

# The IQWiG methodology paper version 1.0

Michael Drummond (Centre for Health Economics, University of York)

Frans Rutten (institute for Health Policy and Management, Erasmus Medical Centre/Erasmus University Rotterdam)

## **1. The reimbursement policy in Germany and the restrictions imposed on IQWiG**

As of April 1 2007, the German legislature stipulates that the Institute for Quality and Efficiency in Health Care (IQWiG) will be commissioned to carry out evaluations of the benefits and cost-benefit ratio of pharmaceuticals. The results provided by IQWiG will support the Central Federal Association of Health Insurance Funds in setting the ceiling price for specific drugs that can not be included in a reference price group. The results may also be used to support the Federal Joint Committee in assessing the efficiency of medical interventions in general (see press statement of 24-01-2008 by IQWiG). In January 2008 a consultation document was published by IQWiG on ‘the methods for assessment of the relation of benefits to costs in the German statutory health care system’. This report has been produced by IQWiG in consultation with an international Expert Panel. In this report we used this consultation document as a basis for our comments on the methods to be used by IQWiG.

As is stated in the preamble to the document, the specific legal requirements according to the German legislation (§35b SGB V), state that IQWiG should value the utility of interventions according to international standards, especially as these are established within health economics. But IQWiG’s mandate to the Expert panel imposed additional constraints, which are rather restrictive and are at considerable tension with the requirement to use methods according to international standards. The most important restrictions are:

(a) *IQWiG should only address the determination of a ceiling price at which a superior health technology in a given therapeutic area should be continued to be reimbursed.*

According to the document an important reason for focussing on a single therapeutic area is that Germany's health care system is not bound to a fixed national budget and therefore should not consider funding priorities across therapeutic areas. It is clear that this is an important deviation from common health economic methodology, where a common measure of benefit is sought and trade offs are made across therapeutic areas and diseases. The rationale for the latter is, of course, that we would not like to spend € 100,000 to gain a unit of health (e.g. a quality-adjusted life-year or QALY) in one therapeutic area while not allowing an intervention in another therapeutic area with a cost per QALY of only € 10,000 per QALY just because we failed to compare the interventions in the 2 disease areas under consideration.

Even if Germany is not bound to a fixed national budget, what is in itself not obvious, it would be unwise to allow such inefficiencies by concentrating on one given therapeutic area at a time and not checking the consistency of decisions across therapeutic areas as is done when a general measure like cost per QALY is used. To have different cost effectiveness thresholds for different therapeutic areas may also be judged inequitable, as patients in one disease area would have earlier access to health care than in another one.

*(b) The costs to be considered should only be those from the perspective of the community of citizens insured by the statutory health insurance.*

This would fall within the variation seen in the guidelines for pharmacoeconomics across national jurisdictions and is therefore in line with international standards.

*(c) The estimation of benefits should be according to standards of evidence based medicine (EBM).*

This is, of course, completely acceptable but the way this is interpreted in the methods section is rather stringent, as EBM seems to be restricted to results from RCTs. Also, although most international guidelines stress the importance of high quality clinical evidence, experience from many settings shows that EBM is a necessary, but insufficient approach for understanding the true value of health technologies. First, the available clinical trials often do not compare the relevant alternatives (for reimbursement decisions), are too short-term and measure only a limited range of endpoints.

Secondly, a recent review of EBM (systematic) reviews undertaken for the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom has shown that these were often inadequate, because a pooled estimate of effectiveness could not be produced, or only produced for a restricted range of outcomes. This is why NICE has strongly supported economic modelling [1].

*(d) IQWiG will assess only those technologies that have been demonstrated to be superior.*

Although this would prevent consideration of highly efficient new technologies (e.g. just a little less effective but much cheaper) other jurisdictions (e.g. the Netherlands) know a similar restriction as the decision making process is organised such that better or equal effectiveness has to be demonstrated first before cost-effectiveness is considered.

*(e) Transferability of economic evaluations to Germany is allowed when adjustments are made for local conditions.*

Again, this is in line with other international guidelines and is not contentious.

We will see in the following sections that these restrictions, especially the first one, form an impediment for performing proper economic assessments in Germany. Therefore it is disappointing that the reasons for imposing these restrictions are not thoroughly discussed in the document, especially as they do not appear to be derived from the legal context. In our opinion these restrictions are not supported by convincing arguments.

## **2. The main impact of the restrictions on the methodology of IQWiG: the efficiency frontier approach**

The methodology section begins by saying that none of the existing methods for economic evaluation are universally accepted and therefore can not be used for ceiling price assessments in Germany. This suggests that cost utility analysis, which is recommended as the reference case in most textbooks and in various national guidelines, is also not to be used in the German context.

Whilst it is true that there are some differences among the various national and international guidelines, there is quite considerable agreement on approach. For example, the reference case proposed by the Washington Panel [2] included QALYs and these guidelines have been widely followed in the literature. They are not even referenced in the IQWiG methods document.

Nevertheless, costs and benefits still need to be compared in a given therapeutic area to arrive at a ceiling price for such area. Let us consider how the document arrives at an acceptable measure of benefit, how it suggests these benefits can be compared to costs and how the comparison may lead to the determination of price ceilings.

In section 2.3.1. it is suggested that accepted ‘clinical measures’ should be used, the advantage being their familiarity to clinicians and their availability from clinical trials. There are various problems with these measures of benefit as also described in the document. Some of these problems are that the measures may not be cardinal (see below), that they may only provide a benefit measure in one dimension and that the relation between the surrogate endpoint and the final outcome to the patient may not be stable across interventions, or over time. Though these problems are being discussed and it is acknowledged that they may provide large problems for the proposed analysis, no further recommendation is provided. Of course, in international studies QALYs have been constructed to overcome these problems but QALYs are definitely not recommended and not even mentioned in the document (except in footnote 1 on page v).

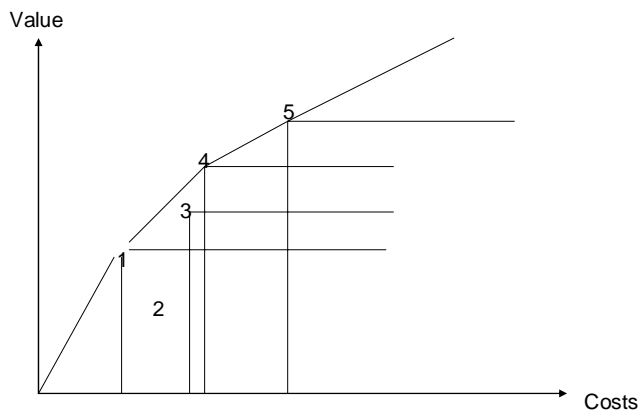
To compare costs and benefits in a particular therapeutic area the document suggests constructing a diagram with costs on the X-axis and ‘value’ on the Y-axis and then to plot the existing therapies in this therapeutic areas as points in the graph (see figure 1). By using arguments of dominance (intervention 2) or extended dominance (intervention 3) the most efficient interventions can be selected (in this case 1, 4 and 5) and these together form an efficiency frontier. The information value of this efficiency frontier graph will depend on several factors:

- the extent to which the measure of value captures the overall benefit to the patient; indeed if this is not the case different efficiency frontiers may apply
- the extent to which the measure of value is cardinal

- whether the information on value and costs for a specific intervention is up to date; this not only relates to the date of the study from which the data are derived but also whether these data are updated with information about costs and benefits in actual practice
- whether all relevant interventions are depicted, even those for which no cost effectiveness information (with the chosen measure of value) was available in the literature
- whether the positions on the ‘efficiency frontier’ really represent efficient decision making in the past; it is not at all clear what we can learn from past decisions especially as these were made in a time when systematic consideration of efficiency was not common.

Each of these factors may cast serious doubts on the value of this frontier to the decision maker.

Fig 1:  
The efficiency frontier based on past decisions on 5 interventions



But it is also very difficult to collect the data required for constructing the efficiency frontier for each therapeutic area! In quite a number of cases new studies would be needed to provide the data for the efficiency frontier especially as old interventions are often not assessed according to their costs and benefits. There may be some analogy with the discussion about the WHO approach on generalized cost effectiveness, where it has proven difficult to determine the counterfactual of the null set of related interventions [3]. Often one needs to reconstruct the past on the basis of incomplete data. Even if economic evaluations have been performed in the past, considerable adjustment and updating would be needed to make the plotted costs and values representative of the actual outcomes in current practice. Finally, foreign studies using cost per QALY as reported outcomes may be of little use in this context as well. In sum, considerable effort would be needed to plot the interventions and the resulting efficiency frontier per therapeutic area; indeed one may expect this effort to be much greater than would be required if IQWiG were allowed to use the same methodology as in other jurisdictions and hence be able to draw on cost effectiveness studies performed abroad.

In sum, it is not clear what the usefulness of this information is for policy makers and it is very difficult and time consuming to construct these frontiers for each relevant therapeutic area. In this respect it is not reassuring that, to date, no practical example has been given of the construction of a frontier for a given therapeutic area, thereby demonstrating the feasibility of the approach.

### **3. How to use the efficiency frontier for decisions about ceiling prices?**

When the frontier has been constructed the next important question is how to use the information for decision making. If one believes that the efficiency frontier represents the relative efficiency of interventions that exist or have been considered in the past in the therapeutic area of interest, then clearly interventions with a value higher than intervention 5 and with a cost lower than intervention 5 are acceptable at the prevailing price (dominating previous interventions, see figure 1). In the same way interventions with higher costs but lower value than intervention 5 are not acceptable

(dominated by intervention 5). Of course, most new interventions will be positioned North East from the position of intervention 5, providing additional value at higher costs. For this highly relevant area it is stated in the document (page 42) that there 'can not be a firm decision rule for health technologies in this zone'. A number of options are sketched, however, that may be considered by decision makers. One may use a rather strict rule by extrapolating the frontier from intervention 5 using the steepest slope of the efficiency frontier (0→1) and allowing only interventions above that position, or being more permissive by using the least steep slope (4→5). One may also use the average slope by extrapolating from the origin through point 5. How to use multiple frontiers in cases where there are multiple relevant benefits, which can not be aggregated in some way, is even more problematic and is not even discussed.

On page 45 IQWiG suggests that the frontier at least provides some framework for the decisions and also states that there is 'no conceptual foundation for alternative approaches that do not directly project the efficiency frontier'. This statement, of course, is untenable as the obvious approach would be to use a common threshold for cost effectiveness, as is done in many jurisdictions. The use of a common threshold would, of course, also guarantee consistency of decision making across therapeutic areas. In this way we avoid that a rather cost ineffective intervention may be approved considering the efficiency frontier if it is lucky to be situated in a disease area where there exist only rather inefficient programs (adding inefficiencies to inefficiencies!) and vice versa.

In some clinical areas there have been examples of new therapies that have been both superior clinically to existing therapies and cheaper (e.g. methotrexate in the treatment of rheumatoid arthritis). This would lead to a backward sloping line on the frontier. It is not clear what that means for the ceiling price for new therapies!

Furthermore, imagine two therapeutic areas having the same relevant measure of outcome (e.g. increased survival). Because of historically differing frontiers it would be possible to pay more for increased survival in one disease area than the other. The common threshold may be very differently positioned in figure 1 than any of the proposed extrapolations of the efficiency frontier.

In sum, much effort goes into the construction of the efficiency frontier but the directions on how to use that information provide little concrete guidance to the decision maker.

#### **4. Other comments on the methodology paper**

##### *Uncertainty*

When decision makers are presented with efficiency data they also need to be informed about the reliability of such data. Recently Claxton [4] suggested that decision makers may use lower thresholds in cases where the uncertainty about the reported cost-effectiveness ratio is larger. Methods for dealing with uncertainty are well addressed in the international health economic literature and established methods are available for constructing confidence intervals for cost effectiveness ratios. In one way it is surprising that this topic is not addressed in the methodology paper. But on the other hand it is not as it is not at all obvious how to present the efficiency frontier framework with due consideration of uncertainty. Again it seems almost impossible to reconstruct the uncertainty around the positions of interventions in the past. We estimate that this would significantly add to the complexity of an already rather complex framework.

##### *Costing*

Most of the comments on costing in the methodology paper seem relatively straightforward. Rather curious, however, is the remark on page 49 is that ‘a clearer categorisation (of costs), unfortunately not often used in economic evaluations, would be into ‘insured’, referring to those the payer covers and ‘not-insured’, referring to those borne by others regardless of what goods and services they are paying for.’ Indeed in textbooks a clear distinction is made between the resources deployed for medical interventions (the costs) and the way of paying for these resources, emphasizing that only the former have to be determined in the context of an economic evaluation. As IQWiG would also allow costs not covered by insurance this alternative categorisation is also not very useful in the context of IQWiG’s methodological recommendations.

Another comment is that the recommendation that productivity costs or benefits should not be treated as a cost or savings but that they should be included on the benefit side (page 52). Though this is consistent with previous recommendations by the Washington Panel [2], it is not done in actual research practice and has several disadvantages [5].



## 5. Conclusion

By imposing the restriction to only consider the efficiency of resource allocation within a therapeutic area and not across therapeutic areas IQWiG has manoeuvred itself into a difficult position. This restriction makes it impossible to conduct economic evaluations to international standards and only allows the presentation of information which is of limited value to the decision maker and gives little guidance on how to decide on the introduction and pricing of medical technologies. Furthermore, by not considering the relative efficiency of interventions across different therapeutic areas it runs the risk of allowing clearly inefficient technologies or rejecting clearly efficient technologies. Finally, constructing the efficiency frontiers for each therapeutic area will consume many resources, only a small part of which would be needed to conduct a standard economic analysis, especially as available information on cost-effectiveness from studies abroad can be used.

In summary, we are in full support of IQWiG's efforts to conduct economic analyses but, unfortunately the methods currently proposed are not up to the task.

## References

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### **Declaration of interests**

In this respect it is appropriate to declare that Frans Rutten was a member of the international expert panel for a short period but decided to withdraw because he disagreed with the restrictions imposed on the work of the panel. Michael Drummond is a member of the Guidelines Review Panel for NICE in the United Kingdom.