Complier Average Causal Effect analysis

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Why is CACE important for cmRCTs?

- cmRCT (TWIC) designs randomly select some eligible patients from the cohort to be offered a treatment

- For an unbiased ITT analysis all eligible patients offered the treatment are compared with all eligible patients not selected

- ITT analysis of everyone gives a valid estimate of the real world, average population treatment effect, but not of the effect in an individual who is treated (because ITT is diluted by non-compliers)
Why is CACE important for cmRCTs?

• If the take up of the offer is low, ITT analysis of cmRCT designs may seriously underestimate the treatment effect.

• And per protocol analysis is wrong. It assumes compliers and non-compliers are the same.

• CACE is a method for adjusting for non-compliance which doesn’t make this assumption.
How does CACE analysis work?

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Compliers with A</th>
<th>Non-compliers with A</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>events</td>
<td>ER</td>
</tr>
<tr>
<td>Intervention A</td>
<td>200</td>
<td>40</td>
<td>0.2</td>
</tr>
<tr>
<td>Control B (TAU)</td>
<td>200</td>
<td>50</td>
<td>?= 0.25</td>
</tr>
</tbody>
</table>

**ITT analysis:** All A vs all B = 0.233 / 0.266 = 0.875

**Per protocol analysis:** Complied A vs all B = 0.2 / 0.266 = 0.75

**CACE analysis:** Complied A vs controls who would have complied = 0.2 / 0.25 = 0.8
CACE analysis assumptions

• In CACE analysis we assume
  1. **Randomisation has worked** – so that, for example, the number of controls who would have been ‘non-compliers with the treatment’ [if they had been offered it], is the same as the number of non-compliers with the treatment who were offered it

  2. Non-compliers who were offered the treatment have the same treatment as controls [as in a single consent cohort trial], and

  3. Simply being offered a treatment doesn’t affect your outcome
Is assumption 2 reasonable?

- Design: (TAU + A) vs TAU
  - Assumption is right
- Design: A vs TAU.
  - Then the question is whether non-compliers with A have TAU or nothing
    - When non-compliance = X-over the assumption is right
    - When A = offer of A, and TAU = no offer, then the assumption is also likely to be right unless the offer of A affects outcome
- Design: TAU + A vs TAU + placebo.
  - Then the question is whether there is a placebo effect
CACE was made for cmRCT trials

- CACE analysis can be used for A vs TAU trials as in cmRCT designs

- It is very helpful for dealing with compliance rather than adherence (i.e., when patients randomised to treatment don’t take it up at all). This is the case in trials of the offer of treatment - as in cmRCT designs

- Some sort of CACE analysis (as opposed to ITT) is essential when compliance is low – as may be the case in cmRCT studies because there is no pre-selection of patients
CACE analysis

- In the simplest case a CACE analysis simply inflates the ITT estimate by the proportion of patients who complied with the treatment
  - For example, if the ITT = +10.0 but only 75% complied, the CACE estimate
    \[ \frac{+10.0}{0.75} = 13.3 \]

- CACE can be used for both binary and continuous outcomes. It is an Instrumental Variable method, and can incorporate adjustment for covariates such as baseline risk and missing data
Thank you

• Compliance/adherence and CACE analysis:
  • I also have some slides showing how CACE analysis works in the simplest situation (email j.nicholl@shef.ac.uk)