



ISPOR GOOD PRACTICES FOR QUALITY IMPROVEMENT OF COST EFFECTIVENESS RESEARCH TASK FORCE

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The following are comments received from the ISPOR Membership in response to the Task Force's Draft Final Report, which is available for review at www.ispor.org/workpaper/healthscience/QI.asp.

COMMENT 1

I have read the report and given the potentially large volume of literature to summarise you and your team have done a great job. I was most interested in Sections 2 and 3 (Guidelines around the globe, and the statistics and science).

Regarding the guidelines section, I agree that measuring the quality of guidelines is extremely difficult to do objectively and without some sort of instrument.

There are some basic features that could be discussed - such as whether it is better to have descriptive guidelines (i.e. if your data are from X, then you can do Y or Z) or whether guidelines should be prescriptive (as in the requiring a unified reference case). This issue should be discussed (i.e. the appropriateness of reference case - as per NICE) and follow this up with a recommendation in the final section.

In addition, a little more discussion on the evolution of guidelines would be useful - for example, the majority of guidelines are for submissions for government (or health insurer) subsidy of pharmaceuticals. Some HEOR guidelines are developed for the evaluation of clinical practices, public health policy etc; and others are developed for the evaluation of medical devices.

All three exist in Australia, and the organisations each have different scope, audiences, and processes for decision-making / recommendations (and hence, substantially different guidelines).

Medical services:

<http://www.health.gov.au/internet/msac/publishing.nsf/Content/guidelines-1>

Pharmaceuticals: (note your ref 11 - this is somewhat out of date - these guidelines have been

updated several times since 2002)

<http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacguidelines-index>

Clinical Practices:

<http://www.nhmrc.gov.au/publications/synopses/cp73syn.htm>

Regarding the statistics and science section - this is all good.

COMMENT 2

This report looks great. I have a few comments. I would like to propose to develop guideline or comparative methods by international regions or health care system. Health insurance or system can be a factor to determine all costs. I think it would be helpful to avoid heterogeneity in cost effectiveness among different countries.

COMMENT 3

First of all I would like to thank you for giving the opportunity to read and comment upon the final draft of the QICER Task Force. It is quite an immense work and I enjoyed reading it.

I think the draft has comprehensively covered most of the areas concerning HEOR. I have one indication and one comment. As to guidelines, please be aware that the Italian Association of Health Economics, chaired by Prof. Giovanni Fattore is about to launch the new guidelines. The QICER Task force might want to get in touch with Giovanni (giovanni.fattore@unibocconi.it) to get an update on Italian guidelines.

The comment mainly relates to the work on "clinical trials based economic evaluations" (Section 3. Statistics and Evidence). More specifically, the QICER's work brilliantly expose on issues and challenges of cost-effectiveness analysis alongside RCTs. I do think that other source of evidence are getting important recently (quasi- non-experimental studies), yet they are not as rigorously studied as RCTs. The issue is that while study designs other than RCTs might fit better certain technologies (i.e. Medical Technology, Implantable Medical Devices), they have not grasped the interest of researchers and health economists as much as experimental studies traditionally did. I therefore think that the issue of source of clinical evidence when dealing with CEA is important to further develop into HEOR guidelines. The work by Drummond, Griffin, Tarricone (Value in health, 2009) shed some light into that direction.

COMMENT 4

The report is well written and makes interesting reading. Just a couple of suggestions/comments provided below as requested:

1. Figure on pg 3 can include 'health policy decision makers' within the circle.

2. Can have a sub-heading " Evaluation of impact of guidelines on HRQOL' before getting into specifics on this topic. Currently it does not seem to separated well to get the reader's attention.

3. Formulary bodies like NICE, PBS etc evaluate HEOR studies or analyses in most cases that are product based and submitted by industry. You might want to expand beyond these to include other organizations evaluating HEOR research in general including those based on academic or public health studies.

4. Might want to add some info in the guidelines section for Taiwan and Singapore - two other countries in Asia with large resources devoted to health care decision making and using cost effectiveness extensively.

5. As part of the recommendations, it might good to include a section on software or analysis tools and list activities (something on updates on versions, validity, flexibility etc.) as done for guidelines, publications etc.

COMMENT 5

Thanks a lot for sending me this report and giving me the opportunity to comment on this. I think this is a great piece and it would be wonderful if there is a guideline for researchers and decision makers. I have little comments on the paper, hope this could give some inputs for the committee.

1. Can we include the feasibility analysis of Guidelines for ISPOR?

2. I have concerns for how to quantify the impact of HE guidelines? For example, for statistical methodology part, there will be hundred of methods in HE research. If the research did not use non-parametric bootstrap for comparison of cost, instead by using Wilcoxon rank test, which is very popular now in literature, so will this paper be categorized as poor and not following the guidelines?

3. If the guideline is going to incorporate the statistical methods, how many will be listed and the recommendations will be a lot for different type of studies, right?

4. How to promote the guidelines in different countries?

It will be fantastic to have specific guidelines for HE researches but I think there is a lot to do to formulate one and to promote to the researches.

COMMENT 6

I would like to take this opportunity of stating that I totally agree with the above-mentioned draft final report of the ISPOR Quality Improvement of Cost Effectiveness Research (QICER) Task Force.

The report reads well and is easy to follow. Major topics have been covered, albeit mostly at a surface level. The fact that the depth is limited is probably ok, given the mission of the Task Force. What I strongly would recommend is an introductory section that discusses "what is new." My fear is that otherwise, the document appears to just review what has already been said and that there is "nothing new in the world of CEA in terms of quality." To highlight what has changed in terms of performance or recommendations would be akin to the same introductory paragraph when new guidelines come out (e.g. JNC VIII will tell us what is different from JNC VII).

COMMENT 7

We have gone through the draft report and have observed that study was extensively designed and guidelines provided are well harmonised and suitable for all countries. The format which was suggested for analysis of data can be modified and make it more suitable for third world countries. We suggest incorporating neutral third world parties in data evaluation process.

We also observed that this study is very implicit and extensive. We suggest for periodic update of guidelines proposed here. We have studied a few guidelines for publications and Journal which were discussed in this study and these guidelines are useful and impressive. We will like to implement few good guidelines for journals published by us. We have three branches of Indian National Associations, namely Indian Pharmaceutical Association, Indian Hospital Pharmacists Association and Indian Community Pharmacists Association. We are publishing Indian Journal of Hospital Pharmacy and online Journal International Journal of Community Pharmacy from Manipal, India. We will take into consideration a few suggestions and guidelines from this study.

COMMENT 8

First, congratulations for this excellent piece of work.

Second, a little comment about France, my home country. The only reference you take into account was issued by the private (although highly reliable) Cercle des Economistes in 2004. You probably know that the "Haute Autorité de Santé" (the French National Authority for Health) has set up a new "Economic evaluation division" which is currently developing several deliverables. I did not find something matching precisely with the global economic assessment of pharmaceuticals, but I would like to assure you that we are not going to have this very "touchy" official institution criticize your excellent work just because they are not mentioned inside ! You might visit them (in English) at

http://www.hassante.fr/portail/jcms/c_5443/english?cid=c_5443

COMMENT 9

I've read through the report. It reads well. The only comment I have is that the Section 5 is a bit wordy. Page 26 first line "Hutton and Brown discussed..." to page 27 end of third paragraph "...at the local level." could be removed as it feels out of scope and doesn't add much facts to report.

COMMENT 10

This is an excellent written document, and should be encouraged to conduct continuous quality improvement activities. One question only, because I am from Taiwan and I know Taiwan has Chinese PE guideline published but it is not included in the Table 1, is it because it is written in Chinese? If not, please be kind to include it in the Table 1. Here is the link:
[http://www.ispor.org/PEguidelines/source/2006 PE Guidelines.pdf](http://www.ispor.org/PEguidelines/source/2006_PE_Guidelines.pdf)

COMMENT 11

One recommendation: start with the recommendations

COMMENT 12

I have had a quick read and think the document is very well written and comprehensive. My only suggestion is to have patients at the centre of your model, ISPOR Vision & Cont. Quality Improvement somehow.

COMMENT 13

After reviewing the report, I cannot agree more on some of the issues of HEOR that were discussed in the report.

My views on the issues are:

1. Guidelines are useful tools, but they have to be adopted to become useful. Guidelines could be too sophisticated for people to follow, or they are not specific enough for people to focus.
2. Being informed the presence of the guidelines sometimes is not adequate for the researchers to follow them. Education is a good tool to go side by side with the guideline. Seminars, electronic newsletters and even on-line courses can help to infiltrate the concepts to the researchers.
3. Seminars and on-line courses of research methodology are useful to provide training.

COMMENT 14

It's obviously easier to critique than to put such a report together, but I did feel that there was some lack of focus in the report. A lot of it dealt with methodological issues in HEOR without any real clear linkage to improving quality. The report mentions many quality assessments of HEOR studies, and I wonder if more space should be devoted to evaluating where the major shortcomings are.

I was also thinking that there is really not much discussion on training and education to improve quality, and this would seem to be critical. I think transparency is also critical, and the issue raised about access to electronic models an important one (though difficult to implement). You might want to consider the recent legal developments in the UK vis a vis provision of electronic models.

Finally, one piece to consider is the role of *Value in Health* in leading the way in terms of the quality of published HEOR studies.

Page 2

“periodically critiqued” should be *“continuously critiqued”*

“Study guidelines” - Not just the guidelines, but the quality of the actual research

Page 4

“All guidances are similar” Really? I would argue that the guidance provided by IQWiG is very different guidance from NICE.

“These studies are often not publically available” But most often they are, even if after a lag between submission and publication in journals.

Page 5

“but these are often small sample size” This sounds like the studies submitted are of small sample size etc. What you mean is that only a small number of studies have been reviewed etc. in these evaluations.

“Although guidelines have not been rigorously evaluated, a number of studies have been published looking at the quality of studies submitted to the guideline-producing bodies”

But at the bottom of page 4 and top of page 5, the statement is made that these have rarely been evaluated that the sample sizes are small, etc.

“No published studies however appear to have measured the relationship between guidelines”

What relationship? Don't the studies just cited do this? And more studies that appear to do this are cited below.

Page 8

“Based on this preliminary review, there are three promising directions in which we could proceed with regard to guidelines as instruments in measuring and improving quality in HEOR”
Are these really three directions? Or one direction with different steps?

“Concurrently, evaluate available instruments or promote development of one to quantify the impact of HEOR guidelines on the quality of HEOR studies. The outcomes of such an instrument

should allow comparison across all guidelines as well as comparison over time, to allow rigorous longitudinal evaluation of quality improvement". How is this different than Item 1?

Page 9

Why the restriction to clinical trial based economic evaluations? What about economic evaluations based on registries, administrative datasets, etc?

"Nevertheless, as our understanding of sampling uncertainty for the comparison of costs and effects has grown, the cases where this interpretation is appropriate have shrunk."

The cases where it is appropriate have not shrunk, they are simply not as common as previously thought.

"When one uses these methods, a finding of significantly lower cost and an indistinguishable clinical outcome need not guarantee that confidence that the significantly less expensive therapy is good value." This is very unclear. If you use the best available methods, and you consider uncertainty, and still find that one therapy is significantly cheaper with no difference in clinical outcome, why would it not be good value? Certainly, there is never any guarantee, but is that really an important point to make. Are you trying to say that without analysis of uncertainty, you could come to the wrong conclusion?

"Alternatively, because it is possible to have more confidence in the combined outcome of differences in costs and effects than in either outcome alone, observing no significant difference in costs and effects need not rule out that one can be confident that one of the two therapies is good value." Indeed, if there is no significant difference in costs and effects, then both may be of good value or both may be of poor value! I understand the point trying to be made, but it is very poorly put forward.

Page 14

"While the quality of cost-utility analyses has improved over time, still current studies do not address all issues appropriately" Why specifically "cost utility" analyses? There are many other types of decision models used in HEOR? Should we not address where the shortcomings are?

"However, in modeling studies, the parameter to be estimated is not only a treatment effect like the odds ratio of having an event. Typically, models contain parameters like transition probabilities between disease states, event probabilities, rate ratios of treatment effects, quality of life or utility values, and costs." It is not at all clear why some of these parameters cannot be evaluated using standard evidence synthesis techniques.

Page 15

"Moreover, the placebo comparator needs to be modeled too, meaning that we are dealing with more heterogeneity than usually remains after the variance in treatment effect has been corrected for the variance in placebo-effect." The placebo comparator certainly does not need

to be modeled! Placebo effects need to be considered when modeling a treatment effect, but that is all. Indeed, modeling 'placebo' is not at all relevant. Modeling 'no treatment' might be if that is a realistic scenario. This makes no sense. Even in a standard meta-analysis of clinical effect, the variance of the placebo effect needs to be accounted for. What point are you trying to make?

“input parameters of the model are varied” as are model assumptions

“Consequently, in the last few years more and more studies include a probabilistic sensitivity analysis, in which all input variables are varied”. I have yet to see a PSA where all input variables are varied. One of the major flaws of published PSAs is the limited number of input variables that are varied (or that the wrong inputs are varied and individual variation is confused with parameter uncertainty).

Page 16

“Such an analysis presents information on all possible outcomes, as well as on the likelihood of these outcomes.” This is overstated.

“study, e.g., to account for other types of uncertainty such as uncertainty relating to the structure and assumption of decision models” Note that assumptions and structure can be integrated into PSA.

“C) Value of information” This section explains what VOI is, but says nothing of quality and improving quality

Page 17

“d) Model validation” This explains what validation is, but nothing about quality. Should we not say something about documentation and reporting of validation?

“internal validation, between-model validation, predictive (or prospective) validation, and external validation” what about technical validation? what about face validity?

Page 18

“There is a clear need for publications in more applied journals that focus on explaining these technical advances in an easily understandable format to conduct knowledge transfer to researchers who need to be applying these newer methods.” I would argue that there is an equally clear need for better training so that researchers can understand more sophisticated techniques.

“Additional efforts to improve the quality of future studies may involve peer reviewers for both funding agencies and journals being critical of studies that fail to apply best practices in cost-

effectiveness research." Isn't this self-evident? What you mean is that they be provided with the tools to be able to do this effectively.

Page 20

Section 4: Why are we not recommending that ViH take a lead role on this? And perhaps a stepped approach, where journals devoted to HEOR use these guidelines/criteria?

"The vast majority (92%) of journals accepted all or some types of HEOR work". Surely this is a biased estimate, as journals interested in HEOR would be more likely to respond.

Section 5: This section seems very unfocussed and does not provide any recommendations. Should we not have explicit recommendations on training of decision makers on best practices which pressure analysts to adopt these. Challenges are discussed and some ideas, but no clear path forward.

Section 6: It's curious to talk about recommendations for quality improvement with no mention of training and education.

Page 30

"Recommendations - Decision-making" Surely, we can provide more recommendations. Training? Support?

COMMENT 15

Thanks for the opportunity to review the draft final report. Overall, I find it well written and very comprehensive, and think it is a sound basis for quality improvement in CE research. However, in Section 5, pages 26 to mid-27, it remains unclear from the text what Hutton and Brown's and to Hoffmann's et al. views are, and what ISPOR's stance is. This part seems lengthy and still very "drafty"; also language/style is less clear.

E.g.: *"Hutton and Brown claims questioned how decisions are made by health authorities for service planning and resource allocation without substantive economic input. In the absence of a clear understanding of the question, they thought economists might be more questioning of the validity of criticism of their work"* (p. 26)

"Counter commentary by Hoffmann et al to Hutton and Brown, agreed that there could be two approaches to addressing the problem" (p. 26),

"Do published cost-effectiveness studies communicate generalizable findings and could they be improved so as to make the generalizable messages self-evident." (p. 27)

"In addition, Hoffmann and colleagues do not agree that there should be reorganization of the NHS decisionmaking process, as suggested by Hutton and Brown, to rectify some of the

problems related to the use of economic evidence in decision-making. They felt such reorganization is likely to merely shuffle the pack rather than bring about real change."

I would recommend to shorten and partially re-write this part of the otherwise excellent paper.

COMMENT 16

This report represents an impressive and comprehensive review of the benefits potentially available and the issues involved in improving the selection and implementation of CER methodologies. Perhaps one noticeable omission is any apparent recognition of the practical constraints under which many target audiences for the results of studies have to operate. Undoubtedly, the development of good practice guidelines and the metrics of their use will obviously benefit some, However many are unable to apply the logical conclusions interests, etc.) Perhaps one area for further research therefore could be to get a better understanding of what the wide diversity of budget holding health care decision makers need most and then fit the application and improvement of the methodologies to those needs.

One other suggestion is that perhaps it might be more appropriate if the diagram on page 3 placed Patients at the centre of the universe and Health Care Researchers on the outside?

COMMENT 17

1. In page 9, the statistical method part, data collection in clinical trial could be addressed, that is because it related to the outcomes of the study.
2. The figure in page 2 needs a paragraph to describe, it is strange to leave it alone and no discussion on it.

COMMENT 18

I have to confess that I haven't done much work in clinical trial based economic evaluations so I am not the best person to comment on the report. That said, I think the report did a great job summarizing methodological considerations in cost effectiveness analyses and made valuable recommendations. I can't agree more with the idea of promoting standard practice and providing richer details of methodology in applied journals. I often find it hard to interpret results from published studies when I don't have the full knowledge of the method used. I will keep the document in my reference library and share it with my colleagues.

COMMENT 19

Overall, I think the report has touched on some very important issues for a very complex topic. For a topic so broad, it can be difficult to establish the appropriate scope of the report.

The introduction indicates that the focus of the task force has been limited to CE research. Broader issues in HEOR such as patient reported outcomes, HRQoL, and software, have been considered outside the scope of this report. I am not quite sure what you are including as part

of CE research vs. topics outside the scope of the report. In Figure 1 on page 22 there are different types of HEOR studies accepted for publication. Are all of these different types of studies within the scope of this report? If so, are different types of guidelines needed for the design and analysis of observational studies (including BOI for epi and cost, registry studies, and database studies), design and analysis of HE data collected in clinical trials (including utilization and cost data for RCTs and naturalistic clinical trials), identification and synthesis of data inputs, and modeling?

I also think the introduction should include some mention of the decision makers' ability to understand the studies and overcoming the barriers to acceptance of CE research. Since CE research is designed to influence decision makers it ultimately needs to be evaluated on that basis to be successful. I would actually like to see this section earlier in the report with specific comments in each of the subsequent sections about how this can be achieved.

In Section 2, Guidelines around the Globe, in the second paragraph the report indicates that a few authors have compared and contrasted different sets of guidelines. The report then states that all guidances are similar across the board, but there are some significant differences, generally due to their intended purpose, the audience to be addressed, regional, cultural, or political variation, or author or sponsor preferences. I think there needs to be more detail added here about emerging controversial issues and potential gaps in the guidelines. Otherwise, why choose an instrument to evaluate them and has harmonization already been achieved? Do the guidelines include issues related to transparency of results so they can be interpreted by people without extensive HEOR training?

The introduction to Section 3, Statistics and Science, indicates that for ease of presentation clinical trial based economic evaluations and decision modeling based studies will be addressed separately.

First, I am not quite sure how clinical trial based economic evaluations are being defined. I think of clinical trial based economic evaluations as models where the model inputs are limited to data obtained from a single or multiple clinical trials. If this is not how clinical trial based economic evaluations are being defined in the report can you please provide a definition?

Second, if you are defining clinical trial based economic evaluations in the way I have indicated above, should there be some discussion in the report about the appropriateness of conducting clinical trial based economic evaluations and when they should be used? I was recently involved with very large clinical trials for vaccines where there were very few protocol mandated visits. Even in these situations, the burden of the illness did not reflect what was found in epi studies. I came to the conclusion that the trials are designed to measure the efficacy of the product and this can be done with resource utilization and cost but I would be very cautious about using the trials to obtain other types of data. The task force may not share

my perspective on this but I think issues related to how protocol mandated care can influence the data collected should be included in the report.

Third, under the clinical trial based economic evaluations, joint comparison of costs and effects and estimation of uncertainty, and analysis of cost data are listed. I would think that these two topics are not limited to clinical trial based economic evaluations. They are issues that are important for all types of economic evaluations.

The topic of decision models begins with methods for evidence synthesis. I think it should start with sections on defining the boundaries of the model and choice of model structures. The section on synthesis should include identifying and synthesizing data. These are the first 3 steps Andy Briggs outlined in his book on Decision Modeling. In the section on identifying and synthesizing data, I think it would be helpful to have some additional detail about how to evaluate the strengths and weaknesses of different sources of data and when synthesis of data is needed. Should it be used in all situations or are there certain situations where it is not appropriate?

Although broader issues in HEOR such as patient reported outcomes, HRQoL, and software, have been considered outside the scope of this report, I think it is important to have at least a paragraph related to the choice of outcome measures used in the decision models. The fact that QALYs are not well understood by people without training in CE and the fact that the benchmarks for determining whether studies are cost-effective are somewhat arbitrary must be addressed in order to promote acceptance of the results on which the economic evaluations are based.

In Section 6 under guidelines I would add one more bullet to develop a report card on the quality of guidelines for journals. Under methodologies, I would add a bullet on educating decision makers as well as developers of models about different aspects of HEOR. If the decision makers are more able to understand the methods used and they expect these methods in economic evaluations, developers will be more motivated to adopt them.

COMMENT 20

This is a good and important report. It covers multiple aspect of cost-effective analysis from different perspective of view. My comments are on the statistical section:

1. For analysis of cost data: Propensity Score Bootstrapping is a novel but promising methodology in analyzing skewed data with cofounder. It worth to reference it in this report. Reference source: Faries D, Peng X, Obenchain R. Analysis of Cost and Cost Effectiveness Data Using Propensity Score Bin Bootstrapping in Analysis of Observational Health-Care Data Using SAS. ed. Faries D, Leon A, Haro JM, Obenchain R. in press. SAS Press, Cary , NC.

2. It may worth to add a paragraph on missing data, though there is one section on censored cost data. People may have different interpreting between censoring and missing.

Overall, this is an important document which gave cost-effective research guidance to researcher, decision maker and journals. I'm looking forward to see the final report.

COMMENT 21

The points of view on this draft as expressed by The Swedish Council of Technology Assessment in Health Care (SBU) were based on the past and present practice as regards assessment of evidence. Since evidence of a health technology, according to the SBU definition, can only be based on empirical studies of relevance for Swedish health care and on studies of higher study quality, very few studies of cost-effectiveness are included in the systematic reviews conducted by the SBU. By saying that, there are rarely any evidence expressed as regards studies of cost-effectiveness in the SBU-reports

However, the SBU finds the aim of the ISPOR task force quite relevant, i.e. to improve cost-effectiveness research in order to facilitate their use for better health care.

As a general comment, this draft was well prepared, covered an impressive amount of relevant references, and included several important issues. From the point of the SBU, the ISPOR vision of a continuity of quality improvement of cost-effectiveness research has a full support. A harmonization of existing tools for evaluation of guidelines based on cost-effectiveness studies is also needed.

Some further comments:

Section 3, sub-title Joint comparison of costs and effects and estimation of sampling uncertainty: The second last phrase on page 10 states that “observing no significant difference in costs and effects need not rule out that one can be confident that one of the two therapies is good value”. It is the opinion of the SBU that medical outcome data showing no significant difference (i.e. if not $p < 0.05$ or less) between two interventions compared, should not be included as any difference of medical effect in the economic modelling of cost-effectiveness either. If there is no difference of medical effect relevant to physicians, economists should not include non-significant differences of medical effects for cost-effectiveness analysis either.

Section 3, sub-title Handling of censored cost data: Page 12, third phrase, the SBU is rather hesitant to follow the task force recommendation that “ignoring small amounts of missing data is acceptable if a reasonable case can be made that doing so is unlikely to bias treatment group comparisons”. That seems to open up for some subjective interpretations.

The section on Decision Models (section 3) includes several important aspects to consider. From the point of view of the SBU, the most important aspect is the need for complete

transparency of a modelling study, and that also includes the availability of a model in an electronic format.

In section 4, although with a low response rate to the survey, it was a surprise to read that only 4 out of 54 responding journals recommended the BMJ health economic guidelines (p. 21) as requirements for publication of studies of cost-effectiveness.

In section 5, the results of the survey once undertaken by Drummond et al and published in 1997, concerns a core aspect on the problem of implementation of health-economic evidence at local level. The need to put evidence of cost-effectiveness into the framework of budget limitations, or limiting possibilities to move resources from one sector of health care to another, must be considered.

Section 6, improvement of recommendations: As stated initially, it is not the objective of the SBU to publish guidelines. However, from a more general point of view of health technology assessment, SBU gives support to what is stated under the headings Guidelines, Methodologies and Publications. However, under the heading Decision-making, recognizing at ISPOR meetings those countries/agencies using cost-effectiveness analysis well, means indirectly an identification of those that are not doing so well. In the latter case, there is a need for concurrent explanations of why some are not doing so well, which quite often boils down to budget limitations.

COMMENT 22

I have reviewed this excellent report. Very well done.

The first section in on guidelines around the globe is a good start but seems less complete than other sections. You have set a fairly comprehensive goal to assess guidelines and their use and then have mostly just listed the guidelines available.

You have already identified guidelines that exist for different jurisdictions and the / countries and stated that they are broadly equivalent to each other. It would be good to have an actual reporting of which elements are the same and where they differ. Given that you find the key elements are the same, these might form the basis for assessing quality of the studies. This would give you core content to compare the existing scales of quality or to make up your own.

In evaluating guidelines it would be good to keep a distinction between which are mandated to evaluate for reimbursement (e.g. Canadian provinces, Australia, NICE in UK) and which are methodological recommendations but not directly tied to reimbursement or purchasing.

The analysis section is excellent and comprehensive. You have identified that it is important to make the best methods methodologically available and this is a nice summary of methods and good practices.

COMMENT 23

Pg 3: A brief description of the figure will be helpful.

Pg 4 Line 3: "*increase credibility and usefulness*" I'm not sure usefulness of what?)

Pg 4: Remove the 1st "or". It would be nice to include at least 3 sentences in 1 paragraph.

Pg 4: Full forms of the acronyms used for the 1st time will be helpful.

Pg 5 Line 7: I'm not sure why it is called "*permutations between*" I think it could be "combination of..."

Pg 9, 2nd para 1st sentence: A citation will be helpful.

Pg 10 line 15: Please consider the grammatical construction of this sentence. Further I cannot understand what sort of "joint" analysis the authors are talking about.

Pg 10 line 20: I am not sure how uncertainty is measured - is it by means of confidence interval approach ?

Pg 15 2nd para: Are the meta-analyses conducted in different settings?

Pg 15 last but one sentence: "*However, such analysis does not pay*" Is this a finding from any study? Further explanation of this concept can be helpful.

Pg 25 1st line: "*Drummond et al. also [add.... stated that] decision-makers*"

Pg 25 2nd paragraph last line: Needs detailed explanation

COMMENT 24

This is an excellent start. I have the following comments:

Major:

-I think net monetary/health benefits should be better explained. They require a lambda (willingness to pay) and are in essence a cost-benefit analysis technique - "Cost minimization" from my view is incorrect. You did not mention their use in EVPI/EVPPI. Ethical concerns against the use of pure cost analysis and cost-benefit analysis are not mentioned. Even the title is not accurate. This section should be revised.

-Analysis of cost data: neither mean nor median are sufficient (median is BTW important in PSA). The entire distribution should be described.

This is not a textbook but should be useful advise for intermediate and advanced researchers.

-Meta-analysis: direct vs. indirect vs. mixed treatment comparison should be explained a bit better (to me this is clear, but can you make it crystal clear?) -VOI, 2nd paragraph, 1st sentence: insert 'maximum' in front of 'amount'. Explain EVPPI better. Is it always 'necessary'? Same goes for EVSI - what if evidence comes in one sample, not in many? How do account for fixed and variable costs?

Minor:

-HEOR is used as an acronym before it is explained -You should mention the search strategy (appendix) and ask readers to submit references in case some guidelines have not been

identified -Section 3: follow ISPOR's terms (ISPOR Book of Terms) -Specify which "*new statistical techniques*" you are talking about -p9, a) One sentence before you go into this would be helpful to understand under which category these methods fall -NMB and NHB are more common acronyms as far as I am concerned -find acronym for the task force

Great work! I love your recommendations.

COMMENT 25

I reviewed QICER draft document. I just have one suggestion for Section 2. I read you mention the countries that have specific guidances and recommendations for HEOR and Mexico has PE guidelines, since November 2008. Maybe you can update QICER draft with Mexican information. I am sending you the guidelines (Guía de Evaluación Económica) and link for reference: http://www.csg.salud.gob.mx/interiores/cb_cat/cuadrobasico_cat.html

In Mexico the formulary evaluation body is General Health Council (Consejo de Salubridad General). When developing the formulary guidelines, two separate working groups (academic/government and industry) considered the draft guidelines and provided input.

The Guidelines are intended to standardize rules and methods for economic evaluation. The guidelines state that a health sector perspective is taken in the evaluation and not consider patient preferences. The principal recommendation is to present a Cost- Effectiveness Analysis, CUA and Budget Impact Model are accepted like a complement. Not cost-effectiveness thresholds has been communicated that would support a successful application. (Some decision-makers use the World Health Organization recommendation, but is not a transparency process for manufacturers).

In general terms the guidelines are aligned with International guidelines.

Obviously Mexico is very young in Pharmacoeconomics subject. By law the requirement to present a PE study just have almost 5 years. Up to now Government and Industry are in a process to improvement PE knowledge.

Despite industry included in submission a PE study, the formulary decisions have been driven primarily by cost considerations. Good epidemiological data are lacking, as well as any standardized cost data bases.

But, the most important thing is that finally Mexico has developed health economic and outcomes research guidances - I think is good beginning.

COMMENT 26

Thank you for the opportunity to serve as a reviewer of this task force report. I hope that these comments will be useful. Here are my main thoughts:

- (1) This is an excellent start on a tough but essential topic for the ISPOR membership.
- (2) I found the sections on guidelines around the world, publication quality, and recommendations extremely useful.
- (3) I didn't quite understand how the sections on statistics and decision makers really fit into this report, since it would seem to overlap with other task force reports with a focus on methods.
- (4) It might be helpful to tie the recommendations directly to each prior section of the report for easy reference.

From my standpoint, I think focusing on development of a single checklist, even if it is broad, would be of great value—something like the old JAMA series “Users Guide to the Medical Research on...”, if that was never done for health economics. And, of course, attempting to monitor the quality of the literature. Finally, some appreciation of where there is not agreement on quality would be useful too, which will allow for more progress in our field to be made.