Randomisation and blinding in clinical trials

**Corresponding Author:**

**Submitting Author:**
Dr. William Kent,
Foundation doctor and Sports Scientist, Royal Sussex County Hospital, Brighton - United Kingdom

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Abstract

High quality clinical trials are designed to reduce bias, to increase the confidence that the reader can place in the conclusions of the trial. This article evaluates the role of randomisation and blinding to prevent bias and how to best implement them in a trial.

Introduction

The quality of a trial can be described as the confidence that the design, conduct, report, and analysis restrict bias.[1] Bias is defined as systematic errors in clinical trials that result in a difference between the results of a study and reality.[2,3] This can lead to inaccurate results and wrong conclusions about the effectiveness of an intervention. Good study design is required to minimise bias4 because it can be introduced at any stage of trial and cannot be measured or controlled for by statistical methods.[2] This article will focus on two methods of preventing bias in clinical trials: randomisation and blinding.

Review

Randomisation

Three possible explanations can account for any difference between groups at the end of a trial: 1) a real effect; 2) chance; and 3) a systematic difference between the groups other than the intervention (bias).[5] Randomisation is a technique used to reduce this third possibility by preventing selection bias and confounding factors. Participants are allocated in a random and unpredictable way to the different groups in the trial.[6] Providing enough participants are involved in the trial the random allocation produces groups which on average are as alike as possible. The assumption being that along with known, measured characteristics, unknown and unmeasured characteristics will also be equally distributed between the groups eliminating their possible influence on the results.[1,2,7] Randomisation also facilitates blinding of treatments which can reduce bias after intervention allocation. It also permits the use of probability theory to express the likelihood that any difference in outcomes between the groups is due to chance.[8]

If randomisation is not used then predictive factors tend to be unevenly distributed between the groups in a trial.[1] This is the result of selection bias through conscious or unconscious manipulation of the allocation sequence by the researchers. For example if a researcher allocates people with a less favourable prognosis to the control group, then (assuming that the intervention is not significantly worse than the control) a positive outcome can be expected for the intervention group irrespective of whether it is in reality any better or not. This uneven allocation may occur because of financial motivation or because of good intentions of the researchers to try and get the best treatments for a patient. Irrespective of the underlying motivation bias is introduced which can invalidate the results of a trial. To avoid this, rigorous methods to prevent researchers from knowing or manipulating the allocation sequence should be implemented. Successful randomisation therefore involves three stages: random sequence generation, concealed allocation, and implementation. Each stage should be adequately described in the methods of a trial so that the likelihood of bias in group allocation can be evaluated.[2].

Random sequence generation

True randomisation is necessary because some methods of allocation such as alternate allocation, or methods based on patient characteristics (Table 1) are not reliably random and are easily predicted and manipulated.[2] In general terms two different types of randomisation exists:

Fixed randomisation: the randomisation method is defined and sequences set up before the start of the trial (eg simple and restricted randomisation).

Adaptive randomisation: randomisation is adjusted as the participants are recruited to account for imbalances in numbers or characteristics of the participants (eg minimisation).[2]

Simple randomisation is equivalent to fair coin tossing whereby each participant has an equal chance of being allocated to each group. However, manual methods such as coin tossing and dice rolling are not used due to issues with concealment, validation and reproducibility. Instead random number sequences generated by a computer or a textbook are usually used. These methods are easy, unpredictable, reliable and have the advantage of producing an audit trail.[8]

Restricted randomisation is used to control randomisation to achieve balance between groups in size (block randomisation) or in size and specified...
characteristics (stratified randomisation).[8] It is especially relevant for sample sizes of less than 200 as due to the play of chance simple randomisation may not produce groups with similar numbers and comparable participant characteristics.[6] However, these methods do not offer any more protection against bias than simple randomisation.[8]

Adaptive or dynamic random allocation methods seek to have balanced groups throughout the study. Minimisation is the only alternative to randomisation recognised by the CONSORT group.[6] The first participant is randomly allocated then the following participants are allocated so as to minimise the imbalance between groups at that time of the study. It ensures balance between groups for size and identified important participant characteristics at all times of the study and is the only method that can guarantee similar groups in a trial.[9]

Allocation concealment
Allocation concealment is used to prevent selection bias before the assignment of interventions and can always be implemented.[10,11] It is different from blinding which is a method used to protect against bias after intervention allocation and cannot always be implemented.[6] Without adequate allocation concealment even random, unpredictable allocations can be corrupted.[1,6] Each investigator in the trial will have an agenda grounded in their personal opinions about the intervention and instances of researchers sabotaging the concealed allocation to subvert the random allocation have been described.[10] The reasons given varied: an intellectual challenge or doing what they believed was right for a patient to deliberate sabotage or manipulation to confirm a belief.[10] Well meaning or not, such tampering undermines the validity of a trial. Most examples of subverted randomisation occur because the methods used to conceal the allocation were inadequate. Robust allocation concealment removes the opportunity for the conscious or unconscious manipulation of participant allocation should therefore be implemented (table 2).

Implementation & Empirical evidence
Strong empirical evidence has been reported that inadequate sequence generation and allocation concealment are associated with overestimates of treatment effects.[1,7,11] These findings support the use of randomisation in clinical trials and as a criterion in critical appraisal. It is therefore important that the methods of randomisation and how it was implemented are adequately described.

Blinding
Blinding is the method of keeping participants, and the researchers involved in a trial unaware of the assigned interventions after allocation. It is utilised to avoid participants’ or investigators’ expectations impacting upon the results.[1] Knowledge, experiences and beliefs can all influence physical and psychological responses to an intervention.[12] Its use is supported by research comparing adequately blinded trials with inadequately blinded trials which found that knowledge of intervention allocation is associated with larger estimates of treatment effects.[13]

Different levels of blinding have been described (figure 2) but their meanings are poorly understood[13-15] and a lack of consistency in their implementation adds to this confusion.[1,13-15] Therefore, the methods used should be explicitly stated to allow readers to assess the adequacy of the blinding and evaluate any impact that bias may have had on the trial.[15] In an attempt to increase and improve the use of blinding, descriptions of blinding methods have been published for both pharmacological[13] and non pharmacological interventions[14] and guidelines have been written for the correct reporting of blinding.[6]

Blinding of different individuals involved in a trial has many potential benefits which can improve the credibility of trial conclusions.[12] Blinding makes unintentional or intentional bias of results difficult, improves compliance, and improves participant retention.[15] Careful consideration needs to be given to the intervention procedures so that differences do not cause unblinding. For example, pharmacological trials should include a placebo or alternative treatment that is identical in appearance (size, colour, weight, feel, odour etc) and route of administration.[4] Nonpharmacological interventions are often harder to blind.[14] The lack of blinding does not automatically indicate a methodologically unsound trial as the design may prevent bias in other ways (e.g. objective outcome measures).[12,13] Furthermore the influence of blinding on reducing bias has yet to be fully ascertained. Studies are required to assess its influence on preventing bias because its actual impact may be considerably different to its theoretical influence.[15]

Discussions and Conclusion

All trials have limitations but good study design reduces the potential for bias and combined with the good reporting increases our confidence in the conclusions of a trial. Randomisation can be used to prevent selection bias and confounding factors in a
trial. Whereas, blinding reduces the opportunity for bias to be introduced after the interventions have been allocated. However, randomisation and blinding do not guarantee a methodologically sound trial especially as these techniques are often poorly understood and implemented. To be successful these methods need to be robustly implemented to prevent even determined individuals from influencing the results of a trial. The methods used must also be explicitly reported so that the overall quality and credibility of a trial and its conclusions can be evaluated with confidence.

References

Illustrations

Illustration 1

Table 1

Examples of inappropriate and appropriate sequence generation methods.[2,6,8]

<table>
<thead>
<tr>
<th>Inappropriate</th>
<th>Appropriate</th>
</tr>
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<tbody>
<tr>
<td>Alternate allocation</td>
<td>Random number tables</td>
</tr>
<tr>
<td>Methods based on patient characteristics</td>
<td>Computer generated random numbers</td>
</tr>
<tr>
<td>Day presenting to clinic</td>
<td></td>
</tr>
<tr>
<td>Case number</td>
<td></td>
</tr>
<tr>
<td>Day of birth</td>
<td></td>
</tr>
<tr>
<td>Day of the week</td>
<td></td>
</tr>
<tr>
<td>Roll of a dice</td>
<td></td>
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<tr>
<td>Coin tossing</td>
<td></td>
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</tbody>
</table>
Illustration 2

Table 2

<table>
<thead>
<tr>
<th>Inadequate allocation concealment</th>
<th>Adequate allocation concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation Posted on bulletin board</td>
<td>SNOSE (sequentially numbered opaque sealed envelopes)</td>
</tr>
<tr>
<td>Translucent envelopes</td>
<td>Pharmacy controlled numbered or coded containers</td>
</tr>
<tr>
<td>Unsealed assignment envelopes</td>
<td>Central randomisation (via telephone, fax, or web)</td>
</tr>
<tr>
<td>Different weight envelopes</td>
<td>Secure computer assisted method</td>
</tr>
<tr>
<td>Unnumbered envelopes</td>
<td></td>
</tr>
<tr>
<td>Allocating more than one assignment at a time</td>
<td></td>
</tr>
<tr>
<td>Different labels</td>
<td></td>
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</table>
Illustration 3

Figure 1

Figure 2. Blinding (masking) definitions

- Open label: All parties are aware of intervention being used.
- Single blind: Either the participants or researcher (usually the participant) is unaware of the intervention allocation.
- Double blind: Both the participant and the researchers (including analysts) are unaware of the allocated intervention.
- Unblinding: The disclosure, planned or unplanned, of the intervention allocation.
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