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BIAS AND CLINICAL TRIALS

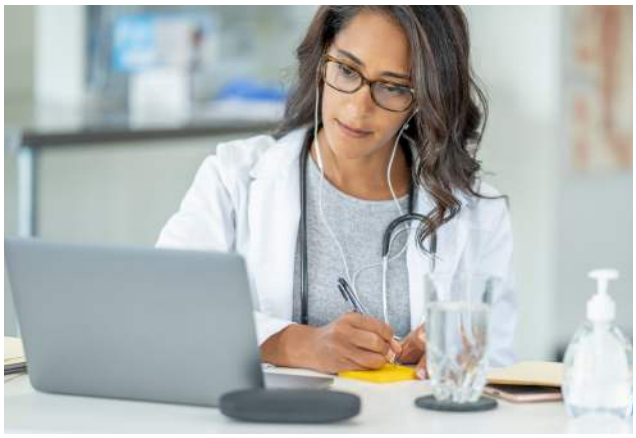
Understanding the behavioral changes associated with enrolling patients in a clinical trial are critical to ensuring that researchers are accurately measuring clinical outcomes and drawing appropriate conclusions about the safety and efficacy of experimental interventions.

Biases and distortions in datasets can arise from many sources in the interactions between patients and clinicians. They can also arise from systematic differences in individuals' willingness to participate in trials and comply with trial requirements. Experimental design is critical to controlling for these biases and can be accomplished with approaches ranging from the gold standard RCT to novel patient engagement strategies. In this paper, we describe the values of different approaches for controlling different types of bias.

DIVERSE BIASES THREATEN THE INTEGRITY OF CLINICAL TRIAL RESULTS

From the moment researchers start searching for potential participants to recruit all the way through to database lock, the interactions between participants and clinical staff and the interactions of both groups with the tools used for data collection all have the potential to induce bias. These biases come in a range of forms[1,2] and below we list some of the most common:

SELECTION BIAS: Selection bias arises when the group of patients recruited into a trial are not representative of the general patient group. If the difference is sufficiently large,



the results of the trial may not be applicable to patients at large, ultimately resulting in failure of the intervention at scale. This bias may be easy to observe as a systematic difference in demographics like age, gender or ethnicity, but it can also be the result of other barriers to recruitment such as geographic location or socio-economic status. The latter kind of selection bias is particularly pernicious because it can be difficult to assess just by looking at the demographics of the study population.

EXPECTANCY BIAS: Expectancy bias (also sometimes called observer effects) results arises when the perceptions of clinicians (or other observers, coders or raters) are

influenced by what they expect to observe as a result of the experimental intervention. Humans have a tendency to look for information that conforms to their hypotheses and overlook information that argues against it. Any subjective rating or coding (behavior, radiological images, etc.) is subject to observer effects, artificially inflating the measured effectiveness of an experimental intervention.

HAWTHORNE EFFECT: The Hawthorne effect occurs when people behave differently because they know they are being watched. For example, when people are asked to keep a diary of eating or exercise behavior, they may temporarily improve their habits during the observational period. In some cases, the observation itself can directly improve the outcome. For example, one recent dementia RCT that showed that the intensity of follow up was correlated with improved cognitive function despite the fact that it was an RCT.[3]

COMPLIANCE BIAS: Compliance bias arises when efficacy measurements are confounded by variations in patient adherence to therapy. For example, if an active compound has aversive side effects, patients may have substantially lower medication compliance, and this may result in an underestimate of the efficacy of the medication. Adherence can also be a surrogate for overall health, and therefore can also inflate the apparent effectiveness of placebo, further complicating the interpretation of data regarding intervention efficacy.

MISSING DATA BIAS: Missing data bias or non-response bias arises when the data set is incomplete. Missing data is relatively common, and the severity of this bias is correlated with the duration of the trial (increased risk of attrition), the difficulty of the assessments, study protocol non-compliance and poor quality of the communication and overall relationship with the patient.[4] These missing data can make it impossible to interpret the outcomes of the study.

PLACEBO EFFECT: The placebo effect arises when the patient's experience of undergoing an intervention produces a beneficial effect, an effect which cannot be attributed to the properties of the intervention itself. Although a large proportion of the placebo effect is attributable to the patient's belief in the power of the intervention, the placebo effect can also be elicited by indirect factors, like the characteristics of researchers or clinicians who interact with patients. For example, clinicians who express more positive nonverbal behaviors (more smiling, use a strong tone of voice, more eye contact, more body gestures) can elicit greater placebo effects than those with negative non-verbal behaviors.[5] This class of bias can be extremely challenging when clinicians or researchers gather data personally in any study that does not use a double-blinding procedure.

MITIGATING BIAS IN CLINICAL TRIALS

Because the causes of bias in clinical trials are so varied, no single approach will mitigate them all.

Some approaches can address multiple biases, and some can mitigate one, but may exacerbate others, so there is no silver bullet for creating a perfect experimental design. For each trial, researchers must prioritize the biases they most hope to mitigate, and then chose a combination of diverse approaches that best address those biases.

Among the most common experimental design feature in clinical trials is a placebo control. In fact, the randomized

placebo control trial (ideally with a double-blinded approach) is considered the gold standard, and with good reason. Under ideal conditions, when a placebo intervention is indistinguishable from the active treatment, and neither clinicians nor patients know which arm the patient is participating in, it can mitigate many of the existing biases that cause distortions in the outcomes of a clinical trial. This is because we expect that most of the biases will influence both experimental and control groups in the same way, so that any difference in outcomes between the two will reflect only the effect of experimental intervention. In reality, however, it is often difficult to create a situation where the active and placebo interventions are entirely indistinguishable – this can be particularly true when the experimental medication has substantial side effects or surgery is too risky – resulting in an awareness of who is receiving the active treatment. Further, for ethical reasons, it is sometimes necessary to perform a comparison trial, where the control group receives the current standard of care, rather than a true placebo. Under these conditions some bias can be almost unavoidable. As a result, there are still many situations in which it is critical to optimize experimental design to minimize the many potential biases as much as possible.

Blinding is another commonly used strategy that can be useful for combating expectancy bias, particularly when used in combination with placebo control. When everyone involved in collecting, rating or coding data is unaware of which arm the data comes from, it can help alleviate the expectancy bias. However, it does not help with the many other biases that can distort trial results, and as described for placebo controls, it is not always possible to keep clinicians and participants entirely blinded to what treatment arm a particular patient is in.

A useful strategy for addressing expectancy bias, however, is automated data collection. When clinicians or raters are not interposed between the patient and outcome quantification, this can mitigate any subjective influences they might have. Where computer, web or mobile based tools are used, the interface with the patient can be replicated across all participants effectively eliminating expectancy bias. These tools can also be useful for mitigating some aspects of the Hawthorne effect, as people tend to be less influenced when observations are made unobtrusively by automated means, even when they are aware that they are still under surveillance.[6]

Using digital data collection tools also enables researchers to control the experience of the patient during data collection, and this approach can also help mitigate placebo effects induced by the personal qualities of the clinician – all patients will be presented with an interface that is equally engaging and which can elicit a more limited response from the patients than is elicited by a

clinician or researcher. It is, however, worth noting that if the interface is very positive, it can induce placebo effects nearly as strong as those induced by traditional clinician or researcher interactions. However, because it is uniformly positive for all participants, it would not be expected to have a differential effect on experimental and control groups, so for placebo-controlled trials this may be less of a concern.

While the positive effects of an engaging interface may induce a placebo effect similar to that produced by human clinicians, the use of engaging digital data collection tools can actually be an important approach for mitigating a host of other biases, including selection bias, compliance bias and missing data bias.

Engaging data collection tools may help with selection bias by creating a patient-centric experience that can make clinical trials more attractive to patients who have traditionally been reluctant to participate in clinical trials. An improved trial experience can therefore potentially improve recruitment overall, particularly for under-represented patient populations, for whom the lack of comfort with clinical trials can be a huge barrier to participation.[7]

Engaging data collection tools can also be used expressly to address compliance bias and missing data bias.

These tools use proven strategies from behavioral and gamification research to motivate patients to complete all trial requirements, such as medication adherence and ePRO completion. Such a system enables researchers to use gamified interactions, alerts and reminders to keep participants engaged in working towards completing all of their trial requirements, make the experience of participation fun and reinforce compliant behavior.

It is nearly impossible to design an experiment completely free of bias. However, by evaluating the greatest potential sources of bias, researchers can choose which of a variety of approaches will be most effective for any particular study. With judicious use of placebo control, blinding, automated data collection and engaging digital data collection tools, researchers can design experiments where much of the expected bias is mitigated.

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