# Analysis

## Is there another way to take account of noncompliance in randomized controlled trials?

Noncompliance is an important issue in the design and conduct of randomized controlled trials (RCTs). It arises when participants do not receive the treatment or intervention to which they were randomly allocated. For example, some participants invited to go through a screening program may not attend. Noncompliance can cause problems at the analysis stage: How do we deal with the people who do not take the treatment or intervention they were allocated?

It is routinely recommended that the primary analysis of an RCT should use intention to treat (ITT). In an ITT analysis, data for each study participant are retained for the original group assignment, irrespective of whether or not the patient received the allocated treatment. A full ITT analysis is possible only when complete outcome data are available for all subjects. The main reason for advocating ITT analysis is that it maintains the baseline comparability achieved by the randomizing process. If the initial random assignment is undermined, then confounding can be introduced and the internal validity of the results is consequently questionable. An ITT analysis provides an estimate that mirrors what would happen in actual clinical practice: it takes account of patients who do not take their medication or do not complete their treatment.

Although it is of interest to makers of policy and public health evaluations to look at such group means or totals, it also matters to look at the effect of treatments on individual patients. For example, if a patient undergoes screening as intended, what is the likely effect upon their condition? Trials with noncompliance that use ITT analysis do not answer this question, because when there is noncompliance, the estimate will be diluted by the data from participants who do not receive the treatment or intervention to which they were randomly allocated.

An ITT approach does answer an important question: whether the *offer* of treatment to the intervention population is effective, a question that is rather different. To answer it at an individual level, some have suggested analysis of data from only those participants who complied with their allocated treatment (i.e., per-protocol analysis) or analyzing data by the treatment actually received instead of that randomly allocated (i.e., on-treatment analysis). For these approaches, the following assumption must be made, to produce an unbiased estimate of the outcome: the probability of taking the treatment is random with respect to all predictors of outcome. If this assumption is untrue, then the results of a per-protocol or on-treatment analysis can be biased.

Many trialists use ITT as the main means of analysis, but also include a per-protocol or on-treatment analysis to try to estimate treatment effectiveness. An alternative approach that (in theory) better estimates the effect of the treatment than either approach is the complier average causal effect (CACE), also called the local average treatment effect (LATE).[1] CACE is a measure of the causal effect of a treatment or intervention on the people who received it as intended by the original group allocation. Because it retains the initial randomized assignment, it overcomes the problems related to per-protocol and on-treatment analyses.

For example, let us consider a trial of fecal occult-blood screening for the prevention of colorectal cancer (CRC)[2] (Table 1). The investigators used an ITT analysis to answer the question, "What would be the reduction in CRC mortality if we offered population screening?" An ITT analysis showed 15% fewer deaths from CRC (Table 2). A per-protocol analysis, applied to answer the question "What would the reduction in CRC mortality be among those who took up the offer of screening?", revealed a 39% reduction in CRC deaths, which is likely to be an overestimate of the screening program effect, since participants who accepted the offer of screening were likely to have characteristics that differed from those who did not attend. In particular, compliers could have been more health-aware and taken other preventative steps.

When a CACE analysis is applied to

**Table 1:** Comparison of rates of death from colorectal cancer among those who attended or did not attend screening during a study of fecal occult-blood screening

| | Intervention group; *n* = *75 253* | | | Control group; *n* = *74 998* | | |
|---|---|---|---|---|---|---|
| Status | Symbol | Deaths ÷ *n* | ER, % | Symbol | Deaths ÷ *n* | ER, % |
| Compliers (53%) | $A_i$ | 138 ÷ 40 214 | 0.34 | $A_C$* | 198 ÷ 39 749 | 0.50 |
| Noncompliers (47%) | $N_i$ | 222 ÷ 35 039 | 0.63 | $N_C$* | 222 ÷ 35 249 | 0.63 |
| Overall outcome | $T_i$ | 360 ÷ 75 253 | 0.48 | $T_C$ | 420 ÷ 74 998 | 0.56 |

Note: ER = event rate (risk of death).
*Quantities on the darker background are calculated rather than observed; see text for explanation.

**Table 2:** Relative risks for the colorectal cancer screening study, by type of analysis performed

| Analysis | Calc. | Data | Result |
|---|---|---|---|
| ITT | $T_i/T_C$ | 0.48 ÷ 0.56 | 0.85 |
| PP | $A_i/T_C$ | 0.34 ÷ 0.56 | 0.61 |
| CACE | $A_i/A_C$ | 0.34 ÷ 0.50 | 0.69 |

Note: Calc. = calculation, ITT = intention to treat, PP = per protocol, CACE = complier average causal effect.

DOI:10.1503/cmaj.051625

this study, we can observe 2 subgroups within the intervention group (the subjects who were invited to attend CRC screening): those who attended screening ($A_t$) and those who did not ($N_t$). To apply CACE, we must make 2 assumptions. The first is that members of the control group have the same probability of noncompliance as do members of the intervention group. If allocation was genuinely random, this statement must be accepted as true, at least for this particular population. The second assumption is that merely being offered the treatment has no effect on outcome.

In the intervention group ($n$ = 75 253), 35 039 participants (47%) did not take up the offer of screening, of whom 222 died from CRC (an event rate of 0.63%). Of the 40 214 participants who attended screening, 138 died from CRC (an event rate of 0.34%).

For members of the control group ($n$ = 74 998), who were not asked to attend screening, we cannot categorize participants based on their actual compliance behaviour was not a factor. However, we know that the total number of control subjects who died from CRC was 420. If we assume that same proportion of participants (47%) would not take up an offer of screening as in the intervention group, we can estimate that 35 249 control subjects would not have attended screening. If we assume again that the offer of screening has no effect on the outcome, then the CRC mortality rate among the hypothetical noncompliers in this group would be the same as that of the actual noncompliers in the intervention group (0.63%). Thus, we can calculate that the number of CRC deaths that could be expected in this group would be 222. The remaining deaths from CRC would have occurred among those in the control group who who would have complied with screening had they been invited ($A_c$ = 198).

We can now compare the outcomes of those who did accept screening with those of a similar subgroup of control subjects who could be expected to have accepted screening had it been offered. As Table 2 shows, the ITT analysis produced the highest relative risk; the per-protocol approach, the lowest. The CACE estimate falls between those 2 extremes.

## Discussion

Although it is widely recommended that the primary analysis of a randomized controlled trial should be ITT, investigators often supplement this with a per-protocol analysis. The main problem with a per-protocol approach is that, as participants self-select into the intervention and control groups, the initial randomization is undermined. Because bias may be introduced, the basis for statistical inference is violated. CACE offers an approach that retains and recognizes the initial randomization and thus overcomes the problems faced by per-protocol and on-treatment analyses.

We have presented the ideas behind choosing CACE to analyze trials involving noncompliance. Statistical methods for estimating CACE have been developed and recently reviewed.[1] Different methods have been used for various types of outcomes (e.g., time to event), for more complex noncompliance situations (e.g., when noncompliance occurs in both groups)[3] and to allow predictors of compliance to be included in the analysis. Moreover, when there is both noncompliance and missing outcome data, the CACE approach can still be used, although further assumptions are required.

One disadvantage of the CACE approach is that it can produce wider confidence intervals than the ITT and per-protocol analyses. However, if variables are included that predict whether participants comply with their allocated treatment or not, then the width of the confidence intervals can be substantially reduced. Most approaches to calculating CACE incorporate compliance as a dichotomous (yes/no) variable, although people sometimes take a treatment intermittently. Again, techniques have been developed to deal with this type of compliance data.

The second assumption of CACE — that merely being offered the treatment has no effect on outcomes — may not be plausible in all trials, and requires careful consideration in each one. For example, being offered screening for CRC may increase someone's awareness of the possibility of the disease; that person may, in turn, take steps to reduce their own chances of experiencing the condition (e.g., by cutting down on their alcohol intake or eating more fruits and vegetables).

Although the ITT approach should remain the primary analysis, some form of CACE analysis should be performed as a secondary analysis instead of a per-protocol or on-treatment analysis.

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This article has been peer reviewed.

**Competing interests:** None declared.

**Acknowledgements:** We thank Trevor Sheldon, Max Bachmann, Craig Ramsay and Diana Elbourne for reviewing an early version of the article and providing valuable feedback.

Funding was provided by the NHS R&D Research Methodology Programme of the National Health Service, United Kingdom.

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