Study designs: Part 5 – interventional studies (II)

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Abstract

In the fifth piece of this series on research study designs, we continue the discussion on interventional studies (clinical trials), in which the investigator decides whether or not a particular participant receives the exposure (or intervention). In this article, we take a closer look at several features which are important to ensure that the findings of such a study represent the real effect of an intervention, such as allocation concealment, blinding, compliance to intervention, the use of co-interventions and participant dropout rate.

Keywords: Clinical trials as topic, random allocation, research design, treatment adherence and compliance

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INTRODUCTION

In a previous article in this series, we introduced the concept of interventional study design.[1] In interventional studies, the researcher actively interferes with nature – by performing an intervention in some or all study participants – to determine the effect that the particular intervention has on the natural course of events. In that piece, we also discussed the importance of "randomization" which ensures that the study participants receiving the intervention being studied (the treatment arm) and those not receiving this intervention (control arm) or receiving an alternative intervention (the comparator arm) are fairly similar, and hence, comparable. This random allocation of the study participants to different arms reduces the risk of bias, i.e., of an invalid conclusion being reached based on baseline difference between various arms and hence allows a stronger inference to be drawn about the effect of the intervention.

There are some additional methodological features which when added to an interventional study design serve to reduce the risk of bias and hence add to the validity of the conclusions drawn. These include allocation concealment, blinding, measurement of compliance, minimizing the dropouts, and handling co-interventions. This article discusses these issues in detail. Other additional considerations that help ensure the validity of results of such studies focus on analytical issues, such as the use of intention-to-treat analysis, ensuring appropriate sample size, and the use of primary versus secondary endpoints; these will be discussed in the next article in this series.

ALLOCATION CONCEALMENT

Allocation concealment refers to procedures that ensure that random allocation is implemented without any bias. This requires that none of those involved in carrying out the study, including the study participants, researchers, health-care providers, and outcome assessors, should be able to decipher in advance as to which intervention the next participant entering in the study would receive. In the absence of allocation concealment, there is a risk of subversion of the random allocation, leading to a differential

enrolment of the study participants to various intervention arms and hence biased results. For example, if an investigator knows in advance what the allocation sequence is, he may be tempted to allocate (or may subconsciously allocate) participants expected to have good outcomes to the treatment arm and expected to have poor outcomes to the control arm. Randomization by itself, i.e., if not combined with allocation concealment, cannot be expected to necessarily result in comparable groups.

A common method to ensure allocation concealment is the use of sequentially numbered, opaque, sealed envelopes (SNOSE). In this, an uninvolved third person creates the randomization scheme and places treatment allocations for individual participants in sequentially numbered opaque envelopes which are then sealed before the study starts. For each participant providing consent for the study, the envelope bearing the next serial number is opened and the intervention is administered as per the assignment. An additional step – requiring the person opening the envelope to write down the particular participant's name on the envelope before it is opened – is often added to further reduce the risk of manipulation.

An alternative method is to prepare sequentially numbered containers containing either a placebo or an active drug, as per the randomization scheme. The participants entering the study go to the pharmacy and receive a container with the next sequential number. This has the advantage that even the pharmacist does not know who has received what.

In recent years, the above methods have been largely replaced by centralized allocation systems, where the site investigator is required to contact a central authority over phone or internet, provide some information that specifically identifies the study participant (e.g., name initials, and date of birth), and is then provided treatment allocation for the particular participant. Of the various approaches, this is currently considered as the best approach, except that it is more resource intensive. In a multicenter trial in the UK and Ireland,[2] the method of allocation concealment changed from SNOSE to central randomization midway during the study. During the SNOSE phase, contrary to what would be expected, the participants allocated to the two treatments were dissimilar. With the introduction of central allocation, the two groups became much more similar.

To summarize, the prevention of allocation bias involves two steps: first, the generation of a randomization sequence and second, concealment of the allocation sequence.

BLINDING

In a randomized trial, knowledge whether a particular person has received active (or new) or inactive (or conventional) treatment may make the study participants or investigators perceive the outcome as more or less positive because of the belief that new treatment is likely to be more efficacious. This can lead to a more positive ascertainment of treatment effect than is actually true (ascertainment bias), due to wishful thinking on part of the investigators (also called as "assessor bias") or of the participants ("respondent bias"). For example, in a study evaluating the role of cyclophosphamide and plasmapheresis in the treatment of multiple sclerosis, unblinded neurologists found a significant benefit with these interventions, whereas blinded neurologists found no evidence of effect.[3]

The term "blinding" (or masking) in the context of a randomized controlled trial refers to making individuals involved in it unaware of the intervention that a particular participant has received. This enables an objective assessment of the effect of intervention in each individual and hence reduces the risk of bias in study conclusions. The people who are made unaware (are "blinded") can include various combinations of the following: participants, investigators, health-care providers, outcome assessors, data analysts, etc., Terms such as "single-blind" (when one of the two main parties – study participants or researchers, i.e., investigators and health-care providers), "double-blind" (both the above parties), and "triple-blind" (also data analysts) were used in the past. The current practice is to avoid these terms and instead explicitly state who all were unaware. In some situations, it is not possible to blind one or more of the parties involved, e.g., in a comparison of hot versus cold compresses for musculoskeletal pain, it would be impossible to hide the nature of treatment received from the participants. In such cases, efforts should be made to blind at least those who are charged with assessing the occurrence of important outcomes.

When the intervention is a drug, blinding is most often achieved through the use of a placebo, defined as an inert substance or treatment which is not designed to have a therapeutic value. The placebo preparation should resemble the active drug in appearance, size, shape, color, presentation, etc., as much as possible, to make the two indistinguishable. If the test treatment involves injections, the placebo should also be injectable – though this raises an ethical dilemma of giving pain without any anticipated benefit to the individual. In studies comparing an oral drug versus an injectable drug, a "double-dummy technique" is used; here, one group receives the active drug tablets and placebo injections, and the other

group receives placebo tablets and active injections at the respective times. When the comparison involves two oral drugs with different schedules of administration, a similar technique can be applied with the use of placebos for each of the two interventions.

However, at times, it may be impossible to achieve blinding using a placebo, for instance, if a drug has a specific characteristic (smell and consistency in case of liquids) which is difficult to reproduce in the placebo or produces a recognizable effect. For example, patients cannot be blinded in a study on rifampicin which leads to distinctive urine color, and physician cannot be blinded in a study on beta-adrenergic antagonists which produce bradycardia.

For studies involving surgery or procedures, blinding is more difficult, but it may be possible to perform a sham procedure, i.e., a procedure where all the steps are carried out as usual, but a crucial step is missed out, in the control group. For instance, in a study to assess the role of vertebroplasty in painful acute osteoporotic vertebral fracture, one group underwent injection of polymethylmethacrylate cement using a bone biopsy needle placed under local anesthesia. In the control group, local anesthesia was administered, a needle was placed in the bone, and cement was mixed in the operating room (to generate mixing sounds and smell to make the person believe that cement was being injected) but was not injected.[4] In another study looking at the efficacy of arthroscopic debridement for osteoarthritis, participants were randomly allocated to receive actual arthroscopic debridement, arthroscopic lavage, or a sham procedure in which skin incisions were made to simulate surgery, but no real surgical procedure was performed.[5]

The use of placebo for controls poses an apparent ethical dilemma when a partially effective treatment is already available for the particular disease condition. In such cases, a useful alternative is to provide the available treatment to all participants, and in addition, the active drug or placebo depending on the random allocation. Thus, the comparison becomes standard treatment alone versus a combination of standard treatment plus the new drug.

MINIMIZATION OF PARTICIPANT DROPOUT

Randomization ensures that the group of participants allocated to one group is comparable overall to that allocated to the other treatment. However, in almost all studies, some participants leave the study midway for various reasons. In this situation, the participants in each group completing the study cannot be taken as being comparable. In particular, if the dropout rate is high or is unequal between various arms, the results may be biased.

Thus, all efforts must be taken to keep the dropout rate as low as possible. These include (i) planning the study such that the overall duration is short and the number of visits per participant is low, (ii) maintaining close contact with the participants and ensuring their convenience during the study visits, and (iii) using outcome measures which are convenient and acceptable to participants (e.g., shorter questionnaire rather than long questionnaires). Furthermore, if a study participant does not wish to continue in the study, the investigator should try to obtain his/her consent to continue to provide data on the most important outcomes even if the drug administration would stop midway and all the data cannot be collected.

COMPLIANCE

Compliance is the degree to which study participants adhere to the prescribed interventions. Failure to comply with the intervention (e.g., missing a large proportion of scheduled drug doses) may interfere with a proper assessment of the study results. This is a particular problem if compliance rates differ between the intervention arms.

Compliance can be improved through reinforcement at each visit and through periodic phone calls or text messages, and can be assessed by asking participants to maintain diaries or by counting the number of unused pills at each visit. The compliance data can also be incorporated into statistical adjustment during data analysis or interpretation of the study results.

CO-INTERVENTIONS

Co-interventions are additional treatments, advice or other interventions that a patient may receive, and which may affect the outcome of interest. For example, in a study on definitive treatment for arthritis where pain control is the outcome of choice, concomitant intake of over-the-counter analgesics or anti-inflammatory drugs may affect the outcome. This is particularly problematic if the usage of such a co-intervention differs between the two treatment arms.

To avoid this, the study design may require either expressly asking the trial participants to avoid such co-interventions, or close monitoring of their use so that necessary adjustment can be done during analysis or interpretation of the study results.

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Conflicts of interest

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