IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

Autumn Symposium 2015

Real world data –

an asset for benefit assessments?

How can registries and routine data contribute?

Introductory and closing speeches by Jürgen Windeler, IQWiG*

27./28. November 2015

*Translation from German.

IQWiG's position (introduction on 27.11.2015)

This year we have chosen the topic "real world data", as it has been increasingly discussed over the last few years. It is also propounded in connection with the discussions about health services research. Many people link the term "real world data" (also called "real world evidence" or "real life data", to name a few variations) to the idea of data treasures, which they envisage with shining eyes and great appreciation. We were of the opinion that we should make this term and its content the topic of the Autumn Symposium, as discussing it is well worth the effort. I'm sure we'll get round to the definition during the course of the afternoon.

Question and discuss one's own position

As IQWiG's Director I am not neutral on this issue, as it is clear to all that IQWiG holds a position here. This position is known and can be viewed in the Institute's methods paper. Likewise, it is traceable in IQWiG's daily work. Nevertheless, questioning and discussing this position form part of the Institute's responsibilities. And this is why for today and tomorrow we have invited several competent and esteemed experts and asked them both to present the results of their work and explain and discuss their points of view.

Small but important difference

First, I would again like to use the opportunity to call to mind the background to IQWiG's position.

For clarification: In the topic selection of the Autumn Symposium the issue is not about whether and which questions can be answered with real world data. This is because an abundance of information can be generated from these data and potentially can also be used for decision-making. Here we are specifically talking about – and only about – whether knowledge on the medical benefit of interventions can be gained with such data. That is a subtle, but important difference.

If we come to the understanding

- that, except for very specific exceptions – see IQWiG's methods paper – the benefit of interventions cannot be assessed by "before-after" observations of treatment outcomes under the heading "The patient has benefited", but
- that one requires comparative studies / comparative data for benefit assessments,

then on this basis one can – without requiring too much discussion – come to the following conclusions that are then condensed into IQWiG's position:

1. To investigate issues of benefit, randomized controlled trials (RCTs) offer the least error-prone study design, as they show high internal validity. RCTs are nearly always – of course I do not say "always" – feasible. They are nearly always defendable. And for one reason alone, they are also ethically well defendable, because with these study designs and their results, one can gain valid knowledge, which in turn can justify the specific study conditions for patients.

2. All other designs – and it doesn't really matter whether "real life" or other labels are stuck onto them – are clearly worse, and unfortunately in practice are even much worse than they would theoretically need to be. This is connected to the extremely great efforts required to control

confounders in order to make these designs internally valid. Unfortunately these efforts are often underestimated, avoided or not adequately implemented.

3. The problems already existing in the reliable identification of RCTs (search options in databases, publication bias) potentiate themselves in other study designs. And this means that, besides the uncertainty and the risk of bias in other designs, uncertainties and sources of error on the meta-level also have to be added.

4. The idea that non-randomized studies, these so-called real life data, have per se higher external validity is wrong. Hence, the above-mentioned particular uncertainty and proneness to error of real-life data versus highly controlled trials becomes even more important.

5. External validity, that is, the question as to whether the study results fit specific decision-making situations is worthless as long as I have to base it on poor, unreliable data. If I think about the question of external validity, the applicability, the precondition is that the studies available show high internal validity.

6. The concept of so-called "effectiveness", from which the definition of daily life and of real-life ideas and their appreciation are derived, stands on shaky ground, to put it carefully. I personally think this concept is simply nonsense. I would like to put it pointedly here – this not only means that the benefit in "daily life" cannot be determined with the methods applied for this purpose, but that it should not be determined at all.

In consequence, this means that we need informative studies, which, if investigating the question of benefit, should be RCTs. These studies should reflect the legal framework and not simply "daily life", but should also dispense with "artificial" elements (run-in).

Lip service

So far in discussions the opinion has often been advocated that the importance of valid, prospective studies, particularly of RCTs, is acknowledged and that real-life data should not replace such RCTs, but only supplement them. I personally have mostly considered this to be lip service. So far it has remained completely obscure how and what to supplement. It is thus also unclear whether this supplementation will contribute to the knowledge pool and, if yes, to what type of knowledge.
It fits the picture that authors of publications – e.g. in analyses of the Swedish Stent Registry – initially infer conclusions on the benefit of interventions from these data, to then state at the end of the respective publication or in discussions about it that the results found now have to be confirmed in an RCT – which of course doesn't happen.

Key questions remain

The following key questions thus arise for our symposium:

- What should the relation of so-called real world data to other evidence look like?
- What precisely should the supplementation of comparative studies comprise?
- Which questions should real world data answer and which requirements should be specified for the data to be able to answer these questions?
- And finally: Can such data represent an asset for the benefit assessment?

There are many suggestions about what one could do with real life data, but relatively few examples of what one has specifically done with them. One could thus ask "Where's the beef?" I look forward to certainly stimulating contributions and an interesting discussion.

Adaptive pathways (introduction on 28.11.2015)

The concept of real word evidence or real world data plays an important role in a specific discussion revolving around so-called adaptive licensing or adaptive pathways. This procedural approach has been discussed for some years. Many events and publications have promoted this concept. However, it has not gone unnoticed to anyone that a large number of HTA agencies, including IQWiG, are highly sceptical or even concerned about this concept, and still see many more open questions than answers.

Open issues

For instance, I ask myself where the evidence is that there is “growing patient demand for timely access to promising therapies” (apart from the fact that the terms “timely” und “promising” are very open to interpretation). Has anyone actually asked patients and also informed them about the consequences, such as the fact of increased uncertainty?

I ask myself in what way the present specific pathways (“orphan”, “conditional”, “compassionate”) are insufficient to solve the specific cases propounded as justification for adaptive pathways.

I ask myself how the promise or hope is justified that companies will still generate evidence after approval. One can actually know that this mostly doesn’t work – and one can even know why.

I ask myself how one can rely on the hope that real-life data can replace conclusions on benefit inferred from RCTs.
I ask myself how the broadly increasing appreciation of patient-reported outcomes (PROs) on an international level is compatible with relying even more than hitherto on surrogates in the approval process. And PROs will not be found in registries with routine data anyway.

I ask myself how the reassuring statements from industry that none of this is new and is restricted to only a few special cases with particular medical needs, are compatible with the statements by advocates. For instance, by Hans-Georg Eichler (2012): “However, adaptive licensing is envisioned as the ultimate replacement for the current development and authorization process / model, and as such would be applicable to most new products.” And in 2015: “will likely make adaptive pathways the preferred approach in the future”.

I ask myself, if – as industry claims – none of this is new and is only restricted to a few special cases, why do we need it so urgently anyway?

Empty promises

The promise to conduct studies after early approval to improve the evidence base is not credible for many – apart from the promise to industry with regard to “an earlier revenue stream and less expensive and shorter clinical trials”. This may partly be connected to the specific German circumstances, where

there is no evaluation of drugs in terms of a fourth hurdle. Hence, in Germany drugs are reimbursable directly after approval. In addition, the use of a drug – even without supplementary evidence – will not be restricted to certain patient groups and the pressure to present further evidence will be very weak. The possibility to sanction cases where evidence is not provided will in effect be zero.

Evidence will become weaker

It is thus certain: the evidence will become weaker. Uncertainty will increase. The compensations are based on hopes. In the past few weeks this has led to more and more critical voices fearing a marked deterioration in patient care.

An article in the BMJ on the situation in the United States presented examples of 3 new drugs that had been regarded as "promising" for the treatment of dementia before their lack of benefit or substantial harm was demonstrated in phase III trials. The authors conclude that efforts to accelerate approval took place "under pressure from Congress and industry". They express the concern that restriction to preliminary data will lead to "high costs in morbidity and healthcare dollars" (then euros in Europe, of course).

A well-known German medical journalist put it in a nutshell: "The announcement to bring interventions onto the market faster and faster can indeed be understood as a threat."

Discussion required

However, these issues are also worthy of discussion and we have invited competent speakers for this purpose, including the main protagonist, Hans-Georg Eichler, Chief Medical Officer of the European Medicines Agency (EMA).

Where is the road leading to? (Closing speech on 28.11.2015)

We are reaching the end of this event and I would like to summarize or comment on a few points:

The term "real world data" is incorrect

From this event I take home with me the conviction to abandon the term "real world data" or "real world evidence". I will also try to avoid using it any longer because it stands in effect for data from non-randomized studies (non-RCTs). I also believe that we are well advised to set this term aside, as it conveys the silly implication that randomized studies have, so to speak, nothing to do with the "real world", while non-randomized studies have everything to do with it. It conveys a false picture and it therefore makes sense to abandon this term.

Different methods for different questions

In various contributions the methods kit has been emphasized as a symbol of the fact that different methods are available for different questions. I assume that everyone can follow this; IQWiG too, of course. I would even go further: If Elisabeth George from the English National Institute for Health and Care Excellence (NICE) says that it is the norm at NICE to use data from non-randomized studies, then I say: this is also the case at IQWiG – namely for questions for which no randomized studies are required. And Mr Augustin explained yesterday that of course one needs to resort to real world data, which, by the way, are found in all of IQWiG's dossiers, for example, to answer the following questions:

- How high is the market penetration of a drug?
- How many patients would be eligible to receive the drug?
- What does the drug, the comparator treatment or best supportive care cost?

For such questions non-randomized study data are the norm. But for other questions investigating the benefit and harm of interventions, other instruments are available in this methods kit. They comprise comparative, informative studies. Of these studies, the randomized study is the best, for several reasons.

In one talks about exceptionally large effects, in particular about the exclusion of certain effects and not about the quantification of effects, then – and this is IQWiG's position too – data may also be sufficient that possibly have a relatively high risk of bias in the sense of high uncertainty.

Can non-RCTs supplement data from RCTs?

I have heard in presentations that non-randomized studies should supplement RCTs. I must confess that, even after attentive listening since yesterday midday, it is still not fully clear to me what this supplementation is actually supposed to comprise.

Many examples named refer to aspects of harm, to signals of harm, to quantification with regard to the question: "Can large effects be excluded?" And here, I think there is no real problem.

There were examples of supplementations in the direction of long-term data that named situations where RCTs are not feasible – in my opinion, here too, relatively high requirements would need to apply. But despite all examples and proposals for variations of supplements, it has not really become clear to me what the particular contribution of non-randomized studies to the benefit assessment is actually supposed to be.

Adaptive pathways – Where is the road leading to?

Elisabeth George appealed, also to IQWiG, to participate in adaptive pathways activities. The decision to participate would be much easier if we knew why one is actually going down this road and where it will lead to. And the question "Where to?" is not trivial.

Mr Paar said earlier that we are currently talking about 6 advisory cases within the framework of adaptive pathways. Of course that is not yet a tsunami; we are right at the beginning of this whole process. But if one looks at publications by Mr Eichler, the adaptive pathways process is to become the preferred process for the future. I did not read about exceptions there. Nor did I read that it is only supposed to apply in certain situations, for which we already have regulations, by the way. According to what has been written, it seems to be a process that seeks a wide area of application. And I don't know how far this is actually supposed to go.

Are studies after approval realistic?

I would find it easier to participate in projects in connection with adaptive pathways if the following points were to be clarified:

1. How can industry be brought to conduct studies after approval?
2. What sanctions and consequences will be imposed if no studies are conducted?
3. How can "managed prescription" or "managed use" be implemented in the German healthcare system? Because it is foreseeable that legal changes are required to implement this in Germany.

IQWiG can gladly participate in such conceptual considerations. But, for the reasons I have stated, we find it difficult to participate in an implementation that is already underway.

Undercutting all evidence requirements

Concerning the regulations on medical devices and methods, we can currently observe how the development is moving from the demand that the *benefit* of an intervention is shown to the demand that a *potential* of an intervention is shown. And we are all currently experiencing what potential – a different word for promise – means in the German system, namely an undercutting of all of the usual evidence requirements. In the drug sector, we do not readily want to go down this road. Elsewhere we would also like to turn back; we are currently working on this.

Ask the general public!

In my opinion the argument is unfair that "there are no studies with certainty of results anyway and that for this reason accelerated approval procedures are feasible". Why? In any case, adaptive licensing / adaptive pathways means that we increase uncertainty. And this with a promise of future certainty, of future evidence then to be provided; I have substantial doubts that this will be realized. And in my opinion this process, which will increase uncertainty, is not actually a process that can be started by the institutions – neither by IQWiG or the German Federal Joint Committee (G-BA), nor by EMA or the European Commission, but is actually a process where the general public must be asked. In this context they should also be informed about the fact that drug safety will be decreased. "Is this what you want?" This question has not been put to them so far.

Adhere to and call for methodological standards!

I would not like to merge the discussion about big data with that of real world data. Although they should be looked at separately, they have one aspect in common – with regard to both forms of data generation and analysis, we should ensure that certain standards are adhered to. We should certainly see to it that methodological standards ensuring that questions are really answered in a valid way are adhered to and called for.