

# Indirect Treatment Comparison Methods Used in Reimbursement Submissions in Canada and the United States: Trends and Applicability of Joint Clinical Assessment Reports

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## INTRODUCTION

- Indirect treatment comparison (ITC) methods are used to compare treatment efficacy when no head-to-head evidence from clinical trials exists
- Results from ITCs often support health technology assessment (HTA) submissions, which are prepared for specific markets where the decision scope can be characterized by the PICO criteria: population(s), intervention(s), comparator(s), and outcome(s)
- The reimbursement process in Europe has gone through an important change with the introduction of the Joint Clinical Assessment (JCA) to coincide with the European Medicines Agency (EMA) regulatory submission
- Current JCA guidelines outline ITC methods based on data availability
- The outcome of this new JCA process is designed to publicize a dossier with comparative efficacy analyses approximately 210 days after EMA submission – likely a much shorter timeline than previous submission activities
- As resulting JCA dossiers may be published before reimbursement reviews occur outside of the EU, such as within North America, it is of interest to understand the impact of these JCA requirements, guidelines, and decisions, particularly towards the comparative analyses that will be included

## OBJECTIVES

- This review aims to survey ITC methods used in Canadian and US-based HTA submissions published since 2020 with a focus on oncology
- We summarized trends and speculated whether JCA dossiers published as a result of the JCA framework will be applicable to the current and evolving reimbursement landscape in North America, by evaluating how closely current submissions align with JCA methodological guidance

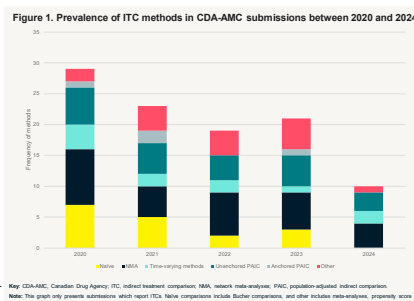
## METHODS

- We conducted a targeted search of public North American submissions in oncology, Canada's Drug Agency (CDA-AMC) and the US Institute for Clinical and Economic Review (ICER) were included
- Our summary was restricted to submissions published between 2020 and 2024, given the evolution in methods used in HTA submissions, often reflecting complex clinical trial designs and treatment innovations in oncology
- We reviewed the available submission materials to identify the use of ITC methods, specifically noting:
  - Data availability (aggregate and/or individual patient-level data [IPD])
  - Base case, subgroup and/or sensitivity analyses
  - Anchored and/or unanchored evidence networks
  - Time-varying or constant hazard ratio analyses
  - Adjustments for clinical heterogeneity, and
  - Details of the proportional hazards assessment
- We compared this to the JCA guidance as outlined in the methodological guidance and the practical guidance (Figure 2), while acknowledging that these guidance documents are not meant to be exhaustive

## RESULTS

### A. Summary of findings

- Based on the inclusion criteria, we identified 96 completed CDA-AMC reimbursement reviews, of which 61 (64%) included ITCs and were evaluated in this review. These evaluations identified 43 specific indications across 43 products. The ICER search identified 42 submissions, but only one that included an ITC in bladder cancer, assessed in 2020
- Of the ITC submissions with a connected evidence base (n = 38), Bayesian network meta-analysis (NMA) was the most commonly used method (n = 28)
- Alternative methods used to analyze connected networks were naïve ITCs/Bucher analyses (n = 9) and anchored PAICs (n = 3), all of which were matching-adjusted indirect comparisons (MAICs)
- Among submissions with a disconnected evidence base (n = 23), the most commonly used methods were unanchored population-adjusted indirect comparisons (PAICs) (n = 15)
- Of the unanchored PAICs, 15 MAICs and one STC were conducted (one submission conducted both an MAIC and STC)
- Other unanchored methods were naïve/Bucher analyses (n = 8), propensity score adjustment (n = 10) and external control arm (n = 1)



### B. Overview of anchored comparisons

- JCA methodological guidance states: *"When indirect comparisons are carried out, only anchored indirect comparisons are appropriate... Useful approaches for indirect comparisons include the Bucher method and the frequentist and Bayesian NMA models."*<sup>1</sup>
- Bucher ITC method: Used in 17 submissions but supplemented with other methods (Bayesian NMA, propensity score analysis [PSA], anchored/unanchored PAICs) in nine submissions
- Frequentist NMA models: Used in three submissions but supplemented with Bayesian NMA in two submissions
- Bayesian NMA models: Used in 28 submissions where 14 submissions included at least one supplemental analysis using a different method
- All cases of analyses with connected networks were conducted with methods outlined in JCA guidance
- When evidence forms a connected network, JCA methodological guidance states: *"For cases in which the property of similarity does not hold, the usual methods for indirect comparisons are invalid. In this scenario, population-adjustment methods might be considered as an alternative approach, provided the network is connected and there is good evidence a priori that such an adjustment is likely to reduce bias."*<sup>1</sup>
- A lack of similarity was assessed and identified in nearly all submissions which included ITCs (n = 60)
- The methods used for adjustment between studies included subgroup and/or sensitivity analyses, and covariate adjustment methods. A lack of similarity was noted in nine submissions, where no further adjustment or methods to address clinical heterogeneity were applied
- The use of multiple methods to address similarity violations adhered to JCA guidance in almost all cases

Figure 2. Hierarchy of methods cited in JCA methodological guidance

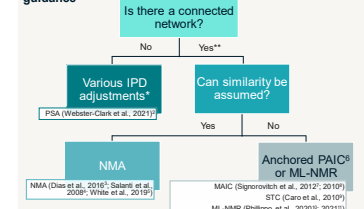
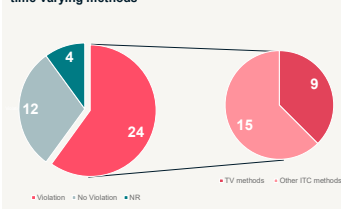


Figure 3. Proportional hazards violations\* and the use of time-varying methods



- When time-to-event outcomes are being analyzed, JCA methodological guidance states: *"...more severe violations [in the proportional hazards assumption] may result in bias and/or the non-interpretability of the hazard ratio as a measure of treatment effect. In these cases, NMA based on parametric survival curves or fractional polynomials can be applied."*<sup>1</sup>
- Of the ITC submissions, 40 submissions assessed the proportional hazards assumption, with violations for at least one outcome explicitly mentioned in 24 submissions. Nine attempted to address this violation with analyses allowing for time-varying (TV) hazard ratios (Figure 3)
- Fifteen submissions where a violation in proportional hazards was noted did not use TV methods. Four submissions did not report any assessment of proportional hazards
- Of the 10 submissions that used TV analyses, 10 used fractional polynomials. Two submissions used other TV methods including parametric and piecewise NMAs
- When the evidence forms a disconnected network, JCA methodological guidance states: *"...When non-randomised evidence is available only at the aggregated data level, there are no adequate methods available for reliable estimation of treatment effectiveness."*<sup>1</sup>
- Nearly all submissions (n = 23) that evaluated an unanchored comparison used an unanchored PAIC (n = 15), with only 10 using propensity score analysis owing to the lack of IPD available for comparator studies
- Under these recommendations, no unanchored analyses would satisfy JCA guidance

## DISCUSSION

- For submissions with a connected network, not all submissions conducted analyses according to JCA guidance and preferred methods (Figure 2)
- Submissions often assessed the exchangeability and more importantly, the similarity assumption
- In cases where proportional hazards violations were noted, TV methods were not always used. Where TV methods were employed, they were not in conflict with JCA guidance
- Upcoming JCA dossiers may provide results with ITC analysis types not often found in North American reimbursement submissions (e.g. time-varying NMA, ML-NMR)
- Unanchored comparisons, by their implementation, deviated from JCA guidance. However, the use of unanchored PAICs remains widespread. There is ambiguity about the acceptability of these within JCA, particularly as it is explicitly stated *"...STC and MAIC without a common comparator are highly problematic..."*<sup>1</sup>, yet unanchored PAICs are also referred to in the practical guidance for assessors
- Our work has some notable limitations
- The applicability of this review is only with regards to the ITC analysis used; the population and comparators within the scope assessed will likely drive much the applicability of these analyses within the North American Market
- Our review only looked at oncology since JCA currently only considers oncology indications. However, this type of work would also be valuable across other indications
- Our evaluation of heterogeneity and use of time-varying models was based on the evidence provided; a more in-depth review may discern additional implications

## KEY TAKEAWAYS

- Within the submissions evaluated, the methods used to conduct ITCs for anchored comparisons were nearly all aligned with methods outlined in the JCA Methodological Guidance<sup>1</sup>
  - Though anchored PAICs and ML-NMR were suggested by the JCA guidelines for those cases where heterogeneity was a substantial concern, there seemed to be low uptake in these recent North American submissions, though this may evolve in the coming years
- For those submissions with disconnected networks, unanchored PAICs were often used – a method that has ambiguous acceptability according to current JCA guidance
  - In these instances, various IPD adjustment methods are specified by JCA guidance documents; however, these methods were rarely used, due to the unavailability of IPD for external studies

## CONCLUSION

In cases where ITCs published in JCA dossiers have methodological issues such as clinical heterogeneity and/or a lack of network connection, it is likely that the results will be applicable and thus could be leveraged in North American reimbursement submissions. This is particularly true in the context of oncology.

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