Improving the Transferability of Global RCT Data to Inform Cost-Effectiveness Models in Japan: A Framework for C2H submission

Putnam Inizio Advisory

Alex Turner[1], Yoshie Onishi[2], Mariko Nomoto[2], Claire Leboucher[3], Clement Francois[4]
[1] Putnam, London, [2] Putnam, Tokyo, [3] Putnam, Lyon, [4] Putnam, Paris

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Introduction

Global randomized controlled trials (RCTs) are frequently used to inform cost-effectiveness (CE) modeling in accordance with health economic evaluation guidelines published by CORE 2 Health (C2H). However, cross-country differences in patient characteristics, clinical practice, and treatment response, raise concerns about the validity of using global RCT data to inform CE models for local decision-making in Japan. The concept of **transferability**, referring in this context to **whether treatment effects estimated in an RCT represent the treatment effects that would be estimated in clinical practice in Japan**, could help in formally assessing validity.

RCTs, which serve as the source population (SP), are used to estimate the Sample Average Treatment Effect (SATE). Health technology assessment (HTA) agencies are interested in the target population average treatment effect (PATE), the treatment effect if all patients from target population (TP) receive the treatment.

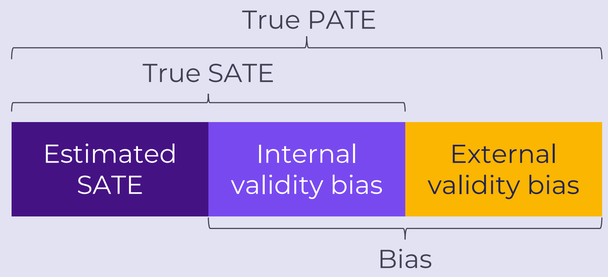
Differences between SATE and PATE are due to:

- Internal validity (driven by sources of bias as confounding) – randomization minimizes the effect of internal validity ➔ estimated SATE = true SATE
- External validity (driven by different TP and SP characteristics) refers to the degree to which treatment effect from an RCT differs from PATE

In this context, external validity is equivalent to transferability. Thus, assessing the transferability of an RCT is effectively an assessment of its external validity.

External validity requires that, either:

- No effect modifiers of the effectiveness exist,
- If effect modifiers exist, their distributions are similar between SP and TP.



Objective

To propose a structured framework for assessing and improving the transferability of global RCT data to support health economic evaluations in Japan.

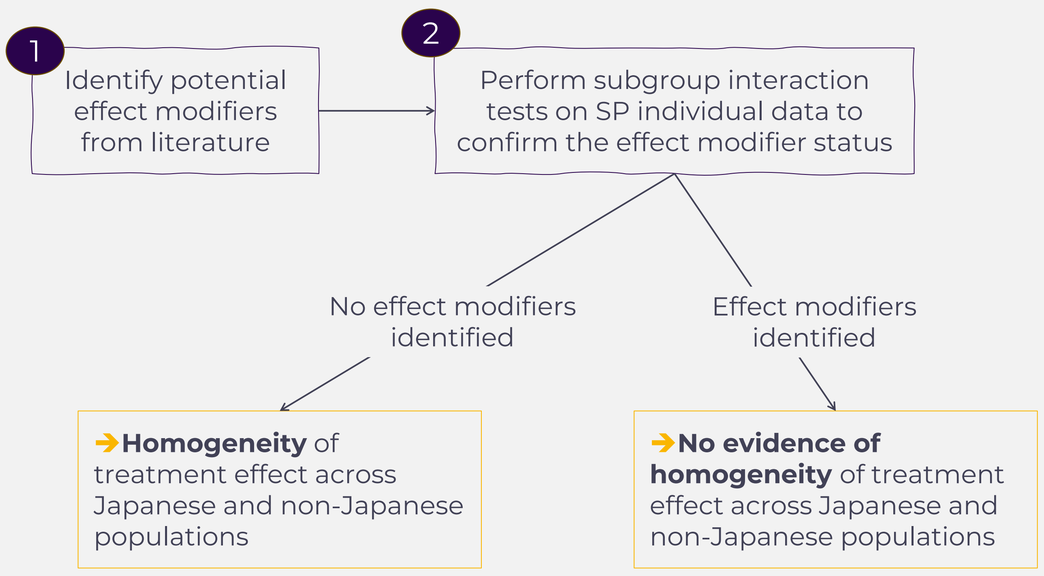
Methods

Following a review of existing publications on transportability, a framework to assess external validity / transferability of RCT has been developed.

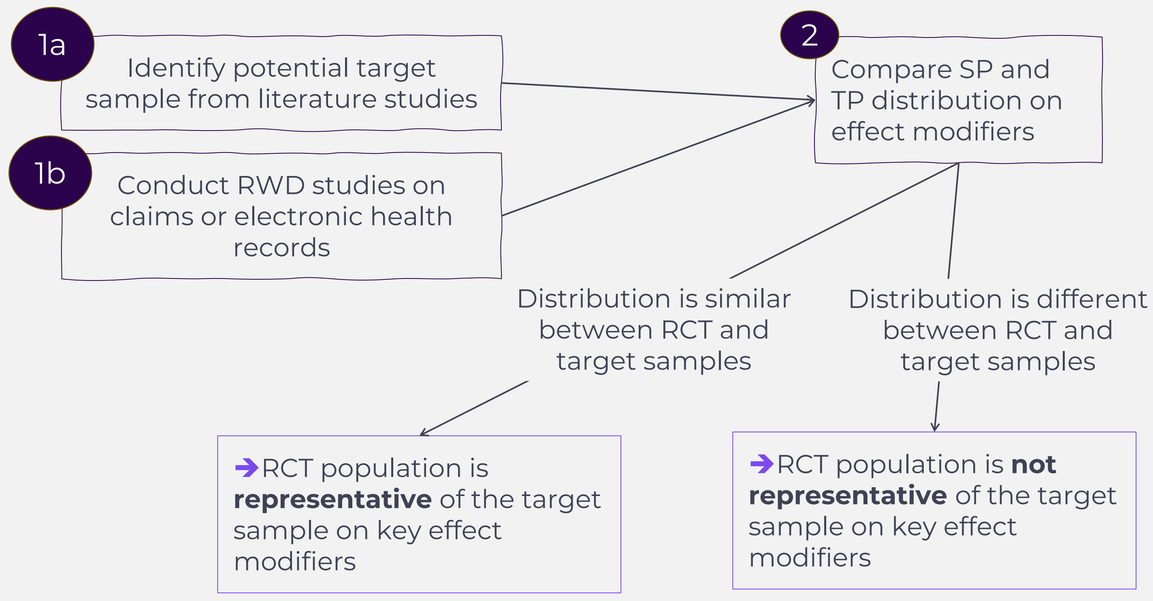
Results

To assess transferability of an RCT, the following process has been developed:

STEP 1: To establish whether there is heterogeneity in treatment effects across Japanese and non-Japanese populations



STEP 2: To examine whether the relevant trial population is representative of clinical practice in Japan



Based on the heterogeneity and representativeness assessment, PATE can be derived from SATE:

	1. Heterogeneity	
2. Representativeness	***Homogeneity***	***Heterogeneity***
Yes	No evidence of external validity / transferability bias ➔ **SATE can be considered as equal to True PATE** ➔ **RCT global data can be used in the cost-effectiveness model**	Potential evidence of external validity / transferability bias ➔ **Adjustment to estimate true PATE from SATE could be considered**
No	Potential evidence of external validity / transferability bias ➔ **Adjustment to estimate true PATE from SATE could be considered**	Potential evidence of external validity / transferability bias ➔ **Adjustment to estimate true PATE from SATE could be considered**

Discussion & Conclusion

A systematic approach combining clinical data analysis, expert input, and use of high-quality Japanese RWD can enhance the relevance of global RCTs for CE modeling in Japan. Early planning and investment in local data are critical to ensuring robust and locally appropriate health economic evaluations for C2H.

To develop a more formal and standardized framework, further research and sensitivity analyses should be performed.

References
Turner A. et al. PharmacoEconomics (2024) 42:165–176; NICE (2022) NICE real-world evidence framework; Degtiar I. et al. Annual Review of Statistics and Its Application (2023) DOI: 10.1146/annurev-statistics-042522-103837;

Abbreviations
RCT: randomized controlled trial; CE cost-effectiveness; C2H CORE 2 Health; SP Source Population; SATE Sample Average Treatment Effect; PATE Population Average Treatment Effect; TP Target Population

Contact
Clément François
Clement.francois@putassoc.com

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