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A primer for clinical researchers in the emergency department: Part 6.

**Measuring what matters – core outcome sets in emergency
medicine research.**

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"Not everything that counts can be counted, and not everything that can be counted counts." – William Bruce Cameron, 1963.¹

Introduction.

Between 2010 and 2013, a series of primers for clinical researchers in the emergency department was published in this journal.²⁻⁶ This paper, the sixth in the series, discusses the selection of outcome measures for research – an important, but often overlooked aspect of study design.

Clinical practice – in all aspects of medicine - involves making decisions. We make decisions during history taking, physical examination, diagnostic test ordering and interpretation, treatment, referral and disposition. These decisions are made with the intention of obtaining the best outcomes for our patients by using knowledge of likely outcomes. This knowledge is gleaned from education, clinical experience, feedback about adverse events, and reading and evaluation of the medical literature.

Understanding the differences between outcomes where there is a choice of therapy can be used to determine which treatment is "best choice" in a particular

situation. Clinicians also use outcome measures for audit, quality and safety improvement, and to determine whether best practice is being delivered.

A critical question, then, is “*which outcome measures should be used?*” This paper will provide an overview of the factors to consider when choosing outcome measures, and the increasing significance of core outcome sets.⁷⁻¹⁰ This is not only important for clinical researchers designing randomised controlled trials, but also for the interpretation of the medical literature, and the use of outcome measures in audit and quality improvement.

The current approach to choosing outcome measures

Two critical questions are posed when choosing an outcome measure: “What should be measured?” and “How should it be measured?”

What is being measured?

A well-designed study should use outcomes which *matter*. Outcomes should be well defined, reproducible, clinically important, and relevant to patients, healthcare providers, and those who fund healthcare.

The choice of outcome measure(s) is dictated by the clinical problem being assessed. For example, quantification of pain is appropriate in many conditions presenting to the emergency department, including ureteric colic, migraine and orthopaedic injuries. However, some additional outcomes are disease-specific,

such as time to ureteric stone passage and need for urologic procedures in ureteric colic, and nausea, vomiting, or need for additional antiemetic therapy in migraine.^{11, 12}

Other diseases with low rates of mortality or without significant complications often use outcome measures based upon clinical scores or pathology test results. For example, the Pediatric Respiratory Assessment Measure (PRAM)¹³ and the Pediatric Asthma Severity Score (PASS)¹⁴ are based upon a combination of symptoms and signs. Unfortunately, to date, such scores have been insufficiently validated,¹⁵ frequently modified, and used in different ways in different study designs,¹⁶ making comparisons between them very difficult.

When choosing outcome measures, there are a number of frameworks, which list types of outcomes – applicable to a range of clinical problems - that are important to consider. For example, the Outcome Measures Framework (OMF) has six categories: survival, disease response, events of interest, patient/caregiver-reported outcomes, clinician-reported outcomes, and health system utilisation.¹⁰ The Outcome Measures in Rheumatology (OMERACT) Filter 2.0 lists three core areas: death, life impact and pathophysiological manifestations; and one strongly recommended area: resource use.¹⁷ Attention to the various categories allows investigators to ensure that all important outcomes are addressed.

The importance of the patient voice is critical to choosing outcome measures, with patients not necessarily determining the same outcomes as important as

health professionals. For example, prior to the OMERACT initiative, trials in rheumatology regularly reported on pain and mobility as key outcomes. While these outcomes are important to patients, considerable importance has also been placed on fatigue and quality of life by patients. These factors have now been incorporated as key outcome measures in trials in rheumatology.^{17, 18}

How are we measuring it?

Once an outcome is deemed to be important enough to measure, the next decision to make relates to *how* the outcome should be measured. In some cases, deciding on an appropriate measurement tool is straightforward – the use of a visual analog scale (VAS) or numeric rating scale for pain measurement is widely accepted and validated in a number of settings.¹⁹⁻²²

However, while a numerical rating scale may change with therapy, and lead to a statistically significant difference, this change may not be clinically important, or may not be the degree of change expected by the patient.^{23, 24} From a patient's perspective, satisfaction with treatment may be more important than changes in a numeric rating scale.

Also, even the assessment of pain using a VAS for an acutely painful condition can lead to difficulties in comparing treatments if the pain is measured at different intervals. Table 1 illustrates the timing of pain assessments for ten recently published trials on acute ureteric colic.²⁵⁻³⁴ Although all studies used a

VAS, it can be seen that making valid comparisons between the studies regarding the 'best' treatment is very difficult.

What are the current problems?

It has been suggested that much research effort is wasted, with problems in choice of research questions, study design and methodology, publication practices, and report quality. Research questions may not match what is important to clinicians and patients.³⁵

Another significant issue is that of outcome-reporting bias – the selective reporting of some – but not all – outcomes from a dataset, often based on the presence of 'statistically significant' results.³⁶ Although this has been somewhat addressed by the increasing utilisation of clinical trial registries, significant outcome-reporting bias still exists.^{37, 38}

Lack of consistent outcome measures also hampers research synthesis. A recent systematic review on outcome measures in cardiac arrest clinical trials identified 160 individual outcomes reported in 61 trials, including 39 different reports of survival measures, 11 of which related to return of spontaneous circulation.³⁹

Another recent publication describes 25 different ways used to categorise response to treatment for cellulitis.⁴⁰ This "outcome heterogeneity" has been acknowledged by the Cochrane Collaboration as a significant issue to address.⁹

Core Outcome Sets: A Way Forward

Wasted research, outcome-reporting bias, and difficulty synthesising research have prompted efforts to develop and apply *core outcome sets*. These agreed, standardised sets of outcomes should be measured and reported in all trials for a specific clinical area.⁸ Core outcome sets have been described as “the minimum that should be measured and reported in all clinical trials of a specific condition and could also be suitable for use in other types of research and clinical audit.”⁷ Important early examples of core outcome sets include those initiated by the World Health Organisation for cancer trials in the 1970s,⁴¹ and the OMERACT (Outcome Measures in Rheumatology) collaboration. OMERACT has set standards for the development and validation of outcome measures for various rheumatic diseases, and has notably included the perspectives of patients in the process since 2002.⁴²

Examples of core outcome sets and/or consensus statements relevant to emergency medicine include those developed for migraine,¹¹ cardiac arrest therapies⁴³ and traumatic dental injuries.⁴⁴ However, many of the currently available core outcome sets have been developed for illnesses less relevant to the episodic care provided in emergency departments, such as adult cardiac surgery,⁴⁵ rheumatoid arthritis,⁴⁶ and eczema.⁴⁷

There are many areas of emergency medicine research that could benefit from the development of core outcome sets. Recently, there has been a call in this journal for the development of uniform data collection and reporting in sepsis.⁴⁸

The authors of this current paper are currently involved in the development of a core outcome set for clinical trials in acute severe paediatric asthma.⁴⁹

How to develop a core outcome set.

The Core Outcome Measures in Effectiveness Trials (COMET) Initiative was launched in 2010, and provides a searchable database of studies relevant to the development of core outcome sets, and various practical and methodological resources useful for those developing core outcome measures.⁸ Figure 1, from the COMET Handbook, provides an overview of the core outcome set development process.⁸ Key initial decision points include; (1) choosing the scope of the outcome set – health condition, target population, and interventions, and (2) determining whether or not a core outcome set exists, or is needed. The need for a core outcome set is supported by identification of outcome heterogeneity and/or outcome-reporting bias. Searching the COMET database can identify existing core outcome sets, as well as those currently in development.⁸

If it is decided that a new core outcome set is required, the next steps are to ensure there is no overlap with work being conducted by other researchers on the same outcomes, and to develop and register a study protocol.⁸

A study steering group is formed, with input from clinicians, researchers, methodologists, and patients and carers. The exact group will depend upon the condition and interventions being studied. For example, development of a core outcome set for emergency department patients with renal colic may need to

assess both long- and short-term outcomes, and should include patients and carers with personal experience of renal colic, urologists, emergency physicians and nurses, and general practitioners. Ideally, a core set of outcome measures should be applicable across a range of health-care settings globally.⁸ Ensuring participation from a number of different settings is likely to increase the generalizability of any findings and make the core outcome set widely accepted, however, poses potentially considerable logistical challenges.

The development of a core outcome set requires consensus. To achieve this, existing knowledge about outcomes must be systematically identified and collated. Additional input is then sought from relevant groups, and an initial set of possible outcomes is developed. The set of outcomes is distributed to all relevant stakeholders, usually through a Delphi survey.⁸

Briefly, the Delphi technique aims to achieve consensus by seeking opinions about the relative importance of the various outcomes from all stakeholders (patients, carers, clinicians, and others). A questionnaire seeking a rating for each listed outcome is administered in a number of “rounds”, with the results of each survey being made available to participants in the next iteration. This allows participants to refine their responses based on feedback.⁸ It has been suggested that feedback allowing stakeholders to view results by each group of participants leads to an improved degree of consensus.⁵⁰

After two or three rounds of the Delphi process, a final face-to-face meeting is recommended to discuss and agree on a final core set of outcomes.

At that point a decision on “what to measure” has been achieved. The next step is to determine *how* to measure each outcome. This may require systematic reviews and possibly further research regarding the best measurement scales for a particular condition, followed by a further consensus process.⁸

Once a final core outcome set has been agreed upon, the findings should be reported according to the appropriate guideline.⁵¹ The core outcome set should be disseminated through appropriate channels to ensure uptake and implementation, and its subsequent impact should be carefully measured.⁸

Conclusion.

Determining *what to measure* and *how to measure it* are critical questions when evaluating a new treatment in a clinical trial, or when examining clinical practice through audit and quality assurance activities. There is a need to identify and focus on measures that are important, to ensure that results are reproducible and can be synthesized and compared between studies. The careful development and widespread use of core outcome sets has the potential to reduce wasted research, limit outcome-reporting bias, and ensure that we measure what matters to patients, families and clinicians.

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Competing interests.

SC, FEB and SRD are Emergency Medicine Australasia section editors for Paediatric Emergency Medicine, while AG is a section editor for Toxicology.

Figure 1. The Core Outcome Set (COS) development process.

Original source: Williamson, et al. The COMET Handbook: version 1.0. Trials 2017, 18 (Suppl 3):280. Used with permission.

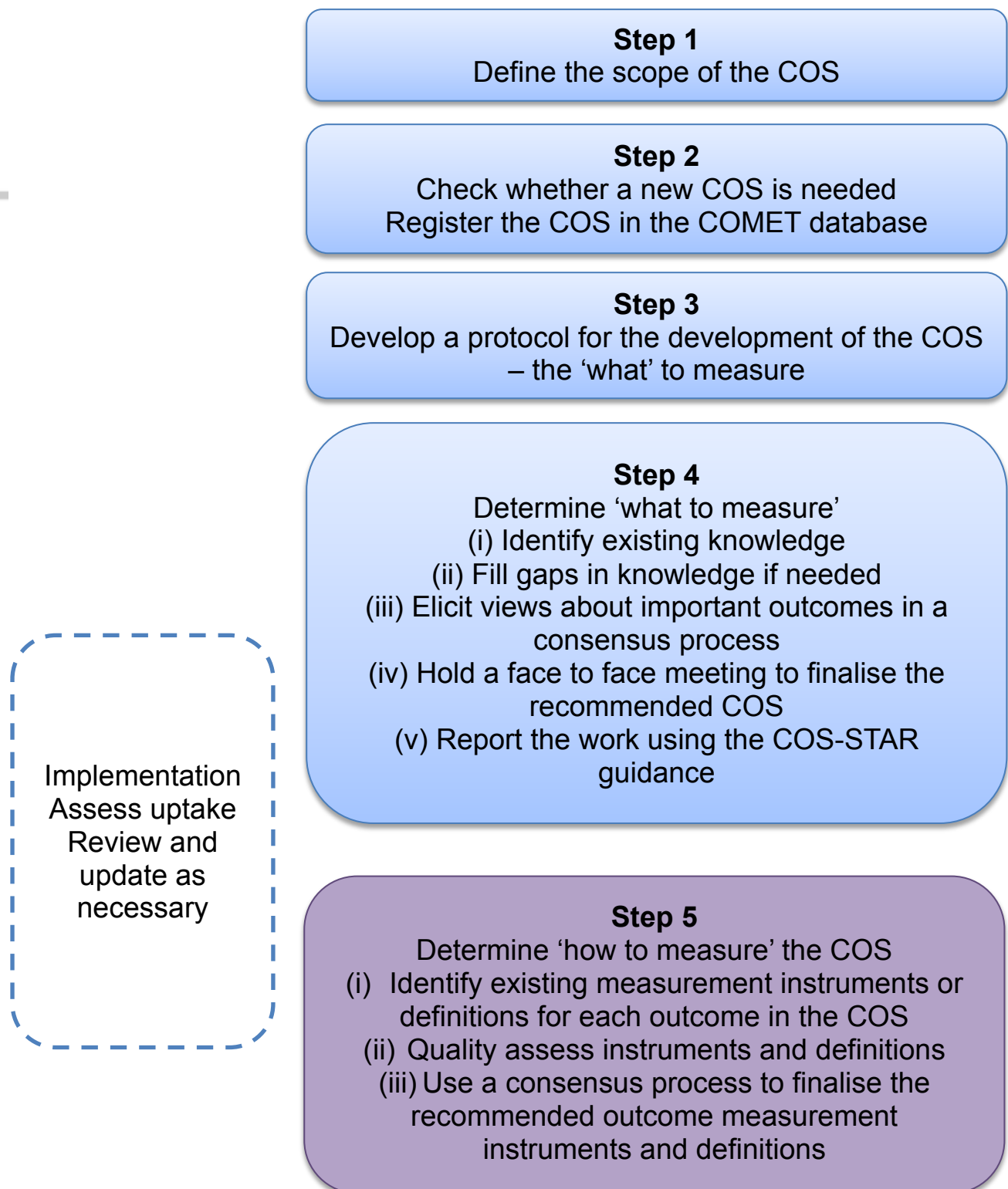


Table 1. Timing of pain assessment in 10 recent RCTs of renal colic

Treatment comparison in each RCT	0 minutes	1 minute	3 minutes	5 minutes	10 minutes	15 minutes	20 minutes	30 minutes	40 minutes	45 minutes	60 minutes	90 minutes	120 minutes
Morphine + Placebo vs Morphine + Ketamine ²⁵	X				X			X			X	X	X
Dexketoprofen Trometamol vs Fentanyl vs Paracetamol ²⁶	X					X		X					
IN Desmopressin vs IV Ketorolac ²⁷	X				X			X			X		
IV Ibuprofen vs IV Paracetamol ²⁸	X					X		X					
IN Ketamine vs IV Morphine ²⁹	X			X		X		X					
Morphine + Ketorolac vs Morphine alone vs Ketorolac alone ³⁰	X						X		X				
IV Fentanyl vs nebulised Fentanyl ³¹	X					X		X					
Morphine + Ketorolac vs Morphine + Ketorolac + Magnesium ³²	X							X			X		
IM Diclofenac vs 12th intercostal nerve block ³³	X	X	X	X				X		X			
Buprenorphine vs Placebo ³⁴	X						X		x		X		

IN=intranasal, IV=intravenous