# How is evidence on comparative efficacy and safety presented for HTA submissions in Japan? A targeted literature review

Putnam Inizio Advisory

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## Background and objectives

- HTA was formally introduced in Japan in April 2019. Guidelines for assessing comparative efficacy and safety, outlining recommended uses of ITCs and preferences regarding local versus global data, were published in 2022 (1)
- To date, there are no studies that have systematically examined the methodologies used in HTA practice and their perception
- This targeted literature review aimed to summarise approaches used in company submissions for HTA in Japan since its inception

## Overview of relevant guidelines for demonstrating comparative effects

Costs, comparators, and target populations should reflect the situation of public healthcare insurance in Japan, with the appropriate comparator selected from technologies widely used in clinical practice and expected to be replaced by the selected technology, if introduced, to treat the target population. Among these, technologies that result in better outcomes should be selected.

Where no RCT studies directly compare the selected technology with the chosen comparator, the additional benefit is evaluated via ITCs, using results identified through systematic reviews.

When ITCs are performed, the following items should be considered:

- When IPD are available, differences in background factors should be adjusted using an appropriate method, such as MAIC
- When IPD are not available, an adjusted indirect comparison using RCT or NMA should be used
- When neither IPD nor results of RCTs are available, a naive ITC may be acceptable. In such a case, the uncertainty of the results should be carefully considered
- Sufficient explanation on the prerequisites for the comparison (e.g., heterogeneity of illness, severity, and patient background) or similarity of the studies is also needed

When there are no clinical data available on the selected technology in humans, the analysis can be performed, assuming that the outcome of the selected technology is equivalent to that of the comparator(s), if appropriate. This is based on considering the approval of the PMDA.

There is a stated preference for data derived from a high-quality research reflective of clinical results in Japan. Data from Japan should be used preferentially if there is an evident heterogeneity between them and the overseas data.

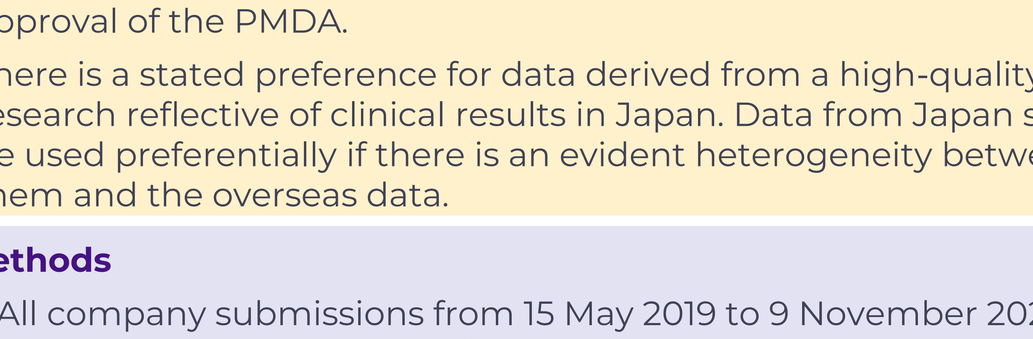
## Methods

- All company submissions from 15 May 2019 to 9 November 2022 for HTA in Japan were screened
- Submissions that were publicly available for review were included
- Information on the evidence presented to demonstrate comparative effects—including methodological information on ITCs, where conducted—and whether the studies included Japanese population only, global population, or both, were extracted
- Feedback relating to comparative evidence from the academic group was summarised

## Results

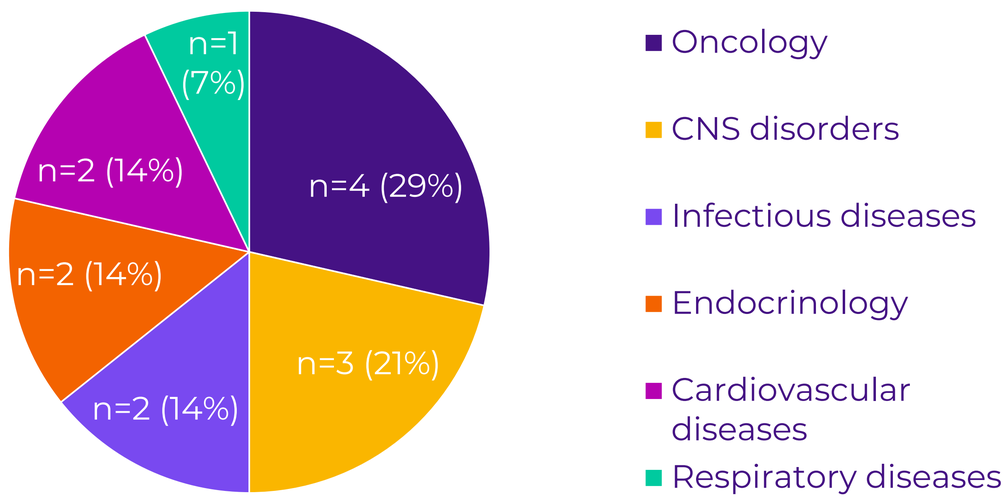
Overall, 27 HTA submissions since 2019 were identified, of which 14 had a public company submission available for review **(Figure 1)**.

**Figure 1. Identification of submissions for HTA in Japan**




Among the included studies, submissions relating to various indications were identified **(Figure 2)**. Oncology and CNS disorders were the most common indications within the identified submissions.

**Figure 2. Indications in the included studies (number of submissions)**




Thirteen submissions (93%) included RCT evidence, of which 6 included studies conducted in the global population, 2 in the Japanese population, and 5 in both global and Japanese populations.

Most submissions presented global clinical trials as their primary efficacy assessment, with some submissions reporting results separately for global and Japanese populations and/or performed pooled analysis to increase the power. Where data from Japan were not used for the ITC, no submissions provided reasons for this.

ITCs were conducted for 6 submissions, with varying specific methodology **(Table 1)**. For some submissions, separate ITCs were conducted for global and Japanese populations; for 1 submission, separate ITCs were conducted for various subgroups and indications. For 8 submissions, no ITCs were conducted.

**Table 1. ITC methodology in included submissions**

| Table 1. ITC methodology in included submissions | Number of submissions |
|---|---|
| NMA | 2 |
| MAIC | 3 |
| Bucher comparison | 1 |

Feedback from the academic groups was mixed, with some criticisms of ITC assumptions and populations. In some cases, academic groups conducted their own analyses.

## Conclusions

- HTA in Japan remains a relatively recent introduction, and there exists heterogeneity across the comparative evidence presented within submissions
- Although few submissions included ITCs, their methodologies varied, covering a range of approaches/complexities
- Some ITCs did not present data from Japanese populations
- When there is a potential for heterogeneity between Japanese and global populations, companies should consider supplementing submissions with comparative evidence focusing specifically on Japanese populations
- Future research should compare approaches used in company submissions for HTA in Japan with submissions for other HTA agencies. This would help to investigate if there is an impact of differing guidelines on the evidence presented to demonstrate comparative effects within these company submissions

**Abbreviations:** CNS, central nervous system; HTA, health technology assessment; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; PMDA, Pharmaceuticals and Medical Devices Agency; RCT, randomised controlled trial

### References

1. Center for Outcomes Research and Economic Evaluation for Health, National Institute of Public Health (C2H). Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council, version 3. 2022. Available at: https://c2h.niph.go.jp/tools/guideline/guideline_en_2024.pdf

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