HTA view on the EMA draft reflection paper and the FDA guidance

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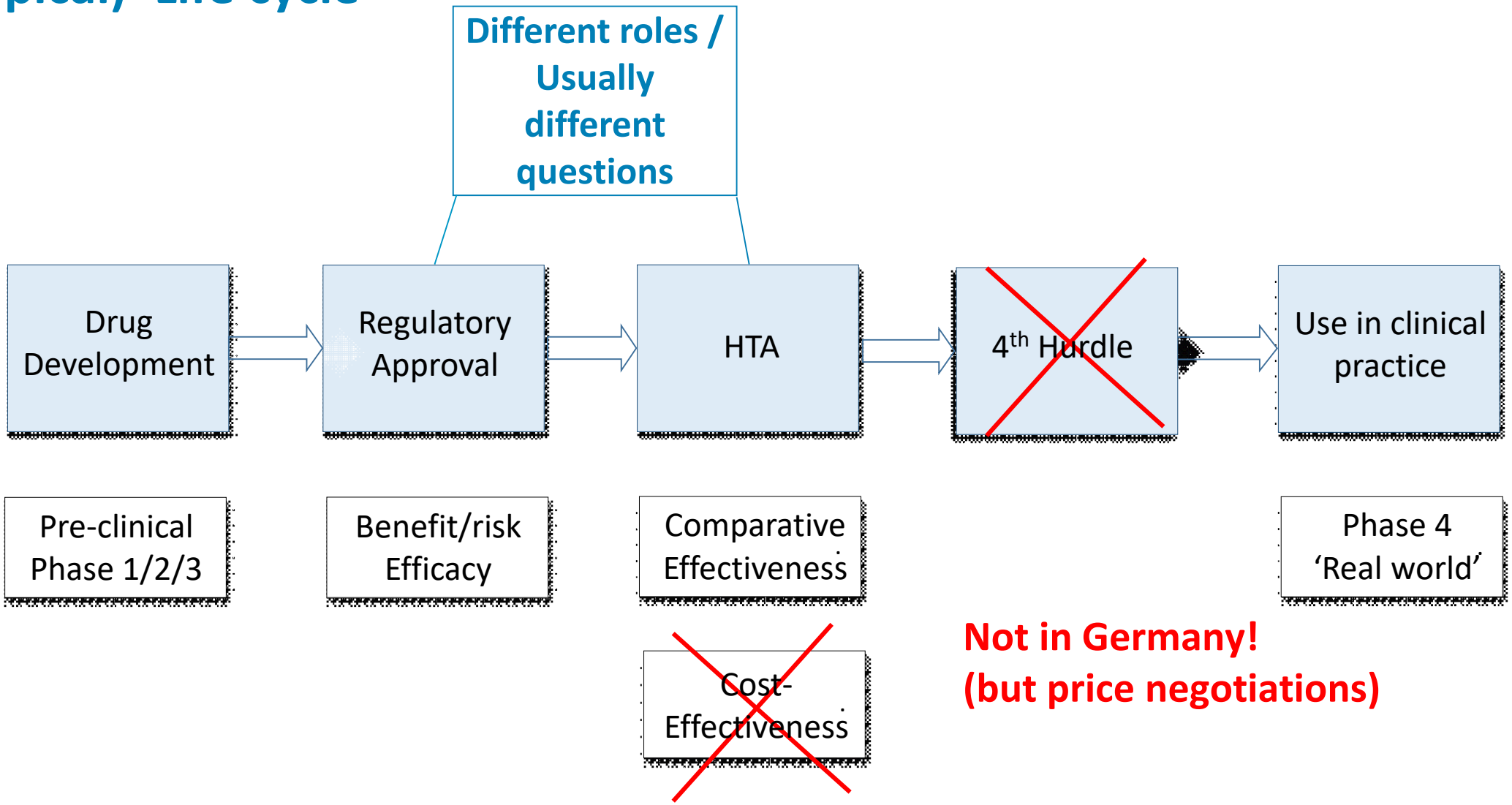
(typical) ‘Life cycle’



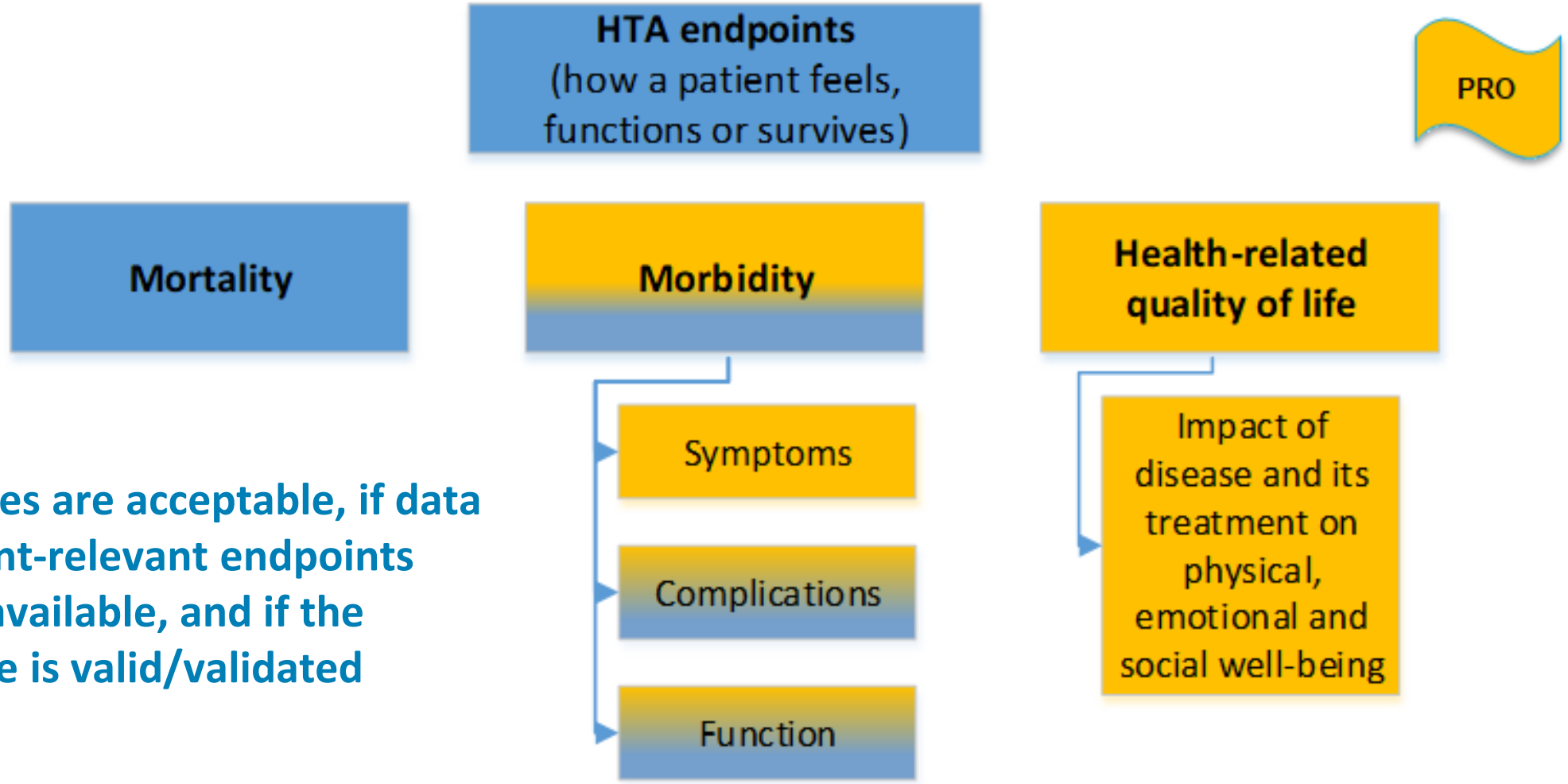
HTA comparators

‘HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. … How well does a new technology works **compared with existing alternative health technologies**? For which population group does it work best?’

(https://eunethta.eu/frequently-asked-questions-for-the-pharmaceutical-industry/)

→ Comparison with standard of care is mandatory (including non-drug interventions and best supportive care [BSC])

HTA endpoints



Surrogates are acceptable, if data on patient-relevant endpoints are not available, and if the surrogate is valid/validated

Laid down in German social code book V (SGB V)

PRO: **P**atient **R**eported **O**utcomes

EMA reflection paper

‘It is the **responsibility of the applicant** to adequately justify to regulators why a SAT*, which deviates from the standard approach of providing pivotal evidence on efficacy through RCTs, can provide clear pivotal evidence of efficacy.’

(https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf)

→ It is not the responsibility of the regulators/assessors to justify why a SAT (or an externally / historically controlled comparison) cannot provide clear pivotal evidence of efficacy or evidence of comparative effectiveness.

*SAT: Single Arm Trial

FDA guidance on Considerations to Support Accelerated Approval of Oncology Therapeutics

‘Accelerated approval is reserved for drugs that are expected to provide **a meaningful advantage (including an efficacy advantage) over available treatment**. To facilitate the demonstration of advantage over available therapies, sponsors should **pre-specify the historical trial(s)** that will serve as the basis for the comparison, and the rationale for the selected trial(s). … FDA recognizes that **it may be challenging, particularly for drugs being developed in molecularly defined patient populations, to identify a historical trial**;’

(https://www.fda.gov/media/166431/download)

“Ultimately, the determination of what constitutes available therapy is made **at the time the regulatory decision is made** rather than at the time the trial was initiated.”

(https://www.fda.gov/media/166431/download)

EMA reflection paper

‘For a SAT the primary endpoint must also be able **to isolate treatment effects** (see Section 3), i.e. it is required that the primary endpoint is such that it is known that observations of the desired outcome would occur only to a negligible extent (in number of patients or size of the effect) in the absence of an active treatment.’

(https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf)

→ For HTA, this requirement is necessary for more than one (primary) endpoint

→ How to estimate treatment effects for endpoints for which isolation (of a treatment effect) doesn’t work ?

→ For HTA, this approach, no matter how convincing it appears is only valid in rare exceptional cases, regardless of whether it may be sufficient for the approval issue.

EMA reflection paper

‘In addition to inclusion and exclusion criteria defined in the protocol, **less tangible and not easily documented selection mechanisms associated with prognosis do occur at the point of recruiting patients**; both due to investigator decisions as well as patients’ choices, or even criteria related to selection of study sites.’

(https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-establishing-efficacy-based-single-arm-trials-submitted-pivotal-evidence-marketing_en.pdf)

→ How to control for this without a (external) control ?

FDA guidance on externally controlled trials

‘A specific design consideration for externally controlled trials involves **prespecifying plans** regarding how to measure and analyze data on important confounding factors and sources of bias.’

(https://www.fda.gov/media/164960/download)

→ It is not sufficient to use the data that is already there (e.g. within a registry), but rather the data that is required

→ How to define / identify ‘important’ confounding factors?

Pufulete M et al. Confounders and co-interventions identified in non-randomized studies of interventions. J Clin Epidemiol 2022; 148: 115-23.

‘Identifying potential confounders in the way that we did is **resource-intensive**.’

FDA guidance on externally controlled trials

‘In contrast, documentation of such data in routine clinical care may not be complete or accurate, and **RWD may therefore lack comprehensive details describing the administration of a treatment or information on the use of concomitant or supportive therapies**. For example, suitable data on additional treatment modalities (e.g., radiotherapy and surgical interventions when treating patients with cancer) may not be available in certain data sources. In addition, management of treatment- or disease-related adverse events may not be predefined or described consistently compared to a trial protocol.’

(https://www.fda.gov/media/164960/download)

→ This will even more the case for the identified important confounding factors

→ It is not sufficient to use the data that is already there (e.g. within a registry), but rather the data that is required

In line with European HTA (EUnetHTA 21 as preparation for HTAR)

‘When a mix between IPD from a single-arm trial and aggregate statistics from another source of data is only available, **unanchored STC*** (Section 5.3.1) and **MAIC*** (Section 5.3.2) have been proposed and applied as a solution for adjusting for confounding bias. However, these analyses without a common comparator (i.e., use of a disconnected network) **rely on the very strong assumption of "conditional constancy of absolute effects"**. This means that the absolute outcome in the treatment arms is assumed to be constant at any given level of the prognostic variables and effect modifiers [64]. **However, in almost all practical applications this strong assumption is not justifiable**. Therefore, STC and MAIC without a common comparator are highly problematic. When treatment effects are estimated from disconnected evidence networks, methods for the analysis of non-randomised data with **access to full IPD* from all studies** should generally be used instead.’

(https://www.eunethta.eu/wp-content/uploads/2022/08/EUnetHTA-21-Deliverable-D4.3.2-Methodological-Guideline-on-Direct-and-indirect-comparisons-V1.0.pdf)

*STC: Simulated treatment comparison, MAIC: Matching-adjusted indirect comparison, IPD: Individual patient data

Gene orphan drugs (completed procedures at G-BA*)

(status: 19.04.2023)

21 Procedures → 6 cancelled (after re-evaluation)

↓

15 Decisions

Worst rating for these procedures (for legal reasons: added benefit given by law not proven by data)

12	Added benefit not quantifiable (‘because the scientific data do not allow quantification’)	Single-arm trials, indirect comparisons with observational (historical) / external cohorts, **populations not comparable**
1	Considerable added benefit	RCT
1	Major added benefit	Single-arm trial (a.o.t.) → historical comparison with (untreated) siblings
1	Added benefit not proven (after regular assessment)	Single-arm trial → comparison with treatment arms of other trials (aggregated data), **populations not comparable**

*G-BA: Joint Federal Committee → decision making body in German health care system

Case study: Onasemnogene abeparvovec (SMA)

Table 6: Influence of disease duration on treatment effect: onasemnogene abeparvovec vs. nusinersen

Outcome category Outcome	Onasemnogene abeparvovec (CL-303, CL-302 and CL-101)		Nusinersen (SHINE-ENDEAR and SHINE-CS3A)		Onasemnogene abeparvovec vs. nusinersen
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Mortality					
Overall survival	Comparison with nusinersen – pooled total populations				
	66	NA 2 (3.0)	101	NA 22 (21.8)	0.14 [0.03; 0.62]; < 0.001

https://www.iqwig.de/download/a21-68_onasemnogene-abeparvovec_extract-of-dossier-assessment_v1-0.pdf

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	Comparison with nusinersen – subgroup ≤ 12 weeks disease duration				
	66	– 2 (3.0)	34[b]	– 3 (8.8)	RR: 0.34 [0.06; 1.96]; 0.260[c]

"A specific consideration involves how well the eligibility criteria can be applied to the external control arm in order to obtain a population comparable to the treatment arm."

(FDA guidance on externally controlled trials; https://www.fda.gov/media/164960/download)

No fair comparison

In addition different in- and exclusion criteria

https://www.iqwig.de/download/a21-68_onasemnogene-abeparvovec_extract-of-dossier-assessment_v1-0.pdf

Target trial emulation (according to Hernán 2016)*

- Design a non-randomized study like a randomized one**, but just omit randomization**
- Choose an alternative to randomization (e.g. propensity score method → consideration of a priori identified relevant confounders → Pufulete et al.)
- Make sure observations start at comparable time ('time zero', ITT-principle, avoid immortal time bias)
- Address impossibility of blinding

→ Not an easy going!

*"Sponsors should **finalize a study protocol before initiating the externally controlled trial**, including selection of the external control arm and analytic approach, rather than selecting an external control arm after the completion of a single-arm trial."*

(FDA guidance on externally controlled trials; https://www.fda.gov/media/164960/download)

* Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183: 758-64.

Conclusions (from an HTA perspective)

- Using non-randomized trial data as ‘convincing’ evidence for comparative effectiveness is an expensive and resource-intensive (even resource-wasting ?) undertaking

‘In many situations, however, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, **regardless of the prevalence of disease**.’

(FDA guidance on externally controlled trials; https://www.fda.gov/media/164960/download)

Conclusions (from an HTA perspective)

- Using non-randomized trial data as ‘convincing’ evidence for comparative effectiveness is an expensive and resource-intensive (even resource-wasting?) undertaking
- Data quality is key and must have the same level as for randomized pivotal trials
- Stand-alone single-arm trials may be convincing evidence for HTA in only (very) rare exceptional cases
- Make use of IPD for externally controlled trials to apply adequate methods for confounder adjustment

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