

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: Incorporating considerations of resources use into grading recommendations

Guideline panellists have differing opinions on whether resource use should influence decisions in individual patients. As medical care costs rise, resource use considerations become more compelling, but panellists may find dealing with such considerations challenging

In this last part of a series describing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to making recommendations we will look at how guideline panellists and clinicians can incorporate matters related to resource use into recommendations and practice. Clinical recommendations inevitably involve judgments about the allocation of resources, judgments commonly referred to as costs. In this article, we will deal with some of the challenges of considering costs, explain reasons for focusing on resource use rather than costs, and discuss how to incorporate considerations of resource use into recommendations.

Cost as an outcome presents special challenges

In one sense, cost is just another potentially important outcome—like mortality, morbidity, and quality of life—associated with alternative ways of managing patient problems. In addition to these clinical outcomes, an intervention may increase or decrease costs. Costs differ from other outcomes, however, in several ways (box).¹ These differences have several implications—including the possible legitimate omission of cost as an outcome in considering a management recommendation—which we will outline in the course of this discussion.

In what way do costs differ from other health outcomes?

- Patients receive health benefits and bear the burden of adverse health outcomes, but healthcare costs are typically shared by society as a whole (as represented by the government), employers, and patients
- Attitudes differ as to whether costs should influence a doctor's decision about treating individual patients
- Healthcare costs may vary widely among and even within jurisdictions and quickly change over time
- What societies can purchase if they forego use of healthcare resources (opportunity cost) varies widely between countries. A year's supply of an expensive drug may pay a nurse's salary in the US and 30 nurses' salaries in China
- When healthcare expenditures demand foregoing expenditures elsewhere, attitudes differ as to whether the health system, public expenditures, or society as a whole should bear the burden
- Matters relating to resource use are highly political and may result in conflict of interest for a guideline panel (for example, panellists may have an association with industry or government)

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This is the last in a series of five articles that explain the GRADE system for rating the quality of evidence and strength of recommendations. Further information is in the version on bmj.com

A balance sheet should be used to assess benefits versus costs

Despite the differences, approaches to resource use are similar to other outcomes in that decision makers require an estimate of the difference between treatment and control. A balance sheet is a simple but powerful way to present the advantages and disadvantages of the management options under consideration, including incremental resource use.² Tables 1 and 2 present an example of an evidence profile informed by a large international clinical trial (carried out in 33 countries) and an associated economic analysis in investigating the usefulness of magnesium sulphate in women with pre-eclampsia.^{3 4}

Evidence profiles should present resource use, not just monetary values

We suggest that guideline developers document best estimates of resource use, not best estimate of costs. Costs are a function of resources expended and the cost per unit of resource. Given the wide variability in unit costs, reporting only total costs leaves users without the information needed to judge whether estimates of unit costs apply to their setting.

Furthermore, specifying resources consumed by alternative management strategies allows users to judge whether the resource use reflects practice patterns in their setting and to focus on the items of most relevance to them (such as drug costs for a pharmacy or hospital costs for a hospital administrator). Finally, users can ascertain whether the unit costs apply in their setting, if monetary values are subsequently assigned to the resources used and, if they don't, substitute unit costs that do.

Tables 1 and 2 show the importance of documenting resource use and specifying the setting. The variation in costs associated with magnesium sulphate, its administration, and the associated hospital costs across countries with high, medium, and low gross national income is large. Our tables document these differences, but many economic analyses will not. Unless resource use is specified, users in settings other than that on which the analysts focus cannot estimate the associated incremental costs of the intervention.

The specific context is crucial for considering resource use

The extreme variability in costs over time and jurisdictions has several implications. Firstly, a guideline

panel should be as specific as possible about the patient population, the nature of intervention, the comparator, and the healthcare setting. The choice of comparator can be a particular problem in economic analyses. If the choice of the comparator is inappropriate (for instance, no treatment rather than a less effective treatment) conclusions may be misleading.⁵

Secondly, a guideline panel may legitimately ignore considerations of resource use, and make recommendations solely on the basis of other advantages and disadvantages of the alternatives being considered. Thirdly, if panellists consider resource use they should, before bringing cost into the equation, decide on the quality of evidence regarding other outcomes, and weigh up the advantages and disadvantages.

A broad perspective is desirable

Conceivably, a recommendation could be intended for a very narrow audience, such as a single hospital pharmacy, an individual hospital, or a health maintenance organisation. Alternatively, it could be intended for a health region, a country, or an international audience.

Few guideline audiences would, however, be happy with a perspective that is narrower than that of the entire health system. For instance, in a publicly funded health system the patient perspective would ignore most of the costs generated. A pharmacy perspective would ignore downstream cost savings resulting from adverse events (such as stroke or myocardial infarction) prevented by a drug, and a hospital perspective would ignore outpatient costs, either incurred or prevented.⁶

An even broader viewpoint—that of society—is the most comprehensive perspective because it includes all costs, regardless of who bears them. This perspective is often preferable, particularly if the health intervention has a broad effect (for example, an intervention for heart failure that improves patients' functioning and reduces the time and cost of family caregivers). Whether cost effectiveness analyses should include the implications of health effects—such as changes in earnings—is more controversial. Economic guidelines advise that such implications are presented separately, instead of as part of the formal cost effectiveness analysis.

Although a particular health plan may bear no downstream costs, it is informative for a host of decision makers to be aware of the incremental long term resource use associated with alternative management strategies. Similarly, although a clinician's responsibility when caring for a patient is to the patient and the patient's family, this responsibility is carried out in a broader context with resource constraints and opportunity costs—resources that are used for an intervention cannot be used for something else and can affect the ability of the health system to best meet the needs of those it serves.

Judging quality of evidence for resource use

As with evidence of rare but serious adverse effects, evidence of resource use may come from sources other than evidence of health benefits. This may be because trials of interventions do not fully report resource use, because the trial situation may not fully reflect the circumstances—and thus the resource use—that we would expect in clinical practice, or because the relevant resource use may extend beyond the duration of the trial.

For resource use reported in the context of trials, criteria for quality assessment are identical to those for other outcomes, as described in the second article in this series; this is the case in table 1. Just as for other outcomes of a trial, the quality of evidence may differ across different resources. For example, when considering magnesium sulphate in pre-eclampsia, we are more confident of resource use associated with the drug itself and administration of the drug than we are of use of hospital resources (table 2).

Formal economic modelling may be helpful

Formal economic modelling results in cost per unit benefit achieved: cost per natural unit, such as cost per stroke prevented (cost effectiveness analysis); cost per quality adjusted life year gained (cost-utility analysis); or both cost and benefits valued in dollars (cost-benefit analysis). These summaries can be helpful for informing judgments. Unfortunately, published cost effectiveness analyses, particularly of drugs, have a high probability of being flawed or biased,⁷ and they are specific to the particular setting.

Table 1 | Summary of findings on whether clinicians should use magnesium sulphate to prevent eclampsia: clinical outcomes

Outcome	Severity of pre-eclampsia	Typical control group risk	Typical absolute effect (95% CI)	Relative risk (95% CI)	No of participants	Quality of evidence
Eclampsia	Severe*	27/1000	16 fewer/1000 (11 to 19)	0.41 (0.29 to 0.58)	11 444	High†
	Not severe	15/1000	9 fewer/1000 (6 to 11)			
Maternal death	Severe	6/1000	3 fewer/1000 (0.6 more to 4 fewer)	0.54 (0.26 to 1.10)	10 795	Moderate‡
	Not severe	3/1000	1 fewer/1000 (0.3 more to 2 fewer)			
Side effects§	Severe and not severe	46/1000	196 more/1000 (165 to 231)	5.26 (4.59 to 6.03)	9992	High†

*Severe eclampsia was defined as (diastolic blood pressure >110 mm Hg on two occasions, or systolic blood pressure >170 mm Hg on two occasions and proteinuria >3+) or (diastolic blood pressure >100 mm Hg on two occasions, or systolic blood pressure >150 mm Hg on two occasions and proteinuria >2+ and at least two signs or symptoms of imminent eclampsia) or for women who had an antihypertensive in the 48 hours before randomisation: (in 48 hours before trial entry, highest diastolic blood pressure >110 mm Hg, or highest systolic blood pressure >170 mm Hg and proteinuria >3+ at trial entry) or (in 48 hours before trial entry, highest diastolic blood pressure >100 mm Hg, or highest systolic blood pressure >150 mm Hg and proteinuria >2+ and at least two signs or symptoms of imminent eclampsia).

†Evidence comes from randomised trials and there was no reason to grade down for study limitations, imprecision, inconsistency, indirectness, or publication bias.

‡The confidence interval was wide so the evidence was graded down for imprecision.

§Mostly flushing. Other side effects include nausea, vomiting, slurred speech, muscle weakness, dizziness, drowsiness, confusion, and headache.

Table 2 | Summary of findings on whether clinicians should use magnesium sulphate to prevent eclampsia: resource use viewed from the perspective of the health system

Resource	Cost*	Typical absolute effect (95% CI)	No of participants (studies)	Quality of evidence	Comment
Magnesium sulphate ampoules (6×10 ml ampoules/patient)					
Setting:					
High income countries	\$20 more/patient		9996	High†	
Middle income countries	\$3 more/patient				
Low income countries	\$5 more/patient				
Administration of magnesium sulphate (1 ampoule/patient)					
Setting:					
High income countries	\$66/patient		9996	High†	Resources for giving magnesium sulphate included midwives' time (main cost), intravenous cannula or needles, syringes, intravenous fluids, and the drug
Middle income countries	\$14/patient				
Low income countries	\$8/patient				
Other hospital resources (varied widely)					
Setting:					
High income countries	\$12 839	\$20 less/ patient (\$0 to \$60)	9.996	Moderate‡	Use of other hospital resources varied greatly in both intervention and control groups. Other hospital costs have been adjusted for on the basis of the influence of eclampsia to control for the many other factors that influenced these costs
Middle income countries	\$1 416	\$4 less/ patient (\$0 to \$10)			
Low income countries	\$157	\$2 less/ patient (\$1 to \$3)			

*\$1=£0.5=€0.7.

†Evidence comes from randomised trials and there was no reason to grade down for study limitations, imprecision, inconsistency, indirectness, or publication bias.

‡The confidence interval was wide so the evidence was graded down for imprecision.

Guideline groups may therefore consider developing their own formal economic model. For guideline groups to consider this option, however, they must have the necessary expertise and resources. The larger the difference in resources consumed by the alternative management strategies, the greater the uncertainty about whether the net benefits of an intervention are worth the incremental costs, and the higher the quality of evidence regarding resource consumption, the more likely it is that a full economic model would help inform a decision.

Modelling, while necessary for taking into account complexities and uncertainties in calculating cost per unit benefit, reduces transparency. In addition, any model is only as good as the data on which it is based. When estimates of benefits, harms, or resources used come from low quality evidence, results of any modelling exercise will be highly speculative.

Criteria are available to assess the credence to give to results from statistical models of cost effectiveness or cost-utility.⁸⁻¹¹ However, these models generally include a large number of assumptions and evidence of varying quality for the different estimates that are included in the model. For these reasons, we do not recommend including cost effectiveness or cost-utility models in evidence profiles. They may, however, inform a guideline panel's judgments, or those of governments or third party payers considering whether to include an intervention among their programmes' benefits.

Tables 1 and 2 allow us to calculate the incremental cost per episode of eclampsia prevented for severe and non-severe pre-eclampsia across high, middle, and low income countries (table 3). Even when—as in this case—cost effective estimates are credible, they do not provide clear answers regarding appropriate action. Most people, however, would consider the cost per episode of eclampsia prevented worth

the money in the case of severe pre-eclampsia. For non-severe pre-eclampsia, particularly in low income countries, the decision is more difficult. Ultimately, decision makers need to weigh the relative value of preventing pre-eclampsia against the benefits that the health system or society would forego in allocating resources to magnesium sulphate administration.

Concluding remarks

Clinical decision making is complex. Guidelines have the potential to help clinicians and patients with complex choices, to improve the quality of care, and to help ensure the best use of limited resources. To ensure that guidelines inform rather than misinform, it is important that they build on the best available evidence and that guideline panels use systematic and transparent processes to make judgments about the quality of the evidence, moving from the evidence to a recommendation, and incorporating considerations of how resources are used.

Clinicians and their patients will be best served by guidelines that use an approach such as the one we have described in this series to explicitly grade the quality of evidence and the strength of recommendations. Front line clinicians or those constructing local guidelines need not replicate the work done

Table 3 | Incremental cost for each episode of eclampsia prevented by magnesium sulphate

National income	Severity of eclampsia	
	Severe	Non-severe
High	\$4125	\$7333
Medium	\$813	\$1444
Low	\$688	\$1222

*\$1=£0.5=€0.7.

by well resourced guideline developers. However, to make the best use of guidelines, they should understand the evidence and judgments underlying a guideline. They should have access to concise summaries of recommendations, including ratings of the quality of the underlying evidence and the strength of the recommendation, and they should understand the meaning of these grades and their implications for clinical decision making.

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SUMMARY POINTS

Costs differ from other healthcare outcomes—costs are shared by patients, employers, and society, and opinions differ as to who should bear the burden; some people think costs should not influence doctors' decisions; costs differ across and within jurisdictions

A balance sheet should inform judgments about whether the net benefits are worth the incremental costs

Evidence profiles should always present resource use, not just monetary values

A guideline panel may legitimately choose to omit costs as a consideration

Formal economic modelling may—or may not—be helpful

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A pair of memorable patients

In my time spent with the renal transplant team I have seen many examples of the immense kindness one person can show to another, but our unit recently performed a live, unrelated transplant that was particularly memorable. The kidney donor and recipient were great friends who had played jazz together for many years. I was involved in the hand-assisted laparoscopic donor nephrectomy, which proceeded without complication under consultant supervision.

A couple of days later at about 2 30 pm, I had just finished a long morning clinic which had over-run. After grabbing a sandwich, I was returning to the offices when the sound of live music echoed up from the floor below. I decided to go and eat in the ground floor atrium, which often has small live concerts at lunchtimes. As I tucked in, I realised the music had stopped and that the two musicians were looking at me. It was the transplant pair from earlier in the week, and amazingly only two days after their surgery they were playing an impromptu jazz session for their friends,

families, and other patients.

The donor was seated at the piano, while the recipient played the saxophone with his catheter bag hidden within a high street shopping bag. I was asked to request the next number and then sat back to enjoy *Take the A-Train*, which has always been a favourite of mine. It had been fantastic to be involved in the operation itself, but to see donor and recipient playing together so soon afterwards was a really special moment. This pair was now truly a team, bonded in an amazing and unique way, and I was thoroughly moved by the scene.

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During their continued recovery, Maff Potts and Andy Williamson have recorded a track with their group, Big Buzzard and the Organ Grinders, to encourage other donors entitled *Live Life then Give Life* (<http://myspace.com/organgrinders>). This will be released as a download single in aid of <http://www.livelifethengivelife.co.uk>, which campaigns on behalf of everyone needing transplants.

Patient consent obtained.



Kidney donor Maff Potts at the piano, and his recipient, saxophonist Andy Williamson, playing a concert two days after their operation (courtesy of A Williamson). See a clip of this performance at <http://bigbuzzard.blogspot.com>