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Lessons Learned from **Confounder Identification**

Insights from German HTA Procedures

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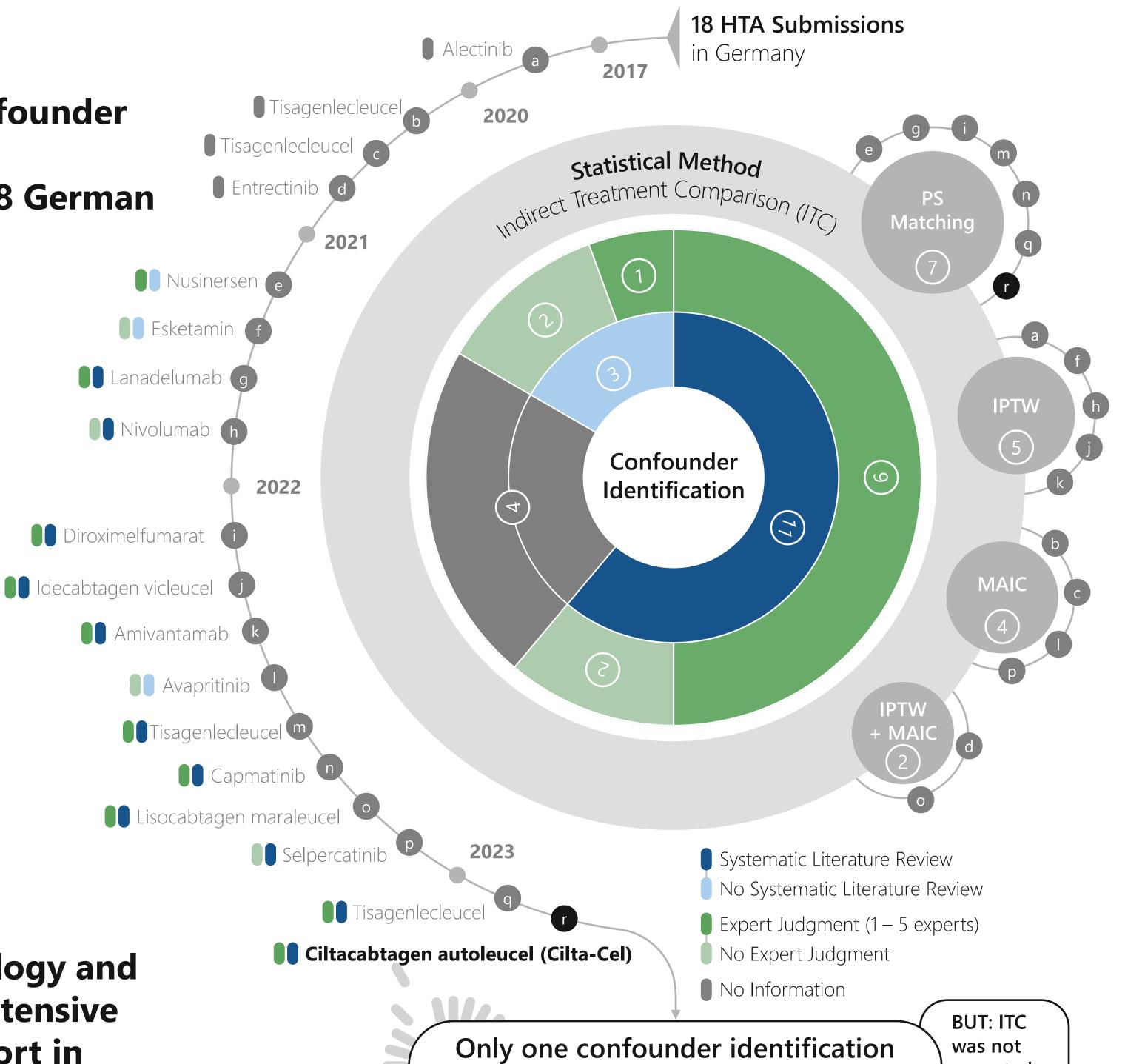


INTRODUCTION

In the **absence of randomized** controlled trial (RCT) **data**, comparisons between populations from different studies are necessary to assess the efficacy of medicinal products, e.g. by **indirect treatment** comparisons.

RESULTS

Despite great efforts, confounder identification was seen as



appropriate according to IQWiG/G-BA

Confounding factors have to be incorporated into these comparative analyses as covariates to adjust for baseline parameters in order to receive unbiased results, e.g. via the use of PS (propensity score) methods.



Challenges

Health technology assessment (HTA) bodies, such as IQWiG and G-BA (Germany), acknowledge the importance of systematic literature reviews and expert judgment in confounder identification.



However, no clear guidance on how to conduct confounder identification is given.

appropriate in only 1 of 18 German **HTA** submissions.

Figure 1 Overview of German HTA submissions reporting confounder identification.

IQWiG Guidance "Confounders must be identified **systematically** (e.g. on basis of scientific literature with involvement of clinical experts) and pre-specified in study planning." IQWiG Rapid Report A19-43 (2020)

Lack of detailed methodology and strong criticism lead to extensive

METHODS

Derivation of methodological requirements for confounder identification from official documents of German HTA authorities.

Review of German HTA submissions employing confounder identification as well as subsequent **authorities'** assessments.

Evaluation of **applied methods** and identification of **potential pitfalls**.

CONCLUSION

Identifying confounding factors for inclusion as covariates in HTA analyses of non-randomized comparisons demands substantial effort in literature reviews and expert judgments, incurring high costs.

approaches with huge effort in systematic literature reviews (SLR) and expert judgments.

Table 1 Requirements vs. approach for confounder identification.

Positive Example referenced by IQWiG **Criticism by IQWiG/G-BA** of previous approaches

Maximum Approach from HTA submissions

was not

accepted

by G-BA

Pufulete et al.: Cohort studies and RCT without restriction

Review

Literature

Systematic

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Extraction with stop criterion (10 consecutive studies without identification of additional confounders)

General:

SLR not recent enough Documentation not transparent

Search strategy:

- Search period restricted Specific search terms
- (e.g. "propensity score")
- Inclusion of endpoints in search

strategy 🕟

Publication types:

Exclusion of observational studies Exclusion of clinical studies

Systematic Literature Review:

Based on indication with a wide range of publication types including secondary literature, interventional and observational studies without any restrictions (e.g. search period, intervention, endpoints etc.)

Example Cilta-Cel:

- > 7000 hits
- > 1000 full texts screened
- \diamond > 250 included sources

Pufulete et al.: Survey: 110 Experts Assessment: 12 Experts

Experts:

Affiliation (independency/bias) Evaluation arbitrary

Independent identification of potential confounders Evaluation of potential confounders with regard to direction of effect, strength, reliability

The lack of detailed guidance on methodology from HTA authorities raises uncertainty about the appropriateness of implemented methods.

Establishing an official, pragmatic, and transparent approach for confounder identification is crucial, especially considering the upcoming EU HTA.

No example referenced: IQWiG requirements ask for accurate description of causal model and its assumptions

Missing ranking Cehj Results-driven, not all confounders considered mog

Example Cilta-Cel: 5 experts

Discerning of true confounders Ranking with regard to relevance • Consideration of interaction between confounders (e.g. as causal diagrams) Letters refer to the respective HTA submissions (see Figure 1)

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References

HTA submissions https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/ (German) IQWIG Guidance https://www.iqwig.de/en/projects/a19-43.html (English) Pufulete et al. Confounders and co-interventions identified in non-randomized studies of interventions. J Clin Epidemiol. 2022 Aug;148:115-123.

Abbreviations

PS: Propensity Score IPTW: Inverse Probability of Treatment Weighting MAIC: Matching Adjusted Indirect Treatment Comparison