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Standardizing end points in perioperative trials: towards a core and extended outcome set

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Varied definitions and inconsistent reporting of outcomes across trials investigating similar clinical problems limit the value of this research.[1 2] Such variability also undermines systematic reviews and meta-analyses aiming to synthesize relevant primary research on a particular question.[3 4] Two key issues underpin this problem, namely which outcomes are selected and what criteria are used to define them. For example, even an apparently simple and binary outcome, such as postoperative mortality, may be reported at different time points (commonly in hospital, 28, 30, or 90 days) and using alternative criteria (e.g. 'all-cause mortality' or 'cardiovascular mortality') in different trials. Likewise, inconsistent definitions of organ injury or composite end points (e.g. morbidity or quality-of-life measures) threaten the validity of any pooled analyses.[5] The findings of medical research should

Table 1 Current Standardized Endpoints for Perioperative Medicine (StEP) working groups. MET, medical emergency team; MACE, major adverse cardiac events; IABP, intra-aortic balloon pump; POMS, post-operative morbidity score

Working groups	Proposed end points
Patient comfort *Chair: Paul Myles*	(i) Postoperative nausea and vomiting (ii) Perioperative pain measurement (iii) Quality of recovery scales (iv) Sleep quality/disturbance (v) Perioperative anxiety/stress (vi) Return of bowel function/ileus
Clinical indicators *Chair: Guy Haller*	(i) Perioperative hypothermia (ii) Perioperative iatrogenic injury (nerve injury, postoperative visual loss, pressure sores, dental damage, post-dural puncture headache) (iii) MET/rapid response calls; cardiorespiratory arrest; unplanned intensive care unit admission (iv) Unplanned hospital readmission; discharge destination
Cognition and stroke *Chair: Lis Evered*	(i) Stroke/transient ischaemic attack (including severity) (ii) Postoperative delirium/confusion (iii) Postoperative cognitive decline
Cardiovascular *Chair: Scott Beattie and P. J. Devereaux*	(i) Composite MACE (e.g. cardiovascular death, myocardial infarction, heart failure) (ii) Myocardial injury after non-cardiac surgery (utility of biomarkers) (iii) Arrhythmias (duration/severity/treatment needed) (iv) Venous thromboembolism (v) Hypotension/requirement for circulatory support (e.g. vasoactive drugs, IABP)
Respiratory *Chair: Rupert Pearse*	(i) Pulmonary complications: how defined and classified; consequences
Sepsis *Chair: Mervyn Singer*	(i) Wound infection (surgical site infection) (ii) Bloodstream infection
Renal *Chair: David McIlroy*	(i) Acute kidney injury (ii) Other renal outcomes
Bleeding and transfusion *Chair: Duminda Wijeysundera*	(i) Blood loss (ii) Transfusion requirements
Organ failure and survival *Chair: Michael Grocott*	(i) Mortality measures (cause/time point) (ii) Composite morbidity scales (e.g. POMS/Clavien–Dindo)
Cancer and long-term survival *Chair: Dan Sessler*	(i) Long-term survival (ii) Disease recurrence (local/distant)
Patient-centred outcomes *Chair: Ramani Moonesinghe*	(i) Patient satisfaction (ii) Health-related quality of life (iii) Disability-free survival (iv) Return to work/normal functioning (v) Functional status/mobility/6 min walk test, other (vi) Home days (days alive and out of hospital)
Healthcare resource utilization *Chair: Rob Sneyd*	(i) Length of stay (intensive care unit/hospital) (ii) Health-care costs (iii) Fitness for discharge; delayed discharge

be replicated before they are considered 'true',[2] and clear and consistent measurement criteria are a prerequisite for replication. There is thus a pressing need to standardize end points in perioperative clinical trials and to agree on a core data set that is common to all trials.

Recent efforts to identify outcome measures for anaesthesia and intensive care studies have been helpful,[6–8] but these were not in accord with current guidelines[9] and did not consider the psychometric properties (validity, reliability, utility, and responsiveness) of the proposed outcome measures;[10 11] further work has been recommended.[6 12] Some measurement scales used in the perioperative setting have not undergone sufficient psychometric validation[13] or have not determined the minimal clinically important difference needed to define a meaningful response to treatment.[13 14] Some candidate end points have existing generic or critical care definitions, or both, that may not be applicable in the perioperative ward or post-discharge setting. Furthermore, the relevance of outcome measures to important stakeholders, including patients, carers, health-care providers and policymakers, may not have been taken into account when designing studies. Other specialties have made good progress in standardizing end points for clinical trials; these specialties include cardiology,[15] respiratory medicine,[16] breast cancer,[17] and stroke.[18]

In June of 2015, the *BJA* sponsored a meeting of experienced perioperative triallists to establish a consensus process of standardizing end points in perioperative medicine. This 'Standardized Endpoints for Perioperative Medicine' (StEP) Group is currently working to provide expert, consensus-based[19] guidelines for clinical outcomes used in perioperative research. This process will feed into a parallel initiative with the aim of identifying a core outcome set (COS) for perioperative studies, the Core Outcomes Measures in Perioperative and Anaesthetic Care (COMPAC) initiative. Together, these two processes seek to standardize both the criteria for and selection of measures for perioperative researchers in order to harmonize outcome reporting and thereby enable the comparison, contrasting, and combination of results from diverse studies. Both the StEP and COMPAC guidelines will be produced according to established standards,[9 20–25] including formation of an expert group to define the scope, methods, and outputs and to oversee all stages of the process. For the StEP process, this will begin with a systematic review of end points, their definitions, and timing of assessment used in large published perioperative studies. The time course of recovery from surgery will be considered when determining the optimal time(s) of assessment. The published performance characteristics of any proposed instruments (i.e. validity, reliability, and responsiveness) will be evaluated and reported. Particular scrutiny will be given to composite end points according to the balance between the burden of data collection and the frequency and coherence of each component of the end point.[5] The StEP group will then make preliminary recommendations and aim to achieve consensus across a broader group of investigators and journal contributors. The final StEP guidelines will be published in one or more anaesthetic journals to maximize their dissemination to target audiences.[19 26] Whereas development of the StEP guidelines is a technical exercise driven in large part by expert interpretation of a complex scientific literature (top-down approach), the COMPAC initiative uses similar methods to achieve consensus between patients, carers, and a broad range of carers as to what are the most important outcome domains to include in a COS (bottom-up approach). Key outcomes from each StEP group will be mapped onto the domains identified by the COMPAC process (e.g. pain/discomfort, quality of life) in order to define a COS for perioperative studies.[27] The COMPAC-StEP methodology is based on an approach that has been successfully used by the Core Outcome Measures in Effectiveness Trials (COMET) initiative over a number of years.[28]

The StEP working groups have been identified (see Table 1). Each group consists of a chair and four to eight members who represent a breadth of relevant expertise in clinical trials and systematic reviews, and where relevant, health services research, biostatistics, psychometrics, and health economics. Where possible, members of each group have been drawn from at least four countries and at least two continents to provide diversity and global representation. Each StEP working group will be asked to identify one or two core outcome measures related to their area of interest that will be candidates for the COS, based on the domains of outcome identified through the COMPAC process. The resulting shortlist of proposed end points and their definitions will then be subjected to a two-stage Delphi process across all the StEP working groups and their clinical research collaborators, plus patient representatives, journal editors, and other relevant stakeholder representatives. We hope to present the final COMPAC-StEP Recommendations for Standardized Endpoints in Perioperative Trials at a workshop during the World Congress of Anaesthesiologists in Hong Kong in September 2016. The completed guidelines will also be published in the anaesthetic literature.

Consensus and consistency in the use of appropriate outcome measures in perioperative clinical trials, and their timing of assessments, should enhance the interpretation and translation of such research endeavours. Standardizing end points will also improve the validity of pooled analysis of clinical trials and assist those wanting to replicate trial results. These latter steps are necessary components of evidence-based practice. Comparison between studies is made easier, and other investigators will have a stronger foundation on which to design future, definitive trials. This will improve the value and efficiency of research.[1 2]

Declaration of interest

P.S.M. is an editor of the *British Journal of Anaesthesia*; M.P.W.G. is an elected council member of the Royal College of Anaesthetists and the Director of the National Institute for Academic Anaesthesia's (NIAA) Health Services Research Centre (to end of March 2016). S.R.M. is the deputy director of the NIAA Health Services Research Centre and will be Director of the NIAA Health Services Research Centre (April 2016).

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Appendix

The COMPAC-StEP Executive consists of Paul Myles (Australia, Co-Chair) and Michael Grocott (UK, Co-Chair), and Bruce Biccard (South Africa), Oliver Boney (PhD Fellow, UK), Matthew Chan (Hong Kong), Lee Fleisher (USA), Cor Kalkman (The Netherlands), Andrea Kurz (USA), Ramani Moonesinghe (UK), and Duminda Wijeysundera (Canada).

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