# Recent Trends in Oncology Submissions to CDA Supported by Single-arm Trials

Yixie Zhang, PhD[1]; Sumeet Singh, BScPhm, MSc[1]• [1]EVERSANA, Burlington, Ontario, Canada

## Background and Objectives

- Many novel oncology therapies are approved based on single-arm studies (SAS)[1], due to practical or ethical barriers in conducting randomized control trials (RCTs).
- The non-comparative nature of these studies presents challenges to Health Technology Assessment (HTA) bodies in interpreting clinical benefits. Often, study sponsors utilize indirect treatment comparisons (ITCs) to generate comparative clinical evidence to support SAS submissions, which can be associated with limitations.[1]
- We reviewed oncology SAS submissions to Canada's Drug Agency (CDA; formerly CADTH) from January 2021 onwards to assess trends and CDA's appraisals of these files.

## Methods

### Search and screening

- We reviewed all reimbursement submissions for oncology treatments to CDA from January 2021 to January 2024. Only submissions with a draft or final reimbursement recommendation were considered. Submissions that had a status of withdrawn, cancelled, or suspended were excluded.

### Data extraction and outcomes

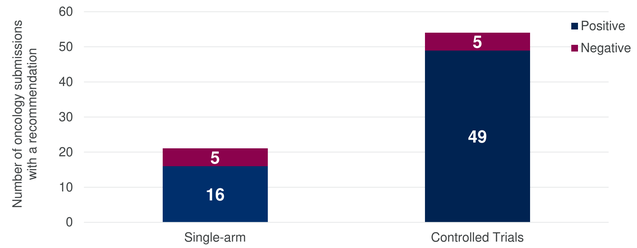
- Among the selected submissions, files supported by at least one SAS were further reviewed. Data on sponsor-submitted ITC methods, and CDA's appraisal of the SAS design and ITC methods, were reviewed and extracted. The CDA recommendation was also recorded.
- Outcomes of interest included CDA recommendation rates, ITC methods used in the submission, and limitations and concerns identified by CDA during the review of the submitted ITCs.

### Statistical analysis

- A standard Chi-square test was used to compared the rate of positive recommendations (with or without conditions) between oncology submissions supported by SAS versus those supported by controlled trials.

## Results

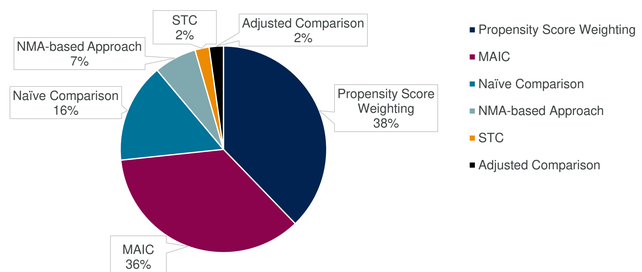
**Figure 1: Comparison of oncology submissions that were supported by SAS or controlled trials**




### Characterization of oncology submissions that were supported by SAS

- Our review identified a total of 75 oncology submissions with a draft or final recommendation from January 2021 to January 2024.
- 21/75 (28%) oncology submissions were based on SAS. The remaining 54 submissions were supported by controlled trials (**Figure 1**).
- 16/21 (76%) SAS files received a positive recommendation, versus 49/54 (91%) files supported by controlled trials ($p$=0.096, Chi-square test) (**Figure 1**).
- In all SAS files, CDA highlighted uncertainty regarding the treatment effect due to the single-arm design. However, CDA commented on the appropriateness of the single-arm design for only 6/21 files (28%).

**Figure 2: Methods used in the submitted ITCs**




### ITC methods

- 20/21 SAS submissions reported a total of 45 ITCs.
- The most commonly used methods were propensity score weighting-based (38%), matching-adjusted indirect comparison (MAICs) (36%), and naïve comparisons (16%) (**Figure 2**).
- Three ITCs used network meta-analysis (NMA) (two based on pseudo placebo arms; one used MAIC in combination with NMA). One simulated treatment comparison (STC) and one unspecified, adjusted comparison were also reported.

**Table 1: Limitations Identified by CDA in Submitted ITCs**

| | Most commonly discussed ITC limitation | Number of ITC (%) (N = 45) |
|---|---|---|
| Between-trial heterogeneity | Patient characteristics | **44 (98%)** |
| | Study design | **27 (60%)** |
| | Eligibility criteria | **16 (36%)** |
| ITC method | Covariate identification and selection | **36 (80%)** |
| | Effective sample size reduction | **28 (62%)** |

### Characterization of issues identified in the submitted ITCs

- In almost all submitted ITCs, CDA noted imbalances in patient characteristics. Additional sources of between-trial heterogeneity identified by CDA included study design (in 60% of the submitted ITCs) and eligibility criteria (in 36% of the submitted ITCs) (**Table 1**).
- Other technical challenges identified included lack of or inappropriate covariate identification and selection, and concerns regarding reduction in effective sample size (**Table 1**).

## Discussion

- **A substantial minority of recent oncology submissions to CDA were supported by SAS. CDA deemed that SAS files had a high degree of uncertainty regarding treatment benefit. Nevertheless, the majority of SAS submissions received a positive reimbursement recommendation, although there was a non-significant trend suggesting that a negative recommendation was more likely than for files supported by controlled trials.**
- **This study characterized the methods used and key limitations identified in the sponsor-submitted ITCs. Overall, the most common methods were propensity score weighting, MAICs, and naïve comparisons. Common concerns raised by CDA were imbalances in patient characteristics and heterogeneity in trial design and eligibility criteria. The main methodological concerns were around covariate identification and selection, and reductions in effective sample size.**
- **In future, guidance regarding the situations in which SAS may be considered acceptable, and optimal analysis and reporting methods for ITCs based on SAS, may be helpful to sponsors of SAS submissions.**

**Abbreviations** CDA = Canada's Drug Agency; HTA = health technology assessment; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; NMA = network meta-analysis; RCT = randomized control trial; SAS = single-arm study; STC = simulated treatment comparison.

**References**

1. US Food & Drug Administration (2023). Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics Guidance for Industry. Available online at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-considerations-support-accelerated-approval-oncology-therapeutics. Accessed: August 21, 2024

**2024 CDA Symposium Shaw Center Ottawa**
**September 4 to 6, 2024**

EVERSANA®