Work Package 7 – Subgroup 3:

Adaptations of JA 1 methodological guidelines

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Adapted EUnetHTA guidelines (JA1) for REA

Topics	Status
1. Applicability	SAG / Public and internal consultation until 9th of Oct.
2. Internal validity (RCTs)	„
3. Criteria for the choice of the most appropriate comparator(s)	„
4. Direct and indirect comparisons	„
5. Clinical endpoints	„
6. Composite endpoints	„
7. Health-related quality of life and utility measures	„
8. Surrogate endpoints	„
9. Safety	Public Consultation from19th of October

What is the story behind the “language adaptations” of JA 1 guidelines?

- Updating / complementing existing JA1 guidelines (for REA of pharmaceuticals) and developing new general methodological guidelines are official tasks of WP7 (Subgroup 3) in Joint Action 2
- Publication of nine JA1 guidelines in March 2013
- Continuous collection of feedback on guidelines by subgroup 3 coordinator from different sources (e.g. surveys, interviews)
- No significant quality problems reported, no need for urgent revisions of documents

Free text answers of WP3 survey 2014 “Problems with guidelines?”

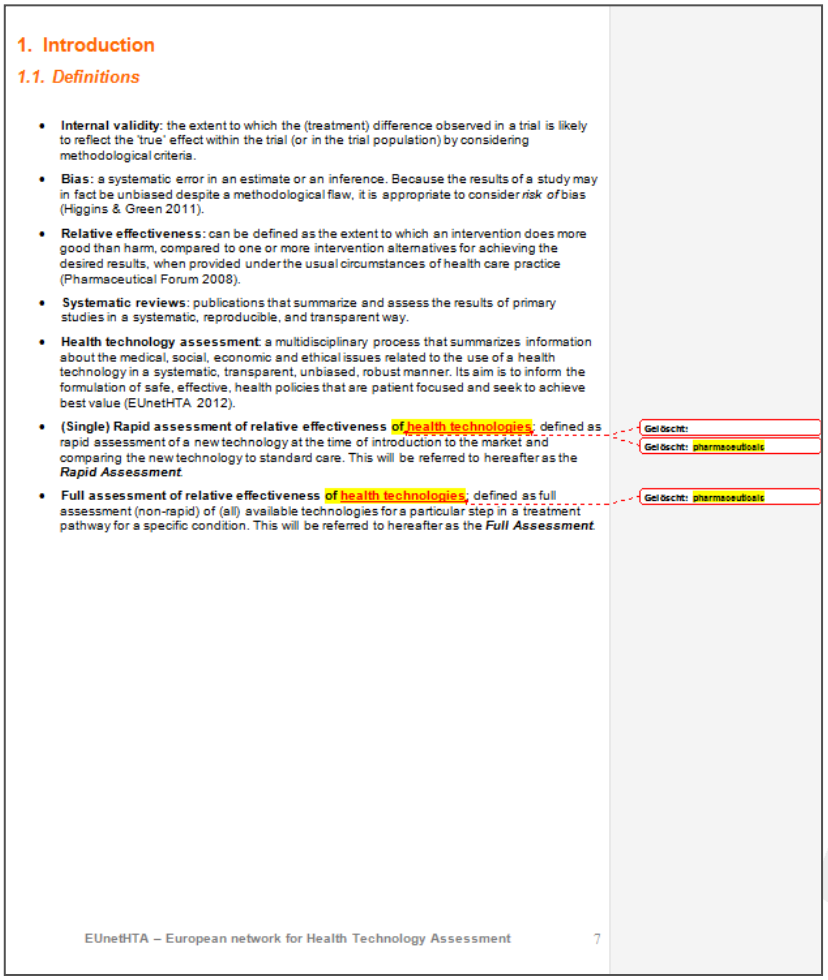
Guideline	Comment
General	The guidelines were published last year, and I think it is very soon to update them
General	All Guidelines should be updated to also meet the need of authors conducting rapid REAs on medtechs etc
Internal validity	GRADE approach should be described
internal validity	more detailed info on the use of GRADE
Levels of Evidence: internal validity	checklists for studies other than RCTs
Levels of Evidence: internal validity	outcome-specific risk of bias analysis difficult to understand
Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison	It is interesting but not enough deep as a practical tool
Indirect Comparisons	Need more information on how to do it in practice
direct and indirect comparisons	more detailed info on indirect treatment methods
Direct and indirect comparisons maybe	in light of the network metaanalysis methodology
Applicability of evidence (no. 9)	Incorporation of non-drug issues
Endpoints: Safety	data sources for safety data for "other technologies"; definition of terms (serious adverse events)
Safety (No. 4)	Incorporation of non-drug issues

What is the story behind the “language adaptations” of JA 1 guidelines?

Decision of WP7 to adapt the JA 1 guidelines to non-drug assessments by minor language changes only, because

- the contents and recommendations of the guidelines are - with a tolerable degree of “imprecision” regarding certain non-drug technologies - valid for and transposable to relative effectiveness assessments of non-drug interventions (with a clear exception of the Safety guideline)
- the new JA2 guideline on therapeutic medical devices would address the need for specific HTA methods deriving from the incremental development of MDs and their user and context dependency, and some implications of the physical mode of action,
- limitation of resources to conduct thorough updates (e.g. new literature search, examples for REA of medical devices) with full consultation processes in addition to the JA2 development of new guidelines
- new guidelines on topics like In-vitro-diagnostics or diagnostics in general could be developed in JA3

How has the JA 1 guideline adaptation been done?



1. Introduction

1.1. Definitions

- **Internal validity**: the extent to which the (treatment) difference observed in a trial is likely to reflect the 'true' effect within the trial (or in the trial population) by considering methodological criteria.
- **Bias**: a systematic error in an estimate or an inference. Because the results of a study may in fact be unbiased despite a methodological flaw, it is appropriate to consider *risk of* bias (Higgins & Green 2011).
- **Relative effectiveness**: can be defined as the extent to which an intervention does more good than harm, compared to one or more intervention alternatives for achieving the desired results, when provided under the usual circumstances of health care practice (Pharmaceutical Forum 2008).
- **Systematic reviews**: publications that summarize and assess the results of primary studies in a systematic, reproducible, and transparent way.
- **Health technology assessment**: a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value (EUnetHTA 2012).
- **(Single) Rapid assessment of relative effectiveness** of health technologies: defined as rapid assessment of a new technology at the time of introduction to the market and comparing the new technology to standard care. This will be referred to hereafter as the ***Rapid Assessment***.
- **Full assessment of relative effectiveness** of health technologies: defined as full assessment (non-rapid) of (all) available technologies for a particular step in a treatment pathway for a specific condition. This will be referred to hereafter as the ***Full Assessment***.

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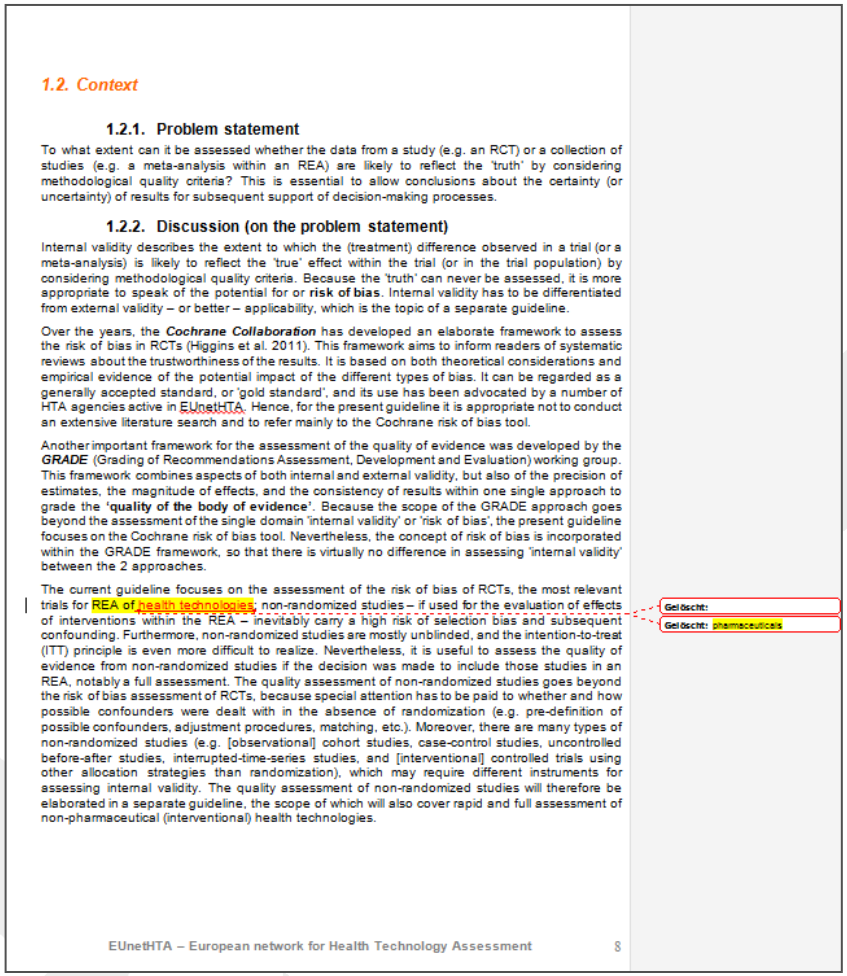

1.2. Context

1.2.1. Problem statement

To what extent can it be assessed whether the data from a study (e.g. an RCT) or a collection of studies (e.g. a meta-analysis within an REA) are likely to reflect the 'truth' by considering methodological quality criteria? This is essential to allow conclusions about the certainty (or uncertainty) of results for subsequent support of decision-making processes.

1.2.2. Discussion (on the problem statement)

Internal validity describes the extent to which the (treatment) difference observed in a trial (or a meta-analysis) is likely to reflect the 'true' effect within the trial (or in the trial population) by considering methodological quality criteria. Because the 'truth' can never be assessed, it is more appropriate to speak of the potential for or **risk of bias**. Internal validity has to be differentiated from external validity – or better – applicability, which is the topic of a separate guideline.

Over the years, the ***Cochrane Collaboration*** has developed an elaborate framework to assess the risk of bias in RCTs (Higgins et al. 2011). This framework aims to inform readers of systematic reviews about the trustworthiness of the results. It is based on both theoretical considerations and empirical evidence of the potential impact of the different types of bias. It can be regarded as a generally accepted standard, or 'gold standard', and its use has been advocated by a number of HTA agencies active in EUnetHTA. Hence, for the present guideline it is appropriate not to conduct an extensive literature search and to refer mainly to the Cochrane risk of bias tool.

Another important framework for the assessment of the quality of evidence was developed by the ***GRADE*** (Grading of Recommendations Assessment, Development and Evaluation) working group. This framework combines aspects of both internal and external validity, but also of the precision of estimates, the magnitude of effects, and the consistency of results within one single approach to grade the **'quality of the body of evidence'**. Because the scope of the GRADE approach goes beyond the assessment of the single domain 'internal validity' or 'risk of bias', the present guideline focuses on the Cochrane risk of bias tool. Nevertheless, the concept of risk of bias is incorporated within the GRADE framework, so that there is virtually no difference in assessing 'internal validity' between the 2 approaches.

The current guideline focuses on the assessment of the risk of bias of RCTs, the most relevant trials for REA of health technologies; non-randomized studies – if used for the evaluation of effects of interventions within the REA – inevitably carry a high risk of selection bias and subsequent confounding. Furthermore, non-randomized studies are mostly unblinded, and the intention-to-treat (ITT) principle is even more difficult to realize. Nevertheless, it is useful to assess the quality of evidence from non-randomized studies if the decision was made to include those studies in an REA, notably a full assessment. The quality assessment of non-randomized studies goes beyond the risk of bias assessment of RCTs, because special attention has to be paid to whether and how possible confounders were dealt with in the absence of randomization (e.g. pre-definition of possible confounders, adjustment procedures, matching, etc.). Moreover, there are many types of non-randomized studies (e.g. [observational] cohort studies, case-control studies, uncontrolled before-after studies, interrupted-time-series studies, and [interventional] controlled trials using other allocation strategies than randomization), which may require different instruments for assessing internal validity. The quality assessment of non-randomized studies will therefore be elaborated in a separate guideline, the scope of which will also cover rapid and full assessment of non-pharmaceutical (interventional) health technologies.

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How has the JA 1 guideline adaptation been done?

- Three person teams (Coordinator, MD expert from IQWiG, and third expert from another member organisation, mostly former first authors) checked the documents consecutively for necessary language changes
- Recommendations and content remained unchanged
- Simultaneous internal and external consultation of adapted guidelines for transparency reasons (tracked changes view)
- Exception: Safety guideline has been supplemented by MD expert from IQWiG, review by experts from AIFA (original author) and KCE (MD expert), internal and now Public consultation (start 19th of October)

Thank you