Connecting Instrumental Variable methods for causal inference to the Estimand Framework

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Abstract

Instrumental Variables (IV) methods are gaining increasing prominence in the pharmaceutical arena in light of the recently published addendum on estimands and sensitivity analysis in clinical trials to the E9 guideline of the International Council for Harmonisation. The E9 addendum emphasises the need to account for post-randomization or ‘intercurrent’ events that act to distort the interpretation of a treatment effect estimate at a trial’s conclusion. IV methods have been used extensively in epidemiology and academic clinical studies for ‘causal inference’, but less so in the pharmaceutical industry setting until now.

In this tutorial paper we review the basic tools for causal inference, including graphical diagrams and potential outcomes, as well as several conceptual frameworks that an IV analysis can sit within. We discuss in detail how to map these approaches to the Principal Stratum and Hypothetical ‘estimand strategies’ proposed in the E9 addendum, and provide details of their implementation using standard regression models. Specific attention is given to discussing the assumptions each estimation strategy relies on in order to be consistent, the extent to which they can be empirically tested and sensitivity analyses in which specific assumptions can be relaxed. We finish by applying the methods described to simulated data closely matching a recent pharmaceutical study to further motivate and clarify the ideas.

Key words: E9 Addendum, Estimand Framework, Causal inference, IV methods, Homogeneity, Monotonicity
1 Introduction

What is the effect of treatment on an individual patient’s health in a trial? In order to answer this question we would need to measure how a patient’s outcome would have changed if they had been given the treatment compared to if they had not. Counter-factual contrasts like this are a popular vehicle for defining a causal effect, but they illustrate the ‘fundamental problem’ of causal inference: It is not possible to directly observe the outcome under both treatment choices for a single individual under identical conditions. In specific settings, such as a crossover trial, or in ophthalmology - where one eye might be treated and the other not - one can come close to this ideal, but specific assumptions must still be made. In an idealised randomized controlled trial (RCT) of adequate size in which all patients adhere to their assigned treatment regimen until their final outcome is observed, the act of randomization ensures that patients on each treatment arm will be sufficiently balanced with respect to all patient characteristics. This provides a solid rationale for attributing any difference in outcomes between the two treatment groups at the end of the trial to the treatment itself, and for unbiasedly estimating this difference (the treatment effect) by comparing patient outcomes across randomized groups. In the field of epidemiology this is referred to as a ‘causal’ effect estimate and the concept of an idealised RCT is routinely invoked in the observational sciences to explain the underlying notion of causality. In spite of this, the word ‘causal’ is rarely - if ever - used within the clinical trials arena. Paradoxically, some high profile journals think it should only be used within an RCT.

When running an RCT in practice, a certain fraction of the patients may not adhere to the assigned treatment regimen, by either skipping a dose, reducing it, or stopping altogether. This could be due to an inability to tolerate a treatment or a lack of efficacy. Such departures are very much part of the standard treatment process. At the same time, understanding what the trial results would have looked like if such departures had not occurred may in some situations also be of interest (in particular when departures can be prevented in a practical setting). Naively accounting for non-adherence via so called As Treated, Per Protocol or Responder analyses can be misleading, whenever patient characteristics that predict non-adherence to treatment also influence the outcome, because of the re-introduction of confounding into trial data. Unfortunately, an intention-to-treat (ITT) analysis of patients according to the original randomized groups (irrespective of non-adherence), is not a catch-all solution either. In particular, the question remains whether estimating an effect in accordance with the ITT principle always represents the effect of greatest relevance to regulatory and clinical decision making. In some settings we may want to know the likely benefit achieved when the treatment is given in the routine care setting, which naturally encompasses a degree of non-adherence within it. Alternatively, we may instead be interested in estimating the effect of treatment for only those who do adhere. So called ‘Instrumental Variable’ methods can be used to go beyond the ITT analysis to answer questions of this nature, which will be discussed in detail in due course.

An important document relating to this discussion is the recently published addendum on estimands and sensitivity analysis in clinical trials to the E9 guideline of the International Council for Harmonisation, which we refer to as ‘E9 addendum’. It defines any such post randomization event that acts to distort the interpretation of a treatment effect estimate at the end of the trial as an ‘intercurrent event’. It stresses the need to pro-actively address the issue of intercurrent events in the design, analysis and report-
ing of studies. The working principles described in the E9 addendum are referred to as the ‘Estimand Framework’ [12, 13], because it accentuates the importance of defining the specific target (or estimand) that is to be estimated, see also [14, 15].

Despite early work on the application of Instrumental Variable (IV) methods to RCTs [16, 17] they have been seldom used in practice. In this paper we consider the application of IV methods for pursing three distinct estimand strategies described in the E9 Addendum:

1. The \textit{Treatment Policy} strategy is one for which an intercurrent event becomes a fundamental attribute of the treatment. A Treatment Policy estimand is therefore the effect of treatment in patients irrespective of whether they experienced the intercurrent event or not.

2. The \textit{Principal Stratum} estimand strategy targets the effect of treatment within a subgroup of patients who would not have experienced the intercurrent event under assignment to one or more treatments;

3. The \textit{Hypothetical} estimand strategy targets the effect of treatment under a hypothetical scenario that the intercurrent event would not have occurred.

We restrict our attention to trials with either a continuous or binary outcome and focus on estimating treatment effects on the mean- or risk-difference scale. In this framework we review the conceptual framework of Principal Stratification [18, 19] for targeting Principal Stratum estimands, and Structural Mean Models [20, 21] for targeting Hypothetical estimands. We use causal diagrams and potential outcomes to explain their rationale and the estimand they target.

In the first part of the paper we explain these methods when the intercurrent event is all or nothing adherence to treatment, as classically assumed within the academic IV literature. To pharmaceutical statisticians, this setting may appear to have only narrow relevance to the problems encountered in clinical trials. In the second part, we thus show how the classical setting can be adapted to better serve this need, using a combination of features from the Treatment Policy, Principal Stratum and Hypothetical estimand strategies.

This is by no means the first review article of this nature, see for example [6, 22, 23]. Our contribution attempts to provide an accessible account of the tools and techniques for IV estimation used in the classical causal inference community for a pharmaceutical statistics audience within the context of the Estimand Framework introduced in ICH E9(R1). To this end, the paper is constructed so that the main body contains a non-technical description of the methods. This is interspersed with figures containing additional modelling details and graphical explanations for the interested reader.

2 Tools for causal inference in clinical trials

Let $R$, $T$ and $Y$ represent the data collected on each patient within a generic two-arm randomized controlled trial. Here, $R$ denotes randomization to the experimental treatment ($R = 1$) or control ($R = 0$). The variable $T$ denotes whether a patient subsequently receives the treatment ($T = 1$) or control ($T = 0$) therapy. We are interested in the scenario whereby post-randomization choices by a patient or their medical care team mean that some patients end up departing from the treatment plan originally assigned to them, which we will take to be the intercurrent event. Consequently, we will consider it possible
in theory for patients in both randomized groups to receive the active treatment or control therapy. Finally, $Y$ denotes the continuous or binary patient outcome of interest, on which the two randomized groups are to be compared.

In many pharmaceutical trial settings, especially when both the patient and clinician are blinded, it may of course be impossible for the control arm patient to receive the experimental treatment, and vice-versa. Furthermore, typically the definition of the intercurrent events is more nuanced in a clinical trial. For example, treatment discontinuation or intake of additional rescue medication might instead be used, with each one being handled with different estimand strategies. We include this simplistic intercurrent event definition for the purposes of clarity and generality, but consider a more contemporary definition in Section 5.

2.1 Causal diagrams

Consider the interpretation of the trial data in an idealised setting where all patients are both expected to take the treatment assigned to them for the duration of the trial and do so - i.e. there is no intercurrent event. This is represented by the directed acyclic graph (DAG)\cite{24} in Figure\textsuperscript{1} (top-left panel) and marked ‘Case 1’. DAGs are a widely used tool in epidemiology, but less so in clinical trials. Here the additional variable $U$ represents all unmeasured factors which could in theory jointly influence the trial outcome and a patient/clinician’s decision to take the experimental treatment or not.

DAGs contain nodes, which in this case are the random variables $R$, $T$, $U$ and $Y$, and directed edges, such as the arrow that goes from $T$ to $Y$ or from $U$ to $T$. An arrow from $T$ to $Y$ indicates that $T$ causally affects $Y$. The variable $U$ is not observed, but allowing for its potential existence is crucial in order to determine if a particular analysis can, in principle, target a causal effect. This, in turn, is relevant for defining subsequent estimands. On an abstract level the DAG encodes a set of relationships about its constituent variables, and these induce certain statistical dependencies between them. Specifically, any two variables are statistically dependent (or associated) if there is an open path between them, and independent if all paths between them are blocked. The status of a particular path can be deduced by the application of three simple rules on the DAG, referred to as ‘d-separation’\cite{24}. This is illustrated in Figure\textsuperscript{1} (top-right panel) for hypothetical variables $A$, $B$ and $C$. In Section 3 we define in more detail what we mean by causal effect (and to whom exactly it applies), but initially suppose the causal effect of interest is represented by the direct arrow from $T$ to $Y$, $T \rightarrow Y$.

In the idealised trial setting (Case 1) there are no post-randomization changes to treatment, so that $R$ is identical to $T$ for all patients. Comparing outcomes across randomized groups (an ITT analysis) is then equivalent to comparing outcomes between those that receive treatment and those that do not (an ‘As Treated’ analysis). Now consider a trial with non-adherence, meaning that not all patients receive the treatment they were randomly assigned to, so that $R$ is not always equal to $T$. In this case variables (e.g $U$) almost certainly exist which simultaneously predict (or confound) the treatment-outcome relationship. This scenario is illustrated by the DAG labelled ‘Case 2’ in Figure\textsuperscript{1}. The ITT and As Treated analyses in Case 2 are now seen to target different estimands. An ITT analysis would reflect the causal effect of $R$ on $Y$ mediated by treatment $T$. An As Treated analysis would reflect the causal effect $T$ on $Y$ plus the association between $T$
and $Y$ due to the confounder $U$. The As Treated analysis includes an additional term because of the open path from $T$ to $Y$ via $U$. This path could be blocked by conditioning on $U$ (rule (ii) in Figure 1), but this not possible when at least some component of $U$ is unobserved. Case 3 in Figure 1 is the same as Case 2 except that now there is no causal effect of $T$ on $Y$. In this scenario an ITT analysis would yield a zero estimate because there is no open path from $R$ to $Y$, whereas an As Treated analysis would estimate the magnitude of the confounding bias, which could be misinterpreted as a treatment effect.

2.2 The Instrumental Variable Assumptions

An ITT analysis is a valid tool for investigating causality (i.e. the presence of treatment effect) in Cases 1-3 because $R$ is an IV, as defined by the following three assumptions:

- **IV1**: $R$ influences $T$, as reflected here by the causal arrow $R \rightarrow T$. This means that they are associated (not independent);
- **IV2**: $R$ is independent of $U$ (as denoted by the lack of an open path from $R$ to $U$);
- **IV3**: $R$ is independent of $Y$ given $T$ and $U$ (as denoted by the lack of an open path from $R$ to $Y$ conditional on $T$ and $U$).

Assumption IV1 is referred to as the ‘Relevance’ assumption, which is guaranteed to hold whenever patients who are randomized to the experimental treatment are more likely to take it than patients who are randomized to the control. This is almost always true. Assumption IV2 is known as the ‘Randomization’ assumption. It justifies why it is not necessary to adjust for patient covariates in a trial analysis to remove bias. Assumption IV3 is sometimes referred to as the ‘Exclusion Restriction’. If it were possible to adjust for all confounders, then in the absence of any treatment effect (Case 3) IV3 implies that the ITT effect is

$$0 = E[Y|R = 1, T = 1, U = u] - E[Y|R = 0, T = 0, U = u] = E[Y|T = 1, U = u] - E[Y|T = 0, U = u].$$

The equivalence of this hypothetical confounder adjusted treatment effect with the ITT effect under Case 3 follows because conditioning on $U$ blocks all paths from $R$ to $Y$ not through $T$, but in this case $T$ itself exerts no direct effect on $Y$. Assumptions IV2 and IV3 imply together that randomization can only influence the outcome through treatment. It is highly plausible in double blind trials, but may be violated in cases where patients become unblinded, and alter their behaviour based on the treatment they know they are receiving. It is important to realise that the Exclusion Restriction is not an immutable property of randomization, its validity is context-specific and depends just as strongly on the intercurrent event one wishes to account for. We will return to this issue in Section 5.

2.3 Potential outcomes

We now introduce the potential outcomes notation which will be used to define estimands of interest. Let $T_i(r = 1) = T_i(1)$ and $T_i(r = 0) = T_i(0)$ denote the potential treatment received random variable for an individual patient $i$, if they were assigned to treatment or control, respectively. In the same vein let $Y_i(r = 1)$ and $Y_i(r = 0)$ denote their potential outcome under assignment to either treatment. Finally, let $Y_i(r = 1; t = 0) = Y_i(1; 0)$, $Y_i(1; 1)$, $Y_i(0; 0)$ and $Y_i(0; 1)$ represent the four potential outcomes for patient $i$ when setting randomised treatment and actual treatment to all possible joint values. Only one
Figure 1: Technical box describing Directed Acyclic Graphs (DAGs), the rules of d-separation, and why an As Treated analyses target different estimands in general.
realisation of each of $T_i(r)$, $Y_i(r)$ and $Y_i(r, t)$ is observable for each patient. For example, if a patient is randomized to the experimental treatment and takes it, we assume that we have observed $T_i(r = 1)$, $Y_i(r = 1)$ and $Y_i(r = 1, t = 1)$ for that patient.

The Exclusion Restriction is often loosely defined as the statement that randomization only affects the outcome through the treatment. Following Hernan and Robins [25], the Exclusion Restriction is defined more formally via the statement that potential outcomes do not depend on $R$. That is:

$$Y_i(r = 0, t) = Y_i(r = 1, t).$$

This implies that a person’s potential outcome given treatment at level $t$ is independent of randomization, so that both

$$Y_i(r = 0, t = 1) = Y_i(r = 1, t = 1) \quad (1)$$

and

$$Y_i(r = 0, t = 0) = Y_i(r = 1, t = 0). \quad (2)$$

Under the ‘full’ Exclusion Restriction, we can simplify the notation by writing $Y_i(0; 1) = Y_i(1; 1) = Y_i(t = 1)$ and $Y_i(0; 0) = Y_i(1; 0) = Y_i(t = 0)$. We will subsequently explore instances where the Exclusion Restriction is fully satisfied, instances where it is ‘weakly violated’ (so that (2) holds but (1) does not), and instances where both (1) and (2) are violated.

3 Etimands and Estimation

3.1 Defining and estimating the Treatment Policy estimand

The Treatment Policy estimand for an individual is the difference between their potential outcomes under assignment to the treatment and control, regardless of the value of treatment received:

$$Y_i(r = 1) - Y_i(r = 0)$$

Since this, or any individual level causal effect is unobservable, we instead define the estimand as a mean difference in observed potential outcomes value across randomized groups:

$$\text{Treatment Policy estimand: } = E[Y_i(r = 1)] - E[Y_i(r = 0)]. \quad (3)$$

It can be viewed as conceptually equivalent to the ITT estimand. Although we may believe that randomization satisfies the IV assumptions with respect to treatment, we strictly only need the second IV assumption, that $R$ is independent of any confounders of treatment and outcome in order to consistently estimate this quantity via a simple comparison of mean outcomes across randomized groups (in the absence of missing outcome data).

3.2 Defining and estimating the Principal Stratum estimand

The Principal Stratum estimand is defined as the treatment effect within the subgroup of participants for whom the intercurrent event would not (or would) occur in the time-frame of the trial under assignment to either treatment. Several possible Principal Stratum estimands can be defined, indeed we introduce a different Principal Stratum estimand
ourselves in Section 5. We start by considering treatment non-compliance as intercurrent event, and assume we are interested in the principal stratum of patients who would take the treatment if and only if they are randomized to do so. That is, those for whom \( T_i(r = 1) = 1 \) and \( T_i(r = 0) = 0 \). This special group are generally referred to as ‘Compliers’ \((c)\) within a conceptual framework termed Principal Stratification [18, 19], which also defines three additional compliance classes:

- Always Takers \((at)\): individuals who would always take the treatment irrespective of treatment assignment, so that \( T_i(1) = T_i(0) = 1 \);
- Never Takers \((nt)\): individuals who would never take the treatment irrespective of treatment assignment, so that \( T_i(1) = T_i(0) = 0 \);
- Defiers \((d)\): individuals who would always dis-respect randomization by taking the treatment not assigned to them, so that \( T_i(1) = 0 \) and \( T_i(0) = 1 \).

This framework presupposes that that each person is a member of only one compliance class and, as such, their potential treatment variables are not stochastic once they were randomized. This makes subsequent development more straightforward but can be relaxed, as discussed in Section 4. The effect of treatment in the Principal Stratum of Compliers, known as the Complier Average Causal Effect (CACE), can be expressed as:

\[
\text{Principal Stratum estimand: } \pi = E[Y_i(r = 1) - Y_i(r = 0)|T_i(1) = 1, T_i(0) = 0] \quad (4)
\]

As a first step to identifying the CACE, we write the expected outcome under assignment \( r = 1 \) or \( r = 0 \) as a weighted average across all compliance classes:

\[
\begin{align*}
E[Y_i(r = 1)] &= E_{1c} \pi_c + E_{1d} \pi_d + E_{1at} \pi_{at} + E_{1nt} \pi_{nt}, \\
E[Y_i(r = 0)] &= E_{0c} \pi_c + E_{0d} \pi_d + E_{0at} \pi_{at} + E_{0nt} \pi_{nt}.
\end{align*}
\]

Here, \( E_{js} \) represents the expected potential outcome under assignment \( r = j \) for compliance class \(* = (c, at, nt, d)\) and the \( \pi \) terms represent their true proportions in the population. Under assumption IV2, these proportions are independent of (or common across) randomized groups. Furthermore, randomization does not affect the outcome for Always and Never Takers, so that \( E_{1at} = E_{0at} = E_{at} \) and \( E_{1nt} = E_{0nt} = E_{nt} \). Taking the difference of the two expected outcomes removes their contribution completely to leave

\[
E[Y_i(r = 1)] - E[Y_i(r = 0)] = CACE \pi_c - DACE \pi_d, \quad (5)
\]

where CACE = \( E_{1c} - E_{0c} \) and the treatment effect in Defiers (Defier Average Causal Effect, DACE) equals \( E_{0d} - E_{1d} \). In order to identify the CACE, it is generally assumed that Defiers do not exist so that \( \pi_d = 0 \). This is referred to as the ‘Monotonicity’ assumption. Alternative assumptions, such as ‘Principal Ignorability’ (see [20] for an overview) could instead be invoked, which are similar to propensity score approaches in observational data analyses. This will not be considered further in this paper. The impact of assuming Monotonicity is three-fold: firstly, equation (5) reduces to the complier fraction times the CACE; secondly, since they sum to 1, \( \pi_c = 1 - \pi_{at} - \pi_{nt} \); thirdly, \( \pi_{at} \) can be estimated by the proportion of patients who are randomized to control but take the treatment and \( \pi_{nt} \) can be estimated by the proportion who are randomized to treatment but take the control. This means the complier fraction can be estimated as

\[
\hat{\pi}_c = 1 - \hat{P}_r(T = 1|R = 0) - \hat{P}_r(T = 0|R = 1) = \hat{P}_r(T = 1|R = 1) - \hat{P}_r(T = 1|R = 0),
\]

8
and the CACE can be estimated as the ratio of the Treatment Policy and complier fraction estimates. The rationale for this procedure is further illustrated further in Figure 2. We note that under the Principal Stratification framework, although the ITT effect in the Always Takers and Never Takers is zero, the treatment effect in these groups is left undefined.

Figure 2: An Explanation of Principal Stratification.

3.3 Defining and estimating the Hypothetical estimand

The E9 Addendum defines the Hypothetical estimand strategy as defining a contrast between treatment and control in a scenario where the intercurrent event is set to specific hypothetical level. When the intercurrent event relates directly to treatment, we could ask what the difference in patient outcomes would have been if all patients had received the treatment compared to if none had received the treatment. This suggests the following Hypothetical estimand:

$$\text{Hypothetical estimand: } \psi = E[Y_i(t = 1) - Y_i(t = 0)]$$

(6)

Unlike Principal Stratification, the Hypothetical estimand (6) describes an effect in the entire trial population rather than a particular sub-group. This estimand, denoted by $\psi$, can be easily identified if the causal effect of treatment is truly constant across all individuals. This is the simplest but most stringent statement of the ‘Homogeneity’ assumption. (We note in passing that this now implies that the treatment effect in Always-Takers and in Never-Takers is not undefined, as it was assumed in section 3.2, but rather that compliance class makes no difference to the treatment effect. Hence, the counterfactual setting for the hypothetical estimand differs from that for the principal stratum estimand: It assumes that compliance could be enforced.) In Section 4.2 we will introduce some alternative, less stringent definitions of Homogeneity, and how it can be formally tested within an extended TSLS model.

Under Homogeneity, and for a continuous outcome, $\psi$ can be estimated by finding the value of the ‘treatment-free outcome’ that is independent of randomization (or equal across groups) for the trial data (see Figure 3 for details). Note that the observed and
treatment-free outcomes are only different for the patients who were actually treated. For a binary outcome the procedure is the same, except \( \psi \) would quantify the shift in probability of response under treatment compared to no treatment. In both cases it can be easily shown that \( \psi \) is estimated to be the ratio of the sample covariance between \( R \) and \( Y \) and the sample covariance between \( R \) and \( T \). The DAG intuition for this estimation procedure is illustrated in Figure 3. Subtracting the treatment effect \( \psi \) from \( Y \) removes the arrow \( T \to Y \). This means that there is no open path between \( R \) and \( Y \), hence their independence.

3.4 Equivalence of estimates in practice

When quantifying the estimand as a mean or risk difference, IV estimates for the Hypothetical and Principal Stratum estimands defined in Sections 3.2 and 3.3 are identical. This equivalence also extends to the setting where the causal estimand is expressed as a risk ratio, but this does not hold when the estimand is expressed as an odds ratio. For further details, see [29]. Therefore, while the estimate of the Principal Stratum estimand assuming monotonicity is identical to the estimate of the hypothetical estimand assuming homogeneity, these assumptions are key in determining who the estimate applies to. In addition to the three IV assumptions, if Homogeneity holds then the estimate is valid for the hypothetical estimand and the monotonicity assumption holds then it is a valid estimate of the CACE. If both assumptions hold as well as the IV assumptions, it is a valid estimate of both estimands, and in this special case the two estimands are identical to each other.

The most straightforward approach for obtaining this common estimate is to use Two Stage Least Squares (TSLS), see Figure 4. TSLS is enacted by firstly regressing treatment received, \( T \), on randomization, \( R \), using a linear model, to give a predicted value \( \hat{T} \). This is identical to the estimated Complier fraction \( \hat{\pi}_c \). The outcome \( Y \) is then regressed on \( \hat{T} \), again using a linear model, and its resulting regression coefficient is taken as the

![Figure 3: Defining and estimating the Hypothetical estimand.](image)
TSLS estimate. The rationale for TSLS is that, whilst the observed value of $T$ and $Y$ are confounded, $\hat{T}$ and $Y$ are not. This follows from assumptions IV2 and IV3. Baseline covariates (denoted by $S$ in Figure 4) can also be easily incorporated into the TSLS model as long as the three IV assumptions are satisfied conditional on $S$. If $S$ does not directly modulate the treatment effect, so that including $S$ in the first and second stage models of Figure 4 does not alter the parameter $\psi$, covariate adjustment can increase the precision of the causal estimate if they help to predict $T$ (given $R$) or $Y$ (given $\hat{T}$), whilst leaving the interpretation of the causal estimate unchanged.

![Diagram of Two-Stage Least Squares estimation](image)

**Figure 4:** Two-Stage Least Squares estimation for quantifying the Hypothetical estimand under Homogeneity or the Principal Stratum estimand under Monotonicity

### 4 Assessing Monotonicity and Homogeneity

#### 4.1 Relaxing Monotonicity for the Principal Stratum estimand

Assessing the plausibility of the Monotonicity assumption is key to determining whether the CACE can be accurately estimated. In specific circumstances it is possible to simply rule out the existence of Defiers altogether. For example, suppose that the intercurrent event is defined as receiving treatment when not randomized to receive it, but no one in the control group has the opportunity to receive the treatment at all. In this case we would assert that the proportion of both Always Takers and Defiers in the trial is zero, and consider the trial to be a mixture of Compliers and Never Takers only. Although one could argue that the make up of the Never Taker stratum would be different in this setting compared to a trial where the control group could theoretically access the treatment, we would still need to apply the framework of Principal Stratification as before to recover the CACE.

When the Monotonicity assumption is violated, the CACE estimate (as given in Figure 3) instead targets

$$\frac{CACE_{\pi_c} - DACE_{\pi_d}}{\pi_c - \pi_d}$$

if (i) the DACE is the same as the CACE and (ii) the proportion of Defiers not equal to the proportion of Compliers (so that $\pi_c - \pi_d \neq 0$), then the CACE can still be consistently estimated without the assumption of Monotonicity. Assumption (i) is essentially saying that the average effect is the same among the Compliers and Defiers. Assumption (ii) can be verified whenever the probability of receiving treatment across the trial is greater when assigned to it than when not (if this probability is equal across randomized groups then
randomization fails assumption IV1 too). In order to allow for Defiers and for violation of (i), a sensitivity analysis could be performed to gauge the impact different values of the DACE and Defier fraction would have on the implied CACE estimand for a given value of the CACE and Complier fraction estimators, as shown in Figure 5. This sensitivity analysis is implemented in Section 5.

**Validity of CACE in the presence of Defiers**

Assume that Defiers do exist as a proportion $\pi_d$ among the trial participants.

\[
\text{Estimand} = \frac{CACE \pi_c - DACE \pi_d}{\pi_c - \pi_d}
\]

Equals the true CACE if: (1) $CACE = DACE$ & (2) $\pi_c - \pi_d \neq 0$

Assess sensitivity to (1) by seeing how the implied estimand changes as function of DACE and $\pi_d$ for a fixed $\pi_c$, and $\pi_c = \pi_c - \pi_d + \pi_d$

\[
CACE = \frac{(CACE (\pi_c - \pi_d) + DACE \pi_d)}{\pi_c}
\]

Condition (2) holds if the proportion of people on treatment is greater in the treatment arm compared to the control arm:

\[
\pi_c - \pi_d > 0
\]

Figure 5: Clarifying what is identified by the regular IV estimator in the presence of Defiers

### 4.2 Relaxing Homogeneity for the Hypothetical estimand.

The Homogeneity assumption facilitates estimation of the Hypothetical estimand, which can be interpreted as the effect of treatment within the entire population. Homogeneity is clearly satisfied if the causal effect is the same for everyone. Although this sufficient condition is implausible, it is not strictly necessary. Several weaker but sufficient definitions of Homogeneity are provided in [25]. For example, when the treatment (or intercurrent event) is binary, the Hypothetical estimand can be identified if either: (H1) the average treatment effect is constant across all levels of the unmeasured confounders; (H2) the strength of association between randomization and the treatment is constant across levels of the confounders; or (H3) the average treatment effect is constant across randomized groups at each level of the treatment:

\[
H1: \quad E[Y(T = 1)|U = u] - E[Y(T = 0)|U = u] = E[Y(T = 1)] - E[Y(T = 0)]
\]

For all values of $U$

\[
H2: \quad E[T|R = 1] - E[T|R = 0] = [T|R = 1, U = u] - E[T|R = 0, U = u]
\]

For all values of $U$

\[
H3: \quad E[Y(T = 1) - Y(T = 0)|R = 1, T = t] = E[Y(T = 1) - Y(T = 0)|R = 0, T = t]
\]

Figure 4 describes how condition H3 can be formalised within an extended two parameter model for $Y_i$. The parameter $\psi_{at}$ in the model represents the Hypothetical estimand with the subset of patients who are randomised to control but who take the treatment. For ease of interpretation we will assume that Monotonicity holds, so that $\psi_{at}$ pertains to the Always Takers. The model parameter $\psi_t$ represents the Hypothetical estimand within
the subset of patients who take the treatment. Under Monotonicity, this is equivalent to the union of the Compliers and Always Takers. As such, $\psi_t$ can be viewed as a weighted average of $\psi_{at}$ and the hypothetical estimand in the Compliers, $\psi_c$, since

$$
\psi_t = E[Y_i(T = 1) - Y_i(T = 0) | T(1) = 1] \\
= \sum_{j=0}^1 E[Y_i(T = 1) - Y_i(T = 0) | T(1) = 1, T(0) = j] Pr(T(0) = j | T(1) = 1) \\
= \frac{\psi_c \pi_c + \psi_{at} \pi_{at}}{\pi_c + \pi_{at}}
$$

The Homogeneity assumption is satisfied if $\psi_t = \psi_{at}$, but is violated otherwise. In this case the Hypothetical estimand does not target $\psi_t$ or $\psi_{at}$, but rather $\psi_c$ since from Figure 3

$$
\frac{Cov(R_i, Y_i)}{Cov(R_i, T_i)} = \frac{\psi_t Pr(T = 1 | R = 1) - \psi_{at} Pr(T = 1 | R = 0)}{\pi_c} \\
= \frac{\psi_t (\pi_c + \pi_{at}) - \psi_{at} \pi_{at}}{\pi_c} \\
= \frac{\psi_c}{\pi_c}
$$

Although this is reassuring on one level, as a practitioner one may instead prefer to report

![Figure 3: Allowing for treatment effect heterogeneity](image)

**Assumed model**

$$Y_i | T_i, R_i, U = \beta_0 + \psi_t T_i + \psi_{at} T_i (1 - R_i) + U_i$$

| Estimand | Potential outcome contrast | Parameter form |
|----------|----------------------------|---------------|
| Hypothetical among treatment arm treated | $E[Y_i(T = 1) - Y_i(T = 0) | T(1) = 1]$ | $\psi_t$ |
| Hypothetical among control arm always takers | $E[Y_i(T = 1) - Y_i(T = 0) | T(0) = 1, T(1) = 1]$ | $\psi_{at}$ |

**Who treatment effect applies to under monotonicity**

$$\psi_t = \pi_c \psi_c + \psi_{at} \pi_{at} \frac{\pi_{at}}{\pi_c + \pi_{at}}$$

$$\psi_c = \pi_c \psi_t + \left( \psi_t - \psi_{at} \right) \frac{\pi_{at}}{\pi_c}$$

$\pi_c$ : Complier fraction

$\pi_{at}$ : Always Taker fraction

Figure 6: Relaxing the homogeneity assumption with a two parameter causal model

$\hat{\psi}_t$ along with the difference $\hat{\psi}_t - \hat{\psi}_{at}$ as a sensitivity analysis to the primary Hypothetical estimand analysis. The advantage of $\hat{\psi}_t$ over $\hat{\psi}_c$ is that the former reflects an effect for an observable subset of patients, whereas the latter does not. Figure 7 describes an extended TSLS model to achieve this aim. It requires a baseline covariate, $S$, which satisfies two properties: Firstly, it does not directly modulate the effect of treatment, as indicated by a zero $T \times S$ interaction in the true outcome model (a main effect for $S$ is allowed). Secondly, it modulates the strength of randomization as an IV across the treatment groups, as indicated by a non-zero $R \times S$ interaction in the model for $T$ given $R$ and $S$. Note that if $S$ were unobserved, this model would itself imply violation of condition H2. For further examples of this approach applied to IV analyses applied in clinical trials and epidemiology
see [27] and [28].

In the first stage of the extended TSLS procedure, \( T \) is regressed on \( R, S \), and \( R \times S \). The fitted value from this first stage regression is then regressed on the two-parameter outcome model along with the covariate \( S \). The corresponding regression coefficients are then consistent estimates for \( \psi_t \) and \( \psi_{at} \) under the stated assumptions. A formal test for homogeneity violation could be constructed based on \( \hat{\psi}_t - \hat{\psi}_{at} \) being significantly different from zero.

**Figure 7: Implementation of the two parameter model with an extended TSLS framework**

### 4.2.1 Simulation example

In order to elucidate the methods described we simulate trial data consistent with the true outcome model in Figure 7 and thus in violation of the Homogeneity assumption. The variables \( R, T \) and the covariate \( S \) are binary. The unobserved confounder \( U \) and the outcome \( Y \) are generated as normally distributed variables. The outcome is generated to have a mean value of 100 in the absence of treatment and a variance of approximately 3. The mean probability of receiving treatment in the treatment arm is 70% and the mean probability of receiving treatment in the control arm is 13%. The true Complier fraction \( \pi_c \) is therefore estimated to be approximately 57%. The average causal effect of treatment for those who are both randomized to the treatment group and take treatment, \( \psi_t \), equals \(-3\) (so that treatment lowers \( Y \) by 3 units). The average causal effect of treatment for those who are both randomized to the control group and take treatment, \( \psi_{at} \), is \(-2\). From this we can infer that the causal effect of treatment in the Compliers, \( \psi_c \), is approximately \(-3.24\) (see Figure 6). Further details on the simulation model are given in Appendix A. Figure 8 (left) shows density plots across 2000 simulated trials (each containing 6000 patients) for:

- The standard Treatment Policy estimate, as assessed by the mean difference in outcomes across randomised groups;
- The basic TSLS estimate, as fitted in Figure 4 without adjusting for covariates, which correctly targets the Principal Stratum (CACE) and Hypothetical estimands under Monotonicity and Homogeneity, respectively; and
- The parameter estimates for \( \psi_t, \psi_{at} \) and \( \psi_c \) obtained from fitting the extended TSLS model under a relaxation of the Homogeneity assumption in Figure 7.

Note that although \( \psi_c \) is not an explicit parameter in the extended TSLS model it can be derived from the estimates for \( \psi_t \) and \( \psi_{at} \) shown in Figure 6.
We see the following: The Treatment Policy estimate is the most precise of all the presented estimates, but also the closest to zero. The basic TSLS estimate has a mean value $-3.24$ as predicted. The extended TSLS model estimates for $\psi_t$ and $\psi_{at}$, fitted under a relaxation of the Homogeneity assumption, are unbiased for their corresponding Hypothetical estimands, but across the simulations the Monte Carlo standard deviation for $\hat{\psi}_{at}$ is approximately 5 times that of $\hat{\psi}_t$ and 25 times that of the Treatment Policy estimate. Using the extended TSLS model estimates for $\psi_t$ and $\psi_{at}$ to derive the implicit CACE, $\psi_c$, we see that it agrees perfectly with the standard TSLS estimate of $-3.24$, as predicted.

Figure 8: Left: Distribution of estimates for the Treatment Policy estimand (black); CACE estimand under Monotonicity or Hypothetical estimand under Homogeneity (black, dashed); the Hypothetical estimands for $\psi_t$ and $\psi_{at}$ under a relaxation of the Homogeneity assumption; the implied parameter estimand $\psi_c$ (orange). Right: Comparison of ‘As treated’ analysis versus a ‘TSLS’ analysis under treatment effect homogeneity and random non-compliance.

4.2.2 When is the ‘As-Treated’ analysis an efficient estimate of the hypothetical estimand?

In Figure 1 we used DAGs to describe why an As-Treated analysis - that is an analysis comparing outcomes between treated and untreated individuals does not in general give a consistent estimate for the causal effect when there is non-compliance. This motivated the use of the IV approach. However, there is a specific scenario where it not only consistently estimates the causal effect, but is more efficient than an IV analysis: namely when non-compliance is random with respect to the outcome: In that case, the use of all patients in the sample (as in the As-treated estimate) does not cause a bias in the estimates of $\psi_c$, $\psi_{at}$, $\psi_{nt}$ or $\psi_d$ since these are all the same. At the same time, the use of all patients without any adjustment for potential compliance class differences is of course more efficient statistically than using an estimate which adjusts for non-existing differences between compliance class outcomes (as the TSLS estimate does). Figure 8 (right) illustrates this. It shows the distribution of the As Treated and TSLS estimates under the same data generating model as before, except that non-compliance is now random and the homogeneity assumption is satisfied ($\psi_{at} = \psi_t = -3$). For these data the proportion
of individuals taking the treatment in the treatment and control arms was on average 68% and 12%, so that the average complier fraction $\pi_c$ was 56%. It shows that both the TSLS and As-Treated analyses unbiasedly estimate the hypothetical estimand (-3), but that the standard deviation of the As-Treated estimate (0.027) is approximately $\pi_c$ times the standard deviation of the TSLS estimate (0.048).

5 Application to a contemporary industry setting

We now discuss how the IV-based estimand strategies introduced thus far can be used to adjust for intercurrent events of more relevance to realistic contemporary clinical trial. Specifically, rather than being non-compliance with the randomized treatment from the start, we will assume that the intercurrent event can also be some other unplanned disturbance of the trial plan and can sit between the initiation of treatment and measurement of the final outcome. In order for IV approaches to be unambiguously fit for purpose, we must have a strong belief that the intercurrent event closely reflects the mechanism by which the treatment affects the outcome. Possible examples include:

1. The presence of disease progression to stage 4 cancer after completion of chemotherapy regimen in a trial measuring overall survival at 5 years;
2. The absence of antibodies to a virus three weeks after being administered a vaccine in a trial measuring re-infection within 2 years;
3. The presence of ‘relapse’ following treatment in patients with secondary progressive multiple sclerosis, before the final disability assessment at 3 months.

To make ideas concrete, we now develop a fourth example, by imagining a randomized placebo controlled trial for which the intercurrent event of interest is measured by a relevant biomarker 1 month after initiation of treatment. The trial outcome is death at or before 3 years. The experimental treatment is hypothesised to work directly through the biomarker so that, if a treated patient does not respond, we believe that the drug has failed to work as planned. Likewise, if a patient does not receive the treatment but nevertheless has a positive biomarker response after 1 month, we may believe that their future health outcomes have been improved or worsened in line with those who took and responded to treatment. The DAG in Figure ?? illustrates our assumed trial set up. Here, $R$ denotes randomization and $T$ denotes treatment received. The randomization and treatment variables $R$ and $T$ are binary as before. We assume that $R = 0$ perfectly predicts $T = 0$, but $T$ is jointly predicted by the baseline biomarker value $B_0$, and unmeasured confounders, $U$, when $R = 1$. This represents a setting where no placebo group patient has access to the experimental drug, but some non-adherence to treatment is present in the treatment arm. $T$ subsequently predicts whether a patient will be a biomarker responder ($B = 1$) or not ($B = 0$) along with $B_0$ and $U$. The binary mortality outcome, $Y$, is assumed to be predicted by $B$, $B_0$, $U$ and (possibly) $T$ itself. The variables $B_0$ and $U$ comprise the set of all confounders of $B$ and $Y$. Our model is purely hypothetical, but loosely inspired by the CANTOS randomized controlled trial [30]. It sought to evaluate whether Canakinumab, a monoclonal antibody which acts to reduce inflammation, was effective in reducing the risk of a major cardiac event in approximately 10,000 patients.

A naive ‘responder’ analysis would quantify the association between biomarker response and mortality via:

$$E[Y|B = 1] - E[Y|B = 0]$$
Contemporary trial setting: intercurrent event = biomarker response

- Treatment predicts the likelihood of being a biomarker responder (B=1), as does baseline biomarker value (B0)
- Randomization a valid IV if it affects outcome Y through B only (exclusion restriction holds)
- Violation if treatment effects Y through alternative mechanism

Compliance Classes

| Compliance Classes | B(r=1) | B(r=0) | Proportion | Estimated by |
|--------------------|--------|--------|------------|--------------|
| Placebo only Responders | 0 | 1 | \( \pi_{tr} \) | \( \hat{Pr}(B=0|R=1) \) |
| Never Responders | 0 | 0 | \( \pi_{nr} \) | \( \hat{Pr}(B=1|R=1) \) |
| Always Responders | 1 | 1 | \( \pi_{ar} \) | \( 1 - \pi_{pr} - \pi_{sr} \) |
| Treatment only Responders | 1 | 0 | \( \pi_{tr} + \pi_{ar} \) | \( \hat{Pr}(B=1|R=1) \) |

Policy Estimand: \( E[Y_i(r=1) - Y_i(r=0)] \)
Hypothetical Estimand: \( E[Y_i(b=1) - Y_i(b=0)] \)
Principal Stratum Estimand: \( E[Y_i(r=1) - Y_i(r=0)|B(1)=1,B(0)=0] \)
(Bornkamp & Bermann) \( E[Y_i(r=1) - Y_i(r=0)|B(1)=1] \)

Figure 9: An Instrumental Variable formulation of a contemporary industry trial with accompanying Treatment Policy, Hypothetical and Principal Stratum estimands.

This does not have a meaningful causal interpretation in its own right, because it directly conditions on the observed (post-randomization) intercurrent event. It is conceptually equivalent to the As Treated analysis in Figure 1. The motivation for the IV analyses is to obtain a fair estimate for the effectiveness of the treatment in (a) principled patient sub-groups defined by biomarker response, or (b) to estimate the causal effect of biomarker response directly, and to achieve (a) or (b) without making the assumption that all founders of biomarker response and the outcome can be measured and adjusted for.

Randomization is a valid IV with respect to the intercurrent event of biomarker response in our context if it is: associated with B (IV1); independent of B0 and U (IV2); and only affects Y through B (IV3). The last assumption, the Exclusion Restriction, means that the arrow labelled ‘?’ linking \( T \) to \( Y \) in Figure ?? must be strictly absent, so that treatment does not affect the outcome through an alternative pathway. This is a strong assumption upon which the validity of standard estimates for the Hypothetical and Principal Stratum estimands rest, and must be carefully justified in each trial context it is applied.

The four traditional compliance classes considered in the trial are as follows: Always Responders (ar) are those for whom \( B(1) = B(0) = 1 \). Never Responders (nr) are those for whom \( B(1) = B(0) = 0 \). Treatment Responders (tr) respond if and only if randomized to treatment, so that \( B(1) = 1 \) and \( B(0) = 0 \). Lastly, Placebo Responders (pc) respond if and only if randomized to placebo, so that \( B(1) = 0 \) and \( B(0) = 1 \).

5.1 Trial estimands

A list of the trial estimands considered for the trial is given in Figure 9. The Policy estimand is the average difference in potential outcomes under randomization to treatment and control, irrespective of whether the intercurrent event (biomarker response) occurred or not. This estimand is identified as long as randomization was adequately performed.
One Principal Stratum estimand would be the Treatment Policy estimand in the sub-set who would have been a biomarker responder under allocation to treatment, and who would not if allocated to the control. We will refer to this as the Treatment Responder Average Causal Effect (TR-ACE) which is directly analogous to the CACE estimand described in Section 3. It can be identified with a valid IV by making the Monotonicity assumption that there are no Placebo Responders. That is, those whose body would naturally produce the correct biological response without treatment, but who would not do so if given the treatment. The treatment itself would therefore have to disturb the body’s natural response in this group. If this is deemed to be implausible then Monotonicity would be reasonable. However, the Exclusion Restriction is also key here: it states that the Policy estimand (or equivalently the true ITT effect) within the Always and Never Responders must be zero (see Figure 3), despite the fact that both patient groups will almost certainly receive far more of the experimental treatment on the treatment arm compared to control.

We can define the Hypothetical estimand in this context as the mean difference in outcomes if all patients had been biomarker responders compared to if all had been non-responders. It can be identified with a valid IV and the Homogeneity assumption that the effect of biomarker response is the same across randomized groups at each level of the biomarker. This would be violated if, for example, the effect of biomarker response is different for treatment and control arm responders.

5.1.1 An alternative Principal Stratum estimand

In follow up work inspired by the CANTOS study, Börnkamp and Bermann [31] proposed methodology within the Estimand Framework to assess the treatment effect in a principal stratum defined by post-treatment inflammation level (or biomarker response) status, as this was a hypothesised mechanism of action for the drug. Specifically, they targeted Treatment Policy estimand, evaluated in the principal stratum who would have been biomarker responders under allocation to treatment, but without restriction as to their biomarker response status under allocation to control, namely:

\[ E[Y_i(r = 1) - Y_i(r = 0)|B(1) = 1] \]

The patient sub-population it applies to is, in effect, the union of the Always Responders and Treatment Responders. In order to identify their estimand, Bornkamp and Bermann assumed that all confounders of biomarker response and the outcome were known. This enabled estimation of all counterfactual estimands by using weighting and standardisation techniques. It can alternatively be estimated using IV methods, by re-writing it as

\[ E[Y_i(r = 1) - Y_i(r = 0)|B(1) = 1] = \sum_{j=0}^{1} E[Y_i(r = 1) - Y_i(r = 0)|B(1) = 1, B(0) = j]Pr(B(0) = j|B(1) = 1) \]

In this context

\[ Pr(B(0) = 0|B(1) = 1) = \frac{\pi_{tr}}{\pi_{tr} + \pi_{ar}}, \]

\[ Pr(B(0) = 1|B(1) = 1) = \frac{\pi_{ar}}{\pi_{tr} + \pi_{ar}} \]

are the conditional probabilities of being a Treatment Responder and Always Responder, respectively, given \( B(1) = 1 \). Under the Exclusion Restriction assumption the mean
outcome in Always Responders is independent of randomization (see Figure 2) and the Principal Stratum estimand can be written as

$$\psi_{tr} \frac{\pi_{tr}}{\pi_{tr} + \pi_{ar}} + 0 \frac{\pi_{ar}}{\pi_{tr} + \pi_{ar}} = \psi_{tr} \frac{\pi_{tr}}{\pi_{tr} + \pi_{ar}}$$

Thereby, this Principal Stratum estimand is equal to the Treatment Policy estimand $\psi_{tr} \pi_{tr}$ divided by the combined proportion of Treatment Responders and Always Responders ($\pi_{tr} + \pi_{ar}$).

### 5.2 Simulated trial example

To make things concrete, we report the results of each estimand strategy and subsequent sensitivity analysis when applied to a single simulated data set of 10,000 individuals consistent with the DAG in Figure 9 (see Table 1). These data are contained in an R work space which is available to download in Online Supplementary Material, along with code used for the data generation and analysis. A summary of the data generating mechanism is also given in Appendix B. Importantly, the trial data is simulated such that the Exclusion Restriction is purposefully violated, because the treatment does not solely effect the outcome through the biomarker, as indicated by arrow marked ? in Figure 9. The simulated data do not share any of the characteristics of the CANTOS trial.

The prevalence of the binary outcome, $Y$, is 50% across the simulated data. No patient in the control group receives treatment and approximately 96% of patients in the treatment arm fully adhere to treatment. In all analyses we take a Policy strategy for the intercurrent event of non-compliance to treatment, considering it to be a natural component of the therapy. The proportion of biomarker responders in the treatment group and control group is 86% and 25% respectively. This indicates that whilst treatment increases the likelihood of a positive biomarker measure, it is not strictly necessary or sufficient.

#### 5.2.1 Results

Estimates for the estimands are given in Table 1. Standard errors are reported for each analysis using a non-parametric bootstrap. The Treatment Policy estimate is approximately 0.022, indicating that randomization to treatment increases the absolute risk of the outcome by 2.2% ($p = 0.028$). This suggests that treatment is, on balance potentially harmful rather than beneficial, despite initiating a significant increase in biomarker response. Next, we report results for the naive Responder analysis. It is equal to $-10.0\%$, indicating that the risk of the outcome is 10% lower in those with a positive biomarker response compared to the biomarker negatives. This is starkly at odds with the Treatment Policy estimate. The Hypothetical estimand is estimated to be 3.5% ($p = 0.028$), indicating that the causal effect of biomarker response is even more harmful than the Policy estimate.

For these data the Treatment Responder fraction (under Monotonicity) is estimated as $\approx 86\% - 25\% = 61\%$. Dividing the Policy estimate this factor an estimate for the TR-ACE of 3.5% ($p = 0.028$), which is identical to the previous Hypothetical estimand for the reasons stated in Section 3. Lastly, the probability of being a Biomarker Responder, $Pr(B = 1|R = 1)$, is 0.86 for these data. Dividing the Policy estimate by this factor yields an estimate for Börnkamp and Bermann’s Principal Stratum estimand of 2.5% ($p = 0.028$).
| Estimand                  | Estimate | S.E  | p-value |
|---------------------------|----------|------|---------|
| Treatment Policy          | 0.022    | 0.010| 0.028   |
| Responder                 | -0.103   | 0.010| < 2 × 10^{-16} |
| TR-ACE & Hypothetical     | 0.035    | 0.016| 0.029   |
| PS(BB)                    | 0.025    | 0.011| 0.028   |

Hypothetical estimand sensitivity analyses

| Biomarker effect heterogeneity |
|-------------------------------|
| ψ_β                           | -0.034  | 0.032| 0.286   |
| ψ_αr                          | -0.202  | 0.099| 0.041   |

| Direct and indirect treatment effects |
|---------------------------------------|
| ψ                                     | -0.295  | 0.139| 0.034   |
| α                                      | 0.201   | 0.086| 0.019   |

Table 1: **Point estimates, standard errors and p-values for the: Treatment Policy estimand; Responder estimand; Hypothetical & TR-ACE estimand; Principal Stratum estimand of Bornkamp and Bermann, PS(BB); Hypothetical estimands for Biomarker Responders and Always Responders, respectively; Hypothetical estimand in Biomarker responders allowing for a direct treatment effect.**

5.3 Sensitivity analyses

5.3.1 Allowing for Monotonicity violation

Figure 10 (bottom) shows how sensitive the TR-ACE estimate is to violations of the Monotonicity assumption (i.e. no Placebo Responders) using the framework described in Figure 5. The estimated Treatment Responder fraction \( \hat{\pi}_{tr} = 0.61 \) implies a plausible range for the true Treatment Responder fraction \( \pi_{tr} \) of (0.61 to 1) and a plausible range for the true Placebo Responder fraction \( \pi_{pr} \) of (0 to 0.61) such that \( \pi_{tr} - \pi_{pr} = 0.61 \). The red and black lines show for all plausible values of \( \pi_{tr} \), the implied TR-ACE necessary to explain the TR-ACE estimate if the true Placebo Responder Average Causal Effect (PR-ACE) were 0.5 times and 2 times as large. This analysis suggests that the TR-ACE could be between 3% and 5%.

5.3.2 Allowing for Homogeneity violation

We now relax the assumption that the causal effect of biomarker response is the same across randomized groups at each level of the biomarker. Figure 11 (top) shows the structural model assumed and an extended TSLS procedure for estimation. As for the analysis in Section 4.2, it requires the utilization of a baseline covariate (in this case \( B_0 \)) that predicts variation in biomarker response rates across groups but does not directly modulate the treatment effect. Under these assumptions it estimates a reduction of −3.4% \( (p = 0.286) \) and −20.2% \( (p = 0.041) \) in the risk of the outcome for treatment and control arm biomarker responders, respectively. Taken at face value, these results suggest that biomarker response does causally reduce the outcome risk, but that the effect is paradoxically greatest in those who do not take the treatment. This implies that the treatment itself may be acting to
increase the outcome risk through another pathway.

5.3.3 Allowing for Exclusion Restriction violation under Homogeneity

Figure 11 (bottom) shows an alternative two parameter model formulation for the difference in potential outcomes to assess the possibility of a full violation of the Exclusion Restriction violation for the Hypothetical estimand. It assumes that the Homogeneity assumption is satisfied, so that $\psi$ represents the true Hypothetical estimand if the Exclusion Restriction in fact held. The parameter $\alpha$ represents the direct effect of randomization on the outcome across randomized groups holding biomarker response fixed. This reflects the magnitude of Exclusion Restriction violation it is necessary to adjust for. This was in fact the model used to generate the data. The parameter estimates for $\psi$ and $\alpha$ are $-0.29$ ($p = 0.034$) and $0.2$ ($p = 0.019$), respectively. The conclusion from this sensitivity analysis is that biomarker response, which the treatment positively influences, could indeed be beneficial in reducing the outcome risk. However, the treatment could exert a direct, negative effect on the outcome through an alternative mechanism, which warrants further investigation to be properly understood.

6 Discussion

In this paper we have attempted to explain the rationale for using Instrumental Variable methods in clinical trials, first from an academic perspective and then within a contemporary clinical trial setting. Here we showed that the Treatment Policy, Hypothetical and standard Principal Stratum estimands can be estimated using a valid IV with the addition of either Monotonicity or Homogeneity. For the Principal Stratum estimand, we described a simple sensitivity analysis strategy for assessing violation of the Monotonicity assump-
Figure 11: Top: Allowing for biomarker effect heterogeneity. Bottom: Allowing for a direct effect of treatment on the outcome.
tion. For the Hypothetical estimand, we described two extended modelling frameworks to assess violation of the Homogeneity assumption and the Exclusion Restriction. Magnusson et al. [32] recently proposed a more formal Bayesian framework for exploring the impact of Monotonicity violation within a Principal Stratum analysis, by specifying prior distributions for the underlying proportion of patients falling into each compliance class. In future work, it would be interesting to see if their method could be extended to jointly model violations of the Homogeneity assumption and Exclusion restriction, and therefore be used as part of a broader sensitivity analysis.

The issue of treatment effect heterogeneity is central to application and interpretation of IV methods, especially Hypothetical estimands, but it has implications beyond causal inference to the general trial setting of subgroup analysis and precision medicine. In trials of a continuous outcome, treatment-effect heterogeneity would imply unequal variances in the outcomes across randomized groups. To this end, Cortes et al. [33] conducted a systematic review of the parallel group trials literature in selected years between 2004 and 2013 and found 208 trials with enough information to test the equal variance assumption. Only 14% of these studies showed evidence of differing variances. These results undoubtedly reflect a lack of power to detect such a difference, which will generally require much larger sample sizes than those justified for detecting a standard treatment effect. The sample sizes needed to fit two-parameter causal models to relax the Homogeneity or Exclusion Restriction assumption will, in fact, closely mirror the size needed to detect a difference in variance. This needs to be understood by trialists when planning the sample size of future trials to enable the primary analysis and sensitivity analyses within the Estimand Framework.

In this paper we have highlighted how two-parameter causal models can be fitted using IV methods combined with instrument-covariate interaction models to estimate violation of the homogeneity assumption as well as direct and indirect effects of treatment. In practice, finding a baseline covariate that strongly and differentially predicts the intercurrent event without modulating the treatment effect may be challenging. Care must therefore be given when selecting a covariate for this role. For a recent example of such an analysis, the AIRWAYS-2 trial [34] randomized patients to receive two types of airway management for out-of-hospital cardiac arrest - Tracheal intubation (TI) or a Supraglottic airway device (SGA). Some non-adherence to randomized treatment was present in both arms of the trial. However, it was impossible to receive the TI intervention, even if randomized to do so, if only one paramedic attended the scene in time (two or more were required). In follow up work, randomization and the interaction between randomization and the binary indicator variable $S=I(≥2$ paramedics attended) were deployed to fully adjust for non-compliance [35], under the assumption that $S$ was a random event that did not modulate the treatment effect in the SGA arm. In this case the interaction induced by $S$ was very strong but also unplanned. Future trialists may consider building such a feature into the design in order to provide the assessment of key assumptions within a causal analysis.

An alternative approach to using IV-interaction models in the estimation of direct and indirect effects would be to use causal mediation methods, which invoke the ‘sequential ignorability assumption’ [36]. In our context this would imply there were no unmeasured confounders of the biomarker response and outcome relationship, conditional on a set of pre-treatment variables as in [31]. In future work we plan to compare the efficiency of this approach to interaction-based IV methods.
In this paper we assumed that the intercurrent event of interest (e.g. adherence to treatment or biomarker response) was a binary variable. This makes it possible to apply the framework of Principal Stratification. In many cases this will be too simplistic a description, but it is in a sense actively encouraged by the Principal Stratification framework. However, this simplification is not inherent when defining Hypothetical estimands. For example, instead of dichotomising patients as biomarker responders and non-responders, it would be possible to treat it as a continuous variable and use randomized treatment and baseline biomarker measurements to predict its value. A resulting Hypothetical estimand could then be constructed to reflect the difference in mean outcomes for all patients if their biomarker level had been lowered by a unit, with the choice of unit being user specified. In settings where the intercurrent event is non-adherence to the full dose of a treatment, Hypothetical estimands could also be constructed using information on the precise percentage of the treatment each patient took. This would be naturally encountered when conducting a survival analysis in late-stage cancer trials, where each patient may spend a proportion of time on or off treatment depending on factors such as disease progression, censoring or death. The Rank Preserving Structural Failure Time (RPSFT) model has been proposed for use in this context, and is based on leveraging randomization as an Instrumental Variable \[37, 38, 39\]. The RPSFT model has been acknowledged as the most statistically principled and robust analysis procedure in health economic settings \[40\], a field where causal inference methods have been embraced. Exploring the application of this approach within the Estimand Framework is an important topic of future research.

Two estimand strategies mentioned in the E9 Addendum but not addressed in this paper are the so called ‘Composite Strategy’ and the ‘While-on-Treatment’ Strategy. Under the Composite strategy, one can choose to integrate the intercurrent event as a component of the outcome variable itself in order to calculate the treatment effect. For a recent example of this, Permutt and Li \[41\] proposed to deal with the intercurrent event of dropout in a trial with a continuous outcome variable by assigning the missing outcomes a value lower than any observed value in the same arm. Outcomes are then ordered within each treatment group, equal proportions of data are trimmed away from each arm (the proportion being at least as large as the proportion of missing outcomes) and the treatment effect estimate is obtained using the trimmed data. Under the While-on-treatment strategy: the value of a patient response up to the time of the intercurrent event may be considered as a valid summary of their outcome. For example, Holzhauer et al. \[42\] consider, amongst other estimands, treatment effects in a Diabetes setting up to the initiation of rescue medication to lower glucose levels. Both of these estimand approaches are of most relevance to the setting where the intercurrent event is dropout, which is thought to materially affect the analysis. This issue is of course ubiquitous in clinical trials, and one which the IV methods we have proposed do not account for. In future work, it will be worthwhile to develop extended IV estimation strategies that address this intercurrent event alongside any others.

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A Data generating model for Section 4.3

The randomization variable $R$, treatment variable $T$, baseline covariate $S$, outcome variable $Y$ and confounder variable $U$ for each subject was generated from the following model:

$$
R \sim \text{Bern}(0.5) \\
S \sim \text{Bern}(0.5) \\
U \sim N(0, 0.5) + 0.1S \\
\eta_T = -2 + 2R + 2RS + U, \quad P_T = \frac{\exp(\eta_T)}{1 + \exp(\eta_T)} \\
T \sim \text{Bern}(P_T) \\
Y = 100 - 3TR - 2T(1 - R) + U + S + \epsilon_y, \epsilon_y \sim N(0, 1)
$$

Under this model, $\psi_t=-3$ and $\psi_{at}=-2$.

B Contemporary trial analysis

R code used to generate the illustrative trial data and perform the analyses discussed can be found in Online Supplementary Methods. The data generating process for $R, B_0,$ and
$T$ is also given below:

\[
R \sim \text{Bern}(0.5) \\
B_0 \sim \text{Max}(N(3, 0.3), 2) \\
U \sim (n, 0, 0.5) + 0.02B_0 \\
\eta_T = -3 + 6R + 0.1U + 0.1B_0, \quad P_T = \frac{\exp(\eta_T)}{1 + \exp(\eta_T)} \\
T|R = 1 \sim \text{Bern}(P_T) \\
T|R = 0 = 0
\]

A continuous underlying biomarker response variable was generated via

\[
B_c \sim N(0.8B_0 - 0.4B_0T + U, 0.4)
\]

from which was generated a binary biomarker response variable $B = I(B_c \geq 2)$, $I(.)$ being the indicator function. The outcome $Y$ was then generated as

\[
P_Y \sim N(0.5 - 0.15B + 0.1T + 0.035U + 0.01B_0, 0.04) \\
Y \sim \text{Bern}(P_Y)
\]

Under this model, the causal effect of biomarker response, which is itself causally induced by the treatment, is a 15% reduction in the outcome risk across the trial population. However, treatment itself causally increases the risk the outcome risk by 10% through other pathways. This is a full violation of the Exclusion Restriction.