Improving the Transportability of Global RCT Evidence to the US Population and Other Target Markets: A Structured Framework for Health Economic Modeling

Claire Leboucher[1], Eric Faulkner[2], Sylvaine Barbier[1]
1 Inizio Ignite Putnam, France, 2 Inizio Ignite Putnam, USA

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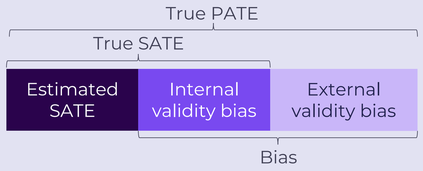
Introduction

Global randomized controlled trials (RCTs) are commonly used to inform cost-effectiveness models in the United States (US). However, trial populations often fail to reflect the demographic and clinical diversity of the US population. These discrepancies raise concerns about the **validity of transferring global RCT** treatment effects to real-world US decision-making, and even more to other ex-US markets.

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 to assess and correct representativeness bias of global RCT populations relative to the US population, and other countries.

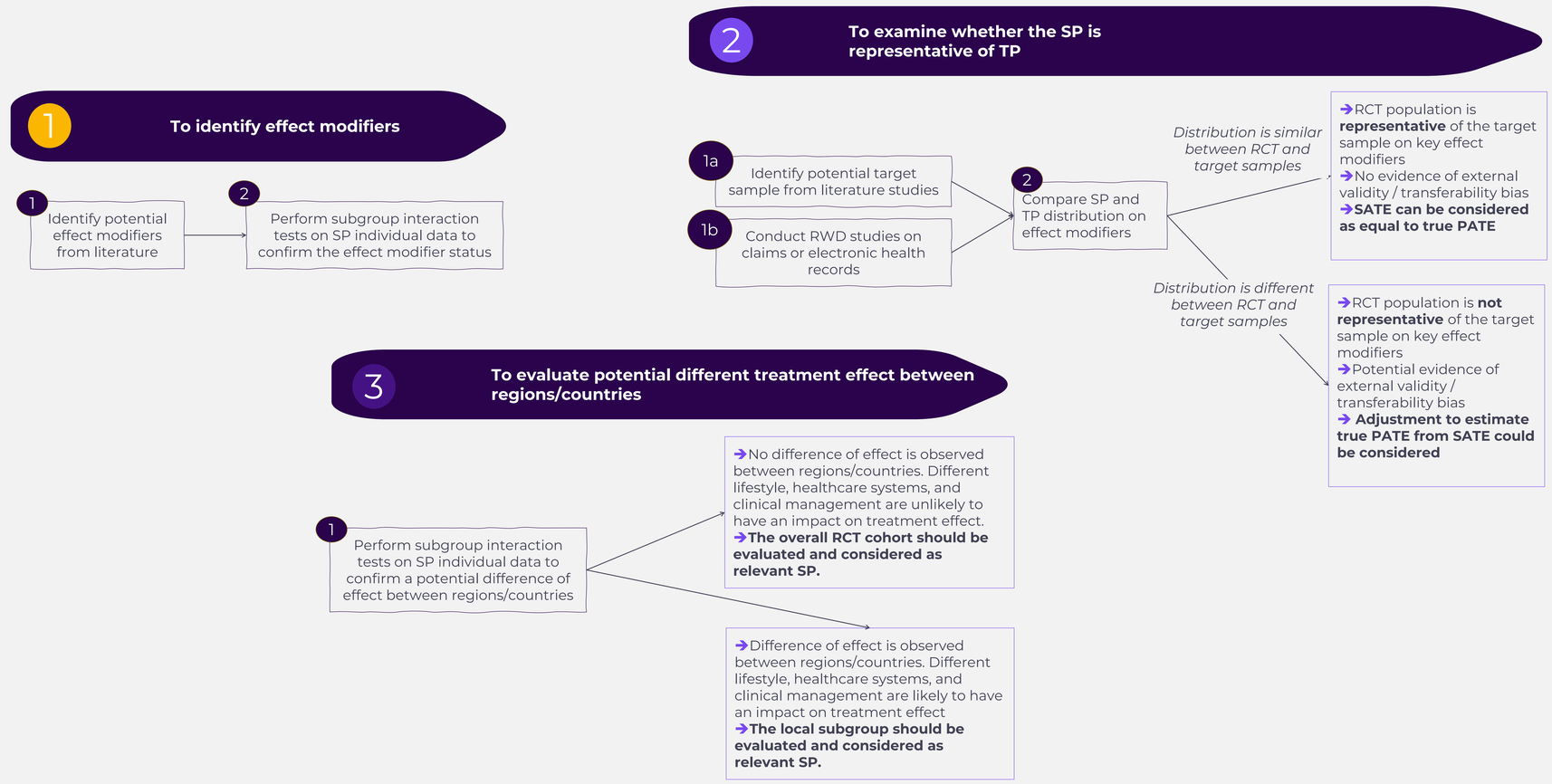
Methods

A framework was developed based on a targeted review of methodological guidance on treatment effect heterogeneity, and transportability methods. It integrates interaction analyses, and statistical adjustment techniques.

Results

A three-step framework was developed.

1. key effect modifiers are identified using clinical expertise and trial data.
the representativeness of the RCT population is assessed by comparing the distribution of these modifiers between the RCT population and a representative
2. US or local target population. When imbalances are identified, statistical methods can be applied to adjust RCT data to better reflect the US/local population.
3. To assess representativeness for ex-US target markets, the framework incorporates additional considerations. If Japan is the target market, the Asian RCT subgroup can be evaluated, to account for contextual differences such as lifestyle, healthcare systems, and clinical management.



Discussion & Conclusion

This framework provides a structured and transparent approach to assessing and addressing population representativeness when using global RCT data to inform US and ex-US cost-effectiveness analyses. By explicitly identifying key effect modifiers and leveraging real-world data and statistical adjustment methods, the framework allows decision-makers to quantify potential bias and improve the relevance of estimated treatment effects for real-world populations. Early consideration on representativeness and targeted investment in local real-world data can support more robust and decision-relevant health economic evaluations across jurisdictions.

References

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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
Eric Faulkner, Partner Evidence and Access
Eric.Faulkner@putassoc.com

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