Enhancing the Acceptance of Externally Controlled Trials (ECTs) in the German HTA System:

Analysis of Guidance Documents From Other Countries

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INTRODUCTION

BACKGROUND:

External controls (ECs) can be used to generate comparative evidence for single-arm trials (SATs).

OBJECTIVES:

With the rise of externally controlled trials (ECTs), regulatory and Health Technology Assessment (HTA) agencies have issued diverse guidelines. This review examines these guidelines, focusing on their application within the German HTA system to enhance the acceptance and integration of ECTs.

METHODS

Seven guidance documents from regulatory (US Food and Drug Administration (FDA), European Medicines Agency (EMA)) and HTA agencies (European Network for Health Technology Assessment (EUnetHTA 21), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care, Germany) (IQWiG), Haute Autorité de Santé (French National Authority for Health) (HAS), National Institute for Health and Care Excellence (England) (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH)) related to single-arm trials, real-world evidence (RWE), and/or external control arms were analyzed. These documents were screened for comments regarding study design, data sources, and analytical methods.

Table 1. Summary „Study Design"

	IQWiG[1]	HAS[2]	NICE[3]	CADTH[4]	EunetHTA[5-8]	FDA[9]	EMA[10]
Early engagement with agency recommended	-	✓	✓	✓	-	✓	✓
Justification that randomization is not feasible/ethical	-	✓	✓	-	-	✓	✓
Access to external data	-	-	-	-	-	✓	-
Target Trial Emulation	✓	✓	✓	✓	✓	-	-
Estimand Framework	-	-	✓	✓	✓	✓	✓
Protocol and statistical analysis plan required	✓	✓	✓	✓	✓	✓	✓
Protocol before SAT is initiated	-	✓	-	-	-	✓	✓
Publication of Protocol and SAP	✓	-	✓	✓	-	-	✓
Immortal time bias	-	✓	✓	✓	-	✓	✓
Specific protocol template suggested	-	-	✓	✓	-	-	n/a

Table 2. Summary "Data Source for External Control"

	IQWiG[1]	HAS[2]	NICE[3]	CADTH[4]	EunetHTA[5-8]	FDA[9]	EMA[10]
Systematic approach for identification of data source	✓	✓	✓	✓	✓	✓	n/a
Preference for prospective data	✓	-	-	-	-	-	✓
Preference for disease registries	✓	-	-	-	-	-	n/a
Preference for local/national data (external validity)	-	✓	✓	-	-	-	n/a
Surrogates accepted (valid but not validated)	-	✓	✓	✓	✓	-	✓
Data quality criteria defined	✓	-	✓	✓	✓	-	n/a
Data assessment tools	✓	-	✓	-	✓	-	n/a

Table 3. Summary Analytic Requirements

	IQWiG[1]	HAS[2]	NICE[3]	CADTH[4]	EunetHTA[5-8]	FDA[9]	EMA[10]
Hierarchical testing	-	✓	✓	✓	-	✓	✓
Preference for patient individual data	✓	✓	-	-	✓	✓	✓
Systematic identification of confounders	✓	✓	✓	✓	-	-	n/a
Selection of confounders	-	-	✓	✓	-	-	n/a
Specific method for adjusting observed confounders	✓	✓	✓	✓	✓	-	n/a
Positivity, overlap and balance to be met	✓	✓	-	-	✓	✓	n/a
Detection of residual confounding	-	✓	✓	✓	-	-	n/a
Effect size important	✓	✓	-	-	✓	✓	✓
Shifted null hypothesis	✓	-	-	-	✓	-	-
Quantitative bias /sensitivity analyses	-	✓	✓	✓	-	✓	✓
Qualitative bias analyses	-	-	✓	-	-	✓	-
Impact Missing data	-	-	✓	✓	✓	✓	✓
Level of evidence for ECT	-	✓	-	✓	-	-	-

✓ = required; - = not required/not mentioned; n/a = not applicable, because out of scope

RESULTS

The evaluation of the guidance documents shows that the requirements for ECTs vary according to the specific mandates of these agencies. Regulatory bodies provide early guidance before pivotal studies, adhering to a hierarchical testing principle, whereas most HTA agencies focus on guidance post-marketing authorization for reimbursement and/or pricing decisions.

Specifically, IQWiG in Germany has unique requirements. In IQWiG's General Methods 7.0, they provide guidance for initial assessments of single-arm trials only by using historical case studies. In their Concepts for the generation of routine practice data (which is included in the General Methods 7.0) the guidance addresses data generation post-benefit assessments for identified evidence gaps. This part of the methods is specific for comparative evidence using non-randomized data.

Table 1-3 list whether or not comments are made for study design, the data source used for the external control and/or any analytical requirements.

DISCUSSION

The analysis reveals that IQWiG aligns with some, but not all, topics addressed by regulatory and other HTA agencies. Compared to these agencies, IQWiG applies stricter criteria for study design and requires prospectively collected data in disease registries. It also places a stronger emphasis on properly matching populations in indirect comparisons, whereas other agencies allow for the quantification of uncertainty or the assessment of data robustness when matching is incomplete.

Most agencies recommend seeking early advice for ECTs before conducting the single-arm trial and/or the external control. When there is consensus that a randomized controlled trial (RCT) is not feasible or unethical, it is possible to conduct quantitative bias analysis, power for surrogate markers (valid but not validated), plan for higher p-values under certain conditions, and adhere to diverse evidence levels. This contrasts with IQWiG's stricter criteria, suggesting a so-called dramatic effect and/or a shifted null (relative risk >10 and p < 0.01) for patient relevant or validated surrogate endpoints.
Table 4 lists modifications and supplementary requirements beyond those defined by IQWiG from other agencies.

Table 4. Modifications and Supplementary Requirements beyond those defined by IQWiG from other Agencies, aimed at enhancing the success probability of Externally Controlled Trials in German HTA.

	HAS[2]	NICE[3]	CADTH[3]	EunetHTA21[5-8]	FDA[9]	EMA[10]
Early Advice Recommended	✓	✓	✓	-	✓	✓
Justification that randomization is not feasible/ethical	✓	✓	-	-	✓	✓
Early discussion of Protocol/SAP for ECT	✓	✓	✓	✓	✓	✓
Effect size must be large but without thresholds	✓	✓	✓	✓	✓	✓
Quantitative Bias Analysis (Residual Confounding)	✓	✓	✓	✓	-	-
Negative-controls (Residual Confounding)	✓	✓	✓	-	✓	-
Surrogatmarkers accepted (valid but not validated)	✓	✓	✓	✓	-	✓
Grading the lower level of Evidence	✓	-	✓	-	-	-

LIMITATIONS:

- The varying requirements for study design, data sources, and analytics may be attributed to differences in mandates of the institutes, such as marketing authorization, reimbursement decisions, or, as in the case of IQWiG, price evaluations.
- The guidance documents vary in focus (single-arm studies, external control arms, or real-world evidence).
- Additionally, the documents from HAS, EUnetHTA, and EMA are not considered final versions for their respective task/agency.

CONCLUSIONS

In situations where RCTs are not feasible or unethical, accepting the inherent uncertainties of surrogate measures and higher p-values may be more beneficial than insisting on stringent criteria, as practiced by agencies like IQWiG and EUnetHTA 21. Stringent criteria could lead to the exclusion of potentially valuable interventions.
By adopting methodologies from other agencies, the quality and acceptance of ECTs within the German HTA system could be significantly improved:

- early consultations with the Federal Joint Committee (G-BA) for single-arm trials to agree on the protocol for the ECT.

when there is consensus on the ECT:

- the use of quantitative bias analysis,
- the use of negative controls,
- the inclusion of surrogate markers

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