Transportability analyses in Sweden

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Tuesday 16th November

Overview

- Registry based randomized trials

- Why do a transportability/generalizability analysis in Swedish data?

Registry based randomized trials (R-RCTs)

SWEDEN

- Sweden has a tax payer funded universal healthcare system
- Everyone that lives in Sweden has a personal number, which is used to capture data every time they use the healthcare system
- There are several mandatory national registers, such as population register, patient register, cause of death register, prescribed drug register etc.
- Also a selection (>100) healthcare quality registries that contain more detailed information on specific diseases. E.g., SWEDEHEART
- Can all be linked using the personal number

R-RCT

Pragmatic randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting

- When a clinician is collecting data for a healthcare quality registry, they are notified if the patient is eligible for an ongoing R-RCT

- If they consent, they are randomized to a treatment arm through a randomization module built into the registry

The registry helps to:

- Identify eligible patients
- Randomize
- Collect baseline and procedure characteristics
- Assist with collecting consent forms
- Identify clinical endpoints (there is no “active” follow up)

WHAT R-RCT'S CAN DO

Evaluate therapeutic options that are available in routine clinical care. We can find out what works best.

WHAT R-RCT'S CANNOT DO

Cannot design RCTs to experiment new pharmaceutical agents or medical devices.

EXAMPLE

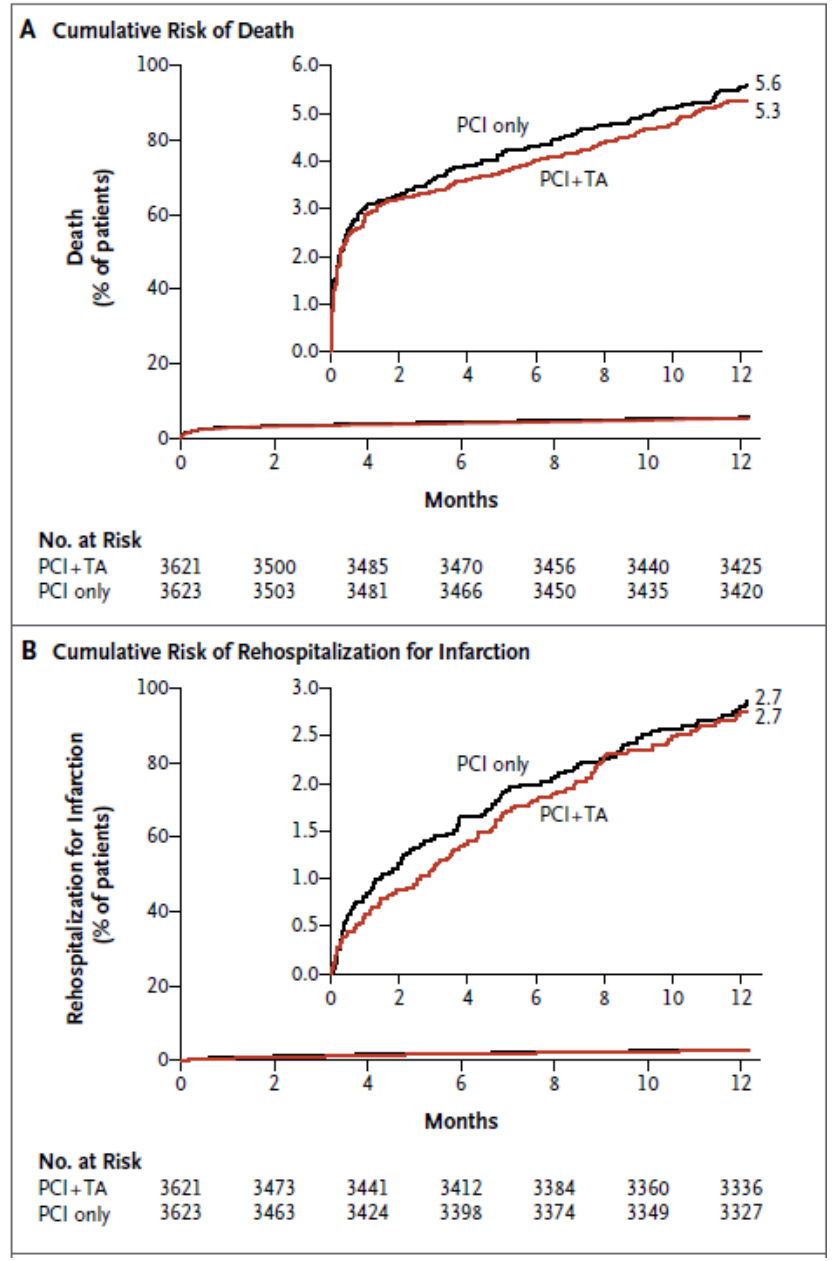
Thrombus Aspiration in ST- Elevation myocardial infarction in Scandinavia (*TASTE* trial):

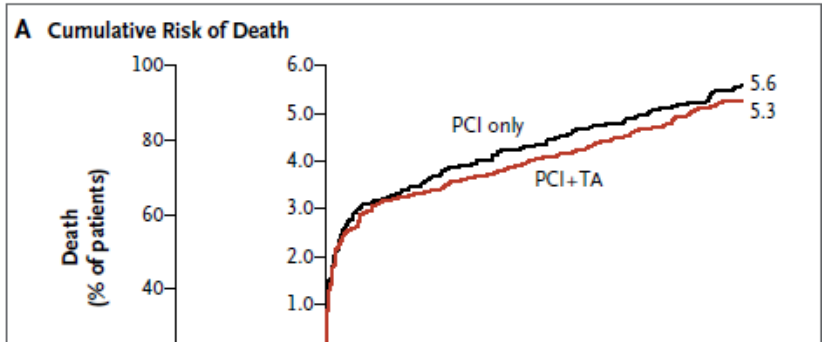
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

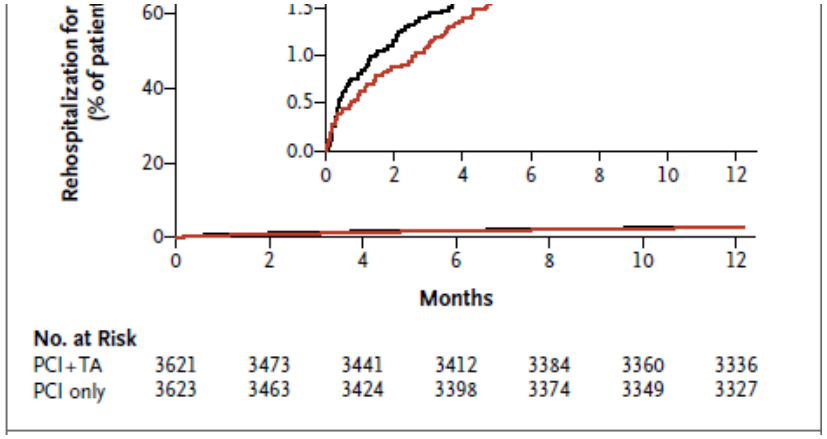
Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Patrik Alström, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Jörg Carlsson, M.D., Ph.D., Olov Collste, M.D., Matthias Götberg, M.D., Ph.D., Peter Hårdhammar, M.D., Dan Ioanes, M.D., Anders Kallryd, M.D., Rickard Linder, M.D., Ph.D., Anders Lundin, M.D., Jacob Odenstedt, M.D., Elmir Omerovic, M.D., Ph.D., Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.


A Cumulative Risk of Death
Death (% of patients)
PCI only
PCI+TA
5.6
5.3
Months
No. at Risk
PCI+TA 3621 3500 3485 3470 3456 3440 3425
PCI only 3623 3503 3481 3466 3450 3435 3420
B Cumulative Risk of Rehospitalization for Infarction
Rehospitalization for Infarction (% of patients)
PCI only
PCI+TA
2.7
2.7
Months
No. at Risk
PCI+TA 3621 3473 3441 3412 3384 3360 3336
PCI only 3623 3463 3424 3398 3374 3349 3327



NO DIFFERENCE IN RISK OF DEATH OR MOCARDIAL INFARCTION BY 1 YEAR BETWEEN THOSE RANDOMIZED TO THROMBUS ASPIRATION OR NO THROMBUS ASPIRATION



TASTE used the SWEDEHEART registry to:

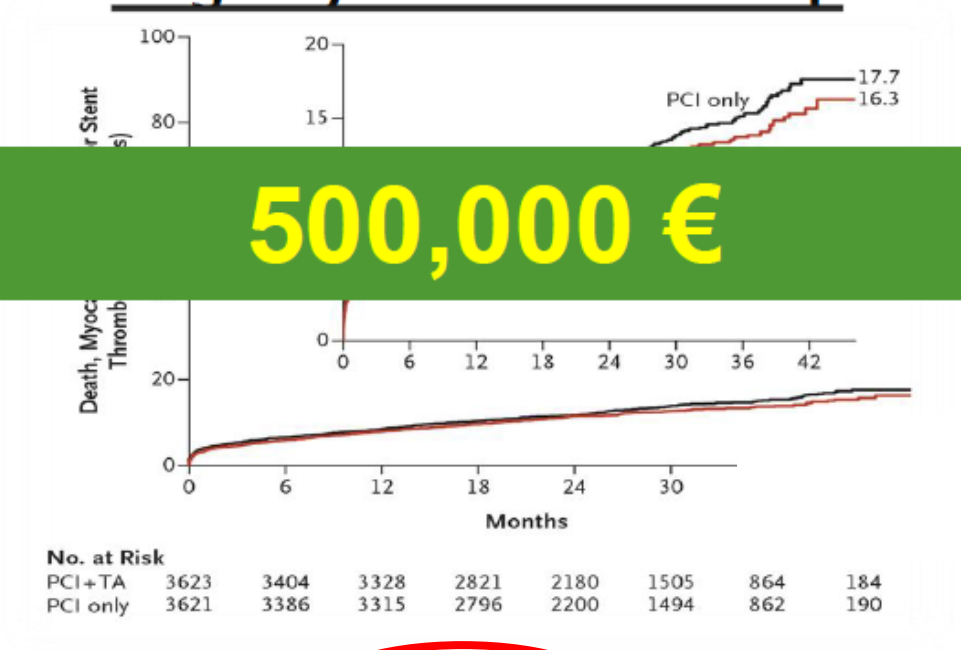
- Identify eligible patients that had an MI and underwent PCI
- Randomize individuals to thrombus aspiration or no thrombus aspiration
- Collect baseline characteristics
- Assist with collecting consent forms
- Identify clinical endpoints of death and myocardial infarction

Embedding the trial within a registry meant TASTE was

CHEAP & QUICK

TASTE

Registry-based Follow-up



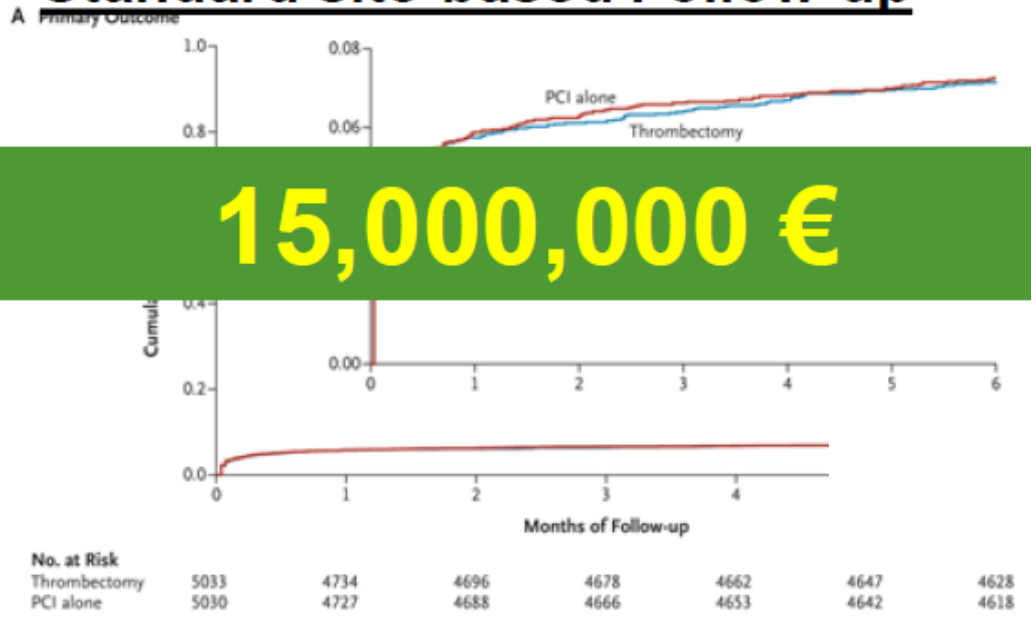
500,000 €

1st patient: June 2010
30 centers
33 months to full enrollment

Fröbert et al. N Engl J Med 2013 Oct 24;369(17):1587-97
Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

TOTAL

Standard site-based Follow-up



15,000,000 €

1st patient: August 2010
87 centers
48 months to full enrollment

Jolly SS et al. N Engl J Med 2015;372:1389-1398

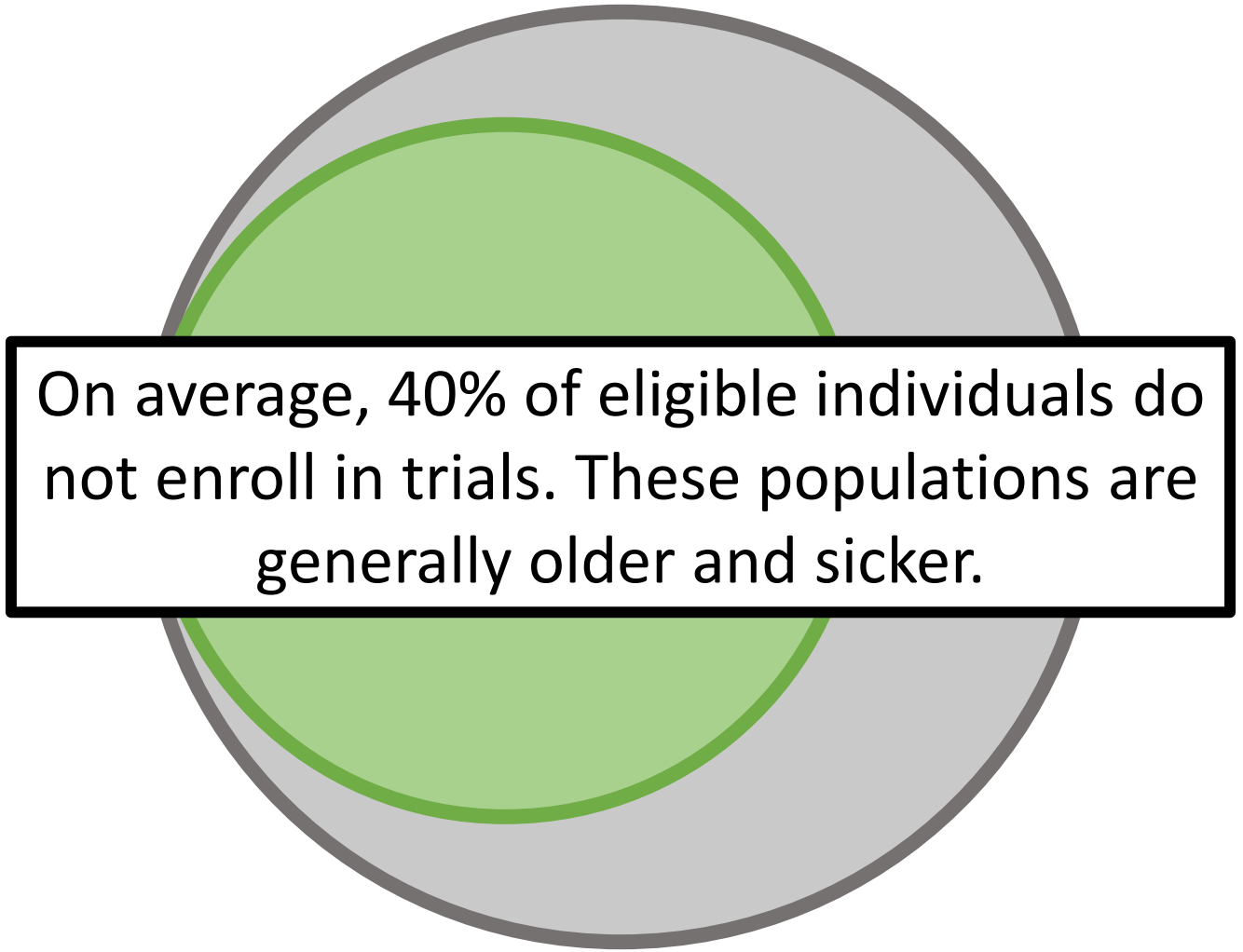
UCR

Why undertake a generalizability/transportability analysis in Swedish data?

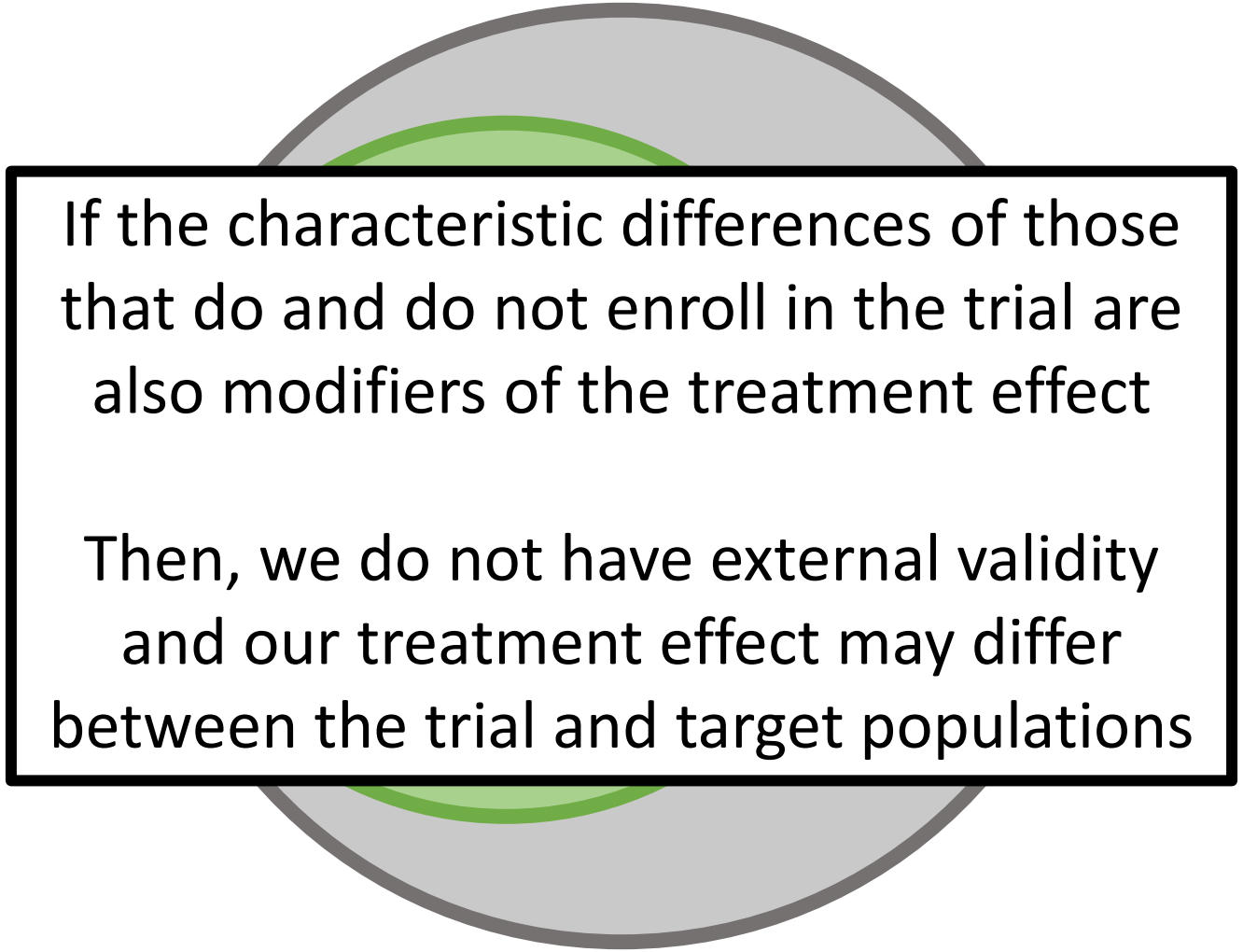
There remain questions around external validity when we undertake R-RCTs

TARGET POPULATION

TARGET POPULATION



TARGET POPULATION



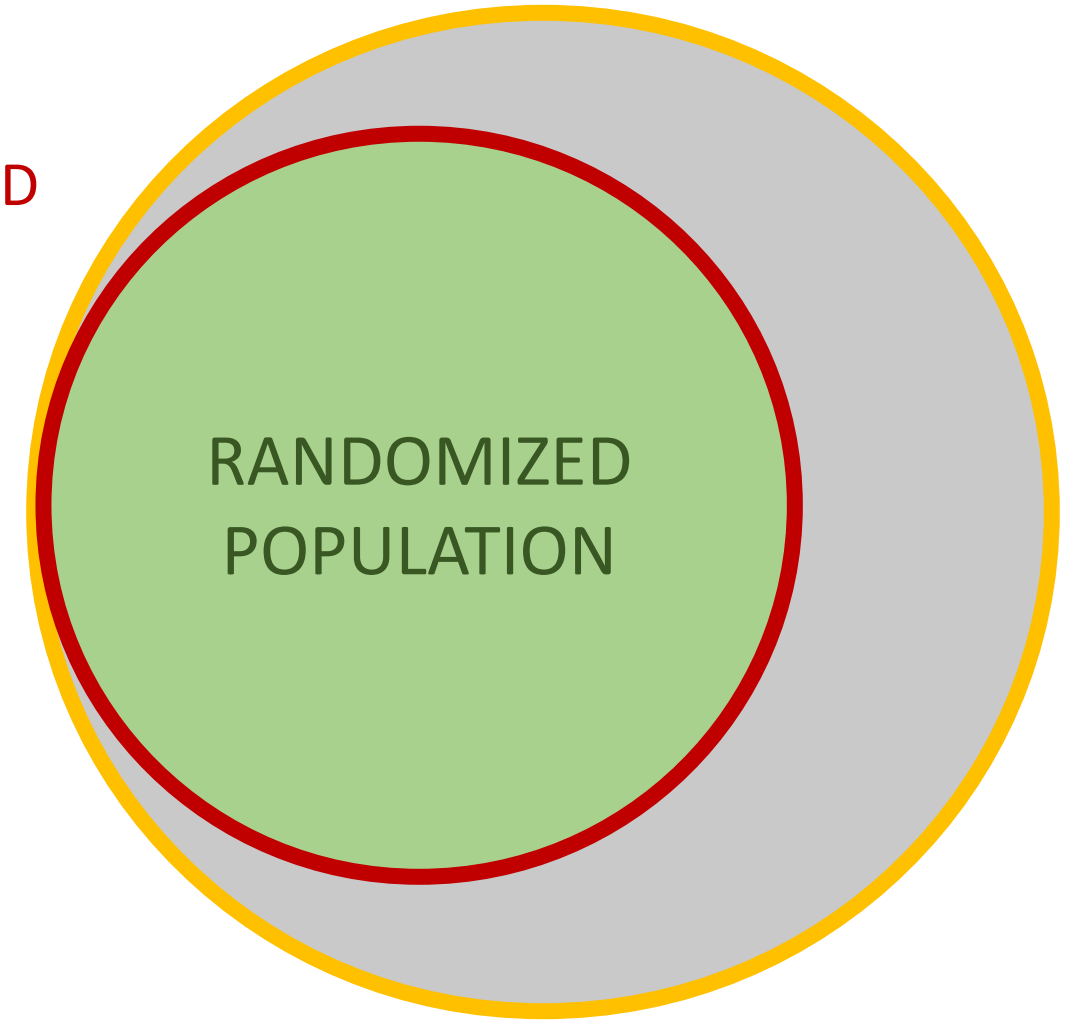
If the characteristic differences of those that do and do not enroll in the trial are also modifiers of the treatment effect

Then, we do not have external validity and our treatment effect may differ between the trial and target populations

TRADITIONAL RCT
BASELINE DATA COLLECTED IN RANDOMIZED POPULATION

TARGET POPULATION

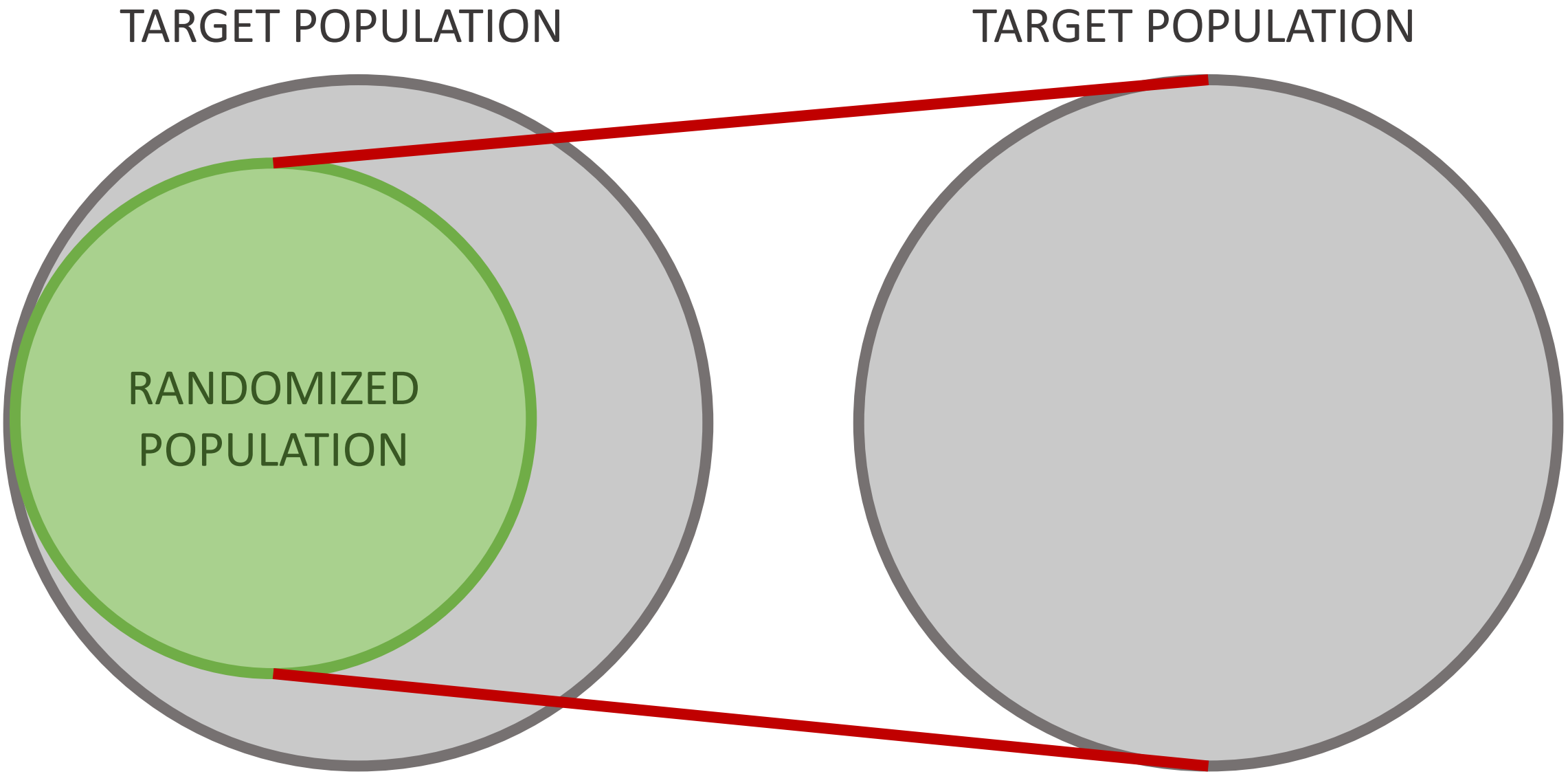
TRADITIONAL RCT
BASELINE DATA COLLECTED IN RANDOMIZED POPULATION

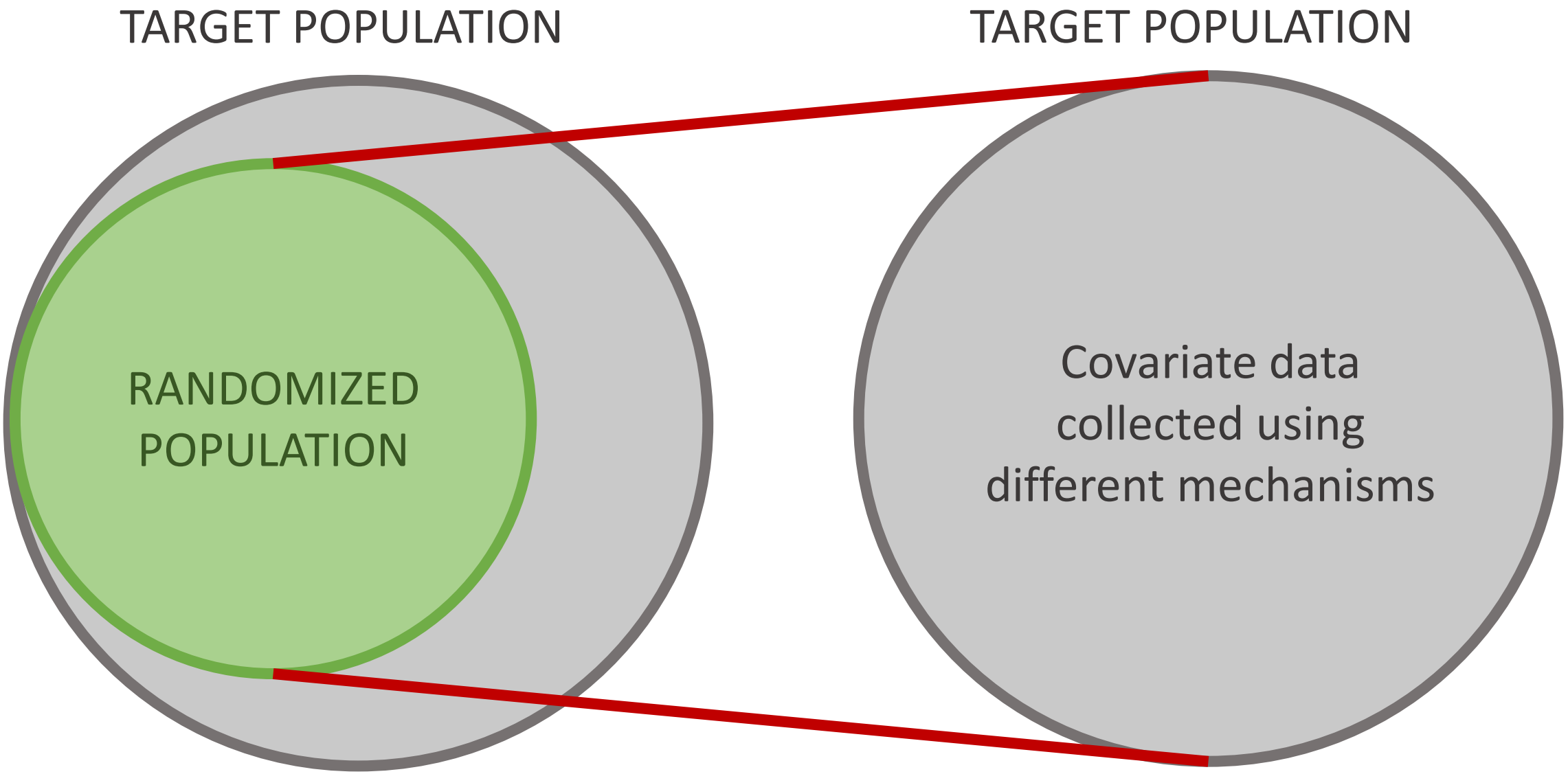


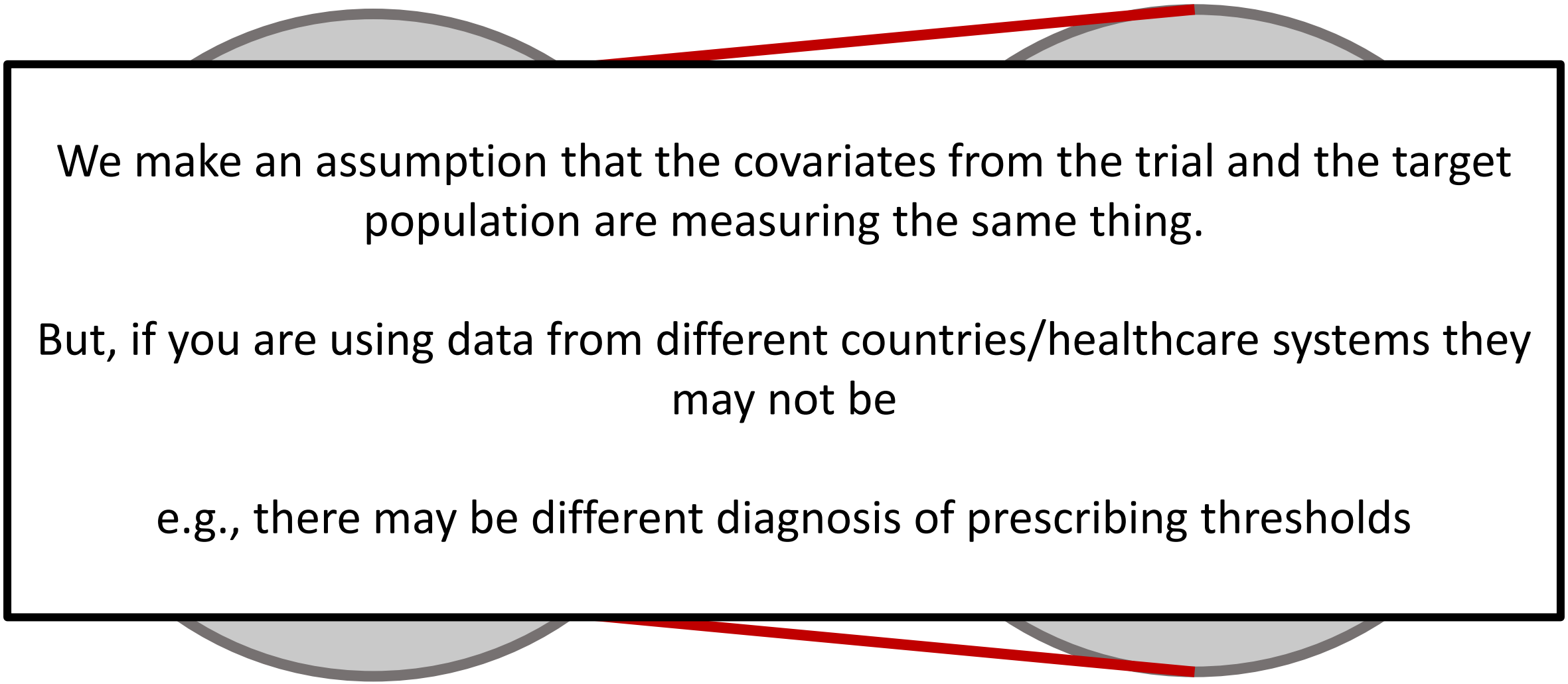
R-RCT
BASELINE DATA COLLECTED IN WHOLE TARGET POULATION

When a trial is embedded within a registry:

- Baseline characteristics are collected in all eligible individuals as part of the standard data collection for the registry
- The data generating mechanism is the same for everyone, regardless of if they take part in the trial
- We can get **the same** baseline data for individuals that were and were not randomized


TARGET POPULATION
TARGET POPULATION
RANDOMIZED
POPULATION


TARGET POPULATION
TARGET POPULATION
RANDOMIZED POPULATION
Covariate data collected using different mechanisms

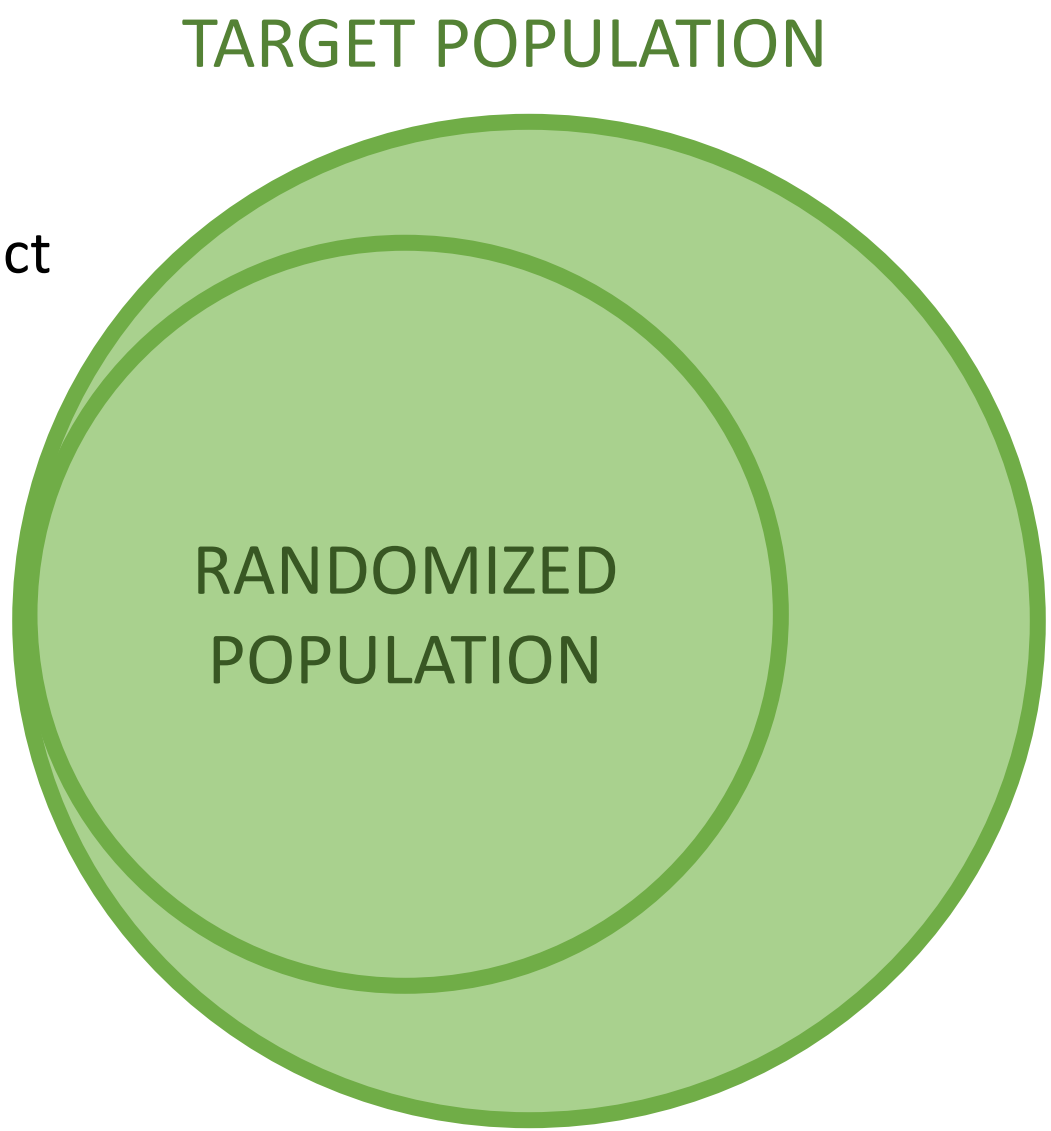


We make an assumption that the covariates from the trial and the target population are measuring the same thing.

But, if you are using data from different countries/healthcare systems they may not be

e.g., there may be different diagnosis of prescribing thresholds

Use baseline data on the potential modifiers of treatment effect to transport (generalize) effect estimates from the randomized to the target population



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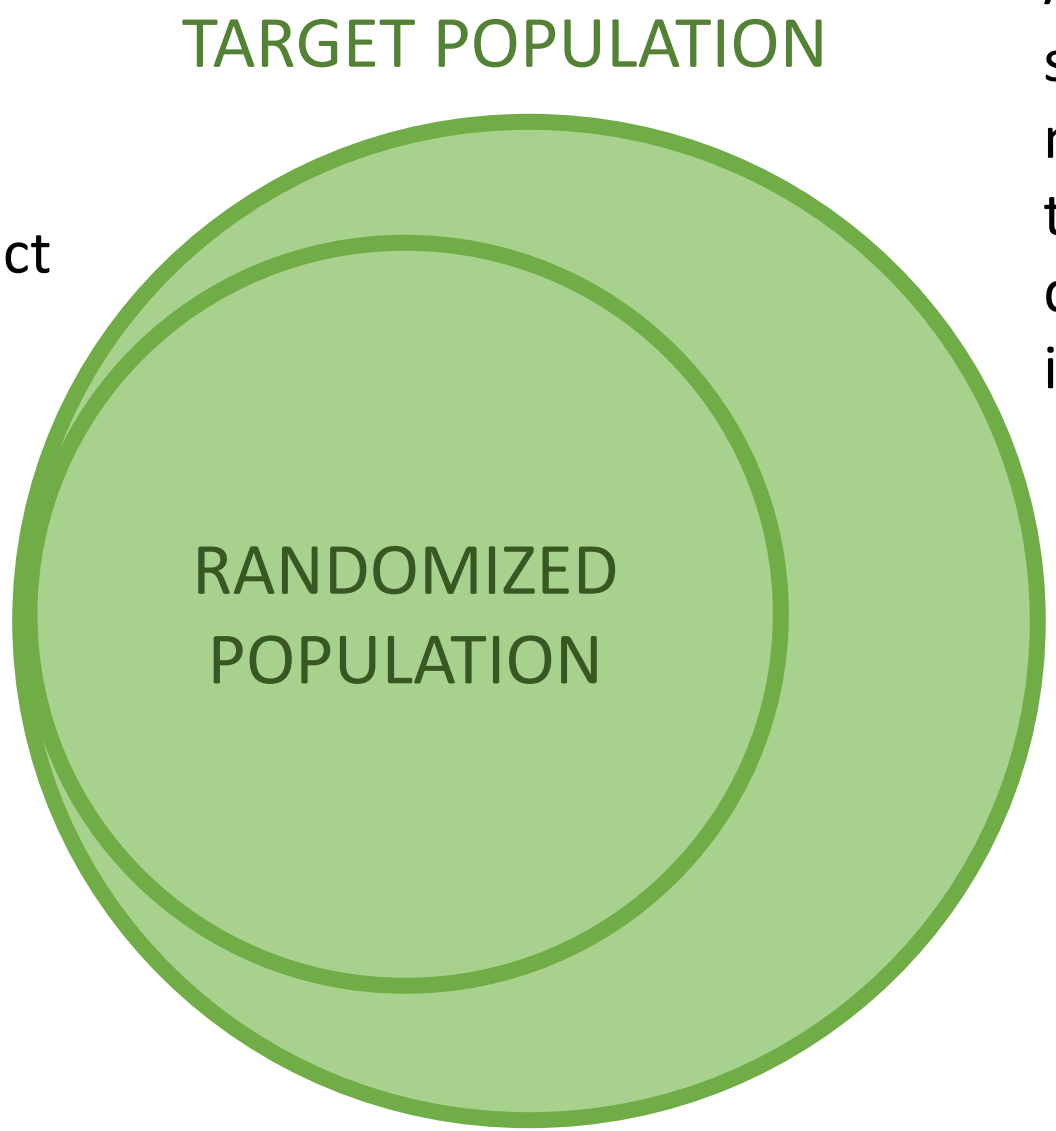

As data are collected in the same way, we don't have to make assumptions that the trial data and observational data are collecting the same info, because THEY ARE

Why undertake a transportability/generalizability analysis in Sweden (or anywhere else that undertakes R-RCTs)?

- There are currently a lot of R-RCTs being undertaken in Sweden (cardiology, cancer, respiratory diseases etc.)

- But these trials still cannot experiment on everyone eligible for the treatments under study – our target population

- We can use data from the SAME registries and perform transportability analyses to estimate the effects in those not included in the R-RCTs

- Because the data are collected from the same registry, we do not have to make assumptions about the data generating mechanisms

QUESTIONS?

- The trial doesn’t answer some questions
  - Don’t know the effect in those that didn’t give consent in Sweden (generalizaibility)
  - Don’t know if the effect is different in populations with different distribution of characteristics (transport to other populations, but have a lot of info on baseline characteristics)

- We need to use observational data to complement these RCT estimates – this is where these methods come in useful

- Say why collecting baseline vars from the registry is important for our work in generalizibility