An approach for using observational data to enhance the external validity of RCTs

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RCTs: what's the problem?

- Heavy investment in RCTs
- Decision-makers want effectiveness for target population
- Fundamental problem: mismatch design and decision
- Often assume external validity without justification
  - 2015 70 RCTs in NEJM, JAMA Lancet
  - 5 (7.1%) studies any quantitative data

- What are we assuming?
- How can we test the underlying assumptions?
- Danger: providing decision-makers with inaccurate evidence

Treatment effects for target population

Population versus sample effects
- Sample average treatment effect for treated (SATT)
  - e.g. treatment effects for treated *within RCT*
- Population average treatment (PATT)
  - e.g. treatment effects for treated in *target population*
- SATT≠PATT if heterogeneity or treatment in RCT is different
- We use observational data to reweight data from single RCT
- Aims to give unbiased estimates for the target population
- Tests whether required assumptions are met

Identifying PATT from RCT
Key assumptions

1. Treatment same effect on outcome in RCT and target population (consistency)

2. Selection into trial is not according to potential outcomes (selection)

General approach

1. Target population defined from observational data

2. Estimate Treatment effectiveness in RCT

3. Use observational data to reweight RCT to target population

4. Assess external validity with Placebo test: reweighted RCT vs target population

5. Treatment effectiveness *after* reweighting to target population

Pulmonary artery catheterisation (PAC)

- Invasive device monitoring flow Intensive care Units (ICU)
- Example setting where device used without trial evidence
- Highly influential observational study: PAC increase mortality
- UK multicentre RCT: PAC no effect on survival, and not cost-effective
- Concern RCT lacked external validity, case-mix too severe
- Prospective non-randomised study (NRS)
- Accessed UK intensive care database over 1.5 million admissions
- Data from 50 centres, where patients had PAC routine practice
- NRS same protocol, casemix, resource use and endpoints RCT

Intervention Pulmonary artery catheter (PAC):
UK RCT and UK NRS: Good overlap

	RCT (Pac-MAN)	NRS
Inclusion	general UK ICUs Admission 01-04	general UK ICUs Admission 03-04
	Equipoise in centre	No equipoise required
	Consent	No consent
	PAC: might benefit	PAC: would benefit No PAC: admitted to ICU
Exclusion	Specialist centres	Specialist centres
	Children, transplants	Children, transplants
N	**506 PACs; 508 No PACs**	**1052 PACs**

Characteristics and outcomes of PAC patients
RCT vs NRS

THETA

Variables	RCT PAC (n=506)	NRS PAC (n=1,051)
Mean Age	64.2	61.9
% Elective surgical	6.3	9.3
% Emergency surgical	28.1	23.1
% Ventilated admission	88.9	86.2
% Teaching hospital	21.7	42.5
Outcomes		
% In hospital Mortality	68.4	59.3
Mean hospital cost (£)	18,612	19,577

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Approach in PAC case study

- Within RCT, for each PAC find matched control, to estimate SATT
- Reweight matched pairs according to target population in NRS

- Placebo tests, contrast weighted outcomes PAC RCT versus PAC NRS
- Pass placebo test- small mean outcome differences, small p values
- Fail placebo test- large mean outcome differences, high p values
    – treatment differs between settings
    – selection into RCT conditional on potential outcome
    – lack power
- Estimate PATT by reweight SATT using covariate from NRS

Placebo tests- in hospital mortality
NRS (PAC) – RCT (PAC)
after reweighting

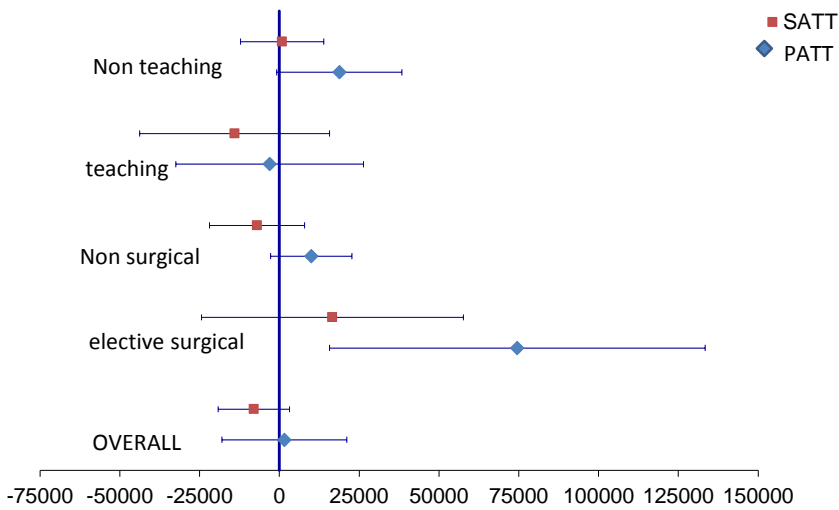|	Mortality difference	P Value	Power	Placebo test
Overall	-3%	0.05	96%	YES
Teaching hospital	-4%	0.12	27%	YES
Non teaching	-3%	0.05	85%	YES
Non surgical	-4%	0.06	83%	YES
Elective Surgery	+8%	0.46	8%	NO

PATT versus **SATT**
In hospital Mortality (PAC - no PAC)
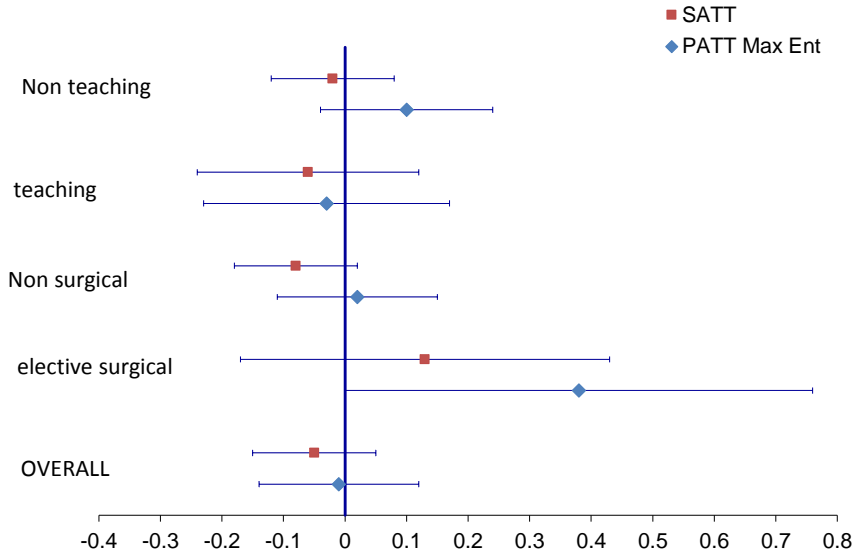
PATT versus SATT
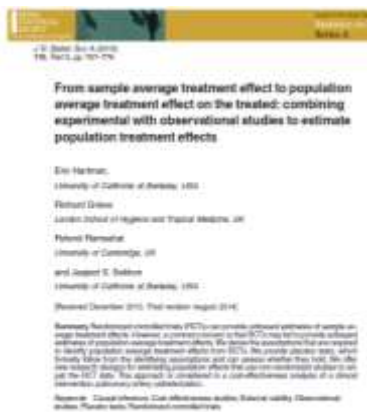## Incremental net benefits PAC- No PAC
£20,000 per QALY

Discussion

- In example, placebo tests passed, overall, not for all subgroups
- Formal use of RWE to assess and improve on external validity
- Illustration setting 'treatment' rolled out before single RCT
- More widely, use RWE
  - define the populations
  - test and adjust for differences RCT vs routine practice
- Nest RCTs within RWE, can help target RCTs to subgroups
- Can also harness with aggregate observational data
- Apply mixed treatment comparisons setting (MAIC)

The framework