IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Institute for Quality and Efficiency in Health Care

Evidence generation for marketing authorisation & adaptive pathways - a HTA perspective

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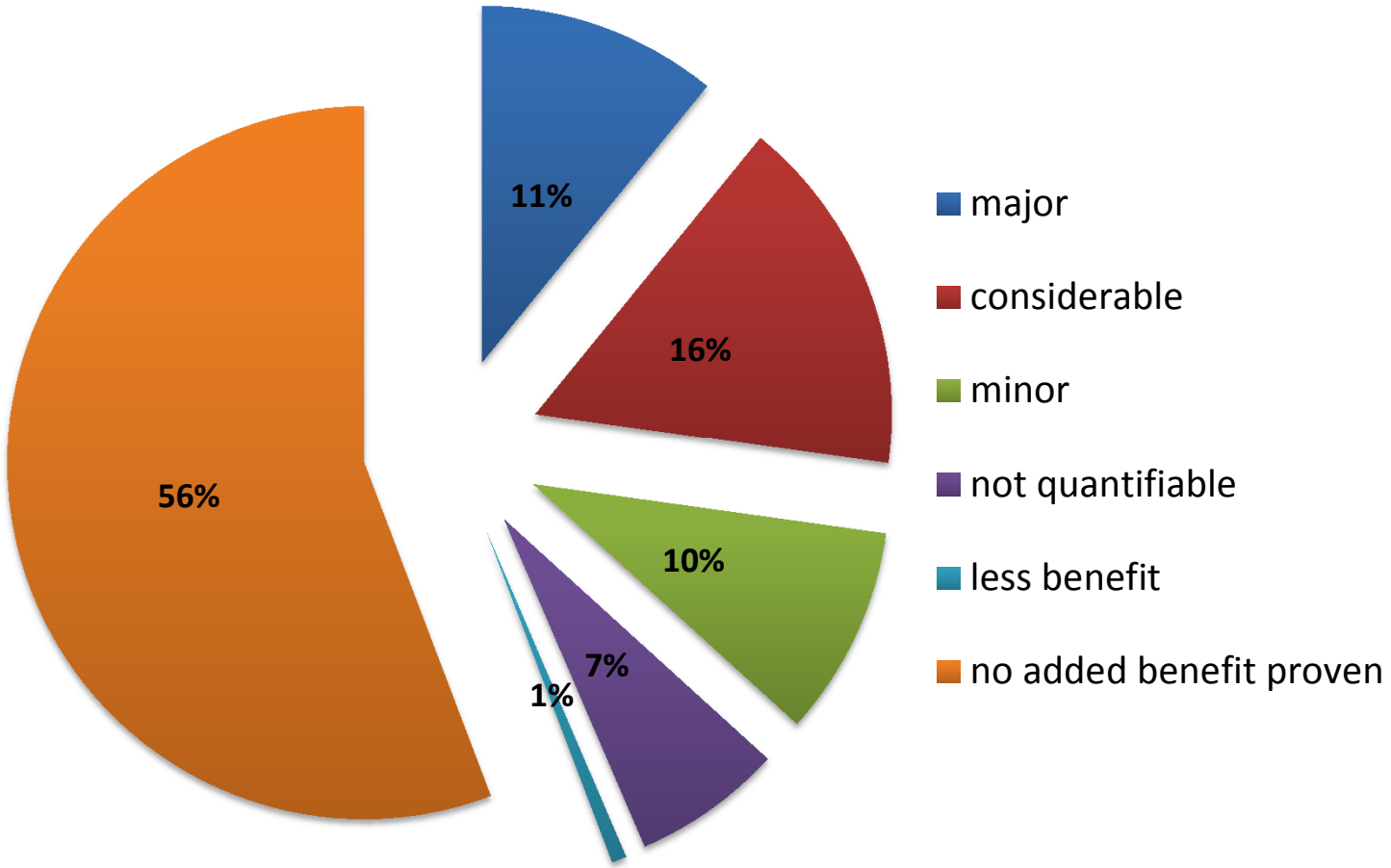
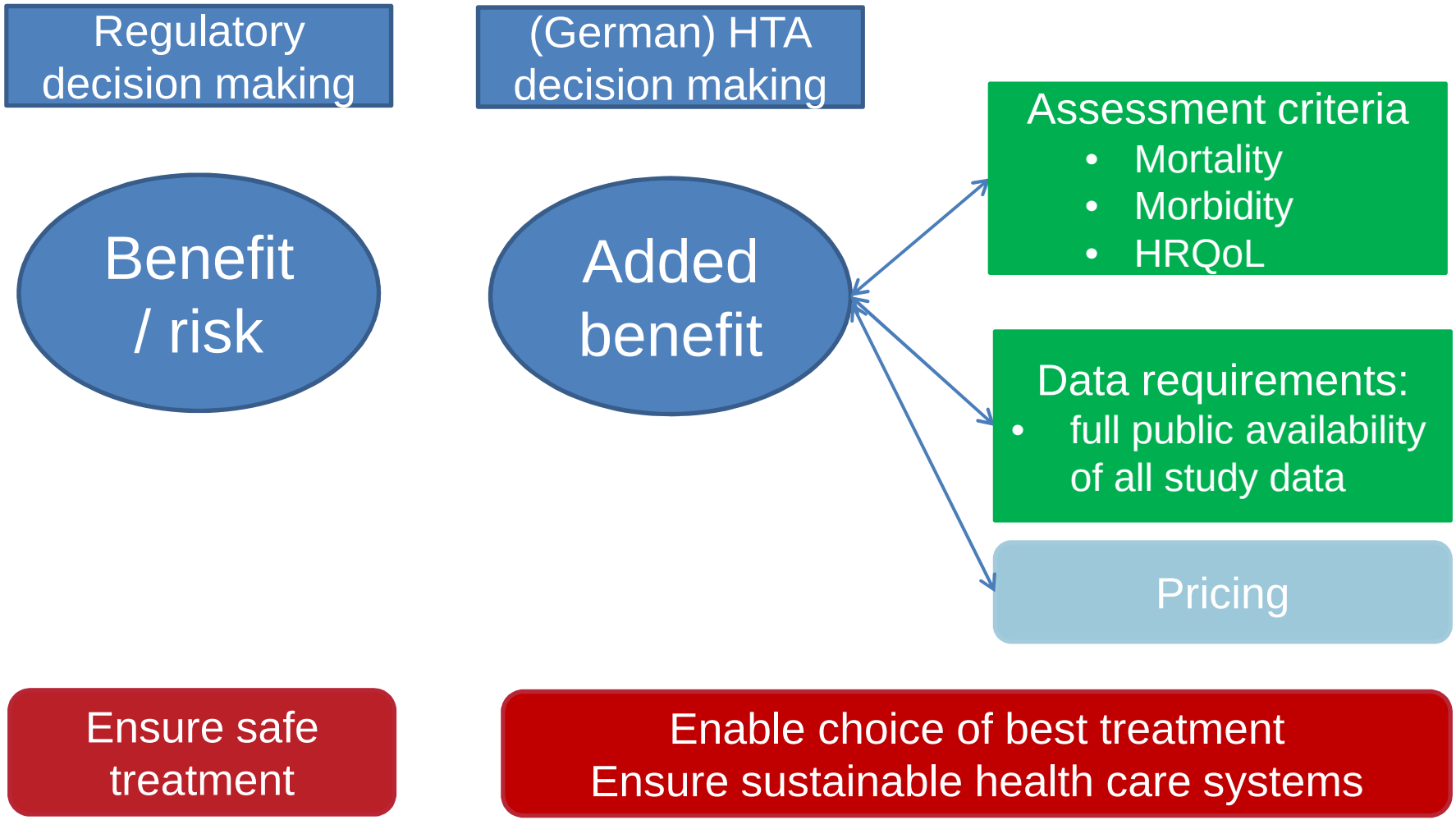
Public conference on clinical drug trials

30 September 2016, Geneva/Switzerland

Results from AMNOG: added benefit (N=147)



Context of benefit assessment



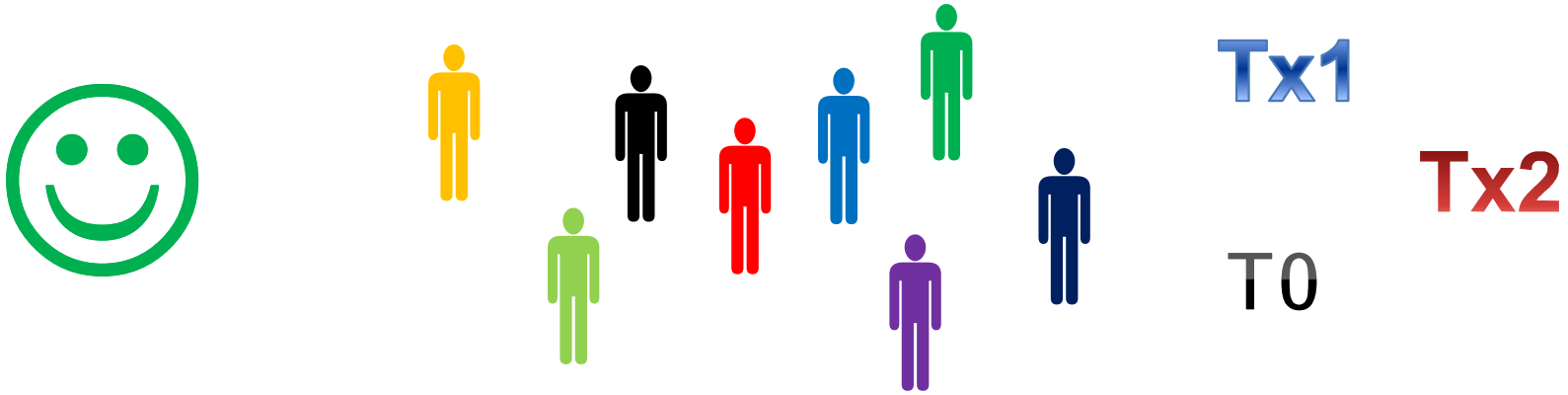
Adaptive pathways and HTA

- IQWiG‘s reservations
  - need of further accelarated approval pathways (beyond procedures already available) is unclear
  - the scope of adaptive pathways is unclear (exception vs. new standard approach)
  - even now we often have insufficient data to describe the benefits of a drug for patients
  - approval of drugs with positive risk/benefit in restricted populations might put patients at risk because restriction of access to approved drugs is difficult in Germany
  - so far negative experience with limited data at approval and with post-approval evidence generation
  - suggested post-approval „real life“ study designs will result in high uncertainty

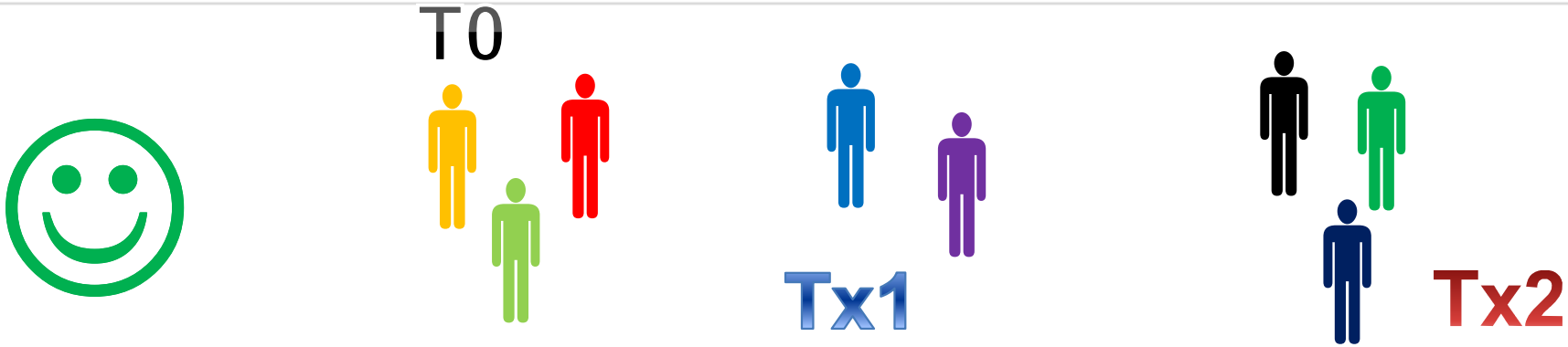
What are we talking about

- „Real life“ data vs. **non-randomised (observational) data**
  - real life data is defined as non-randomised, non-interventional, observational studies (e.g. registries, routine health care records)
  - pragmatic (real life) RCTs are not included

- **Assessment of treatment effects** vs. other uses
  - HTA is aiming to compare benefits and harms of medical interventions (i.e. assess treatment effects)
  - other uses of observational data are out of scope of todays‘ discussion (e.g. data on size of patient population, uptake or use of new drugs, ressource use etc.)



Doctors don‘t treat patients randomly



Doctors don‘t treat patients randomly

Uncertainty of non-randomised data

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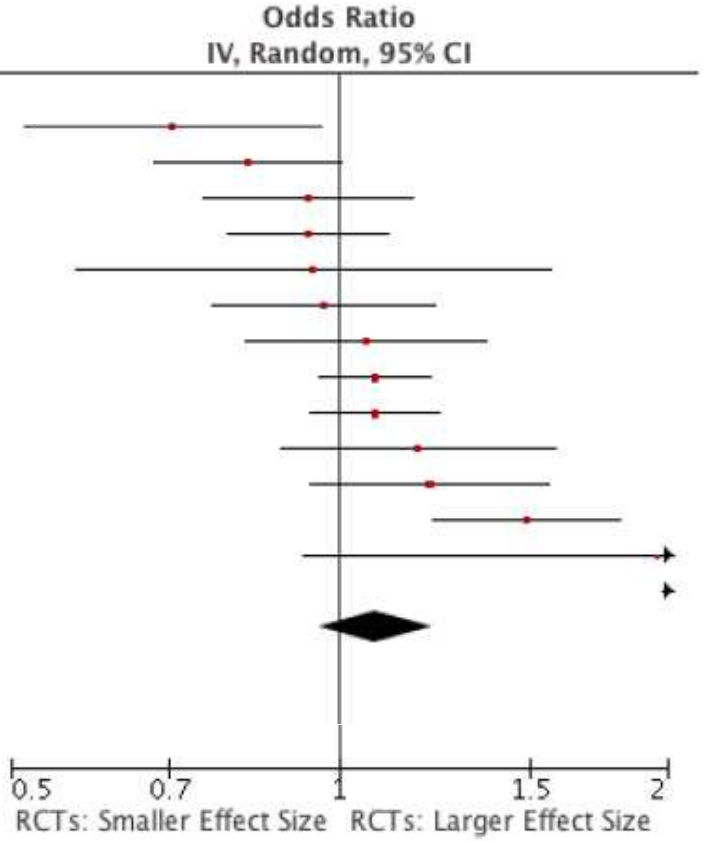
Anglemyer A, Horvath HT, Bero L.
Healthcare outcomes assessed with observational study designs compared with those assessed in randomized trials.
Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: MR000034.
DOI: 10.1002/14651858.MR000034.pub2.

Cochrane Library
Cochrane Database of Systematic Reviews

Study or Subgroup	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 RCT vs All Observational		
Bhandari 2004	6.4%	0.71 [0.52, 0.96]
Beynon 2008	8.7%	0.83 [0.68, 1.01]
Oliver 2010	8.2%	0.94 [0.76, 1.17]
Kuss 2011	9.3%	0.94 [0.80, 1.11]
Benson 2000	3.8%	0.95 [0.58, 1.55]
Shikata 2006	7.9%	0.97 [0.77, 1.22]
Lonjon 2013	7.5%	1.06 [0.83, 1.36]
Concato 2000	10.2%	1.08 [0.96, 1.21]
Golder 2011	9.8%	1.08 [0.94, 1.24]
Edwards 2012	6.8%	1.18 [0.89, 1.57]
Ioannidis 2001	7.6%	1.21 [0.95, 1.55]
Müeller 2010	8.7%	1.48 [1.22, 1.80]
Furlan 2008	2.1%	1.94 [0.93, 4.05]
Naudet 2011	2.9%	3.58 [1.96, 6.53]
Subtotal (95% CI)	**100.0%**	**1.08 [0.96, 1.22]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 48.19$, df = 13 ($P < 0.00001$); $I^2 = 73\%$
Test for overall effect: $Z = 1.27$ ($P = 0.20$)



Uncertainty of non-randomised data

PROTECT: key results and recommendations

… PROTECT recommends that conducting multi-centre database studies requires very detailed common protocols and data specifications that reduce variability in interpretations by researchers. It was found that a priori pooling data from several databases may disguise heterogeneity that may provide useful information on the safety issue under investigation, and it should be avoided. PROTECT rather advocates to analyse databases in parallel and explore reasons for heterogeneity through extensive sensitivity analyses. This approach will eventually increase consistency in findings from observational drug effect studies, or reveal causes of differential drug effects. The design and analysis of studies should also be tailored to the specific drug-adverse event association of interest with a consideration to case-only designs that were found to add insight into associations because of the different assumptions. Furthermore, no universal recommendations on which method to control for confounding variables could be made from the findings: this should be assessed on a case-by-case basis. …

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500204179.pdf

Déjà-vu

Richard Peto

„A lot of money has been spent on nonrandomized outcomes research because the claim was made that is was going to give us reliable comparisons between the main effects of different treatments. It has utterly, totally, and predictably failed to do so.“

Science **1994**, 263, 1080-1081

Experience from EMA‘s adaptive pathway pilot

- … The majority of the **plans were vague** in terms of the purpose of collection of real world data to supplement RCTs, and on the practical elements for implementation there was **insufficient detail** in the submitted proposals to explore the **refinement of the safety profile**, and **even less about to what extent efficacy could be confirmed or augmented** in the post-authorisation phase. A **critical discussion** on the quality, potential for bias, and reliability of the data acquired in the post authorisation setting, and their **suitability for regulatory and HTA purpose, was lacking**. …

Better evidence from better RCTs

- Use the advantages of randomisation while avoiding the shortcomings of many current RCTs
  - pragmatic (real life) RCTs
  - relevant (real life) inclusion criteria
  - develop data collection in routine care context that works
  - larger sample sizes (also allowing for analysis of effect modification by patient characteristics)
- Make use of full information from available RCTs
  - full transparency of methods and results
  - availability of de-identified indvidual patient data
- Explore use of non-randomised observational studies for situations in which RCTs are really not possible

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