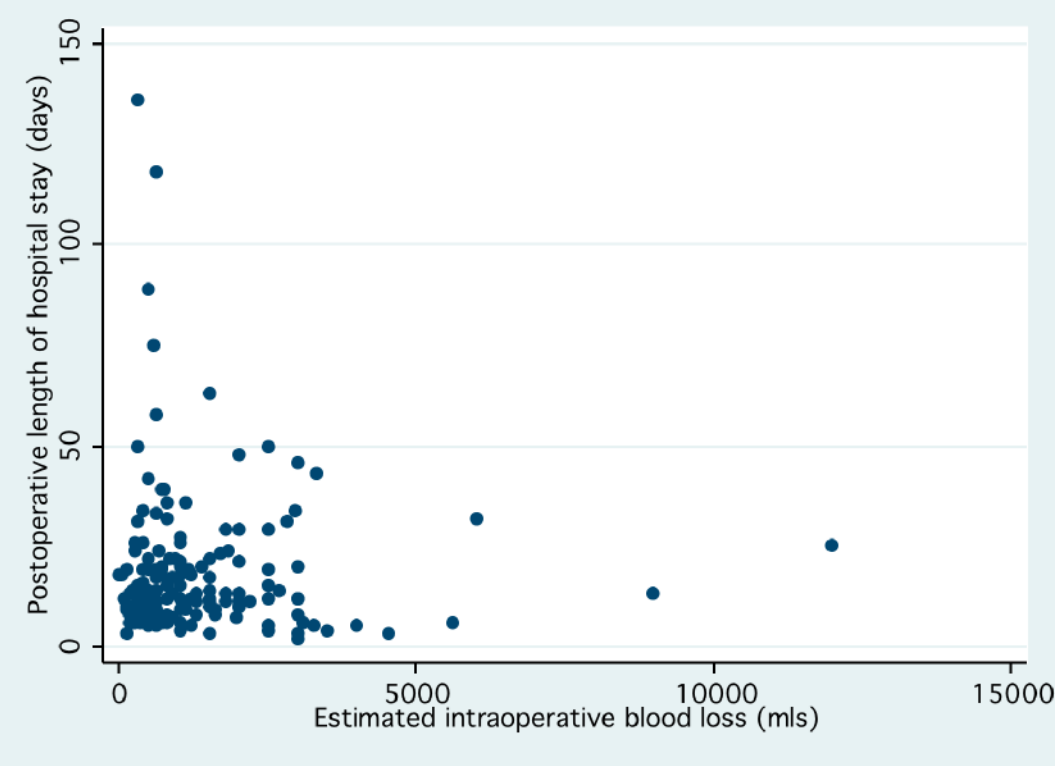



**Figure 17** Scatter plot of estimated intraoperative blood loss (mls) against postoperative length of hospital stay (days)

Two hundred and eighty nine patients (65.8%) underwent orthopaedic surgery, 101 (23.0%) had general surgery and 49 (11.2%) had urological surgery. Patients undergoing orthopaedic surgery (mean 65.2 years) were slightly older than those undergoing general (60.2 years) and urological surgery (55.2 years), but were judged to be at lower risk of post-operative morbidity using POSSUM criteria (24.4% versus 48.5% for general surgery and 42.0% for urological surgery patients). POSSUM physiology scores were slightly higher in patients undergoing orthopaedic surgery (mean 17.2, median 17) than in patients undergoing general (mean 16.1, median 15) or urology (mean 16.1, median 15) surgery. POSSUM operative severity scores were higher for urological surgery (mean 15.9, median 17) and general surgery (mean 17.3, median 17) than for orthopaedic surgery (mean 10.2, median 9). Duration of surgery was longer for urological surgery (mean 268 minutes, median 285 minutes) and general surgery (mean 282 minutes, median 255 minutes) than for orthopaedic surgery (mean 183 minutes, median 168 minutes). Estimated blood loss was greater for urological surgery (mean 2173 mls, median 1700 mls) than for orthopaedic surgery (mean 1084, median 650) or general surgery (mean 942 mls, median 700 mls).

The POMS was administered to those members of this cohort who remained in hospital on post-operative days three (433 patients), five (407 patients), eight (299 patients) and fifteen (111 patients).

### 4.3.2 Prevalence and pattern of post-operative morbidity

The percentage of patients with and without POMS-defined morbidity, by surgical specialty, for all post-operative time points is reported in Table 26. POMS-defined morbidity was present in 75.1% of in-patients on day three, 56.8% on day five, 46.2% on day eight and 63.1% on day 15. The most common sources of morbidity were gastrointestinal (recorded in 47.4% of all 439 patients at one or more than one post-operative time point), infectious (46.5%), pain (40.3%), pulmonary (39.4%) and renal (33.3%). Wound (11.2%), haematological (10.5%), cardiovascular (3.6%) and neurological (2.3%) morbidities were relatively rare.

Orthopaedic patients were much more likely to avoid any form of POMS-defined morbidity over the course of their hospital stay (29.4% versus 2.0% for general surgery and 6.1% for urological surgery, $p < 0.001$). However, they were also more

likely to remain in hospital despite having no form of POMS-defined morbidity (e.g. 55.0% remained in hospital with no morbidity on day five compared to 19.4% of general surgery patients and 22.5% of urological surgery patients, $p < 0.001$). The prevalence of each type of morbidity for the different surgical specialties at each post-operative time point is shown in Table 26. Patterns of morbidity are shown graphically in Figure 18 (PODs 3 and 5) and Figure 19 (PODs 8 and 15). The most extreme discrepancies in specialty-specific morbidity rates were observed in the gastrointestinal domain on day three (20.1% for orthopaedic surgery versus 91.1% for general surgery and 51.0% for urological surgery).

The five categories of morbidity that occurred with relatively high prevalence (>25% frequency at one or more postoperative time point) followed consistent patterns across specialties. For the gastrointestinal, pulmonary and pain domains, morbidity prevalence was general > urology > orthopaedic surgery for all PODs. For the renal domain morbidity prevalence was urology > general > orthopaedic surgery for all PODs. For the infection domain morbidity prevalence was urology > general > orthopaedic on PODs 3,5 and 15 but not on POD 8.

**Table 26** The Middlesex hospital postoperative morbidity study (n=439). Percentage of patients with postoperative morbidity (as defined by POMS) according to discharge status by surgical speciality. Percentage of patients with morbidity in each POMS domain by surgical speciality at all postoperative timepoints.

| | **Orthopaedic (N = 289)** | | | | **General (N = 101)** | | | | **Urology (N= 49)** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Day** | | | | **Day** | | | | **Day** | | | |
| | **3** | **5** | **8** | **15** | **3** | **5** | **8** | **15** | **3** | **5** | **8** | **15** |
| Discharged | 1.7 | 6.9 | 34.9 | 83.0 | 0 | 3.0 | 15.8 | 53.5 | 2.0 | 18.4 | 46.9 | 69.4 |
| In hosp - POMS | 35.6 | 51.2 | 40.5 | 8.7 | 2.0 | 18.8 | 34.7 | 12.9 | 6.1 | 18.4 | 18.4 | 6.1 |
| In hosp + POMS | 62.6 | 41.9 | 24.6 | 8.3 | 98.0 | 78.2 | 49.5 | 33.7 | 91.8 | 63.3 | 34.7 | 24.5 |
| Pulmonary | 30.1 | 7.3 | 2.4 | 1.7 | 58.4 | 19.8 | 12.9 | 5.9 | 36.7 | 22.4 | 8.2 | 6.1 |
| Infectious | 26.6 | 21.5 | 14.5 | 7.6 | 43.6 | 28.7 | 18.8 | 11.9 | 59.2 | 36.7 | 14.3 | 16.3 |
| Renal | 24.9 | 8.7 | 2.8 | 1.0 | 39.6 | 21.8 | 5.9 | 3.0 | 53.1 | 30.6 | 10.2 | 4.1 |
| Gastrointestinal | 20.1 | 15.9 | 7.3 | 1.0 | 92.1 | 65.3 | 37.6 | 25.7 | 51.0 | 40.8 | 18.4 | 10.2 |
| Cardiovascular | 0.7 | 1.4 | 0.3 | 0 | 3.0 | 4.0 | 1.0 | 1.0 | 2.0 | 2.0 | 0 | 0 |
| Neurological | 1.7 | 0.7 | 0.3 | 0 | 3.0 | 2.0 | 0 | 0 | 0 | 0 | 4.1 | 0 |
| Wound | 1.7 | 5.5 | 5.9 | 2.4 | 0 | 1.0 | 6.9 | 6.9 | 0 | 2.0 | 4.1 | 4.1 |
| Haematological | 7.3 | 2.4 | 1.0 | 0.3 | 4.0 | 2.0 | 1.0 | 0 | 16.3 | 2.0 | 0 | 0 |
| Pain | 30.8 | 4.2 | 1.4 | 0.7 | 58.4 | 24.8 | 10.9 | 5.9 | 49.0 | 20.4 | 2.0 | 2.0 |

***Notes to Table 26:*** *Discharge = Discharged from Hospital, In hosp – POMS = Patients remaining in hospital with no morbidity as defined by the POMS, In hosp + POMS = Patients remaining in hospital with morbidity as defined by the POMS.*

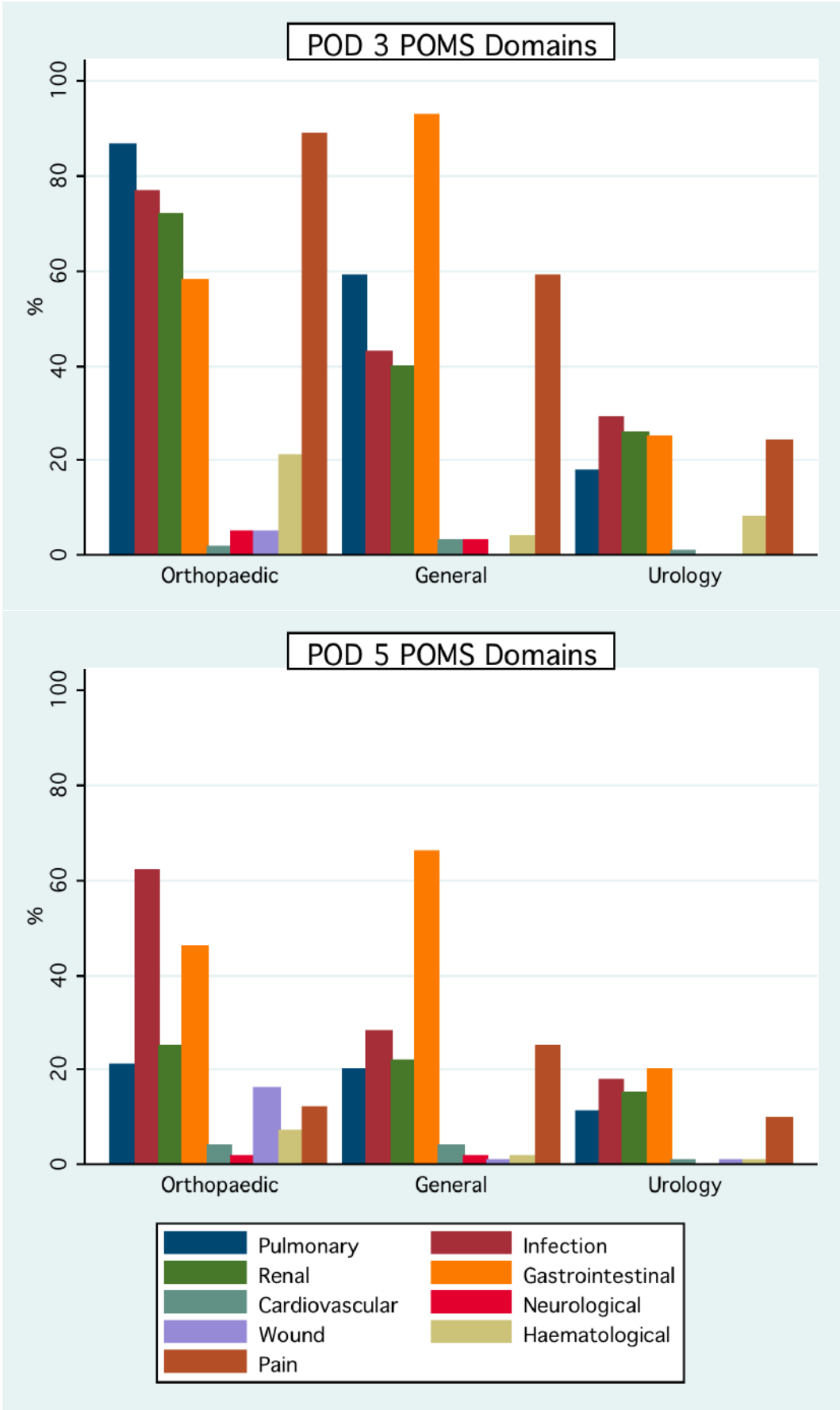



**Figure 18** The Middlesex Hospital postoperative morbidity study (n=439), frequency of POMS domains on postoperative day 3 (POD 3) and postoperative day 5 (POD 5) by surgical specialty

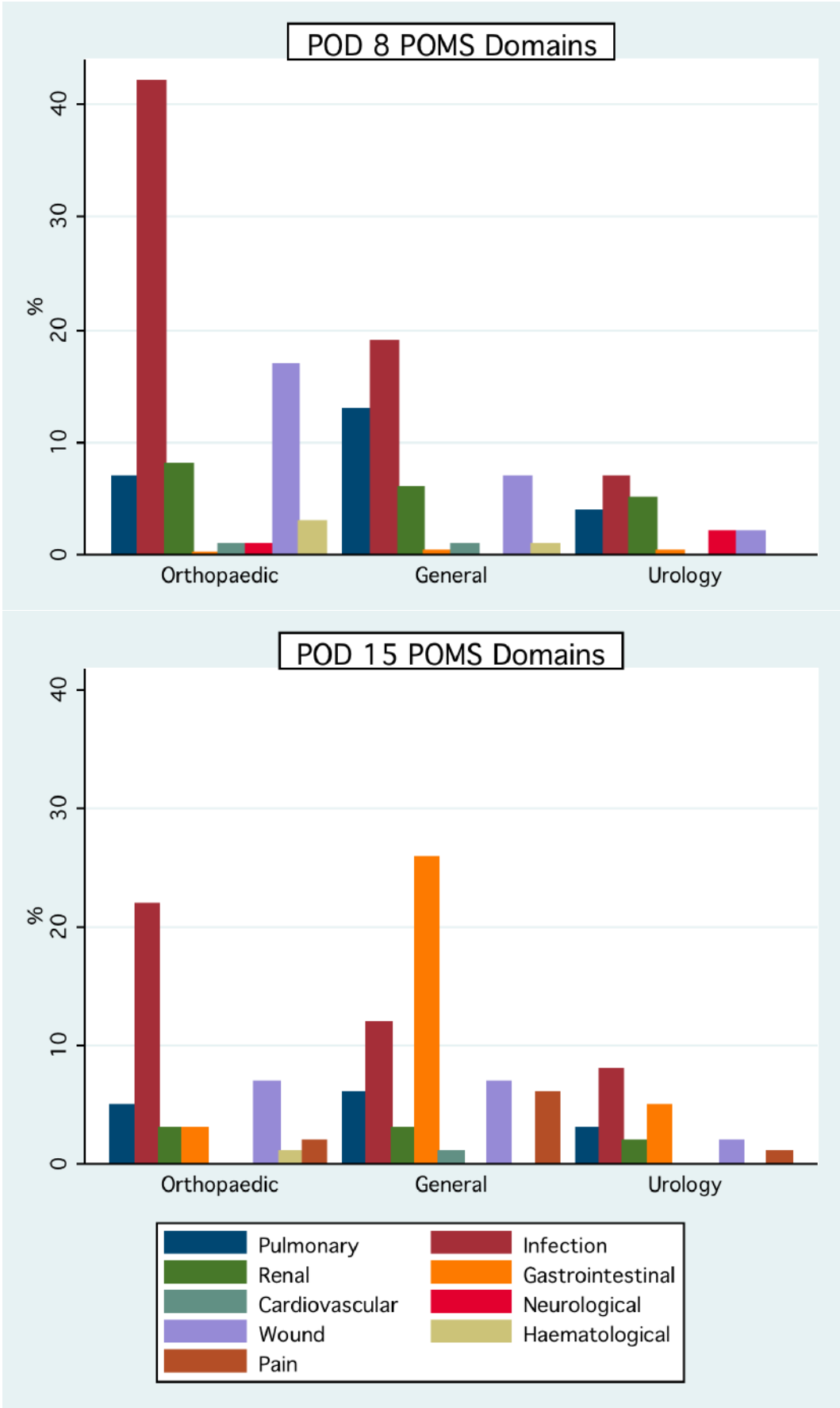



**Figure 19** The Middlesex Hospital postoperative morbidity study (n=439), frequency of POMS domains on postoperative day 8 (POD 8) and postoperative day 15 (POD 15) by surgical specialty

### 4.3.3 Relationship between postoperative morbidity and stay in hospital

Many patients remained in hospital in the absence of POMS defined morbidity (Table 26 and Figure 20): 108/433 (24.9%) on POD 3, 176/407 (43.2%) on POD 5, 161/299 (53.85%) on POD 8 and 41/111 (36.94%) on POD 15.

Patients undergoing orthopaedic surgery remained in hospital without POMS defined morbidity more frequently than those undergoing either general or urology surgery on all PODs and this was statistically significant on PODs 3 and 5.

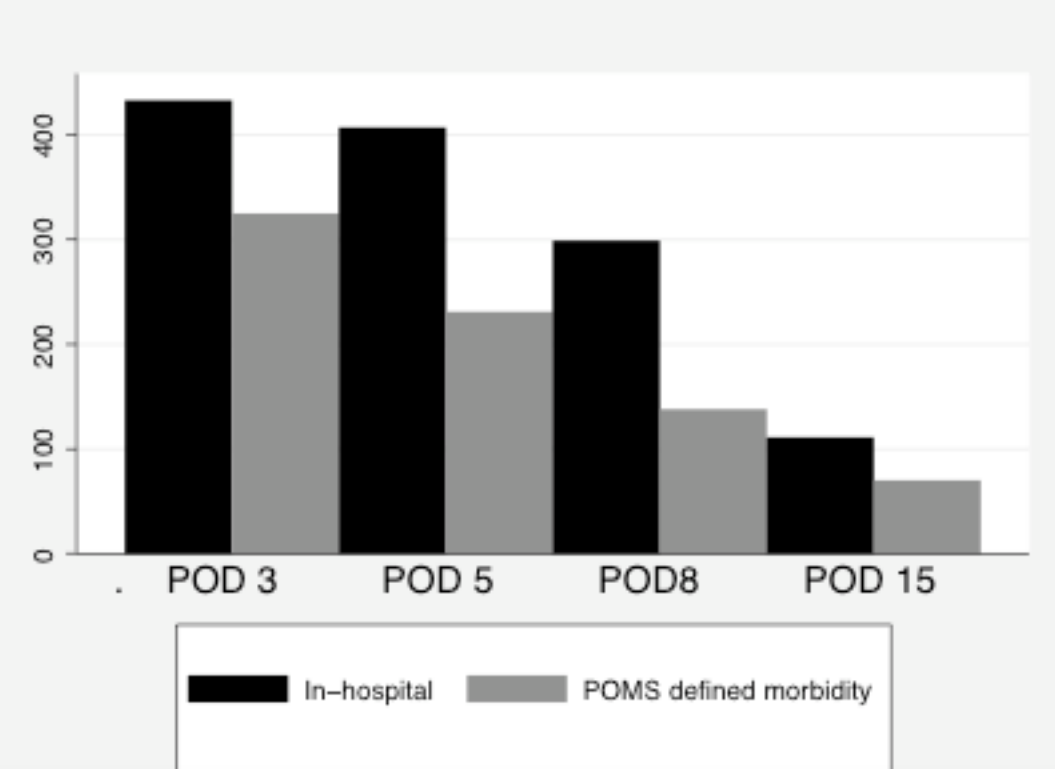



**Figure 20** The Middlesex Hospital postoperative morbidity study (n=439), the frequency of patients remaining in hospital with prevalence of postoperative morbidity (POMS defined) on postoperative days 3,5,8 and 15 (PODs 3, 5, 8 and 15).

For the last 200 patients enrolled into the study, if no POMS defined morbidity was identified, we recorded alternative reasons for remaining in hospital and did not identify any additional unrecorded morbidity. Common reasons for non-discharge included mobility problems (41 patients on day eight, 8 patients on day 15), awaiting equipment at home (14 patients on day eight, 3 patients on day 15), social problems (3 patients on eight, 3 patients on day 15). Four patients on day eight and 1 patient on day 15 remained in hospital without any identifiable reason.

For those patients remaining in hospital without morbidity the mean subsequent length of stay was 5.7 days on POD 3, 4.7 days on POD 5, 4.7 days on POD 8 and 5.1 days on POD 15. The total subsequent length of stay in hospital (product of mean subsequent length of stay and number of patients remaining in hospital without morbidity) was 2314 days (4.8 days per patient).

A sub-group of patients identified as remaining in hospital without morbidity subsequently developed new morbidity (Table 27).

**Table 27** The Middlesex Hospital postoperative morbidity study (n=439), frequency of developing subsequent POMS defined morbidity after being morbidity free as defined by POMS

| In hospital without morbidity on: | Post operative day 3 | Post operative day 5 | Post operative day 8 |
|---|---|---|---|
| Postoperative day 5 POMS | 17/114 (14.9%) | | |
| Postoperative day 8 POMS | 12/114 (10.5%) | 16/208 (7.7%) | |
| Postoperative day 15 POMS | 5/114 (3.6%) | 8/208 (3.8%) | 10/301 (3.3%) |

## 4.3.4 Comparison with US data

### *4.3.4.1 Patient and surgery characteristics*

When compared with the UK (Middlesex) cohort (n=439), the USA (Duke) cohort (n=438) was slightly younger (mean age 59 vs. 63 years), included more men (47% vs. 41%, NS) and tended to have higher ASA-PS scores (5/52/38/5 vs. 18/58/23/1 for ASA-PS scores I/II/II/IV respectively, p = 0.007)) (Figure 21). Although the inclusion criteria were the same (elective major surgical procedures expected to last more than two hours or with an anticipated blood loss greater than 500 milliliters) there are differences between the included list of procedures identified by these criteria (Table 28), which reflect underlying differences in the surgical procedures undertaken at the two institutions. For example the Middlesex cohort included first-time lower limb joint replacement and colorectal surgery which were not included in the Duke cohort, whilst the Duke cohort

includes abdominal aortic aneurysm and major gynaecological surgery which are not included in the Middlesex cohort.

In-hospital death occurred in 6/439 (1.4%) in the Middlesex cohort and 7/438 (1.6%) in the Duke cohort (p = NS). Postoperative length of stay was greater than 7 days in 114/438 (26.0%) of patients in the Duke cohort and 299/439 (68.1%) of patient in the Middlesex cohort (p <0.001).

#### *4.3.4.2 Prevalence and pattern of postoperative morbidity*

A comparison of POMS domains frequencies and number of patients remaining in hospital on POD 5, 8 and 15 is presented in Table 29**.** Infection (p <0.001 all PODs) and gastrointestinal (POD 5 p = 0.008, POD 8 p = NS, POD 15 p <0.001) morbidity occurred more frequently in the Middlesex Cohort. Conversely, cardiovascular and neurological morbidity tended to occur more frequently in the Duke Cohort (p = NS all comparison). Morbidity levels were similar in both cohorts for the remaining POMS domains.

ASA-PS score was associated with the presence of postoperative POMS defined morbidity (recorded in one or more domains at one or more than one post-operative time point) in both cohorts (p ≤0.001).

#### *4.3.4.3 Patients remaining in hospital with no POMS defined morbidity*

In the Duke cohort 98% (95% confidence interval, 96-100%) of patients remaining in hospital at POD 8 or thereafter had POMS defined morbidity. In the Middlesex cohort only 46% (95% confidence interval, 40-52%) of patients remaining in hospital at POD 8 or thereafter had POMS defined morbidity.

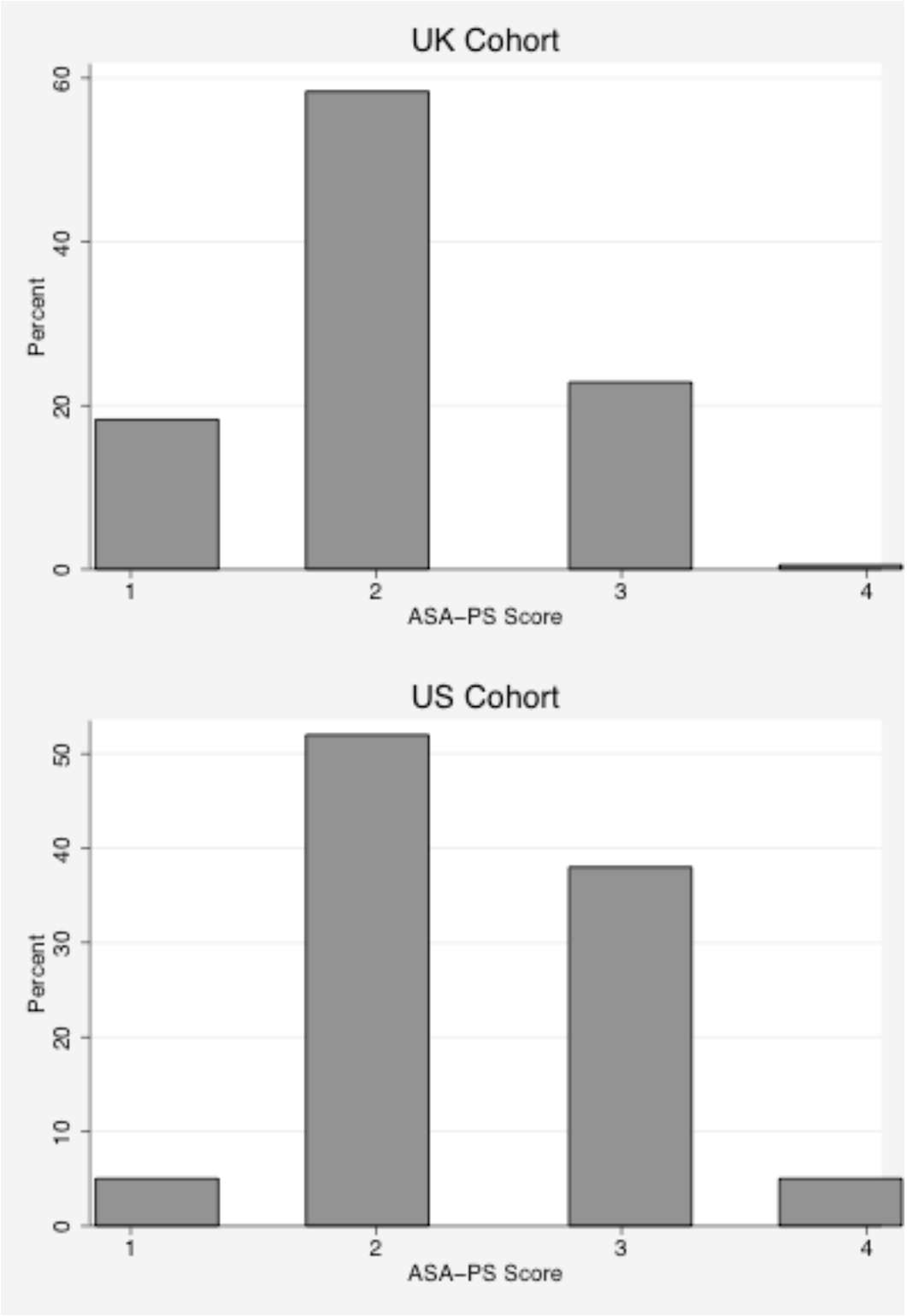



**Figure 21** Comparison of the ASA-PS score distribution between the Middlesex postoperative morbidity study (UK cohort) (n=439) and the Duke postoperative morbidity study (USA cohort) (n=438)

**Table 28** Surgical procedure categories included in the Middlesex postoperative morbidity study (UK cohort) (n=439) compared with those included in the Duke postoperative morbidity study (USA cohort) (n=438)

| **Middlesex Cohort, UK** | **Duke Cohort, US** |
|---|---|
| Revision Hip Arthroplasty | Revision Hip Arthroplasty |
| Total Hip Replacement | |
| Total Knee Replacement, | |
| Fusion/instrumentation of multiple lumbar or thoracic vertebrae | Instrumentation of multiple lumbar or thoracic vertebrae |
| Any Laparotomy expected to last > 2 hours | Any Laparotomy expected to last > 2 hours |
| Partial Hepatectomy, | Partial Hepatectomy |
| Pancreatic surgery | Pancreatic surgery |
| Re-operative colon surgery | Re-operative colon surgery |
| Abdominoperineal resections | |
| Anterior resections | |
| Panproctocolectomies | |
| Hepatobiliary bypass procedures | |
| Radical Prostatectomy | Radical Prostatectomy |
| Radical Cystectomy | Radical Cystectomy |
| Radical Nephrectomy | Radical Nephrectomy |
| | Abdominal Aortic Aneurysn Repair |
| | Gynaecological Cancer Debulking Procedures |
| | Abdominal Hysterectomy |

**Table 29** Comparison of POMS domain frequencies and the number of patients remaining in hospital on postoperative days 5, 8 and 15 between the Middlesex postoperative morbidity study (UK cohort) (n=439) and the Duke postoperative morbidity study (USA cohort) (n=438)

| | **Postoperative Day 5** | | | **Postoperative Day 8** | | | **Postoperative Day 15** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **UK** | **US** | **P** | **UK** | **US** | **P** | **UK** | **US** | **P** |
| In Hospital | 407 | 176 | **<0.001** | 299 | 114 | **<0.001** | 111 | 21 | **<0.001** |
| Pulmonary | 52 | 30 | **0.011** | 24 | 29 | 0.473 | 14 | 6 | 0.071 |
| Infectious | 109 | 20 | **<0.001** | 68 | 15 | **<0.001** | 42 | 9 | **<0.001** |
| Renal | 62 | 46 | 0.103 | 19 | 24 | 0.430 | 8 | 4 | 0.246 |
| Gastrointestinal | 132 | 97 | **0.008** | 68 | 58 | 0.343 | 34 | 11 | **<0.001** |
| Cardiovascular | 9 | 16 | 0.154 | 2 | 10 | **0.020** | 1 | 3 | NA |
| Neurological | 4 | 25 | **<0.001** | 3 | 11 | **0.031** | 0 | 1 | NA |
| Wound | 18 | 5 | **0.006** | 26 | 14 | 0.053 | 16 | 5 | **0.015** |
| Haematological | 10 | 14 | 0.405 | 4 | 18 | **0.002** | 1 | 3 | NA |
| Pain | 47 | 40 | 0.436 | 16 | 25 | 0.148 | 9 | 2 | 0.034 |

Only two patients in the Duke Cohort remained in hospital without morbidity on POD 8 or POD 15; one was awaiting commencement of chemotherapy and one was awaiting a diagnostic test. This contrasts with 181 patients in the Middlesex Cohort who remained in hospital without morbidity on POD8 or POD15 (or both); reasons for remaining in hospital are reported in Section 4.3.3 (above). No patient in the Duke Cohort had morbidity on POD 15 that had been morbidity free on POD 8. Readmissions were not reported in either study.

## *4.4 Discussion*

### 4.4.1 Summary of findings

In this first use of the POMS in a UK setting, gastrointestinal, infectious, pain-related, pulmonary and renal problems were the most common sources of morbidity following major surgery. Many patients remained in hospital despite having no morbidity, but no patient free of morbidity as defined by the POMS was found to have a morbidity-related reason for remaining in hospital: the POMS captured all relevant morbidity in in-patients. A variety of non-medical reasons were identified as being responsible for prolonged hospital stay. Morbidity levels were lowest in patients undergoing orthopaedic surgery but these patients were also more likely to remain in hospital without any form of morbidity.

### 4.4.2 Epidemiology of POMS defined morbidity

The epidemiology of postoperative morbidity observed in this study reflects the health of the study population, the nature and severity of the surgery undertaken and the definitions of morbidity used.

Although patients undergoing orthopaedic surgery were marginally older and less fit than patients undergoing urological or general surgery this was not reflected in the overall prevalence of morbidity for the three surgical groups. The differences in overall morbidity levels between surgical groups seem predominantly to reflect severity of surgery as indicated by differences in the Operative Severity Score of the POSSUM and differences in the duration of surgery. POSSUM operative severity score, and therefore POSSUM predicted morbidity level, and duration of surgery were all greatest in patients undergoing general surgery, less in patients undergoing urological surgery and substantially lower in patients undergoing orthopaedic surgery. Interestingly, estimated intraoperative blood loss, which has previously been used as an index of severity of surgery, was similar for orthopaedic and general surgery but greater for urological surgery.

Whilst severity of surgery is reflected in the overall prevalence of morbidity, the nature of surgery is reflected in the pattern of morbidity. For example gastrointestinal morbidity was observed most frequently following general surgery (operation directly involving gastrointestinal tract) and least frequently following orthopaedic surgery (operation site remote from the gastrointestinal tract) whereas renal morbidity occurred most commonly following urological surgery. The interaction between severity of surgery and type of surgery follows a predictable pattern: within each specialty the pattern of morbidity is consistent but the prevalence of each type of morbidity increases in proportion to operative severity.

### 4.4.3 Comparison with other postoperative morbidity estimates in the literature

Estimates of morbidity prevalence are always contingent on the population under study and the definitions used. Previous reports have classified postoperative morbidity using alternative approaches to that taken by the POMS. They have

commonly focused on defined diagnoses (e.g. Deep Venous Thrombosis) [68] rather than looking to capture all morbidity relevant to patients. They have often not recorded morbidity that did not fit into this type of diagnostic categorization (e.g. failure to tolerate enteral feed). As an example, comparison with other studies assessing pain is difficult because I used an operational definition for presence or absence of pain at predefined times whereas most pain studies use objective testing methods (e.g. visual analog scores) [295-297] and/or cumulative recording (e.g. total morphine usage) [295,298-299] yielding continuous variables rather than a point prevalence. Additionally most previous studies which have recorded postoperative morbidity have not collected data such as POSSUM scores that would permit risk adjustment and meaningful comparison with this study.

Recognizing these limitations, it seems that relationships between different categories of morbidity and length of stay observed in my study are broadly consistent with previous reports. Pain and gastrointestinal dysfunction were common and associated with prolonged duration of stay in hospital. In a day surgery setting prolonged length of stay was associated with postoperative nausea and vomiting, dizziness, drowsiness, pain and cardiovascular events [300]. Other studies of outcome following surgery have shown that delayed enteral feeding is not uncommon following gastrointestinal [174,260] or non-gastrointestinal surgery [301]. A study of outcome following gastroenterological surgery in patients having lower risk operations than were included in my study found 13.9% (70/503) of patients had delayed oral intake (still receiving iv fluids > 1 week after surgery owing to postoperative ileus) [302]. This is comparable to the day 8 GI morbidity of 37.3% (inability to tolerate enteral diet) reported in my study. However it is notable that in our study gastrointestinal morbidity, which is by definition distressing to the patient (unable to tolerate enteral diet), is not uncommon (> 15% on POD3 and POD5) even following orthopaedic surgery. This suggests that much of this type of morbidity is not simply related to direct disturbance of the gastrointestinal tract but may be associated with the overall physiological disturbance consequent upon major surgery of any type: it is likely to be a marker of the whole body response to injury rather than a specific local effect. Previous attempts at recording perioperative outcome have often not recorded this dimension of patient

morbidity or have recorded "postoperative ileus" [303], a much less clearly defined outcome [304].

In my study the wound domain was not strongly associated with increased length of stay and occurred less frequently amongst those with a greater preoperative risk as defined by ASA grade of POSSUM. This finding was consistent across surgical sub-groups. This is in contrast to previous epidemiological [305] and case-matching [306,307,308] studies which have reported clinically significant "attributable" increases in length of stay associated with surgical site infection (SSI). The lack of association in my study is striking because the POMS definition of wound morbidity has a stricter criterion than many other reports with the result that the POMS should only identify the most serious or severe wound morbidity. However this is not universally reported: a case series of patients following colorectal surgery did not demonstrate an association between SSI and length of hospital stay using multiple regression analysis [309].

Both cardiac and neurological domains occur infrequently (<5%) in all types of surgery. Although cardiac risks are commonly perceived to be greater my results are consistent with large-scale surveys of the risk of major cardiac complications in non-cardiac surgery [124,310-312] but lower than levels identified if intensive monitoring techniques (e.g. continuous ECG monitoring for ST depression) [313] or biochemical tests [314] (e.g. Troponin T) are used.

### 4.4.4 POMS and stay in hospital (bed occupancy)

The observation that patients remain in hospital in the absence of a clinical indication is not new [315-322]. A recent UK report of post-operative bed occupancy reported that 31% of patients were occupying beds inappropriately [323]. Although the POMS was not designed as a bed utilisation review tool the striking difference in prevalence of "morbidity-free" days between the Middlesex and Duke cohorts discussed below suggests contrasting levels of "appropriate" bed use and emphasizes the potential for improvements in discharge efficiency in the UK hospital. Shorter hospital stay as a result of improved discharge efficiency will reduce cost per patient and increase patient throughput. Screening for postoperative morbidity using the POMS may be useful to identify patients

remaining in acute hospital beds unnecessarily. The POMS may have utility as a tool for recording bed occupancy and for modelling bed utilisation.

### 4.4.5 Comparison between the Middlesex (UK) and Duke (US) Cohorts

Our study also provides an opportunity for direct comparison of outcome following major surgery between a UK and a US institution [172]. The pattern and prevalence of morbidity was very similar but the relationship between morbidity and bed occupancy was not: nearly all (> 98%) patients remaining in hospital in the US hospital had identifiable morbidity [172] whereas many patients (54% on day 8) in the UK hospital did not.

The comparison between the Middlesex and Duke cohorts may provide interesting insights into differences between two contrasting systems of care. The Middlesex cohort tended to have higher levels of morbidity than the Duke cohort despite a lower level of risk according to the ASA-PS scores. The general pattern of morbidity was similar for the two cohorts. Overall, gastrointestinal, pulmonary, renal and pain tended to more common whereas cardiovascular, neurological, haematology and wound morbidity tended to be less common (never > 6% of total patients). Comparing the two cohorts, wound morbidity tended to more common in the Middlesex Cohort whilst neurological, cardiovascular and haematology morbidity tended to be more common in the Duke cohort. The most striking findings were that patients in the Middlesex cohort were more likely to remain in hospital (> 2 fold difference, p <0.001, all PODs), more likely to remain in hospital in the absence of POMS defined morbidity (>20 fold difference, p <0.001, PODs 8 and 15) and had a higher prevalence of infection morbidity (> 4 fold difference, p <0.001, all PODs) when compared with the Duke cohort.

Whilst inter-cohort variation in distribution of surgical specialty, operation types and risk (ASA-PS score) may contribute to these observed differences, it is unlikely that they provide a full explanation, given the broad similarity in overall morbidity and mortality levels. The difference in infection morbidity may reflect a true difference in rates of infection or might result from differences in prescribing practice. The POMS criteria for infection morbidity are either "Currently on antibiotics.." or "..temperature >38°C in the last 24 hours." If clinicians attending the Middlesex cohort had a lower threshold for prescription of antibiotics they

might elevate the measured level of infection morbidity in the absence of a true difference. However the higher prevalence of wound morbidity ($p < 0.05$ on POD 5 and 15, $p = 0.053$ on POD 8) is suggestive that at least some of the observed difference in infection prevalence may represent a true infection morbidity signal.

The striking differences between length of hospital stay and the much greater number of patients in the Middlesex cohort who remain in hospital without POMS defined morbidity are strongly suggestive of differences in the way that care is delivered. In the cost driven healthcare environment of a "private" (non-state) US hospital discharge policies seem to be substantially more efficient than in the NHS institution. However identifying these differences as solely due to efficiency differences, depends on the assumption that once patients become morbidity free they are fit for discharge home and will not subsequently develop "new" morbidity. The reoccurrence of morbidity in some patients in the Middlesex cohort who remained in hospital whilst free of morbidity challenges this assumption. Unfortunately hospital readmission rates are not available from either study. It is therefore uncertain whether patients who had been discharged home subsequently developed morbidity meeting POMS criteria, thereby suggesting that their discharge may have been premature. Comparisons between UK and US institutions are not common in the literature. A comparison between UK (Queen Alexander Hospital and St Mary's Hospital, Portsmouth Hospitals NHS Trust, Portsmouth, UK) and US (Mount Sinai Hospital, New York, NY, USA) institutions suggested a four-fold difference in POSSUM risk adjusted mortality following major surgery in large (>1000 patient) cohorts [19]. Consistent with this (but with a smaller effect magnitude), a risk-adjusted comparison of outcome following liver transplant surgery between UK (> 5000 patients) and US (>40000 patients) cohorts showed increased early (<90 days) mortality in the UK cohort (hazard ratio 1.17; 95% CI 1.07 to 1.29) [324]. Interestingly however, there was no mortality difference between 90 days and 1 year, and a trend towards reduced mortality in the UK cohort after > 1 year [324]. In the Middlesex POMS study, mortality was similar to that observed in the Duke cohorts, although ASA-PS scores were significantly higher in the Duke cohort. Further studies utilizing direct prospective comparisons across several centres within each system may illuminate differences in patterns of outcome and delivery of care of potential benefit to both systems.

Such data could be obtained simply, by harmonizing perioperative datasets for institutions in different environments.

### 4.4.6 Limitations of POMS and this study

A potential weakness of this study is uncertain generalisability. We focused on adult orthopaedic, general and urological surgery and our study was limited to one UK teaching hospital. However, a similar prevalence study (using identical recruitment criteria for the same types of surgery) in a US teaching hospital found a similar pattern and levels of morbidity [172]. We have not demonstrated that the POMS is a valid index of morbidity for other types of surgery (e.g. vascular surgery, cardiac surgery and paediatric surgery). We would expect to see distinct patterns of morbidity in these groups reflecting different patterns of surgical injury and underlying disease. In some cases specific comorbidities are associated with underlying risk factors for the problem requiring surgery (e.g. increased level of ischaemic cardiac disease in patients undergoing surgery for peripheral vascular disease). Separate work is underway on the development of alternative versions of the POMS that are specific to cardiac and paediatric surgery. Strengths and limitations of the POMS that relate to the criteria for individual POMS domains and the validity of the POMS as a measure of postoperative morbidity are discussed in Chapter 5.

## *4.5 Summary*

1. The POMS identified gastrointestinal, infectious, pain-related, pulmonary and renal problems as the most common sources of morbidity following major surgery in a UK setting. The type and severity of surgery was reflected in the frequency and pattern of POMS defined postoperative morbidity.
2. Many patients remained in hospital despite absence of post-operative morbidity as defined by the POMS. Screening for post-operative morbidity using the POMS may be useful to identify patients remaining in acute hospital beds unnecessarily. The POMS may have utility as a tool for recording bed occupancy and for modelling bed utilisation.
3. Comparison between similar UK and US cohorts highlights striking differences in delivery of care and outcome that merit further investigation.

# CHAPTER 5: Validation of the POMS in adults

## *5.1 Introduction*

This chapter describes the validation of the POMS as a descriptor of Postoperative Morbidity using a clinimetric approach. First inter-observer reliability of the POMS was explored: reliability of a measure is a pre-requisite for validity. Second, the extent to which the nine domains of the POMS represent a single underlying construct was tested to establish whether further development of a score (based on a sum, or weighted sum, of POMS domains) was appropriate. Third, in the absence of a criterion "gold standard", construct validity of the POMS was explored for individuals POMS domains, and the presence or absence of POMS defined morbidity. Testing for construct validity involves the testing of hypotheses relating to the definition of the measure under consideration e.g. patients in groups known to be at greater risk of postoperative complications would have a higher frequency of POMS defined morbidity; patients with POMS defined morbidity would be expected to stay in hospital longer than those without. Finally the results of this validation analysis are discussed along with the implications of these findings.

## *5.2 Methods*

### 5.2.1 Overview

Recruitment of the validation cohort and data collection methods are described in detail in Chapter 4 along with patient characteristics and a quantitative description of the patterns of morbidity. In this chapter I report the acceptability to patients of the data collection process, reliability of the collected data, and the validity of the Postoperative Morbidity Survey as a descriptor of morbidity following major surgery.

### 5.2.2 Acceptability

No formal approach to assessing acceptability to patients was undertaken. Both research nurses noted acceptability of the POMS to patients separately.

### 5.2.3 Reliability

Thirty-four patients were administered the POMS by both research nurses to assess inter-rater reliability. Inter-rater reliability was analysed using the Kappa coefficient of agreement [325].

### 5.2.4 Scaling properties

In order to establish whether or not it was acceptable to evaluate a Post-Operative Morbidity Score derived from the POMS (by summing the POMS domains) the internal consistency of the POMS domains was explored using the Kuder-Richardson formula 20 (KR20) [202]. This test examines the extent to which the nine POMS domains measure a single unidimensional underlying construct (internal consistency) by covariance. Internal consistency was evaluated on POD 3, 5, 8 and 15. A criterion of 0.7 was accepted as indicating adequate internal consistency for further development of a score [325].

### 5.2.5 Validity: Construct validity

The predictive validity of POMS was explored first on a univariate basis using t-tests to compare the mean subsequent length of stay of patients with and without POMS-defined morbidity. A multivariate linear regression analysis was then performed to determine the independent predictive strength of each POMS domain: the raw differences in length of stay, between patients with and without morbidity on each POMS domain, were adjusted to take account of morbidity in other domains.

To test 'known-groups' construct validity the extent to which POMS domain frequencies were higher in patients with a greater risk of post-operative morbidity was examined: patients with preoperative ASA-PS score I and II were compared with patients with ASA-PS scores III and IV using chi-squared tests. Chi-square tests were also used to compare POMS domain frequencies in patients with < 50% risk of post-operative morbidity (as defined by the POSSUM assessment) with those with ≥ 50% risk.

### 5.2.6 Statistical Approach

All p values are 2-sided and p values lower than 0.05 were considered statistically significant. Stata/IC software (Release 10.0) [StataCorp, TX, USA] was used for all calculations.

## *5.3 Results*

### 5.3.1 Summary of findings

Within the limits of the available data the POMS was found to be acceptable to patients and reliable. The scaling properties of the POMS (internal consistency) precluded further development of a "POMS score". The POMS was found to be a valid measure of postoperative morbidity based on hypothesis testing of "known-groups" differences and the association of POMS defined morbidity with subsequent length of hospital stay (predictive validity). All results are presented for POD5 followed by a comparison with PODs 3, 8 and 15. At POD5 recorded morbidity was considered likely to be "real" rather than due to "routine" care (which may occur at earlier measurement points). However, on POD 5 a majority of patients remain in hospital with morbidity (in the validation cohort) resulting in optimal statistical power to discriminate between "known groups".

### 5.3.2 Acceptability

Acceptability to patients was subjectively reported by the research nurses to be good. Specifically they commented that that there was little or no dissatisfaction among patients during POMS administration and that the patients appreciated their visits and used them as an opportunity to talk about problems and concerns.

### 5.3.3 Reliability

Inter-rater agreement for 11 items was perfect (Kappa = 1.0), with Kappa = 0.94 for six further items. Agreement was slightly lower on one item (assessment of nausea, vomiting or abdominal distension; Kappa = 0.71) and a more precise definition, which included the prescription of anti-emetics as a criterion, was subsequently adopted.

### 5.3.4 Scaling properties – internal consistency

The internal consistency values of the nine POMS domains (KR20) for PODs 3, 5, 8 and 15 are presented in Tables 30-33. KR20 coefficients for POD 3, 5, 8, and 15

were 0.60, 0.56, 0.49, and 0.54 respectively. Accepted minimum standards for internal consistency (0.7) [325] were not met on any of these PODs. This indicates an insufficient level of homogeneity among the nine POMS domains to regard the survey as a scale addressing a unified underlying construct. Given this lack of unidimensionality, the nine POMS domains were treated separately in subsequent statistical analyses. In addition the dichotomous variable of "POMS defined morbidity" was defined by the criterion that morbidity occurring in at least one POMS domain, and analysed separately from the POMS domains.

### 5.3.5 Validity

#### *5.3.5.1 Construct validity*

Across all nine POMS domains, patients with morbidity on POD5 had a longer subsequent mean length of stay than those without morbidity (Table 35). In four domains (pulmonary, infection, gastrointestinal and pain) these differences were statistically significant. The largest domain-specific difference was between patients with and without pain-related morbidity (21.1 versus 7.6 days) and the smallest was for wound-related morbidity (10.3 versus 9.2 days). When taking account of morbidity in other domains using multivariate linear regression the only statistically significant independent predictors of length of stay were gastrointestinal and pain-related morbidity. On POD 5, patients with renal morbidity tended to have a shorter adjusted subsequent length of stay than those without.

Consistent with POD5, on PODs 3 (Table 34), 8 (Table 36), and 15 (Table 37), patients with morbidity had a longer subsequent mean length of stay than those without morbidity, except for two domains (wound, haematological) at POD8 and one domain (haematological) at POD15. These differences were statistically significant for four domains (pulmonary, infection, gastrointestinal, pain) on all PODs, and for one additional domain (renal) on only PODs 8 and 15. The largest domain specific differences were for neurological morbidity (18.4 versus 10.4 days) on POD3, and pain-related morbidity on POD8 (28.2 versus 7.9 days) and POD15 (44.7 versus 9.8 days). However, in the multivariate analysis the following domains tended to have a shorter adjusted subsequent length of stay when morbidity was present (haematological and renal on POD 3, haematological and

wound on POD 8, and renal, cardiovascular, haematological and wound on POD 15).

Comparing patients with and without POMS defined morbidity (all domains), patients with morbidity had a longer subsequent mean length of stay on POD3 (12.2 vs. 5.7 days), POD5 (12.6 vs. 4.7 days), POD8 (14.0 vs. 4.7 days and POD15 (17.1 vs. 5.1 days) ($p<0.001$ in all cases).

Patients in higher preoperative risk categories (ASA-PS scores III/IV and those with ≥ 50% risk of post-operative morbidity as defined by POSSUM) tended to have greater POMS-defined morbidity on POD 5 (Table 39) for all domains except 'wound'. The POMS tended to discriminate more clearly between patients in lower and higher POSSUM risk categories, than between those in lower and higher ASA-PS score category.

On POD 3 a similar pattern was observed, the exception being that 'haematological' morbidity occurred less frequently in the high-risk (ASA defined) category when compared with the low-risk (Table 38). However, several domains had a lower level of morbidity in the high-risk compared with low-risk (POSSUM defined) category on POD 8 (infection, cardiovascular, haematological, wound)(Table 40) and POD 15 (pulmonary, infection, renal, heamatological, wound, pain)(Table 41). Similarly several domains had a lower level of morbidity in the high-risk compared with low-risk (ASA defined) category on POD 8 (haematological wound, pain) and POD 15 (infection, gastrointestinal, cardiovascular).

Only one comparison reached statistical significance when the differences between POMS-defined morbidity levels of patients with low and high-risk ASA-PS scores on POD 5 were compared: patients with ASA-PS scores I or II had a lower risk of infection morbidity than patients with ASA-PS scores III or IV. In contrast, the same comparisons for patients with low versus high-risk of POSSUM-defined post-operative morbidity showed significantly higher levels of POMS-defined morbidity in the high-risk group for all but the neurological and wound domains.

On POD 3 pulmonary, infection and pain-related morbidity were significantly more common in high-risk (ASA defined) than low-risk patients whilst pulmonary, infection, renal, gastrointestinal and pain–related morbidity were significantly more common when POSSUM morbidity risk was the criterion used to define risk category. On PODs 8 and 15 there were no significant differences between low-risk and high-risk patients (ASA defined) whereas when risk was defined by POSSUM morbidity risk category, gastrointestinal and renal morbidity occurred significantly more frequently in high-risk patients on POD 8 and gastrointestinal morbidity was significantly more common on POD 15.

POMS defined morbidity (all domains) occurred significantly more frequently in high-risk (POSSUM defined) compared with low-risk patients on POD 3 (96.1% versus 69.4%), POD 5 (82.9% versus 46.3%), POD 8 (55.3% versus 26.5%) and POD15 (43.3% versus 10.2%)($p < 0.001$ in all cases). However patients in the high-risk category (ASA defined) had a significantly greater frequency of POMS defined morbidity (all domains) than low-risk patients only on POD 3 (87.3% versus 69.9%, $p = 0.002$) and POD 5 (62.8% versus 50.0%, $p = 0.027$). On POD 8 (38.2% versus 29.5%) and POD 15 (20.6% versus 14.8%) this difference did not reach statistical significance.

**Table 30:** Middlesex postoperative morbidity study (UK cohort) (n=439). Kuder-Richardson coefficient of reliability (KR-20) for the 9 domains of the POMS on postoperative day 3 (433 patients remaining in hospital on Day 3).

| Item | Observations | Item Difficulty | Item Variance | Item-rest Correlation |
|---|---|---|---|---|
| Pulmonary | 433 | 0.3788 | 0.2353 | 0.5012 |
| Infection | 433 | 0.3464 | 0.2264 | 0.2800 |
| Renal | 433 | 0.3187 | 0.2171 | 0.3755 |
| Gastrointestinal | 433 | 0.4065 | 0.2413 | 0.3464 |
| Cardiovascular | 433 | 0.0139 | 0.0137 | 0.0757 |
| Neurological | 433 | 0.0185 | 0.0181 | 0.0988 |
| Wound | 433 | 0.0115 | 0.0114 | -0.0233 |
| Haematological | 433 | 0.0762 | 0.0704 | 0.1566 |
| Pain | 433 | 0.3972 | 0.2394 | 0.5117 |
| **TEST** | | **0.2186** | | **0.2581** |

**The KR20 coefficient for the 9 domains of the POMS on Day 3 was 0.5995**

**Table 31:** Middlesex postoperative morbidity study (UK cohort) (n=439). Kuder-Richardson coefficient of reliability (KR-20) for the 9 POMS domains on postoperative day 5 (407 patients remaining in hospital on Day 5).

| Item | Observations | Item Difficulty | Item Variance | Item-rest Correlation |
|---|---|---|---|---|
| Pulmonary | 407 | 0.1278 | 0.1114 | 0.4537 |
| Infection | 407 | 0.2678 | 0.1961 | 0.2552 |
| Renal | 407 | 0.1523 | 0.1291 | 0.3689 |
| Gastrointestinal | 407 | 0.3243 | 0.2191 | 0.3446 |
| Cardiovascular | 407 | 0.0221 | 0.0216 | 0.2164 |
| Neurological | 407 | 0.0098 | 0.0097 | 0.1486 |
| Wound | 407 | 0.0442 | 0.0423 | -0.0350 |
| Haematological | 407 | 0.0246 | 0.0240 | 0.1287 |
| Pain | 407 | 0.1155 | 0.1021 | 0.4203 |
| **TEST** | | **0.1209** | | **0.2557** |

**The KR20 coefficient for the 9 domains of the POMS on Day 5 was 0.5610.**

**Table 32:** Middlesex postoperative morbidity study (UK cohort) (n=439). Kuder-Richardson coefficient of reliability (KR-20) for the 9 POMS domains on postoperative day 8 (299 patients remaining in hospital on Day 8).

| Item | Observations | Item Difficulty | Item Variance | Item-rest Correlation |
|---|---|---|---|---|
| Pulmonary | 299 | 0.0803 | 0.0738 | 0.3591 |
| Infection | 299 | 0.2274 | 0.1757 | 0.3608 |
| Renal | 299 | 0.0635 | 0.0595 | 0.3360 |
| Gastrointestinal | 299 | 0.2274 | 0.1757 | 0.2344 |
| Cardiovascular | 299 | 0.0067 | 0.0066 | 0.0183 |
| Neurological | 299 | 0.0100 | 0.0099 | 0.0545 |
| Wound | 299 | 0.0870 | 0.0794 | -0.0312 |
| Haematological | 299 | 0.0134 | 0.0132 | 0.1950 |
| Pain | 299 | 0.0535 | 0.0506 | 0.4123 |
| **TEST** | | **0.0855** | | **0.2155** |

**The KR20 coefficient for the 9 domains of the POMS on Day 8 was 0.4915.**

**Table 33:** Middlesex postoperative morbidity study (UK cohort) (n=439). Kuder-Richardson coefficient of reliability (KR-20) for the 9 POMS domains on postoperative day 15 (111 patients remaining in hospital on Day 15).

| Item | Observations | Item Difficulty | Item Variance | Item-rest Correlation |
|---|---|---|---|---|
| Pulmonary | 111 | 0.1261 | 0.1102 | 0.3688 |
| Infection | 111 | 0.3784 | 0.2352 | 0.2990 |
| Renal | 111 | 0.0721 | 0.0669 | 0.4504 |
| Gastrointestinal | 111 | 0.3063 | 0.2125 | 0.2803 |
| Cardiovascular | 111 | 0.0090 | 0.0089 | 0.2214 |
| Neurological | - | - | - | - |
| Wound | 111 | 0.1441 | 0.1234 | 0.1846 |
| Haematological | 111 | 0.0090 | 0.0089 | -0.0088 |
| Pain | 111 | 0.0811 | 0.0745 | 0.3027 |
| **TEST** | | **0.1408** | | **0.2623** |

**The KR20 coefficient for the 8 (of 9 in total) domains of the POMS where morbidity was identified on Day 15 was 0.5433**

**Table 34** Middlesex postoperative morbidity study (UK cohort) (n=439). Remaining length of stay (days) in patients with and without POMS-defined morbidity on postoperative day three.

| Morbidity type | With morbidity | | Without morbidity | | | Independent predictive strength of each POMS domain based on multivariate regression analysis | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | P | Adjusted difference in length of stay (days) beyond Postop day 3 | P | 95% CI |
| Pulmonary | 269 | 13.8 | 164 | 8.6 | **<0.001** | 2.7 | 0.065 | -0.2 to 5.7 |
| Infection | 283 | 12.7 | 150 | 9.5 | **0.014** | 1.7 | 0.189 | -0.9 to 4.3 |
| Renal | 295 | 12.3 | 138 | 9.8 | 0.051 | -0.1 | 0.949 | -2.9 to 2.7 |
| Gastrointestinal | 257 | 13.4 | 176 | 8.6 | **<0.001** | 2.7 | **0.043** | 0.1 to 5.3 |
| Cardiovascular | 427 | 16.2 | 6 | 10.5 | 0.281 | 3.8 | 0.467 | -6.4 to 14.0 |
| Neurological | 425 | 18.4 | 8 | 10.4 | 0.082 | 5.3 | 0.238 | -3.5 to 14.2 |
| Wound | 428 | 12.2 | 5 | 10.6 | 0.776 | 2.0 | 0.715 | -9.0 to 13.1 |
| Haematological | 400 | 10.7 | 33 | 10.6 | 0.968 | -1.9 | 0.062 | -6.4 to 2.6 |
| Pain | 261 | 13.8 | 172 | 8.5 | **<0.001** | 2.7 | **< 0.001** | -0.1 to 5.6 |

**Table 35:** Middlesex postoperative morbidity study (UK cohort) (n=439). Remaining length of stay (days) in patients with and without POMS-defined morbidity on postoperative day five.

| **Morbidity type** | **With morbidity** | | **Without morbidity** | | | **Independent predictive strength of each POMS domain based on multivariate regression analysis** | | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **N** | **Mean** | **P** | **Adjusted difference in length of stay (days) beyond postop day 5** | **P** | **95% CI** |
| Pulmonary | 52 | 16.3 | 355 | 8.2 | **<0.001** | 1.7 | 0.43 | -2.5 to 5.8 |
| Infection | 109 | 12.4 | 298 | 8.0 | **0.002** | 2.5 | 0.07 | -0.2 to 5.3 |
| Renal | 62 | 12.1 | 345 | 8.7 | 0.056 | -1.8 | 0.31 | -5.4 to 1.7 |
| Gastrointestinal | 132 | 14.1 | 275 | 6.9 | **<0.001** | 4.3 | **0.002** | 1.6 to 7.1 |
| Cardiovascular | 9 | 15.4 | 398 | 9.1 | 0.143 | 0.1 | 0.98 | -8.7 to 8.9 |
| Neurological | 4 | 18.0 | 403 | 9.1 | 0.172 | 5.4 | 0.40 | -7.3 to 18.0 |
| Wound | 18 | 10.3 | 389 | 9.2 | 0.719 | 2.6 | 0.37 | -3.1 to 8.4 |
| Haematological | 10 | 14.9 | 397 | 9.1 | 0.159 | 3.4 | 0.39 | -4.4 to 11.2 |
| Pain | 47 | 21.1 | 360 | 7.6 | **<0.001** | 10.6 | **< 0.001** | 6.4 to 14.9 |

**Table 36:** Middlesex postoperative morbidity study (UK cohort) (n=439). Remaining length of stay (days) in patients with and without POMS-defined morbidity on postoperative day eight.

| **Morbidity type** | **With morbidity** | | **Without morbidity** | | | **Independent predictive strength of each POMS domain based on multivariate regression analysis** | | |
|---|---|---|---|---|---|---|---|---|
| | **N** | **Mean** | **N** | **Mean** | **P** | **Adjusted difference in length of stay (days) beyond Postop day 8** | **P** | **95% CI** |
| Pulmonary | 275 | 17.8 | 24 | 8.2 | **0.001** | 2.3 | 0.478 | -4.0 to 8.6 |
| Infection | 231 | 14.0 | 68 | 7.6 | **<0.001** | 3.9 | **0.044** | 0.1 to 7.8 |
| Renal | 280 | 16.9 | 19 | 8.5 | **0.011** | 0.1 | 0.978 | -6.5 to 6.7 |
| Gastrointestinal | 231 | 17.7 | 68 | 6.5 | **<0.001** | 7.8 | **<0.001** | 4.1 to 11.6 |
| Cardiovascular | 297 | 15.0 | 2 | 9.0 | 0.547 | 6.3 | 0.494 | -11.9 to 24.5 |
| Neurological | 296 | 17.7 | 3 | 8.9 | 0.285 | 8.7 | 0.251 | -6.2 to 23.5 |
| Wound | 273 | 7.0 | 26 | 9.2 | 0.455 | -1.6 | 0.562 | -6.9 to 3.8 |
| Haematological | 295 | 6.6 | 4 | 9.0 | 0.747 | -12.6 | 0.067 | -26.1 to 0.9 |
| Pain | 283 | 28.2 | 16 | 7.9 | **<0.001** | 14.3 | **<0.001** | 6.7 to 22.0 |

**Table 37:** Middlesex postoperative morbidity study (UK cohort) (n=439). Remaining length of stay (days) in patients with and without POMS-defined morbidity on postoperative day fifteen.

| Morbidity type | With morbidity | | Without morbidity | | | Independent predictive strength of each POMS domain based on multivariate regression analysis | | |
|---|---|---|---|---|---|---|---|---|
| | N | Mean | N | Mean | P | Adjusted difference in length of stay (days) beyond Postop day 15 | P | 95% CI |
| Pulmonary | 97 | 32.9 | 14 | 9.8 | **<0.001** | 11.9 | **0.019** | 2.0 to 21.8 |
| Infection | 69 | 19.0 | 42 | 8.8 | **0.004** | 8.4 | **0.009** | 2.1 to 14.8 |
| Renal | 103 | 25.5 | 8 | 11.7 | **0.043** | -2.1 | 0.743 | -14.9 to 10.6 |
| Gastrointestinal | 77 | 22.3 | 34 | 8.4 | **<0.001** | 7.3 | **0.032** | 0.7 to 14.0 |
| Cardiovascular | 110 | 27.0 | 1 | 12.5 | NA | -3.2 | 0.850 | -36.2 to 29.9 |
| Neurological | 111 | NA | 0 | 12.7 | NA | NA | NA | NA |
| Wound | 95 | 12.8 | 16 | 12.6 | 0.973 | -4.8 | 0.254 | -13.2 to 3.5 |
| Haematological | 110 | 5.0 | 1 | 12.7 | NA | -8.0 | 0.600 | -38.4 to 22.3 |
| Pain | 102 | 44.7 | 9 | 9.8 | **<0.001** | 25.5 | **<0.001** | 13.7 to 37.4 |

**Table 38:** Middlesex postoperative morbidity study (UK cohort) (n=439). Rates (%) of POMS-defined morbidity on postoperative day 3 in patients with different ASA-PS score categories* and in different POSSUM-defined morbidity risk categories.

| **Morbidity type** | **ASA-PS score category** | | | **POSSUM risk category** | | |
|---|---|---|---|---|---|---|
| | **I/II (n = 327)** | **III/IV (n = 101)** | **P** | **< 50% (N = 358)** | **≥ 50% (N = 75)** | **P** |
| Pulmonary | 34.6 | 49.5 | **0.018** | 32.7 | 62.7 | **0.000** |
| Infection | 30.3 | 47.5 | **0.003** | 31.6 | 49.3 | **0.003** |
| Renal | 29.7 | 38.6 | 0.223 | 29.1 | 45.3 | **0.006** |
| Gastrointestinal | 40.7 | 42.6 | 0.167 | 33.0 | 77.3 | **0.000** |
| Cardiovascular | 1.2 | 2.0 | 0.821 | 1.1 | 2.7 | 0.297 |
| Neurological | 1.8 | 2.0 | 0.949 | 1.7 | 2.7 | 0.562 |
| Haematological | 7.7 | 6.9 | 0.561 | 7.5 | 8.0 | 0.892 |
| Wound | 1.5 | 0.0 | 0.440 | 1.4 | 0.0 | 0.303 |
| Pain | 35.8 | 54.5 | **0.001** | 34.6 | 64.0 | **0.000** |

*Based on 428 of 434 POD 3 in-patients where pre-operative ASA-PS score was known.

**Table 39:** Middlesex postoperative morbidity study (UK cohort) (n=439). Rates (%) of POMS-defined morbidity on postoperative day 5 in patients with different ASA-PS score categories* and in different POSSUM-defined morbidity risk categories.

| **Morbidity type** | **ASA-PS score category** | | | **POSSUM risk category** | | |
|---|---|---|---|---|---|---|
| | **I/II (n = 305)** | **III/IV (n = 98)** | **P** | **< 50% (N = 333)** | **≥ 50% (N = 74)** | **P** |
| Pulmonary | 11.2 | 18.4 | 0.131 | 10.8 | 21.6 | **0.012** |
| Infection | 22.6 | 39.8 | **0.004** | 24.6 | 36.5 | **0.037** |
| Renal | 13.8 | 20.4 | 0.196 | 12.3 | 28.4 | **0.001** |
| Gastrointestinal | 32.1 | 34.7 | 0.339 | 26.4 | 59.5 | **0.000** |
| Cardiovascular | 1.6 | 4.1 | 0.343 | 1.2 | 6.8 | **0.003** |
| Neurological | 1.0 | 1.0 | 0.980 | 0.6 | 2.7 | 0.097 |
| Haematological | 2.3 | 3.1 | 0.868 | 1.5 | 6.8 | **0.008** |
| Wound | 4.9 | 3.1 | 0.673 | 4.8 | 2.7 | 0.426 |
| Pain | 10.8 | 14.3 | 0.497 | 8.1 | 27.0 | **0.000** |

*Based on 403 of 407 POD 5 in-patients where pre-operative ASA-PS score was known.

**Table 40:** Middlesex postoperative morbidity study (UK cohort) (n=439). Rates (%) of POMS-defined morbidity on postoperative day 8 in patients with different ASA-PS score categories* and in different POSSUM-defined morbidity risk categories.

| **Morbidity type** | **ASA-PS score category** | | | **POSSUM risk category** | | |
|---|---|---|---|---|---|---|
| | **I/II (n = 219)** | **III/IV (n = 77)** | **P** | **< 50% (N = 227)** | **≥ 50% (N = 72)** | **P** |
| Pulmonary | 7.3 | 10.4 | 0.607 | 7.5 | 9.7 | 0.543 |
| Infection | 21.9 | 24.7 | 0.803 | 22.9 | 22.2 | 0.904 |
| Renal | 5.5 | 9.1 | 0.483 | 4.4 | 12.5 | **0.014** |
| Gastrointestinal | 22.8 | 23.4 | 0.637 | 15.9 | 44.4 | **0.000** |
| Cardiovascular | 0.5 | 1.3 | 0.730 | 0.9 | 0.0 | 0.424 |
| Neurological | 0.5 | 2.6 | 0.265 | 0.9 | 1.4 | 0.706 |
| Haematological | 1.8 | 0.0 | 0.477 | 1.8 | 0.0 | 0.257 |
| Wound | 9.1 | 7.8 | 0.812 | 10.1 | 4.2 | 0.118 |
| Pain | 5.5 | 5.2 | 0.914 | 4.0 | 9.7 | 0.059 |

*Based on 296 of 299 POD 8 in-patients where pre-operative ASA-PS score was known.

**Table 41:** Middlesex postoperative morbidity study (UK cohort) (n=439). Rates (%) of POMS-defined morbidity on postoperative day 15 in patients with different ASA-PS score categories* and in different POSSUM-defined morbidity risk categories.

| **Morbidity type** | **ASA-PS score category** | | | **POSSUM risk category** | | |
|---|---|---|---|---|---|---|
| | **I/II (n = 79)** | **III/IV (n = 32)** | **P** | **< 50% (N = 66)** | **≥ 50% (N = 45)** | **P** |
| Pulmonary | 8.9 | 21.9 | 0.061 | 13.6 | 11.1 | 0.694 |
| Infection | 36.7 | 40.6 | 0.700 | 42.4 | 31.1 | 0.228 |
| Renal | 5.1 | 12.5 | 0.170 | 7.6 | 6.7 | 0.856 |
| Gastrointestinal | 35.4 | 18.8 | 0.084 | 21.2 | 44.4 | **0.009** |
| Cardiovascular | 1.3 | 0.0 | 0.523 | 0.0 | 2.2 | 0.224 |
| Neurological | 0.0 | 0.0 | NA | 0.0 | 0.0 | NA |
| Haematological | 0.0 | 3.1 | 0.114 | 1.5 | 0.0 | 0.407 |
| Wound | 13.9 | 15.6 | 0.817 | 15.2 | 13.3 | 0.789 |
| Pain | 6.3 | 12.5 | 0.281 | 9.1 | 6.7 | 0.646 |

*Based on 111 of 111 POD 15 in-patients where pre-operative ASA-PS score was known.

## *5.4 Discussion*

### 5.4.1 Acceptability

In this study the POMS had good acceptability to patients. However this aspect of POMS performance was not formally assessed, but based on the subjective views of the research nurses involved in data collection. Consequently the potential for observer bias limits the significance that can be attached to this result, and further investigation in a separate study may be appropriate.

### 5.4.2 Reliability

The POMS had good inter-rater reliability. According to the subjectively derived classification of Landis and Koch [326] all domains except gastrointestinal achieved perfect or "almost perfect agreement". The gastrointestinal domain achieved "substantial agreement" before the adoption of a more precise definition that included an additional criterion (prescription of anti-emetics as an inclusion criterion for nausea) after which agreement was perfect (1.0). This data is from senior research nurses with long experience (> 5 years) of handling study data and more than a year's experience of collecting POMS data (and working together as part of a team). The reliability of the POMS when recorded by less experienced data collectors in different settings may not reach the levels measured in this sample. The use of standard operating procedures describing the procedure and criteria for collecting POMS along with periodic testing of reliability on sample subpopulations is likely to result in higher quality data.

### 5.4.3 Internal consistency

The low level of internal consistency amongst the POMS domains argues against the concept that there is a single underlying construct that is being measured by the POMS. In addition this lack of homogeneity indicates that the POMS does not have the scaling properties necessary to generate a total score that could be used as an index of overall morbidity and therefore does not support the development of a scale derived by summing different domains, as if they were all measuring elements of the same underlying construct. Consequently, subsequent validation focuses on the validity of the individual domains and of the overall presence or

absence of morbidity (defined as present if morbidity is present in one or more domain) as measures of postoperative morbidity.

### 5.4.4 Validity

#### *5.4.4.1 Criterion validity*

There is no criterion "gold standard" with which to compare the POMS as a tool for identifying postoperative morbidity therefore testing of criterion validity is not possible. The absence of a "gold standard" along with the lack of evidence of a measurable underlying construct defined by the POMS raises two questions. Does morbidity exist as a concept that can be defined and measured? Is there any value in measuring an indefinable variable? These questions will be revisited in the final Chapter 6.

#### *5.4.4.2 Face validity*

Face validity (the instrument appears "on the face of it" to be measuring the attributes it claims to be measuring [327]) of the POMS as a composite measurement tool for postoperative morbidity rests on demonstration of its ability to identify clinically relevant postoperative morbidity. There was evidence that POMS captured all clinically relevant morbidity: patients remaining in hospital who did not meet criteria for POMS did not complain of morbidity that had not been captured by the POMS. The reasons given for remaining in hospital were predominantly process related e.g. awaiting equipment at home (see Chapter 4). The exception to this was patients who had problems with mobility. On the basis that these mobility problems were new postoperative occurrences, a case could be made for including mobility as an additional domain within the POMS. Implicit in the use of the POMS is the assumption that patients who have been discharged from hospital do not have morbidity of a severity sufficient to meet POMS criteria. Given the magnitude of morbidity required to meet the domain criteria this seems likely to be true, however this has not been formally explored.

Face validity of the domains is dependent on the credibility of the domain criteria as representative of significant magnitude of morbidity (e.g. parenteral opioids or regional analgesia represent a non-trivial level of pain relief). Face validity of the domains is also supported by the fact that for each domain the criteria are objective and simple to assess.

#### *5.4.4.3 Construct Validity*

*A priori* hypotheses that the POMS would discriminate between patients with different known levels of morbidity risk, and predict length of stay were generally supported through observation of data trends.

Subsequent length of stay tended to be greater in patients with morbidity than those without for all but 3 out of 32 comparisons of POMS domains. These differences were statistically significant for the pulmonary, infection, gastrointestinal, pain domains and for the overall POMS defined morbidity on all PODs. The adjusted subsequent lengths of stay, derived from a multivariate analysis, tended to be shorter in patients with morbidity for 8 of 24 analyses. Patients with gastrointestinal and pain morbidity had significantly longer subsequent length of stay on all PODs. These findings are consistent with the hypothesis that patients with POMS defined morbidity would be expected to stay in hospital longer than those without, and this 'predictive validity' supports construct validity of the POMS.

For 'known groups' comparisons where patients were categorised to be at higher and lower risk of postoperative complications (morbidity) by ASA-PS scores or by POSSUM morbidity risk prediction the results were less consistent. On PODs 3 and 5, patients categorised at higher risk where more likely to have morbidity in almost all cases and this association was stronger (statistically significant for more domains) with POSSUM than with ASA-PS score. However on PODs 8 and 15 several domains had a lower frequency of morbidity in the higher risk category whichever criterion was used to define risk. The only significant differences were an increased frequency in the high POSSUM morbidity risk category of renal and gastrointestinal morbidity on POD 8 and of gastrointestinal morbidity on POD 15. These findings are broadly supportive of the hypothesis that patients in groups known to be at greater risk of postoperative complications would have a higher frequency of POMS defined morbidity. However, the results on POD 8 and 15 are inconsistent and in some cases contradictory of this hypothesis and these data merit explanation if construct validity is claimed.

Three factors that may be responsible for these data are the heterogeneity of surgical type in this cohort, the known limitation of the ASA-PS score with respect to discrimination between moderate levels of risk, and the high number of patients remaining in hospital with no POMS defined morbidity.

Three distinct types of surgery were represented in the validation cohort (orthopaedic, general, urological). Patterns of postoperative morbidity vary between these types of operation (see Chapter 4) reflecting both the underlying disease process and surgical insult. Distributions of risk descriptors also vary between these different types of surgery (See Figure 22). Differences in POSSUM defined risk are mainly due to variation in Operative Severity Score rather than the Physiological Score (see Figure 23). This variation is a potential confounder in the relationship between morbidity domain frequencies (in a heterogeneous cohort) and risk category or subsequent length of stay. Furthermore, the frequency of the less common categories of morbidity (e.g. wound, cardiovascular, neurological, haematological) at PODs 8 and 15 are very low and non-significant differences should be interpreted with caution. For this reason I did not explore surgical specialty subgroups further in this cohort. In a larger cohort with large homogeneous subgroups more valid results might be obtained.
The ASA-PS score divides risk into a limited number of categories whereas the POSSUM regression analysis provides a continuous spectrum of expected morbidity. In this cohort only 2 of 439 patients were classified ASA-PS score 4, with the result that the ASA-PS score distribution effectively had only three categories. The threshold between low and high risk for ASA-PS score category in this study was between 2 and 3. It is well documented that attribution to ASA-PS scores between these two categories is unreliable [328,329]. Consequently the known limitations of the ASA-PS score (low precision discriminator of risk with lack of reliable attribution between ASA-PS scores II and III) are likely to be contributing to the weaker association between ASA-PS scores and POMS domains frequencies than those that occur with POSSUM predicted morbidity risk, which is not thought to exhibit these weaknesses. Whilst the reliability of POSSUM has not been formally tested, the objective nature of many of the criteria (e.g. laboratory measured values) suggests that reliability may be superior to the ASA-PS.

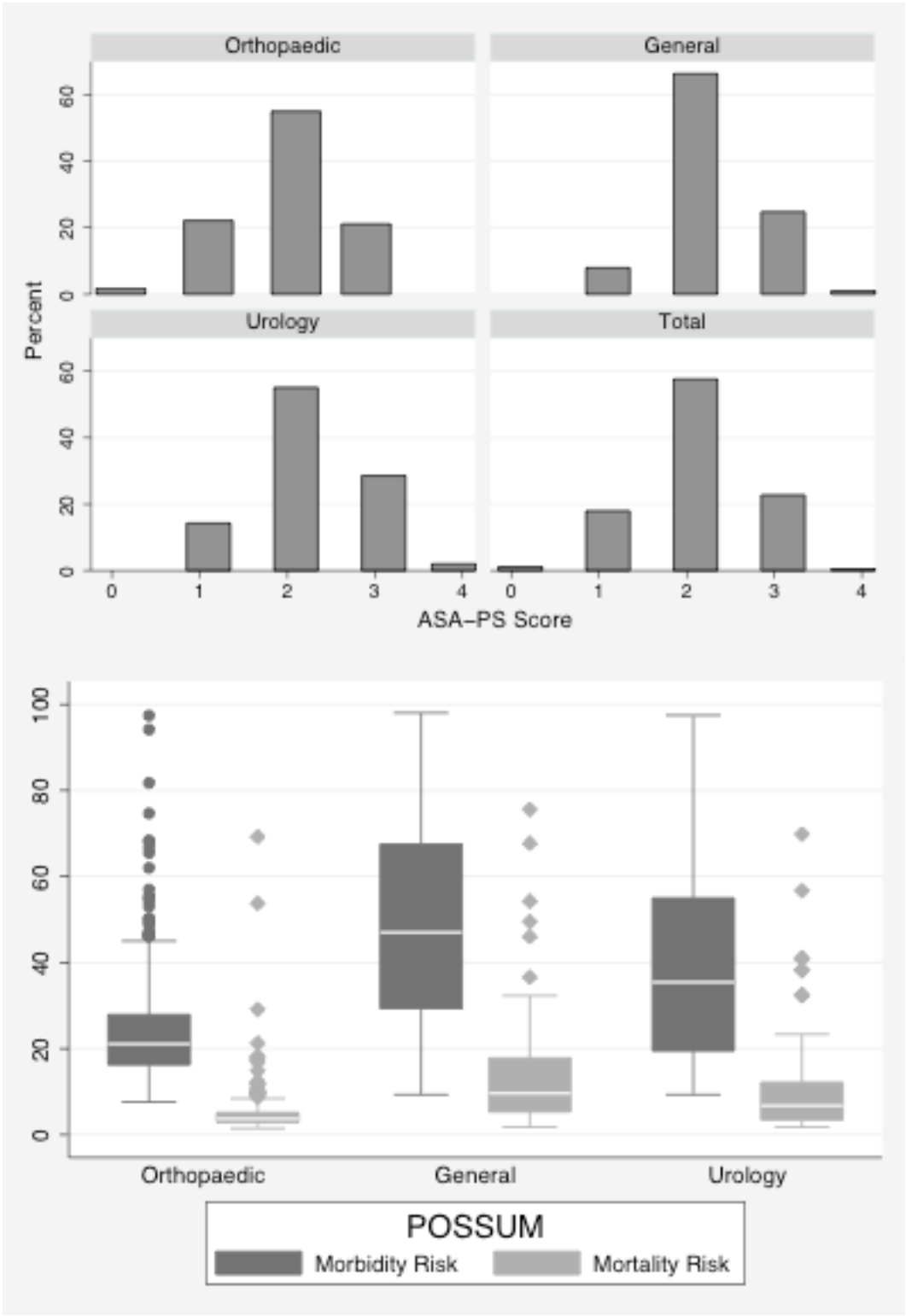



**Figure 22** Distribution of ASA-PS Score and POSSUM Morbidity and Mortality Risk by Surgical Specialty in the Middlesex postoperative morbidity study (n=438).

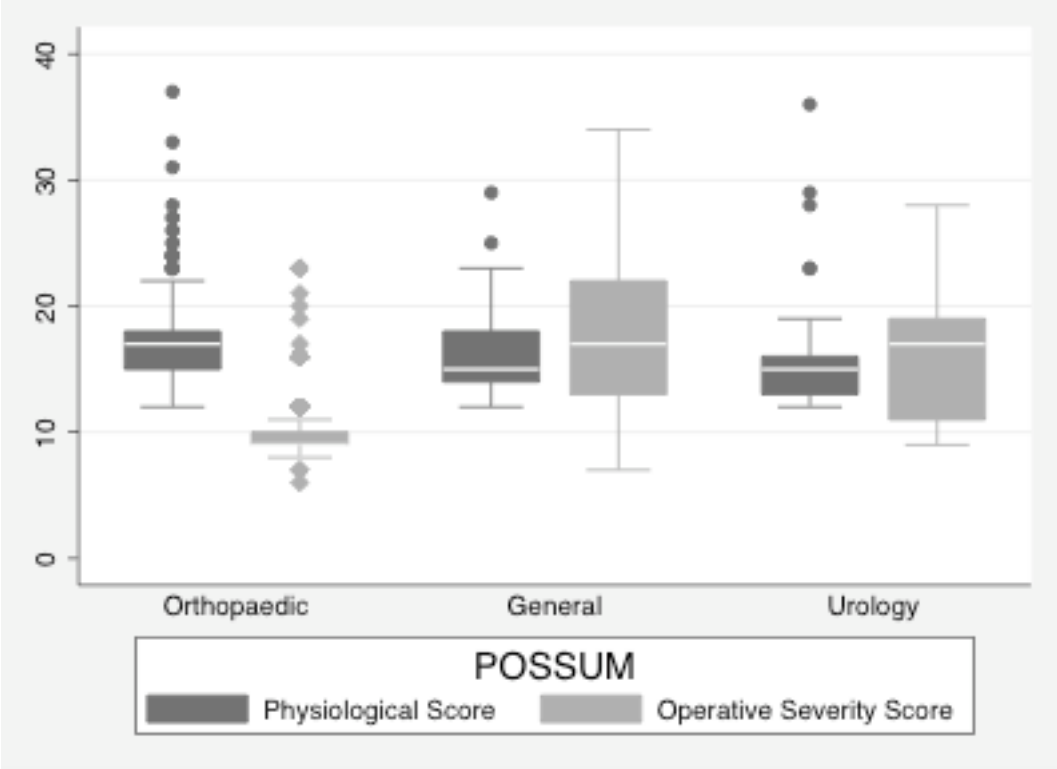



**Figure 23** Distribution of POSSUM Physiological and Operative Severity Scores by Surgical Specialty in the Middlesex postoperative morbidity study (n=438).

### 5.4.5 POMS domain criteria

The definitions of morbidity used for each domain of the POMS will influence measured prevalence of morbidity types. For example if the definition of pain were altered to include taking oral analgesics the measured frequency of pain would be much higher. Additionally for some domains there may be threshold effects whereby morbidity significant to a patient is not recorded (e.g. blood loss resulting in anaemia and fatigue, but not meeting transfusion triggers). However the finding that patients in hospital without morbidity as defined by the POMS were not there because of unrecorded morbidity supports the notion that the POMS records morbidity significant to patients and clinicians. A tool more sensitive for lower levels of morbidity (e.g. mild headache or mild exercise limitation) would be a poor discriminator of postoperative outcome following major surgery.

The definitions within individual domains record phenomena which may be pathophysiologically related. There is therefore the potential for redundancy between domains. For example an acute myocardial infarction might be recorded under pain (parenteral opiate prescription), cardiovascular (tests for ischaemia), pulmonary (supplemental oxygen) and infection domains (fever) domains. Pathophysiological interactions might also result in interactions between domains. For example the pain and gastrointestinal domains might be associated due to the effects of parenteral opiates on gastrointestinal function leading to inability to tolerate enteral diet.

Limitations of the domain criteria are that in some cases they are dependent on administered treatment, that they are composed of variety of different types of data and that the binary nature of the domains (presence or absence of morbidity) might result in threshold effects whereby significant morbidity would go unrecorded. These limitations are discussed below.

The definitions used in POMS may be criticized as being too dependent on administered treatment: routine prophylactic interventions might be confused with 'true' morbidity. This is particularly true in the first three days after certain types of elective surgery, where, for example, there may be routine use of pain

medication, urinary catheter, antibiotics, and respiratory support and in some cases withholding of oral nutrition. However, the routine use of these treatments should be rare beyond the first three post-operative days and morbidity identified subsequently should be 'true' morbidity. The recent development of "fast-track" or "enhanced recovery" care packages following major surgery, particularly for patients undergoing colorectal surgery [330], will tend to reduce the duration of time following surgery when any of the interventions used as criteria for POMS domains might be considered routine. This in turn may increase the validity and value of POMS recorded earlier in the postoperative phase (e.g. POD 3). Such changes highlight the fact that variation in clinician practice relating to the context of use of the POMS may confound measurement of "true" morbidity. They also emphasize the importance of using POMS in an environment where "routine" postoperative care is clearly defined in order that morbidity may be operationally defined by deviations from the "routine" (see below).

A distinct but related issue arises because of the use of administered treatment within some of the POMS domain criteria. The effectiveness of the POMS in measuring "postoperative morbidity" rests on the assumption that the institutional settings in which it is used will be competent to recognize and treat morbidity as it arises. Where this assumption is violated, the POMS may produce the paradoxical result that hospitals with lower standards of care record the lowest level of morbidity. For example, a hospital with inappropriately low parenteral opiod prescription could fail to record POMS-defined pain morbidity. It is therefore important that POMS data is always interpreted in the context of an understanding of local post-operative treatment protocols and guidelines.

Many of the POMS definitions include more than one type of data. For example the POMS definition of renal morbidity includes a laboratory finding (increased serum creatinine (>30% from pre operative level)) a treatment (urinary catheter in situ) and a physiological observation (oliguria < 500ml/24hours). However, this is consistent with the clinimetric approach to index development [331] [183]. Strengths of this approach are that face validity is improved and that the POMS has good sensitivity and specificity for significant morbidity requiring hospital care when applied in an environment with a tightly defined discharge policy [172]. Using

observable treatment to define morbidity leads to high inter-rater reliability in combination with acceptable levels of sensitivity and specificity for clinically significant morbidity. Additionally this approach eliminates much of the variation arising from subjective assessment of conditions such as wound infection, pain and respiratory distress.

## *5.5 Summary*

1. The POMS is a reliable and acceptable to patients.
2. The POMS should not be treated in statistical analyses as though it is a unidimensional scale: a POMS score derived by summing POMS domains would not be valid in this context.
3. The POMS is a valid descriptor of short-term post-operative morbidity in major surgical patients. Limitations of the performance of the POMS in this analysis are likely to be related to heterogeneity of type of surgery and the limitations of the measures against which the POMS is being validated.

# Chapter 6: Conclusions and further work

## *6.1 Summary of contents of thesis*

Outcome following surgery is a significant public health issue. Quality of surgical care can be defined in a variety of ways. The distinction between structure, process and outcome is important, as is the perspective of the measurer. In the UK quality has been subdivided into safety, experience and effectiveness.

Risk adjustment of outcome data is essential to minimise confounding by patient and surgical characteristics if effectiveness of care is to be evaluated. Clinically important short-term outcomes following surgery include mortality and morbidity. Duration of hospital stay is commonly used as a surrogate measure of outcome. Description and measurement of morbidity following surgery are inconsistent limiting comparisons of effectiveness of care.

Measurement of an unobservable phenomenom, such as postoperative morbidity, is dependent on measurement of hypothesised manifestations of the phenomenom. Reliability and validity are essential requirements in a clinical measure and are critically dependent on the context of testing. In the case of an unobservable phenomenon such as postoperative morbidity, a criterion measure may not be available in which case testing of construct validity is required.

A systematic review of the efficacy of a specific perioperative haemodynamic management strategy was performed to explore the balance between therapeutic benefit and adverse effects. Whilst mortality and length of hospital stay were reduced in the intervention group, pooling of morbidity data for between-group comparisons was limited by the heterogeneity of morbidity reporting between different studies. Classification, criteria and summation of morbidity outcome variables were inconsistent between studies, precluding analyses of pooled data for most types of morbidity. A similar pattern was observed in a second systematic review of randomised controlled trials of perioperative interventions published in high impact surgical journals.

The Post-operative Morbidity Survey (POMS), a previously published method of describing short-term postoperative morbidity, lacked validation. The POMS was prospectively collected in 439 patients undergoing elective major surgery in a UK teaching hospital. The prevalence and pattern of morbidity was described and compared with data from a similar study using the POMS in a US institution.

The type and severity of surgery was reflected in the frequency and pattern of POMS defined postoperative morbidity. The POMS identified gastrointestinal, infection, pain-related, pulmonary and renal problems as the most common sources of morbidity following major surgery in a UK setting. Many patients remained in hospital despite absence of post-operative morbidity as defined by the POMS. Screening for post-operative morbidity using the POMS may be useful to identify patients remaining in acute hospital beds unnecessarily. The POMS may have utility as a tool for recording bed occupancy and for modelling bed utilisation. Comparison between the similar UK and US cohorts highlighted striking differences in delivery of care and outcome that merit further investigation. In this comparison, patients in the US cohort were less likely to remain in hospital in the absence of POMS defined morbidity and had a lower prevalence of infection morbidity.

The POMS was found to be reliable and acceptable to patients. The POMS should not be treated in statistical analyses as though it is a unidimensional scale: a POMS score derived by summing POMS domains would not be valid in this context. Limitations of the performance of the POMS in this analysis are likely to be related to heterogeneity of type of surgery and the limitations of the measures against which the POMS is being validated. Inter-rater reliability was adequate and a priori hypotheses that the POMS would discriminate between patients with known measures of morbidity risk, and predict length of stay were generally supported through observation of data trends, providing good evidence of construct validity. The POMS was a valid descriptor of short-term post-operative morbidity in major surgical patients.

## *6.2 Outstanding questions*

### 6.2.1 Current literature

Systematic reviews of preoperative risk metrics and of postoperative outcome measures would be valuable.

### 6.2.2 POMS internal validity

Internal validity of the POMS might be improved if POMS domain criteria could be simplified (e.g. cardiovascular) without loss of POMS performance. A simplified version of the POMS might have utility for monitoring morbidity on days when the full POMS is not currently collected. For example, only collecting the most prevalent domains (gastrointestinal, infectious, pain-related, pulmonary) might provide much information at the cost of minimal resource. The possibility of replacing some of the domains with biomarkers (e.g. Brain Natriuritic Peptide as a marker of cardiac injury) may merit exploration.

The assumption that patients discharged from hospital do not have (or develop) clinically significant morbidity merits further investigation. This might be achieved using post-discharge telephone surveys or patient completed scorecards. Investigation of readmission rates and post-discharge medical contact (e.g. general practitioners) may also provide useful information in this area.

Where an "index" measure of morbidity is required, which postoperative day best quantifies "true" morbidity (the optimal balance between patients remaining in hospital and "contamination by routine care") merits investigation in different populations. Changing patterns of care (e.g. introduction of "fast-track" care packages) may cause this to evolve over time.

### 6.2.3 POMS external validity

An important element of future work will be to validate the POMS in other populations (e.g. vascular surgery, cardiac surgery, neurosurgery and paediatric surgery). The distinct patterns of morbidity in some of these settings (e.g. neurosurgery, cardiac surgery) might be expected to require the development of a modified tool specific to this type of surgery. In the paediatric surgical population one might hypothesize that both the pattern of morbidity and the expression of

"unwellness" (e.g. different reasons for not tolerating enteral feeding) might be different to the adult population, necessitating a modified POMS tool.

### 6.2.4 Does perioperative morbidity constitute a syndrome?

Two modes of investigation may contribute to answering this question. First, statistical analysis of extant POMS databases using techniques such as factor analysis may illuminate relationships (e.g. clustering of POMS domains) within the data. Second, measurement of cytokines, both pro-inflammatory (e.g. interleukin-6) and tissue injury markers (e.g. BNP), may contribute to the data supporting the concept of postoperative morbidity being a "mild" variant of MODS resulting from "mild" SIRS.

### 6.2.5 POMS applications

Further exploration of the partial dependence of the POMS on administered care may have value. A study to test the hypothesis that use of the POMS in an environment with more tightly defined and audited management pathways (in particular for the interventions included within the POMS morbidity definitions) might be expected to further improve validity and utility.

#### *6.2.4.1 Quality of care studies*

The POMS may have utility as a tool to explore improvements in bed management efficiency and to evaluate the success of these changes when implemented. Furthermore the POMS may be used to explore determinants of prolonged bed occupancy (e.g. socioeconomic status).

Models incorporating preoperative risk profiles, surgery characteristics and postoperative morbidity assessment could be developed which would predict surgical bed occupancy and be responsive to the level and pattern of morbidity in current in-patients.

#### *6.2.4.2 Prognostic studies*

Further exploration of the relationships between morbidity (POMS) and more acute and more chronic outcomes following surgery may have value. The value of early warning scores in the immediate postoperative period merits further investigation. Similarly, the relationship between POMS and long-term outcome (e.g. function in a replaced joint, mortality) should be explored.

#### *6.2.4.3 Efficacy and Effectiveness studies*

The POMS has potential utility as an outcome measure in RCTs and studies of implementation of novel clinical interventions.

## *6.3 Conlusions*

In clinical practice, the POMS can be envisaged as a component of an integrated system of practice evaluation incorporating tightly defined care pathways and recording of case-mix (risk) adjusters, post-operative morbidity and mortality, resource utilisation (length of hospital stay, cost) and quality of life data. In this context, the POMS may be a useful tool to inform clinical decision-making, resource utilisation, in clinical governance activities and in effectiveness research.

The POMS has great potential as a standard outcome measure in quality of care, prognostic and effectiveness research. As the only validated measure of postoperative morbidity this would permit comparison of both the level and pattern of post-operative morbidity and allows comparison between different studies and different environments (e.g. institutions, countries). Comparing outcomes that occur more frequently (e.g. morbidity rather than mortality) allows smaller studies whilst retaining statistical power to detect significant differences between groups. In addition the POMS permits the relative separation of process and outcome assessment in prognostic and effectiveness research thereby reducing confounding by process related factors.

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# Appendix 1: Published manuscripts arising from this MD thesis

1. Grocott MP, Browne JP, Van der Meulen J et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of Clinical Epidemiology*. 2007;**60**:919-928.

2. Sinha S, Sinha S, Ashby E, Jayaram R, Grocott MP. Quality of reporting in randomized trials published in high-quality surgical journals. *Journal of the American College of Surgeons*. 2009;**209**:565-571.