The Acceptance of Indirect Treatment Comparisons in Pharmacoeconomic Analyses by the Dutch Healthcare Institute (ZiN)

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Indirect treatment comparisons introduce uncertainty in cost-effectiveness analyses but are not principally rejected by the Dutch health technology assessment authority. Methodological guidance could improve the quality of submitted analyses and add to consistency in decision-making.

Background

In April 2023, the European Medicines Agency published a reflection paper on the use of single-arm trials as pivotal evidence in marketing authorization applications for new therapies.[1] Single-arm trials lack a comparator arm and therefore do not include a relative treatment effect of the new therapy versus a comparator therapy like in randomized controlled trials (RCTs).

Health technology assessment (HTA) necessitates a comparison against the current standard of care. Indirect treatment comparisons (ITC) estimate the relative effectiveness when no direct head-to-head data is available for the new therapy and its relevant comparator. In the case of single-arm trials, unanchored ITCs can be conducted, utilizing data from other clinical trials or real-world external control arms.

Historically, ITCs have been included as part of submissions to the Dutch healthcare institute (Zorginstituut Nederland; ZiN) in both pharmacotherapeutic and pharmacoeconomic analyses. Nevertheless, there exists a lack of established ITC guidelines for evaluating this methodology in the context of HTA in The Netherlands, especially in determining the cost-effectiveness of novel therapies.

With the growing prevalence of marketing authorization applications relying on single-arm trials, it is important to understand the various ITC methods employed in past cost-effectiveness analyses (CEA) and their acceptance by ZiN.

Objective

This study aimed to evaluate the reimbursement decisions and critiques on ITCs in CEA for oncology therapies reviewed by ZiN.

Methods

A review was performed of ZiN reimbursement dossiers from January 2017 to June 2023. All ZiN reimbursement dossiers that consist of a CEA with an ITC were included for full-text review.

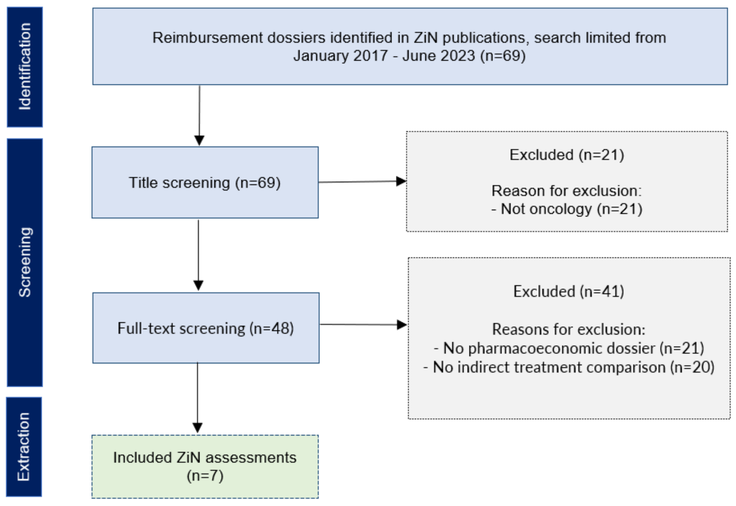
Data on the following items were extracted from the reimbursement dossiers:

- Pivotal trial design
- Applied ITC method(s)
- Critique from ZiN on the applied ITC method
- Reimbursement decision

Results

The search yielded a total of 69 reimbursement dossiers, of which 21 dossiers were excluded because they concerned non-oncology indications. Furthermore, 41 dossiers were excluded because they did not include a CEA, or an ITC was not used to determine comparative effectiveness. Seven reimbursement dossiers that included a CEA using the results of an ITC were included after full-text review (**Figure 1**).

Figure 1. PRISMA diagram



Abbreviations: ZiN, Zorginstuut Nederland (Dutch Healthcare Institute)

After full-text review, all seven CEAs were included for data extraction (**Table 1**). Two out of seven identified CEAs were the initial and resubmission of the same therapy and indication.

The reason for conducting an ITC was the single-arm design of the pivotal clinical trial in four of the seven CEAs. The three other CEAs did have pivotal evidence from an RCT. These CEAs included an ITC to assess comparative efficacy against a relevant comparator that was not included in the RCT (2/3), or because of immature overall survival in the trial (1/3). In two submissions the ITC was not considered as part of the base-case analysis by ZiN for different reasons (see **Table 1**).

Four CEAs based on ITCs used external patient-level data from a real-world evidence study and one was based on an external RCT to inform the comparator's survival data. For daratumumab and venetoclax + rituximab the data source was not reported as the ITC was not assessed.

Table 1. ZiN submissions including ITC

ZiN submission	Year	Indication	Trial design	ITC method	ZiN Critique on ITC	Reimbursement decision
Brexucabtagene autoleucel (resubmission)[2] vs mix of SoC therapies	2023	Mantle cell lymphoma	SAT	Unanchored propensity score-matched analysis ▪ Unweighted comparator curve in base case ▪ IPW comparator curve tested in scenario	ITC results in uncertainty around the estimated relative cost-effectiveness and is inferior to a direct comparison	Accepted
Ciltacabtagene autoleucel[3] vs mix of PCT therapies	2022	TCRMM	SAT	Unanchored propensity score-matched analysis, nearest neighbor	▪ ITC results in uncertainty around the estimated relative cost-effectiveness and is inferior to a direct comparison ▪ Impact of variables and other matching methods were not tested in scenario analysis	Rejected due to quality of CEA
Brexucabtagene autoleucel[4] vs mix of SoC therapies	2022	Mantle cell lymphoma	SAT	Unanchored propensity score-matched analysis • Unweighted comparator curve in base case • IPW comparator curve tested in scenario	ITC results in uncertainty around the estimated relative cost-effectiveness and is inferior to a direct comparison	Rejected due to model structure
Venetoclax + rituximab[5] vs bendamustine + rituximab	2019	CLL	RCT	Propensity score-matched analysis	MAIC was presented to compare against an external comparator for a specific subgroup. ITC method (MAIC) not considered in CEM due to the absence of therapeutic added value (CEA was not needed)	Accepted
Axicabtagene ciloleucel[6] vs chemotherapy +/- alloSCT	2019	DLBCL/ PMBCL	SAT	Naïve indirect comparison ▪ Scenario with population adjusted comparison	▪ Patient characteristics of pivotal and external comparator trial are not representative of Dutch patient population ▪ Comparator survival curves not presented in dossier	Accepted (pay for performance)
Daratumumab[7] vs bortezomib + dexamethasone	2017	Multiple myeloma	RCT	Network meta-analysis	ITC method was not assessed because it was not applied for the main comparator therapy	Accepted
Palbociclib[8] vs letrozole vs fulvestrant	2017	Advanced breast cancer	RCT	HR from an external clinical trial assessing everolimus + exemestane was applied to determine OS versus fulvestrant	▪ Applying a HR from a trial assessing a different therapy is not desirable. ▪ The uncertainty surrounding the CEA results are mainly caused by the estimation of OS	Accepted

Abbreviations: alloSCT, allogeneic stem cell transplant; DLBCL, diffuse large B cell lymphoma; CEA, cost-effectiveness analysis; CLL, chronic lymphocytic leukemia; IPW, inverse probability weighting; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PCT, physician's choice of therapy; RCT, randomized controlled trial; RR, relapsed/refractory; PE, pharmacoeconomic; PMBCL, primary mediastinal large B cell lymphoma; SAT, single-arm trial; SoC, standard of care; TCRMM, triple class refractory multiple myeloma; vs, versus

Despite their absence in Dutch modelling guidelines, five out of seven ITCs applied adjustment for differences in population. In all cases, ZiN expressed concerns around the potential bias and uncertainty due to the use of an ITC. It is likely this has contributed to two CEAs being considered of insufficient quality and subsequently receive a negative recommendation.

Therapies were more likely to receive positive recommendations when:

- Results of the ITC were published (3/7 CEAs)
- When the certainty in the treatment effect and its direction was substantial.
- Sensitivity analyses were provided to quantify the bias and uncertainty caused by the use of the ITC and its method.

Despite critique on the use of ITCs, no specific methods were rejected in principle. There was a substantial variation in submitted analyses and how they were criticized.

Conclusions

This review highlights how ITCs introduce substantial uncertainty to CEAs as part of HTA submissions to ZiN. ITCs were previously endorsed only when no other alternatives were available, such as in the case of single-arm pivotal trials. The increasing prevalence of pivotal single-arm trials makes it imperative to employ ITCs more frequently in CEAs. There is a pressing need for additional guidance from ZiN to outline how uncertainty arising from ITCs can be effectively managed in CEAs.

References

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Disclosures

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