The following are comments received from the ISPOR Membership in response to the draft paper which is available for review at http://www.ispor.org/workpaper/RWD_TF/RWTFDraftReport.pdf

The comments are divided into three groups: Scope of Paper, Content of Paper and General Comments.

**Scope of Paper:**

In general, I find the report accurate and well written. My compliments to the authors. I have some suggestions:

- The recommendations contained in the report, at times, seem to be in several locations and often appear more as suggestions (or it is unclear if they are suggestion or recommendation). It would help if all recommendations were bolded, laid out consistently, and perhaps numbered, similar to the way they are found in clinical guidelines. In the same way, while I appreciate the need for offering alternatives, I was hoping the report would contain more recommendations to give guidance and eliminate unacceptable alternatives in the use and analysis of real world data.
- You clearly address the benefits and limitations of real world data. However, I do not find any discussion of how the data can be used to make decisions about clinical matters, or even the concepts of coverage and reimbursement that you mention at the beginning. Perhaps this was beyond the scope of your task force. If so, you should probably clarify it and remove the references to "coverage and reimbursement" since I don't find anything in the report that is unique to those issues; either that or expand it to state how "coverage and reimbursement" are impacted by real world data.
- A fundamental reason for the use of real world data, as you point out, is to gather effectiveness over efficacy data. However, what makes it even more useful to decision makers is the idea that it represent real patients typical in the practice. To that end, you are right when you talk about the impact of confounders and bias. But, I believe a discussion on the things that make real world data unique, such as outcomes, perspective, setting, definition of resources, etc. would add something to this paper. It would show that real data studies can be tailored to meet the needs of the user, and the things that need to be taken into account.

**Comment 2:**

Congratulations on a well-written and thoughtful paper.

I have only one comment and concern - the title Real World' Data in Coverage and Reimbursement Decisions is somewhat misleading and should be changed for the actual publication in Value in Health. As it is, the title indicates that the focus is both on RW data AND coverage and reimbursement decisions.
Actually, the paper is an overview of RW data, period. The reader is left with very little indication of HOW to use RW, just WHAT it is and is not. It may sound like hairsplitting, but you don't want to raise expectations when literature searches are done, and the title causes disappointment, regardless of it being a good paper. A simple modification such as "Understanding real world data for coverage and reimbursement decisions" may be sufficient.

Comment 3:

Thanks a lot for the paper which I have read carefully and found very much interesting. The topic is important and I share your view that much still needs to be debated and agreed upon.

My general comment is that while the topic of RW data has been “technically” analysed in great details, the paper misses a “conclusive” part where clear indications on when RW data are to be used, who is to be in charge of paying for RW data and evidence, whether decision makers are to use common and global guidelines to conduct (or pay for conducting) non-experimental studies are given. By reading the paper it seems (at the end) that one of your goals is to provide indications on the above issues but there are not or they do not come out clearly enough. I think that your paper is an excellent piece of paper and that further analysis and clarification/indications on the above points would contribute a lot to the debate around the issue.

Comment 4:

Broadly, the paper seems well constructed and I particularly liked the section on sources of real-world data.

As for suggestions, my first is about the definition of real-world data. I appreciate this has been controversial within the task force. But “data used for decision making that are not collected in conventional controlled randomized trials” seems too broad. As stated, it includes everything from decision analytic models to systematic reviews. I don’t imagine you intended the definition to cover data that are secondary syntheses of primary data, even if they might be valuable evidence for decision making. I suggest the definition be restricted to primary data collected at patient level by methods that minimise the imposition of artificial constraints. This might include pragmatic clinical trial designs as well as other approaches lower on the classic epidemiological hierarchy of evidence.

The paper might acknowledge that the controversy between explanatory and pragmatic designs to answer questions of clinical effectiveness, let alone cost-effectiveness, has been simmering for many years (Schwartz D, Lelouch J. Explanatory and pragmatic attitudes in therapeutic trials. Journal of Chronic Disease 1967; 20: 637-648). So it’s relevant beyond and predates the modern era of pharmacoeconomics and outcomes research.

I wasn’t entirely comfortable with the definition of economic outcomes, though I accept many people tend to use the word “economic” to refer to resource utilization and costs only. My rationale is that economics in the context of reimbursement and adoption decisions is (or should be) about choices for efficient allocation of scarce resources. We need to emphasize that both costs and outcomes play into this. This isn’t just splitting hairs – I think it’s important because saying “economic outcomes” when we mean “costs” serves to perpetuate the idea among certain decision makers that health economics is just about saving money and that the economic criterion for acceptance of a new intervention should be whether it saves money, as opposed to providing improved outcomes at reasonable incremental cost. I suggest replacing “economic outcomes” with cost or opportunity cost.

The short paragraph on modelling looked like rather an afterthought! It left me wondering about how the topic applies to decision-analytic models, and whether this is a whole topic in itself. Models are usually constructed as a vehicle for cost-effectiveness analysis. This begs all sorts of questions about the criteria used for decision making, be they disaggregated outcomes such as clinical effectiveness, PROs, costs; or a modelled synthesis of these in a formal cost-effectiveness analysis. That in turn takes us into questions of whether all the available evidence, whether pragmatic/real-world or explanatory should be thrown into the same pot. Should your scope include using primary real-world evidence as an input to secondary analyses, such as modelling. If so, this would merit a full section. If not, perhaps leave out the...
mention of modelling and state that your terms of reference are the use of real-world data as primary evidence.

The construction of the sentence at the end of page 4 I found jumbled. Do you mean “Both DERP and IOWiG emphasize RCTs for clinical evidence to project real world effectiveness, as opposed to synthetic modeling approaches such as those used by NICE?”

I hope these brief comments are of some help. From my perspective in consultancy, the demand for real-world studies in Europe is growing as decision makers resist betting too heavily on modelling predictions. Keep up the great work!

Comment 5:

Thank you for the opportunity to comment on the work by this Task Force. Following are my comments:

- It seems that this report was written by those individuals with mostly pharmaceutical experience - the content is only suggestive of pharmaceutical studies. This report does not recognize the differences between the medical device and pharmaceutical industries.
- The report lays out a list of possibilities for developing real world clinical/economic evidence. Many medical device companies have followed the Medical Device Amendments (1976) which standardized the safety and efficacy clinical trial model, which, as a result of the task force, would now become the starting point for the clinical program.
- The report also touches on definitions of the types of evidence that could be gathered and little about how one chooses which are most appropriate and in what circumstances - will the task force continue their work in that direction?
- I would recommend that ISPOR note in the abstract that this applies to pharmaceutical studies only.

Comment 6:

Thank you for the opportunity to preview this document and to comment.

My first thought after reading the document was "Where's the beef?"

This was an easy to read review, but fell short of your stated mission: to develop a framework to assist health care decision-makers in dealing with 'real world' data/evidence and information in 'real world' health care decision, making, especially related to coverage and payment decisions. The document draws attention unresolved issues but offers no suggestions for resolution. The only new issue raised is who is going to pay for this research.

I can offer 2 suggestions: Add a section about group, such as the Cochran Collaborate which conduct systematic reviews and offer methodological standards for dealing with the inherent biases and other limitations of real world data. Expand the scope to global and cross-cultural issues. After all, ISPOR is an international organization.

Regarding the conflict between the terms real world “data” and “evidence”: Data collected for any purpose or source can be utilized to provide real world evidence. Administrative claim can used to determine some clinical outcomes. Clinical data from RCT's plus economic data are used in real determining economic evidence. I see no downside to using the term “real world evidence”? But there is a downside of using the term RW “data”. Unfortunately, too many observational studies articles describe the study design by the data source (e.g. retrospective database study or registry study).

The Task Force Report supplies some useful definitions and highlights the limitations currently encountered when attempting to use real world data to make coverage and payment decisions (which we encounter on a daily basis).
However, if the underlying purpose is to help health care decision-makers use real world data, this document falls short of that goal. In our opinion, no framework was provided to "help health-decision makers deal with real-world data and information in dealing with health care decision-making." In addition to outlining the problems in dealing with real world data, it would be helpful to offer some potential strategies for solving them. For example, there is a start on providing specific tools in section 4.6, with regard to value of information (VOI) analysis, but more useful would be an example of its use and references to resource materials.

Comment 7:

I think that the frame of the study is very interesting and of global form I believe that yes it is necessary to obtain real information to be able to improve the Health policy. Nevertheless, I consider that the decisions for the health coverage are very different considering the country in which one resides.

In Spain, Health coverage is guaranteed almost universally for everyone, for what the decisions, although increasingly they are guided by results of clinical and economic studies, bases on others prescripts. Although we have universal health coverage, we need to evaluate outcomes based on clinical, economic and PRO studies, so we are be able to offer better health assistance.

On the other hand, although I think that it is essential to develop real world data, but as important is also to evaluate the reliability and consistency of outcomes. For example, in reference to the PRO studies, the used instruments have been improving, but sometimes they are used in an inadequate form (well, because they were not designed for the studied pathology or for the absence of PRO knowledge) or they are designed in such a way that they only reflect some of the adverse effects and others do not (for example, in transplant fields, the health related quality of life questionnaires often evaluate just the adverse effects of an specific immunosuppressor). The same happens with the economic studies.

So, the framework made by the Task Force will be very useful for the health care decision-maker.

Thank you for taking my comments accounted.

Comments 8:

Overall the report looks good. I had few suggestions -

- The report focuses on coverage and reimbursement - I wonder if it also has implications for cost-effectiveness and quality of health care
- Use of health surveys for understanding prescribing behavior and quality of care

Comment 9:

I really appreciate you for sending me such great draft over real world data. It was really interesting and I learned a lot from the draft, especially the task force showed systematically variety of real data with its characteristics. Also I got fully apprehended necessity of the real world data for decision-making.

Even though I am good at the US context, but I would like to make some points. Please consider that I am from South Korea and my comments based on my own knowledge and experiences in Korea.

- which level of decision makers do you target? It is ambiguous to figure out what level of policy makers need "real world" data, I don’t think that you mean the draft is only targeting decision makers in government level. Because there are many levels of policy makers in the US, and the way the task force discussed is more instructive to decision makers of each HMO or PBM or insurer level rather than government level.
- it should be defined whose perspective is mostly considered? I am much afraid that the ISPOR real world task force draft should be distinguished from argument of pharmaceutical companies. Even though I fully understand how much we need to match clinical outcomes, claims data and registries to get ideal evidence, I think it is necessary to consider not only privacy of patients, but each country’s policy. Some countries require pharmaceutical companies to submit data for
reimbursement, and the governments have no responsibility to support drug use data with claims or etc. Thus pharmaceutical companies usually buy commercial data like IMS. Even though it looks very easy and cheap to argue claims data should be shared in NHS or NHI countries, but it should be discussed if the country have complete system to protect privacy and confidentiality. System of IRB was mentioned in the draft, but it is not universal system in global, I think.

- in the scope, US vs. global focus, I cannot agree with that the focus group extend their implication to global with very limited experiences from US and NICE, IQWiG. Even though NICE, IQWiG are referenced to make up for limitation of the draft, it does not seem appropriate that findings be global in reach.

Thanks so much for sharing the draft and giving me a chance to comment.

Comment 10:

Thank you for the chance to read and comment on your Task Force’s draft report. I read it with great interest, and found it to offer a balanced and pragmatic review of the availability and use of real world data.

I have one general comment: it seemed to me that there was little consideration of the automated, anonymised longitudinal patient records databases that already exist, especially (but not only) in the UK where patients register with a particular primary care physician or practice, and the PCP acts as the gatekeeper to health care resources. Because of the fact of patient registration in the UK, there is good denominator information, and all disease areas are potentially covered. These are not claims databases but capture clinical data directly from the electronic patient record as maintained by the physician for his/her own ongoing clinical management of the patient. Your report makes only a brief mention of EHRs, appearing to suggest that this is a type of data source for the future and not the present, and it does not appear to consider these longitudinal clinical records databases to be EHRs; nor are they patient registries in the way defined in that section.

I wonder whether due account has been taken, therefore, of the work already undertaken using these databases, not only for pharmacoepidemiology but also, increasingly, for HEOR studies. I would be interested to know how the Task Force positions these databases, and what they see as being their value in assessing real world outcomes.

Comment 11:

The report was excellently written, the only comment I had was the focus – the title mentions reimbursement decisions, however, the text focused more on the strength of different methodologies and very little on impact of each on reimbursement decisions. Could there be more added or an appendix on how this impacts reimbursement and coverage. May be a separate report on factors impacting reimbursement and coverage and then try to combine the conclusions of this report could be more productive.

Comment 12:

The draft report looks good! I have a few comments about the draft report. When dealing with real world outcomes, we look more at the overall effectiveness of the drug. Therefore, it’s important to include information about a drug’s probability of causing adverse events (variable considered when doing CEA). This leads us to an important topic that needs to be mentioned as a potential objective of this report, and that is, patient safety (Patient Safety and Quality Improvement Act of 2005- key topic in one of President Bush’s speech).

Also, data differs from evidence because data is collected for more than one purpose (billing, payment, research etc) while evidence is collected solely for research purposes.

Other Benefits of RW
• Allows us to know the net monetary benefit of a treatment
• Allows us to indirectly compare the effectiveness of a treatment in more of a crossover type setting i.e. the same patient but switch treatment to its ineffectiveness
• Allows us to explore new drug indications
• Fosters an environment of continuous research

Comment 13:

I appreciate your initiative. As naturalistic studies to generate RW data are not accepted as classic RCTs it is a great challenge to bring the importance of this trials and data into attention and to establish the methods as valid tools.

Now please find my suggestions below. I focused on ups and downs of RW studies and classic RCTs and chapter 3.3 and 3.4. I hope my comments are not too specific. Chapter 4, covers most of my comments but I think some aspects need more explanation or specification before.

In general I’m missing a part which focuses on timing. That means at which time point the collection of RW data must start to get the data in time. As fare as I know RW data are often not available at the time of launch or are generated by using the piggy back method. On the other hand NICE starts the appraisal process before / around launch. This "discrepancy" should be pointed out.

• From my point of view "real world data" is the perfect term. It is a clear differentiation compared to data coming for classic RCTs.
• Evidence hierarchies: is a very important point regarding the acceptance of RW data. In chapter 3.3 and 3.4 it looks like that RW data generated by "naturalistic studies" do not fulfill criteria of high evidence. One of the most important may by most important criteria of EBM is randomization. It should be pointed out that "naturalistic studies" should be randomized trials whenever possible.

Some aspects might be more pronounced:

• RW data coming from "naturalistic study" often have a totally different primary end point as classic RCTs ( PRO, health care utilization, direct/indirect cost vs. efficacy)
• The limitation of classic RCTs: mostly a comparison drug A vs. drug B but not focusing on treatment procedures in total. Economic aspects/ data are often collected by using the "piggy back". I have attached three articles from Freemantle at al which are dealing with the limitations of these different study types.
• Pragmatic trials: There might be also the possibility to run pragmatic trials randomly (randomization on center level for non interventional observational trials). Again I think randomization is a very important factor to increase the acceptance of RW data. In the report you mentioned the German IQWIG. The IQWIG only accept published data of the highest class of evidence (I think this is not best practice and not correct, hence it’s the reality in Germany). I don’t agree that costs for a pragmatic trial increase by the large number of patients and setting if the collected data reflect daily medical practice, only. Additional visits and documentation of aspect not really needed to answer the scientific question will increase the costs for sure. That means: define the question and document what is really needed.
• RW data coming from registries: There are ups and downs. As far as I know no real international conventions regarding quality standards and quality insurance exist. Mostly a protocol including a definition of endpoints and hypothesis and a standardized statistical analysis plan do not exist. So it might be complicate to compare data generated by different registries. On the other hand by using a registry it is possible to generate a large data set.
• RW data coming from "retrolective studies" (as some people named them). I have attached a presentation from Hubert Kolb held at EASD 2004. I like this study design. The main advantage is
to combine retrospective and prospective aspects in one setting. Using this design it is possible to generate naturalistic RW data in a short time period.

In conclusion:

- Randomization will increase the level of evidence. As I am a member of the international real world study steering committee (trialist) you understand that I prefer to generate RW data by using a randomized naturalistic study designs. Pragmatic trials should be randomized. The retrospective design is an attractive alternative to registries. May be you will add it into chapter 3.4

I apologize my comments are very short but I’m back in the office since Sept 4th. My mailbox is like a disaster. It will be a great pleasure to work together with the real world data task force in the future. I’m highly interested.

Comment 14:

It is an interesting report. Would it be worth also discussing the reliability and consistency (or lack of) in the actual coding of health data as it is entered at the point of care - particularly in relation to the limitations of electronic health records?

Content of Paper:

Comment 15:

Thank you for the opportunity to review the draft document. My comments are as follows:

- Strongly agree with use of data vs. evidence in describing RW data.
- What about the concept of using RW data in a CQI approach to validate or refute RCT design and results on a case by case basis vs. broadly focusing on the limitations of RCTs? Also, what about detailing the use of RW data to guide the development of follow-on trials vs. the positioning them as a “higher level of evidence”?
- I would disagree that RW data provides a higher level of evidence then the traditional RCT as stated on page 9. There are far too many bias and data integrity issues for this position. There are 12 bullet points citing the advantages of RW data vs. the 1 paragraph on its limitations. This does not seem balanced. Bias and data quality are substantial issues that may/may not be adequately addressed statistically. RW data has utility ONLY when there is mutual validation with RCT results, clinical practice and the results of systematic reviews.
- Where is the role of high quality systematic reviews in guiding RW data methodology and interpreting results?

In summary, this draft seems very biased towards the utility of RW data. I think all consumers of clinical information would be better served by emphasizing an ongoing continuum of cross-supportive methodologies. RW data, while useful and a key piece of the overall evidence equation, should still be ranked after high quality systematic reviews and well designed RCTs.

Comment 16:

- This is a good start for dialogue, as it is intended.
- Although they may be often used, the term Practical or Pragmatic clinical trials, are quite misleading. Also you tend to put more emphasis on their “real-world” aspect than truly exists. They are still clinical trials and subject to the limitations of clinical trials (e.g., sample selection).
- I understand you are trying to shape this to address the ISPOR audience, but there is a much larger health economic audience that shapes policies formed by payors, including the federal government, which seems to be ignored. They also use “real world data”, that has a differing set of challenges.
• Pg 6 paragraph 1 “This is not to say that data from RCTs are irrelevant or not used by decision makers: indeed, they remain the critical foundation for almost all coverage and reimbursement decisions.”

Comment: This statement seems a bit strong given multiple mandates and policy requirements that are at play. Furthermore we know that it is impossible to utilize RCTs for all treatments.

• Pg 6 The use of real world “data” is most appropriate, especially given that this paper is intended to combat the idea that the term evidence is typically thought to be associated with randomized controlled trials, hence the idea is not to define evidence, but to help the reader understand what needs to go into building evidence. One study is never enough, regardless of its quality.

• Pg 7 Focusing on coverage and reimbursement decisions limits this to evidence based medicine for the insured. Therefore, if you are hoping to stress that this type of research is focused on evidence-based medicine, it will weaken your argument. Furthermore, it emphasizes the need to clearly define limited populations in comparison to international data that is based on the national populations (i.e., national coverage vs. us insurer selected coverage).

• Section 3.1 Are you characterizing the data or defining types of analyses??? Suggesting that data is actually a type of analysis implies that you are creating this data to support the outcome you want, not collecting data to support a specific type of study. Many datasets can be utilized for a variety of analytics (economic and clinical)

• Section 3.2 Try to balance the subsections. It seems you are putting more weight behind patient reported outcomes. I am not sure this is the intent, but given the amount of commentary it appears that way.

• Section 3.4 paragraph 1 – I would include panel surveys as a separate type of real world data. It incorporates a time dependent aspect, has long been used in economic and health economics to support health policy decisions, and requires a separate set of skills to analyze. I suppose this could go under health surveys, by expanding that section a bit as it doesn’t address some of the large sample size that would be found in a panel survey, etc.

• Pg 17 claims databases – You did not mention that one of the biggest problems with claims databases is that they typically do not include inpatient care data. Given that this is one of the largest healthcare expenditures, it would be imprudent to consider this type of data for an economic analysis for decision making, or to evaluate health outcomes for that matter. Furthermore, they only include reimbursable data.

• Section 4.4 (one of the better sections)

• P. 21 last paragraph, last sentence. The prior sentences do not support your statement that this will ensure that informed consent is in place.

• P22 THANK YOU, for including information pertaining to the endogeneity bias! This is far too often overlooked in the pharma field.

• Section 4.7 Would like to see an emphasis on replacing predictive models with Real World Data, rather than an amalgamation of all types of data to produce a result. This would help with the transparency issue that is brought up in the last paragraph of this section.

• Page 26 paragraph 1 – I will go back to an earlier comment and state that you are limiting the potential of “real world” data by continually listing a few favored types of data by the panel.
Comment 17:

Thank you for the opportunity to review the above mentioned report. I appreciate that there was considerable work spent on this important issue. Overall the report is well structured and reads easily.

I would like to start with some general comments on the report before providing some specific comments by page. As already mentioned during a session at the last European ISPOR meeting I believe the report would benefit from setting a clear perspective for whom the report is meant to be. Form my perspective there is a “provider” of such RW data that needs to be acquainted with “good practice” in generating and presenting RW data. The provider in rare instances could be the same as the addressee, meaning that reimbursement agencies themselves may generate or commission to generate such data. However, in practice, more often we have the situation that reimbursement agencies request RW data (as general policies or as a specific data request) and then the focus would be on how to interpret/appraise the provided RW data. Some more clarification of this would be beneficial (stating for example on page 5 what the report is NOT about AND maintain the perspective throughout the report).

The report would benefit a lot from a summary table on the strengths and weaknesses of the different sources of RW data. It is difficult to arrive to some comparison by only reading the narratives. The table rows could be addressing such issues as “sources of bias”, “methodologies available to address biases”, “external validity”, “typical population addressed”, “available guidelines on good practice for conducting research” etc. with appropriate references. And then most importantly statements on the level of evidence the Task Force believe these data sources can provide if research is conducted properly. If not done in this report, then it should be a next step to completely fulfil the objectives of the Task Force to guide decision makers in their appraisal.

It would be useful to state that primarily coverage decisions will have to be made without RW data on the product/intervention after marketing authorisation (based on phase II and III data). This coverage will make the collection of RW data possible, without at least some coverage the possibility to collect RW will be very limited if not impossible. RW data will then mostly be used to revisit the coverage decision at a later stage by the nature of the data.

By page comments:

- Page 2, “background” last sentence: reads difficult
- Page 3, 1.1.: Mention high internal validity of RCTs
- Page 4: I am not sure the AMCP dossier is a good example of RW data request since it is been written and provided initially shortly after marketing authorisation acknowledging that RW data at this point in time do not really exist. Rather than serving as an example for RW requirements it may serve as an example for standardisation of data requests.
- Page 4: “effectiveness and safety” is used, but it should read “efficacy and safety”, given the topic of the report
- Page 5: Real world data and “real world outcomes” should not be used interchangeably since not all RW data will be “outcomes” data (e.g. the often requested prescription data per country to assess “realized” budget impact).
- Page 6: “…they remain critical for almost all coverage and…” Add “initial” coverage and…
- Page 7: besides the P&T committees for formulary decisions in the US, add examples of national reimbursement bodies like in Canada, Australia, most European countries. This will underline the point you want to make even more since those bodies make most often national decisions for the whole population of a country rather than one P&T committee making it for the covered lives of a single health plan in the US.
- Page 7: add “for example” before NICE and IQWiG in second last sentence of this page
- Page 9: Sentence on observational studies: add “provided that potential biases have adequately been addressed”.

9
Comments to Using ‘Real World’ Data Task Force Report

- Page 10: since PRO is the overarching term it does not seem to be appropriate to speak about "quality of life and patient-reported outcomes". Also it is often been emphasized to speak not about quality of life but "health-related" quality of life.
- Page 10: last paragraph sounds as if the US was the front-runner in PRO inclusion in reimbursement decisions. However, I do not believe this was the intention nor would I endorse such a notion.
- Page 11: PRO in label and promotional claims is of course not the only reason why manufacturer include PRO instruments into clinical development trials. Should be worded more broadly.
- Page 13, 3.4. first sentence: correct grammar
- Page 13: use PRO/quality of life consistently (see previous comment)
- Page 14: another issue is that in some countries randomisation requires the sponsor to provide study drug which is a huge deviation from real world prescribing.
- Page 15: first parenthesis, add "for example, more likely to use..." since the differences are not only restricted to this but much broader like having a research infrastructure available with research staff, level of experience in conducting research etc.
- Page 15: "and determining value or reimbursement levels". I do not understand this sentence part.
- Page 16: There are clearly databases that are NOT claims databases, like GPRD or MEMO in the UK. This section should therefore be expanded to be broader. Most of the biases however are in common between claims databases and the above mentioned databases.
- Page 18, 4.1., starting paragraph on RCTs: The most important feature is missing which is randomization. Only this feature makes statistical analyses possible in the way it is confirmatory conducted.
- Page 18: Decision makers may not necessarily be the ones synthesising the RW data. It may well be that providers have to synthesize the data and present them.
- Page 19, second bullet point: Many RCTs for regulatory approval do not only contain placebo since it is for example a requirement of the European Agency (EMEA) to conduct comparative trials vs. standard treatment for regulatory approval.
- Page 19, 5th bullet point: I don’t understand: "broader range of outcomes (i.e. quality of life and symptoms)", since these outcomes are nowadays collected in most RCTs (at least in phase III).
- Pages 13-18 already include in parts appraisals of the limitations (so beyond description what it is) generating overlap with the limitation section starting on page 20 (4.2). Either the sections are merged or more clearly separated avoiding already discussion of limitations in the description part.
- Page 21, section 4.4.: Should be written from the primary perspective of the report on the USE of the data not the generation, meaning that users have to check on whether good research practices have been followed and then giving examples
- Section 4.6 Add some references to this section since concept and practical applications are not yet widely embraced nor conducted. Contact person could be Karl Claxton for suitable references.
- Section 4.7. Before starting on “modelling” there should be a paragraph what frameworks there are available to synthesize the RW data, models being one of them.

Comment 18:

Thank you for the opportunity to comment on this draft report. Below are my comments.

- Re: “Practical clinical trials have the important strength of randomization, which minimizes bias in the estimation of treatment effects.”

Comment – In my experience the term “practical clinical trials” or others cited do not necessarily indicate the clinical trial is randomized - and the term clinical trial does not mean it is a randomized trial. Think perhaps some clarification – or perhaps warning to examine the methods
needed around this issue. Don’t assume randomization because the type of trial was listed as a “clinical trial”

Practical Trials – also usually more long term – not just larger – adds to cost also – but also adds to ability to detect more “final” outcomes than shorter “registration trials”

- Under: Claims Databases: “Results should be reported in a clear and transparent fashion, so that other researchers are able to understand and reproduce the analyses.”

Comment – think this may have been meant to refer to “Methods should be…”

Overall – may want to cite need to educate formulary/coverage decision makers on types of real world studies and related benefits and drawbacks. Researchers may know this – but I doubt many on P&T committees do.

Comment 19:

I would like to congratulate you on producing a clear and comprehensive report. I have the following comments:

Section 3.2 Page 10:

- Is the list of clinical outcomes presented too restrictive? Should it include changes in physiological markers of disease e.g. blood pressure, cholesterol etc? Should symptoms listed here be better included in patient-reported outcomes?

- To match with FDA terminology it would be better to include ‘health-related' before quality of life.

Section 3.4 Page 13:

- Long-term follow-up of patients who have been in RCTs is another potential source of data.

Page 16

- Since registries are usually set up after product launch should their use in initial reimbursement decisions be discussed?

- Is it worth discussing the difficulties of obtaining measures of efficacy in claims databases?

Section 4.5 Page 23

- I feel that this discussion would be improved if it also covered circumstances under which RW data could have a greater influence on a decision.

Section 4.6 Page 23

- This section gives a clear indication of how to determine the value of collecting additional data but it is not explicit on who should fund it although that appears to be the focus from the first sentence.

Overall comment

- The question of whether RW studies can be conducted internationally or RW studies conducted in one country can contribute to a decision elsewhere is not addressed.
Comment 20:
The report is generally well written. I have the following specific comments.

pp. 8-10.

- The three categories of RW data – clinical outcomes, economic outcomes, and patient-reported outcomes – are not only broad but meld into each other. For example, cost/benefit or cost/effectiveness ratios are economic outcomes with clinical outcomes and patient-reported outcomes entering into the denominator. The implication that economic outcomes pertain only to costs (the numerator) is a narrow and incorrect interpretation of economics.

pp. 16-17.

- Re administrative claims databases, it should be noted that, if they occur randomly, miscoding and missing data are non-issues especially with very large databases. They seem to pale in comparison to protocol driven results of RCTs and surveys. The major limitation of claims databases is the absence of detailed patient information. Selection bias becomes less of a problem with more patient information. If medical records and other patient information can be merged with claims data, then randomization (the main advantage of RCTs) becomes less necessary. Claims and medical records data are generated for purposes other than research, making their marginal costs for research purposes minimal. Because of their size and diversity, relatively low costs, and freedom from protocol bias, merged electronic databases should be at the top of the evidence hierarchy.

p. 21.

- Re “good practices for collecting and reporting RW data..” These suggestions seem to have very limited application to RW data collected for purposes other than research, such as claims and medical records data. Modifications to data collection protocols may not only impose additional costs but may interfere with the main purposes of the data (payment/reimbursement and patient record keeping).

Comment 21:
Overall I think this is a well written and informative document. I have a few comments:

section 3.4.:

- description of real world data sources. I think that RCTs are inherently not real world, by design, even when we try to collect the 'big ticket' resource utilization items.

section 3.4. :

- EHRs. This section should be more elaborate. First by describing EHRs that exist in Europe (e.g. GPRD, THIN and others) and US (HE CDS data), second by at least discussing the emergence of more EHRs as a result of investment in HIT.

in general:

- the document is US focussed. Would be interesting to understand the application of real world data by out of US authorities, of have an idea on ex-US surveys.

Comment 22:
A few comments on the Real World Data report:
• in general a good report
• personally I would like to see more discussion about pros and cons of various types of RW data (for example the type of discussion that can be found on page 15 regarding data from registries)
• perhaps it could be mentioned that it will take some time before RW-data will be available for new drugs. Hence, initial price and reimbursement decision will usually have to be based on RCTs
• I am skeptical to the value of bringing in VOI in this context; I wonder how useful it is in real life

Comment 23:
I have some minor changes to suggest:

• Page 12, Para 2, Line 6. Period after ‘expert opinion’
• Page 13, Section 3.4, Line 1: Delete ‘is’
• Page 13, Section 3.4, Line 4: Period after ‘health records’

Comment 24:
Thank you for the opportunity to review the draft document about “Using ‘Real World’ Data in Coverage and Reimbursement Decisions”. It is much needed and important. I believe one of the most important issues is the recognition by the policy makers of the complexity, limitations and challenges of real world data as opposed to information obtained from randomized controlled trials.

I have a few comments:

• regarding 3.4 I noticed that all types of data listed have both strengths and limitations outlined except for health surveys. I would suggest adding some limitations of health surveys. They include among others the problems with validity of subject-derived health information (e.g. patient-reported diagnostic information), issues of subject recall, lack of physical examination and lab tests availability in case of interview surveys (as opposed to interview and examination surveys) and others.
• regarding 4.2 I believe that potential bias in observational research is associated with a specific research question and study design rather than being an intrinsic characteristic of a particular type of data (RW data in this case). RW data can be e.g. obtained in large simple trials where randomization would minimize potential for selection bias.
• regarding 4.2 I would suggest changing the phrase “observational or database studies”. I believe that most database studies are observational in nature.
• regarding 4.4 perhaps it would be worth mentioning that there are some existing guidelines on the evaluation of pharmaceutical products in real life e.g. the ISPE Good Pharmacoepidemiology Guidelines (see at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm)

Comment 25:

• Data to prove to added value of a new therapy in daily practice. And not to prove that a NCE should be reimbursed.
• 100% effective based on registration data. <100% effective in real life, mostly has nothing to do with the drug but with the surrounding circumstances (co-morbidity, doses variation, patient compliance, etc.)
• This lower effectivity still needs a political decision on reimbursement. But what is known about the standard therapy in real life?

Comment 26:
I have a couple of comments here:
• Page 6, "Data vs. evidence"

I would like to say "Data may be considered, which can be used for information, but evidence is thought as information that provides proofs or beliefs."

• Page 7, "Focus on coverage and reimbursement decisions"

I think the paragraph, "We recognize the decision......and the health outcomes they obtain," is somewhat irrelevant to the title of the section. Rather, we need to describe regarding the scope and definition of the "coverage and reimbursement". Especially, because real features of coverage and reimbursement are different in the real world, we need to show how the approach in this paper can be transferable across countries.

• Page 23, "The need to consider the costs and benefits of data collection"

This tile may produce misunderstanding, as which this paper handles cost-benefit analysis of using real world data.

I prefer the title as "The need to consider the merits and demerits of RW data collection"

Comment 27:

I just quickly read through your report on Using Real World Data in Coverage and Reimbursement Decisions. I believe that this is an extremely important topic and agree that at times observational data may be more useful than data for RCTs. Overall I believe that the report is well written however I would also encourage that you create an annotated version that covers is a few pages with some tables the key points of the report - I believe that your message will get to a much wider audience if you can summarize your key points.

Just some additional points of discussion. You mention that RW data can be used to determine how a drug is actually being dosed and used in the clinical practice. This is something that only can really only be determined from RW data and is extremely important in making coverage decisions. A drug may be shown to be very effective and cost-effective for a given indication but what happens when other non-studied indications become the predominant use of the drug. Obviously this can change the dynamics of the situation and it may be impossible to do a cost-effective analysis if data on the alternative uses does not exist.

Some additional analysis that can be performed with RW data is what happens when a drug is not covered, covered at a higher co-pay, covered only after another drug fails, or covered only with a prior authorization. Restricting access to drugs may have unintended consequences. For example increasing co-pays may decrease adherence to medication producing poor patient outcomes. Prior authorization may lead to certain patient receiving a drug that is less effective or more toxic because they could or did not negotiate the prior authorization process.

Comment 28:

I read the report in detail and am somewhat at a loss on how to respond. I found no particular problems with the report, but I'm not sure how useful it will be. It carefully enumerates a number of cautions to be observed in using 'Real World' data but does not provide seem to provide much in the way of useful guidance. In trying to evaluate it I thought of the reports from the panel on cost-effective in healthcare and Medicine. Those reports provided specific guidance on what to report, how to use the data, and most importantly how to deal with uncertainties and report thoroughly on what analysis was done and what its limitations are. I am not familiar with what exact charge the task force was given, so I don't know what possible advice might be useful. As pointed out in the report 'real world' data is being used increasingly to inform coverage and payment decisions. I guess that I would have hoped that the report might detail what a "panel worthy" analysis might be and how one might grade different analyses that might be constructed for the same situation. this may have been beyond the Task Force mandate and be part of some future
effort. In trying to assess the report, I tried to think of what I might do differently having read through it. I could not think of any single thing. It was a good introduction to the material, but was short on specific guidance. Economic analyses are troubled by having an embarrassment of riches, that is many resources could be used in many different ways. Information on standardizing some types of outputs and specifically dealing with uncertainties would be a welcome addition but not addressed in the report. No doubt these are areas of ongoing research and not yet to be settled, but the data is being used now and the process of "validating" an approach and knowing what level of confidence can be had in any particular analysis is a challenge that needs to be met each day.

I hope that these observations are of some use but fear that they might not.

Comment 29:

Thank you for the opportunity to comment on the draft for the ISPOR Task Force on Real World Data. It is obvious that much effort has gone into the preparation of the document.

As a strong believer in the values of real world data, I was concerned about the order of presentation in Section 3.1 Characterizing RW Data. The paragraph concerning hierarchies of evidence might be re-organized so that it leads with the strengths of RW data and then comments on the traditional hierarchies.

An example would be:

“RW data can provide a more complete picture of RW data, especially in the ability to add generalization to results that cannot be found in RCTs. The traditional hierarchies rank evidence based on the research design. Typically, data from RCTs sit atop the hierarchy followed by data from non-randomized intervention studies, followed by epidemiological studies and so forth. Indeed, some would argue that observational data can often provide a higher level of evidence regarding patient outcomes in actual clinical practice than can a registration RCT.”

Regarding the issue of ranking, I hope this committee can spend time in the future creating a ranking for real world sources, such as comparing the methods of validation used by data purveyors, levels of "adjustment" in DRG identification systems that maximize payment, and source of actual input (physician, technician, input specialist).

In Section 3.2 Types of Outcomes, the description of clinical outcomes might be enhanced by adding the phrase "physical measures" to the types of measures available. Several systems are linking lab and clinical measures to their administrative data.

In Section 3.4 Sources of Real World Data, the strength of the report might benefit from the order of listing of the sources. I suggest inverting the order to lead with Electronic Records and end with Supplements to RCTs.

Thank you for asking for comments. I read the document quickly and I have a few comments that I hope are helpful.

Comment 30:

First, when I began to read the document I thought this was about economic outcomes only. It was not until page 8 when the three types of outcomes are mentioned did I realize that the document was about real world data for each. I would suggest making a statement earlier about 3 types of outcomes.

That said, I found it a bit contradictory to say that physicians make decisions that affect individual patients and that the real world data addressed here would be used by bodies making decisions about groups (aggregate) -- and then include clinical data and patient reported outcomes as sources of information on which to make these policy decisions. Many times these types of data are used for individual patient decisions. I think they are used along with economic data, and in aggregate to make 'formulary' or policy decisions. At a minimum, I would suggest that you include that the clinical and patient reported outcomes
data you are referring to is aggregate data, not data applied to individual patients. I would also venture further by saying that neither clinical or PRO data can be used in isolation at a policy making level, economic data is the major driver in many decisions at the levels you are talking about.

On page 4 at the end of the first paragraph, the word alternative is used. I cannot think of a better word and I know what you mean, but on first pass, I thought you were referring to alternative or complimentary medicines (non prescription, herbal etc). The term ‘Alternative therapies’ probably means different things to different people.

Lastly, and I would be happy to discuss this further because it may be that I did not 'get it' - I do not understand how or if the objective of the task force was met. The mission to develop a framework to assist decision makers. I did not see how the document was a framework. I was looking for some more declarative instructions, such as decision makers should consider this data for formulary decisions. While all of the information contained within was informative, and the task force does a great job of bringing up ongoing debates (data vs. evidence), I just could not see by reading the document how a framework was developed.

Comment 31:

I applaud the important and substantial efforts of the Task Force to draft a framework designed to assist health care decision-makers with evaluating "real world" data and to report the findings. For the high-level reader this should serve as an important document when it is finalized and published. My only concern is that the framework is quite vague in key areas that the Task Force recognized would be important to coverage and payment decision applications. Although it may be difficult if not just time-consuming to cite important "real world" (if I may take leave) examples of the benefits of these data, such examples are conspicuously missing from Section 4.1 of the draft report. My experience suggests that decision-makers are likely to look to this type of document for concrete situations in which benefits, limitations, and methodological challenges of applying real world data have been undertaken, so that they can (most importantly) relate the situations to their own. One has but to look to recent articles in Value in Health and clinical journals or abstracts in scientific conference proceedings for the examples I am suggesting. It may be extremely helpful if the Task Force could substantially increase the value of this report by focusing future resources on the presentation of examples to frame the available "real world" data and how it is already employed for research and clinical guidance purposes.

Thank you for the chance to comment on the draft report. Even in its current state it should prove to be valuable, but with additional work its value could increase substantially.

Very useful information to a variety of stakeholders, especially the working definitions and the compare and contrast of the data sources.

- Section 3.4 – Sources of RW Data - Registries, p. 15
  Comment: May want to incorporate verbiage that registries may be hypotheses generating.

- Section 4.4 – The need for good research practices for collecting and reporting RW data – p. 21
  Comments: May want to incorporate verbiage delineating monitoring conducted for RCTs from remote site monitoring and “for cause” monitoring.

Consider verbiage to address importance of conducting data quality audit to verify accuracy of the data stored in the study database.

Comment 32:

A couple of minor comments include:

- p.5. Why was the framework to assist decision-makers rather than also analysts?
• p.10. Why differentiate between clinical outcomes and health outcomes - is that used anywhere in the text?
• p.13: An "is" in the first sentence of section 3.4 should be omitted.

Comment 33:
I think this is a very good summarization all the sources of information available both quantitative and qualitative. It is also a good summary of all the challenges I have faced in outcomes research over the last 20 odd years. I'm very glad you have composed this framework, and I am very interested to hear what will come of it.

My only comment on content is that I might have added more on the specific methodologies, how they compare and how and when they should be used since you provided similar information on all the information on the different types of data.

Comment 34:
The report is excellent in that it makes a good case for the use of RW data for making sound coverage, payment and reimbursement decisions, while discussing both the pros and cons of RW data over randomized clinical trials... It discusses all the other alternatives to the current gold standard, such as practical clinical trials, observational registries, claims databases, etc. The authors acknowledge the many challenges. One of the challenges they don't address in detail is Institutional Review Board (IRB) involvement and or the use of patient databases, working with deidentified data and if necessary patient consent. In RTCs all these issues are strictly controlled by IRBs. How will patient information be protected using other methods? Maybe an alternate to the over protection of patients rights by IRBs and their current stifling of all research by constant nitpicking and changing positions will herald a new progressive era.

Comment 35:
I have read the document. It is well thought out and I appreciate the amount of work and effort that has gone into it.

However, I wish to suggest that there should be a comment on sample size to serve as a guide when using real world data for pharmacoeconomics research and decision making. The issue of sample size can be a real problem for researchers and guidelines appear to be silent on this.

Comment 36:
Firstly, the report is well written, and does an excellent job of setting out the types of data and data sources and the issues relating to both. I have the following comments:

• The definition of RW data as that which is not collected in conventional RCTs is a useful definition but I think it needs to be made clear if randomisation is a defining factor of what is not RW, as well as non-representative patient sample populations. This seems to be implied in the rest of the document, but should be made explicit
• For me, the evidence hierarchy is the most useful way of framing the discussion of the relevance of RW data for policy making. The report correctly diagnoses too rigid application of traditional EBM hierarchies as an obstacle to best possible analysis to support decisions. Each category of evidence also has to be judged on its own merits, with research design and methodological rigour and relevance the main criteria. I do not disagree with the conclusion that RCTs remain the gold standard in evidence, but would like a little more advocacy, in the conclusion, of the sort of approach recommended by the Scottish Intercollegiate Guidelines Network and the Oxford Centre for EBM

The report identifies the use of RW data in measuring effect as the most difficult area, and health technology assessment bodies do not yet seem to have developed transparent rules for dealing with this
issue. Is it possible for the report to go further than it currently does and be more specific about when RW data should be considered as good evidence of effect?

Comment 37:
In general, I found the document to be well written. I have two comments to make:

- One I appreciate the difficulty in differentiating between evidence and data. So here is my two cents worth of comments: “data remain data until adequately designed study is conducted to where data may become evidence. On the other hand, evidence is as solid and convincing to the extent that data upon which the evidence was structures are strong and used by capable researchers.

- On page 8, I am a bit troubled by differentiating clinical efficacy from patients reported outcomes. First we want the clinical folks to believe that what is collected on our behalf is relevant to their process. second, there are indications where PROs constitute the crux of the clinical efficacy. For instance in most pain centered indications such as arthritic conditions, PROs are most likely the primary efficacy endpoints.

Comment 38:

- The table of contents could be provided in the beginning of the paper. This is the guideline which lets readers easily follow the whole structure of the article.

- On page 5 the objectives, nothing is mentioned why information in 'real world' health care decision-making is especially related to coverage and payment decisions. Some illustration could be given for the

- On page 13, the sources of real world data has six types. I think it is good to make a table to summarize the comparisons for those six data sources, such as the application, the advantage, disadvantage or the limitation of the data sources. It is easy for readers to go through this section quickly.

- On page 19, the benefits of RW data are listed in 12 items. I think they could be categorized to reduce the difficulty in comprehension.

Comment 39:
These are my general comments:

- The term 'Real World', though self-explanatory, is not defined precisely. I suggest removing the term 'conventional' as instead mentioning as data that is not collected from RCTs.

- On page 7, the differences in assessing drugs and medical technologies can be noted - the latter does not have 'good' RCTs because (a) the lifespan of technology is around 18 months compared to years for drugs (b) there are ethical issues around denying medical devices to patients (for use in control group settings) and (c) the trial size will always be much smaller than for drug trails. In some cases, the disease is so rare that there cannot be a RCT.

- On page 10, might want to note opportunity cost as one of the standard costs for consideration during economic analysis.

- On page 14, another reference to note is GRADE Working group (BMJ 2004;328:1490-1494)

I agree strongly with the need to look at RW data for coverage and payment decisions. This need to be formalized in a structure. Right now, any evidence other than from RCTs is considered "WEAK". This type of analysis need to be changed. Also, evidence from grey literature (speaking to experts in the field) may somehow need to be given higher standing and regard.

Comment 40:
Thank you for this opportunity to comment this excellent paper. I have one comment only
• page 10. in the sentence: "For purposes...patient-reported-outcomes. Quality of life is one type of PRO i.e., the sentence should be revised: "...which include patient-reported-outcomes such as quality of life."

Comment 41:

• I think you may want to make reference to the fact that many, many non-RCTs are published yearly (probably many more than true RCTs anyway) in the background or justification sections
• While you decided to stick with the term ‘Real World’ data, I would suggest that ‘Real’ may be not an appropriate word. Is there a fantasy world (or other worlds) that needs distinction from this world.
• The beginning sections (prior to section 4) drag on for too many pages. The meat of the paper seems to be section 4, but it takes too long to get there. Consider vastly shortening those pages and pages of definitions and evidence schemes – take away from the main message.
• I was disappointed that there weren’t more recommendations or policy statements made. The draft seems to make a case for real-world data, but doesn’t do enough to talk about how to handle it as a decision maker, or provide enough ‘best practices’ for its collection use. (I assumed the paper was going to cover the later to when I began reading.)
• You may wish to consider moving section 2.3 to an appendix. I don’t think the average reader will care about this section.

Other Comments

• On page 4 near the bottom, the abbreviations for the German authority don’t match each other – one uses a ‘O’ and one use a ‘Q’
• Page 10 near bottom, the abbreviation ‘CDC’ is given – this may need either further explanation here as it may be confusing to some people.
• Page 10 near bottom, the abbreviation ‘CMS’ is given, but hasn’t been previously defined in the preceding pages (also appears on page 25). This term may not be readily known to non-US citizens. I suggest spelling it out here.
• First sentence of section 3.4 has an extra ‘is’ in it.
• Page 17 – Something is not quite right with the sentence ‘Surveys use design features that methodologically rigorous …’ Might the word ‘are’ be missing between ‘that’ and ‘methodologically’.
• On page 10, resource utilization is made into an abbreviation (RU). Given that it is a fairly short phrase, only appears two more times (pages 14 & 16), is too close to the abbreviation of the thrust of the paper (RW), and may not be appropriate to abbreviate in the first place, I suggest spelling out the three instances of it.

Comment 42:

General Comments:

• Need to standardize how real-world is denoted: real world, real-world, or RW. A variety of these forms are found throughout the document.

• I am struck, in reading this manuscript, by a lack of mention of the use of electronic data capture (EDC) to collect real-world data. There is a brief mention of electronic health records, yet this is only one facet of the use of electronic means to collect data. For example, clinical trials are frequently done with EDC by both sponsors and CROs. Real-world data are valuable to those involved in making policies when it can be timely. Electronic collection (e.g., RCT, practical CT, registries) and analysis provides further
assurance that the data are current, therefore more relevant and frequently cleaner, as it is more feasible to data manage and run algorithms to detect anomalies. It may be more relevant and informative if this subsection (Electronic Health Records) was changed to Electronic Data Capture and its use for collection of real-world data. Within that context, EHR may be included, along with mention of their potential ability to provide real-world data (albeit with the challenge of transforming data for research purposes).

Specific comments:

- Page 9, third paragraph: “Data sources”. Given the movement for greater utilization of electronic data capture and associated technologies (e.g., IVR, PDAs etc) the use of the term “data source” may introduce some confusion. Perhaps it may be clearer to the audience to use a term such as “data-generating/collection activity” to refer to the resource.
- Page 12, third paragraph, last line: a period is missing
- Page 13, section 3.4, first paragraph: “categorized is” should read “categorized”
- Page 15, Registries section, second paragraph, 3rd line: “…studied in phase III RCTs; therefore they may better reflect real-world….”. “may” should not be in this sentence since registries are capturing routine clinical practice and are therefore reflecting real-world patients.
- Page 15, Registries section, second paragraph, 5th line: “Most registries have very few, if any, required visits, evaluations, or procedures….” Registries, as outlined in the first sentence of this section, are observational, consequently there should be no influence on the care provided, including mandating visits. Perhaps this sentence would be more accurate and appropriate as, “Given the observational nature of registries, there are no required visits, evaluations or procedures outside of the standard care for a given condition and/or with a particular agent; therefore, the treatment patterns reflect the everyday clinical decision-making……”
- Page 15, Registries section, second paragraph, line 11/12: “therefore, registries may not be suitable to test hypotheses.” This is absolutely correct but it may also be worthwhile to mention in a follow-on sentence that registries, given a greater breadth of patient representation (in terms of numbers, co-morbid conditions and concomitant medications) are valuable assets for hypothesis generation- ideas which may be tested in an appropriately controlled trial.
- Page 16, Registries section cont’d, 2nd line: “Registries often include sites that are not experienced in conducting research, and without appropriate oversight, data integrity could be in question”. I don’t believe that often is appropriate. Registries may include sites not experienced in conducting research but it is too great a generalization to say often.
- With respect to data integrity, the recent adoption of electronic data capture for registries has greatly facilitated data monitoring and data integrity. This may be an appropriate place to interject that this is the direction that registries are moving. In addition, the real-time surveillance afforded by electronic data capture provides a significant means to capture AEs and SAEs in the real-world setting and suggests that more appropriate representation in terms of the frequency of such events (numerator) and the population at risk (denominator) can be captured. This is a very relevant consideration for policymakers, including those involved with coverage and payment decisions.
Page 17, Health survey section, second paragraph, second line: “Surveys use design features that are methodologically ……”

- Page 18, Electronic Health records section (see note above; if section is not to be altered): “Finally we note that…… (and other future technologies…..)” Future is not necessary in this context since numerous other technologies already exist and are actively employed in data capture for a variety of clinical settings and activities.

- Page 18, Section 4.1, second paragraph, 3rd line: “…in the restricted trial setting” or “in restricted trial settings”

- Page 19, Bullet point #8: semicolon is needed at the end of “Data in situations where it is not possible to conduct an RCT (egg, narcotic abuse);

- Page 19, a potential bullet point: perhaps it is worthwhile mentioning that real-world data can provide the basis for the development and/or revision of treatment guidelines, especially in therapeutic areas where clinical trials may be difficult to conduct based due to cost and low numbers of eligible patients, among other items.

Comment 43:

Overall the report is excellent. My input to the report is in the form of comments or suggestions that the taskforce might consider when revising the document. My comments or suggestions are as follows.

- On the subject of the definition of “Real World” Data, I think that the definition should reflect data used for decision making that are not only collected in conventional controlled randomized trials but also in well designed studies.
- On the subject of Data vs. Evidence, I advocate the use of data (vs. evidence) because evidence implies processed information and thus users might feel compel to accept or reject it without fully understanding the context upon which the processing was derived. I think providing the decision makers and analysts with the tools to obtain the best raw material – data and the analytic tools to process data will have higher utility and benefit. One reason is that unique conditions in various environments need to be factored in the processing procedure.
- Characterizing RW Data – The rankings suggested is good. However developing weights that could be applied to quality of design issues (or elements), such as generalizability of evidence and sampling to achieve representativeness of target population, to mention a couple, need to be considered. Combination of such weights and the current ranking might improve on the evidence hierarchies relative to research design that currently exist.
- Though implied in the report, it would be useful if it is explicitly indicated that the use of post-marketing surveillance (Phase IV Clinical Trials) data be used as part of the RW data.
- It is important to explore meta-analytic techniques that might improve the effective use of various data sources.

Comment 44:

I have reviewed the draft report on real world data. My comments are included as sticky notes on pages 11 and 18 in the attachment. See document for track changes (track changes #1.pdf)
Comment 45:
I've put in a morning's work into it. Please see the attachment. See document for track changes (Track changes #2.pdf)

Cheers,

Comment 46:
See document for track changes (track changes #3.pdf)

General Comments

Comment 47:
Many thanks for the opportunity to comment on this report which provides a valuable roundup on the current perception of RW data.

Given the argument in favour of RW data for some applications is well made perhaps the next step is to consider whether we need to move in the direction of defining a 'gold standard' approach to collecting data on effectiveness and resource use in line with the use of RCTs for efficacy.

Comment 48:
Thanks for the chance to comment. Nice to see this all in one place. It's well done. Some quick thoughts:

My gut reaction to the conclusion that RW data are "essential" and "critical" was "hyperbole." I do agree RW data are useful to strengthen coverage and reimbursement decisions.

- I have a lingering concern that HIPAA confidentiality requirements may harm the ability of some researchers to do RW studies. I don't know if this paper can/should address that, but I see it as a potential challenge.
- The suitability of RW data for assessments of fast changing technologies in the device area may be another challenge. Should the paper get into that?
- Evidence hierarchies are troubling to me since they are used to suggest some data types are better or worse than others. I believe a more accurate view to propose is that all types of data have strengths and weaknesses that need to be understood before one can evaluate the rigor or usefulness of a study. I'd rather see an evidence circle, or some other representation that better deals with this.
- Lastly, the registries discussion beginning on page 15 suggests they prospectively collect clinical, economic and PRO information. I may have a dated view, but I see them as more commonly being narrow, limited purpose efforts with minimal planning to collect safety events as is noted on page 16, or patient information for possible later use such as a recall. If they were really well designed to collect comparative clinical, economic, and PRO information that informs coverage and reimbursement decisions, I'm not sure I could tell someone the difference between a registry and a practical/simple clinical trial.

Comment 49:
I read the report on "Real World" data with interest. It gave a very concise overview of the types of "real world" data and their strengths and limitations vis-à-vis RTCs. The report seems to argue that while RTCs are the strongest design for internal validity they often lack external validity and are costly. Whereas observational data tend to have the opposite strengths and weaknesses. My sense is that researchers and policy makers are still not convinced that observational data has enough internal validity
to allow decision making on relative effectiveness. That is, can we ever be confident enough that we have controlled for selection bias in observational studies that we can make decisions based on it? Are the methods for checking for selection bias that can give us greater confidence or is it typically unknown? Or are there certain decisions that we are willing to make with observational data? For example, clearly most people would not argue that the FDA use only observational data for drug approvals, but should they be using it to monitor possible adverse events? If they see adverse events in observational data should they make decisions based on it such as “black boxes” or should they conduct further studies to confirm the observational data such as RTC re-analyses and physiological studies? Also, the report doesn’t seem to discuss the use of observational studies for purposes other than determining effectiveness such as burden of illness studies, adherence studies, diffusion studies, etc.

Thank you for the opportunity to comment on this important report.

Comment 50:

I think the text is very well written.

Real world data are essential when you have different populations, health status and economic differences, specially across countries.

In order to avoid methodological bias, perhaps some guidelines about using real world data should be developed. That would be very useful in my country for example.

Comment 51:

Congratulations to the draft report “ISPOR Real World Task Force’.

I just have a small comment regarding chapter 4.8 the need for ongoing dialog.
I worked with original data of the phampro database.

This database comprises all prescriptions being paid by the German Statutory Health Insurance AOK, covering 45% of the German population.

It was possible to track down the prescription behaviour of each individual physician per month per drug brand name and package.

Unfortunately, this enormous database is released for the use by the AOK only.

As a positive example we see real world data on resource consumptions per German Diagnosis Related Groups provided by 220 German hospitals in 2004 including 1.8 million patient cases, being released for public use.

In other words: We have to overcome "mistrust" in order to enable conjoint analysis.

Economic real world data is on hand.

Comment 52:

I have read the document, it is very well written, and think it is terrific. A few thoughts to consider as you finalize this to make it more applicable.

- Are there accepted standards with which to grade the quality of real world studies; either prospective observational cohort studies, or claims analyses?
- I think what we are missing is a section on the “application” of RWD studies. One major problem is the frequent “misuse” of studies for other purposes both in the world of pharmacoconomics but also by payers more generally. For example, a claims database analysis not really capable of a comparative effectiveness analysis being used as such or a hypothesis generating study being used to argue for causal relationships. What I am suggesting is a section on the appropriate use of RWD studies based on their capabilities (design) and limitations. Another example is that
payers may use a systematic review to document lack of data regarding comparative effectiveness to argue that the agents are “the same” or there are “no differences” (e.g. absence of data = no difference), this is the flip side of the coin about the “misuse” of data.

- In the section on the statistical limitations of claims analyses, this could be clarified and expanded to serve audiences that may not be as statistically inclined.

Comment 53:

I have made a number of comments using the note function.

- One key point is that Randomisation into EHR is going to become a major player in the Observational world- it avoids all the issues of confounding and channelling and is inexpensive to conduct -about 1/10th the cost of a P3 clinical study.

I have added notes in places where this seems to have been missed. See document for track changes (Track changes #4.pdf)

Comment 54:

Thank you for sharing your work. The draft is a very good summary of the different types of RW data and the pros and cons. As a continuing of the task force's work I would appreciate a discussion around the utilisation of these data sources in decision making and specifically health-economics (which is my field ;-). For this year's ISPOR meeting in Europe, I was planning to organise an "Issue panel" on the topic "Researchers access to primary clinical data for health economic assessment" but I had to drop it as I could not find a suitable discussant from the "don't touch my registry"-sphere. I share the abstract with you. Perhaps it is something that you may find interesting.

Please keep me updated on your progress. See attached document (Ola Ghatnekar abstract.doc)

Comment 55:

Here are some reflections of me with regard the draft document on “using RW Data in Coverage and reimbursement Decisions Task Force Report”

- The term Real Word Data is good because this is already used by the Belgian Health Authorities. In Belgium, providing real world data is especially important for submissions of reimbursement of products of class 2 (products with the same level of clinical evidence as already existing products) or revision studies which are asked for 3 years after a product of class 1 (higher therapeutic level of clinical evidence).
- In our environment we prefer to use the term Real World Evidence because this implicates a higher level of scientific validity and as I read that observational studies, … has to be well conducted with a clear research question, an appropriate design, well defined perspective, quality control, … I suppose that in that context RWE is more appropriate. Maybe both terms RWE and RWD can be used in function of the specific data that are presented.
- Maybe it is important to create guidelines which could be recognized by EMEA, FDA and/or other agencies which give companies more support in presenting their files to their specific authorities.

Comment 56:

I agree with this report that Real World data will always be the best way to have information for making decisions, but in order to have precision and quality in that information for the patients, doctors and the pharmaceutical companies, it will be more expensive to work only with Real World data instead of using modeling. Real World data is the basis for making a model and in the beginning of a study or research it will be useful, but it can take more time and more costs than making a trusted model.

My advice is to use both considering the dead line of the research and the costs that it will take, using Real World data as the basis and using models to "predict" the results or have a future scenario. I think
that this combination (RW/modeling) will help decision makers to make the best decision in order to give a quality service without spending a lot of money.

Comment 57:

Overall I enjoyed reading this report and found it very well written!

A 'major' comment that I would like to see being addressed is the issue that if decision-makers/payers start requesting real-world (RW) evidence on new medical products for decisions on reimbursement, companies are almost in a catch 22 area. Prior to launch, a lot of these RW activities are difficult to perform as the product is not on the market. However, if the company cannot launch the new product, these data will be impossible to generate as the product is still not on the market... I appreciate that egg. practical clinical trials can be performed, but this is at least true for many of these RW design options. Will/should this speak in favor of conditional reimbursement?

Comment 58:

I would very much like to express my comments to supporting this initiative.

- To my knowledge, in the pharmacoeconomics and outcome research, we usually emphasize on RCTs as a golden standard (pre-marketing study) and neglect on the observation study, i.e., real world data (post-marketing study). the task force report fills the gap of our knowledge.
- ISPOR chairs and four group's head have made the contribution on RW data task force report. I wonder if we can use the word of ECHO model to express the type of outcomes (clinical, economic and humanistic patient-reported outcomes).
- In data collections, regarding to the drug safety, specially the adverse event (ADR), I think the notification system and surveillance data also are important source of evidence.
- although the report gives an analysis framework for policy makers to using the real world data. I feel the contents are lack practical method to guide policy makers to use the real world data on coverage and reimbursement decision.

Comment 59:

I have read with much interest the "Using 'Real World' Data in Coverage and Reimbursement Decisions Task Force Report" and I have a comment on it.

- I suggest that the group proposes a kind of "standardized report", some kind of format which summarizes the main information to be used in health economics analysis, so in the medium term the organizations manage the information in a form that can be "friendly" to analytic tools of health economics.
- I suppose this won't be an easy work to do, but maybe it put the basis to make rules on the registration of information and in the future the information collected would be more reliable and useful.

Comment 60:

After reviewing Using 'Real World' data Task Force Report (draft), I am interested in knowing answers to the following questions:

- Types of outcomes
  
  If decisions are to be made for reimbursing mental health services, how will RW data be useful in this regards? What method and/or data source will be used to capture mental health outcomes?

- Types of sources of data
  
  Can Hospital Discharge Data be an appropriate source for RW data?
Comment 61:

As a clinical researcher /expert psychopharmacologist in management of schizophrenia, the methods outlined have been essential in gaining reimbursement in Australia. The case in point is Risperidone CONSTA. Unfortunately the company trials were hardly extensible/applicable to usual care patients and a broader strategy was required to influence the decision makers. The FDA efficacy/safety trials have become reified as some arbiter of reimbursement with total disregard for efficiency (efficacy in the RW).
I support your initiative.

Comment 62:

For us in Brazil this task force report will be very useful to start our local discussion. For our local decision makers will be very important to define the concepts of real word data power and utilization. In the moment I don’t have any consideration, because for me the considerations of the task force are very complete.

Comment 63:

The economic value of prescription drugs relative to alternative therapies is considered to be an increasingly important issue. Health care decision makers are therefore currently interested in real world (RW) outcomes when dealing with the coverage and payment policies. ISPOR has set a Task Force to assess the definitions and use of RW data for these purposes. We would like to give insight on our unique approach to RW data that integrates evidence from several sources and gives a more accurate picture on several of the outcomes aspects with a system that is scientifically vigorously guided.

GeneOS Ltd. is a private Finnish health care bioinformatics company that co-operates with a variety of institutions and individual researchers in Finland to study the treatment and outcomes in common chronic diseases from relevant perspectives, including cost-effectiveness of different therapies. Finland has complete medical records of every individual treated in the country. These include specific pharmacy data, clinical diagnosis information, diagnostic test results and overall cost to treat a patient. Therefore, GeneOS is well positioned to provide feedback to Real World Data issues. GeneOS has developed the relationships and infrastructure to tie all these data sources together enabling in silico analysis of an individual suffering from chronic diseases.
We have set up a unique scientific approach to the evaluation of clinical, economic, patient-reported outcomes as well as adherence to therapies from the provider and patient perspectives. The first objective of this study (AST study) was to understand why patients suffering from asthma and COPD respond very differently to treatment, but as the methodology and infrastructure have evolved, additional therapeutic areas will be included. With our RW data, all types of interventions can be evaluated, i.e. drugs, devices, health programs, procedures, and the overall care provided, for evaluation of effectiveness impact in the general population. GeneOS in collaboration with Helsinki and Uusimaa Hospital District (HUS) obtained the IRB approval for this AST study by the Coordinating Ethics Committee at HUS in Nov 2004. We set up a Clinical Research Unit at Meilahti for enrolling patients. Our AST study officially kicked-off in January 2005 with our first mailing campaign inviting patients to our visit our Clinical Unit and consent in person to participate in the AST study. Our overall goal is to recruit up to 8000 AST study subjects in Finland.

Participants agree to provide us with access to last 10 years of medical data and to have us follow them up for the next 10 years. All the following data types are being linked on individual basis enabling to build a complete health care history of a person:

- Physicians’ medical records
- Hospital records
- Diagnostics results (all laboratory and diagnostic measurements, imaging)
- Prescription information
- Pharmacy data
- Quality of Life and disease specific questionnaire filled by each patient annually
Participants agree also to donate blood samples and to be re-contacted for enrollment into other GeneOS studies.

Using validated and secure IT systems GeneOS team of biostatisticians and MDs deploy an exhaustive analytical strategy to mine this unique database and gain insights into real-world disease determinants, treatments outcomes from the clinical, economical and patient perspective, and adverse effects. This is done by examining and comparing biological data and the long term treatment history and health records of patients. Our programs are reviewed and approved by regulatory authorities to ensure that we use healthcare data appropriately and have comprehensive patient consents. All relevant findings shall be published in peer-reviewed journals and presented at medical and other relevant congresses. GeneOS Ltd. has had three poster presentations at ISPOR congresses previously and a podium presentation is due in Copenhagen.

In summary:

- GeneOS conducts research to understand the effectiveness, safety and cost-utility of medical therapies and enable development of molecular diagnostics.

- GeneOS bases its research on various medical records and registries of people who consent to participate in our efforts. Participants join GeneOS' studies by enrolling at our partner hospitals. The hospital collects the participant's records and samples, removes the patient's identification and sends the information to GeneOS for analysis.

- GeneOS provides the results of our research to a variety of customers including healthcare providers, reimbursement agencies, and pharmaceutical companies. Only GeneOS has access to the research database.

- Whenever possible, GeneOS will publish the results of our research in scientific forums in order to help advance the use of appropriate therapies in healthcare.

ISPOR Task Force recommends that RW data can be characterized by type of outcome, 1. Clinical as in biological measures of morbidity (symptoms, acute events, side effects) and mortality, 2. Economic as estimation of medical and non-medical resource utilization and their costs and 3. Patient-reported outcomes (PRO)/quality of life as in patient provided reports on a health condition and its treatment (symptoms, functional status, HRQoL, treatment satisfaction, preference and adherence). We agree on the outcome classification since GeneOS' RW data gives insight on all abovementioned types of outcomes and could be useful in decision making in the drug approval processes.

ISPOR Task Force report also underlines the hierarchies of evidence (strength of research design). That is a very important aspect since more scientifically sound the research is more impact the results are for the decision-making process. In an agreement, we use a strict documentation all study protocols, appropriate analytical techniques and strive for internal consistency. Our results are, as ISPOR requires, applicable to a broader population and truly reflect actual clinical practices.

ISPOR Task Force report also highlights the type of data sources and limitation of these studies, e.g. retrospective and prospective data. Both data type are of value since GeneOS type of data is a unique blend integrating different sources and is both retrospective and prospective in nature. Our data gives insight on the natural history of the diseases studied, in the safety and effectiveness of therapies, and evaluates quality of care. It is unique in its ability to reflect everyday clinical decision-making and cost-effectiveness data is easily available.

We believe there are no limitations to the amount of data collected and fixed intervals are used for gathering additional cross sectional prospective data. Data integrity can be questionable in studies based on registry data solely, but as we use a blend of PROs, laboratory results, medical records and surveys, cross-validation gives additional strength to our material.
In Finland as still in many developed countries, most of the retrospective data extracted from medical records is still paper format which includes the clinical data in a free text format. As the Task Force report states, transforming this information for research purposes is challenging. Through our own experience we believe that this complex process can be successfully accomplished and we are currently adding available electronic health records for the detailed information required by the Task Force including disease specific symptoms at the personal level.

RW Task Force report summarizes that there is a definite need for RW data that has to have external validity and generalizability into larger population. Important factor to support this aspect is that studies based on RW data are published in peer-reviewed forums. Multiple sources of data are necessary as well as integration of data from different sources. GeneOS Ltd. approach has these advantages, and we can see the true effectiveness of alternative interventions or clinical strategies in clinical practice. This type of data gives an estimation of long-term and rare clinical benefits and adverse effects. All types of outcomes can be evaluated in all types of patients observed in true clinical practice and data on resource use for economic evaluation is available. Physician behavior patterns and patient levels of compliance and adherence can be evaluated.

RW data has a potential for bias, but every effort is needed to recognize the effect of missing variables, measurement errors, incorrect functional forms and simultaneity bias by a team of MDs and statisticians. We agree with the Task Force that well-defined questions and timeframes for the duration of data collection are necessary. In our study protocols are rigorously applied, all data collection tools are carefully designed and quality control is present. Also, GeneOS Ltd. uses monitoring to ensure quality of its data, informed consents are obligatory and utmost care is taken of the privacy concerns.

It has been acknowledged by the Task Force that real world outcomes data should come from real world situations. We believe that RW data gives a unique opportunity for reimbursement decisions.

I appreciate for having the opportunity to provide my feedback, and truly wish all the success to RW Data Task Force in its valuable work.

Comment 64:

I have read the draft report on real world data with great interest and believe it is a valuable contribution to the ongoing discussion on how to use real world data in decision making.

No comments to the draft version.

Comment 65:

Difficult to comment on the document as it covers general aspects of the issue of collecting the data and the sources. Overall it appears to be a good reference piece for those attempting this effort.

Comment 66:

I thought the report was excellent. I really have nothing to add at this point.

Comment 67:

I have reviewed the draft report from the ISPOR Task Force on Real World Data. The report does an excellent job of outlining the different types of real world data and I have no editorial comments on the contents. It remains an ongoing challenge to work with reimbursement agencies that rarely have an RCT that directly addresses key issues of patient groups where the drug may eventually be used and about real world effectiveness so I appreciate the absolute need for real world data contrasted against the quality issues that are often difficult to assess in real world data. The report does an excellent job on providing input into the continuing debate on real world data. Sorry I don't have anything more substantive to add.
Comment 68:

Thought report is an excellent overview of the opportunities and challenges with the use of "Real World" data. I don't have any substantive suggestions for changes.

Comment 69:

Thank you for your excellent report. As such I have no comments. Good luck on finalizing the report!

Comment 70:

I found the report well very timely. WR studies are becoming a necessary component for managed care reimbursement and education on validity of study design must be emphasized. WR studies are a requisite for patient safety, to determine costs associated with adverse events including loss productivity, total health care costs, etc.