Fool's gold? Why blinded trials are not always best

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ANALYSIS

Fool's gold? Why blinded trials are not always best

Blinding is intended to reduce bias but can make studies unnecessarily complex or lead to results that no longer address the clinical question, argue **Rohan Anand and colleagues**

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The essence of blinding is withholding information about treatment assignment from people involved in the trial. Trials in which patients, clinicians, and researchers are blinded to the allocated intervention are usually regarded as the gold standard of clinical research and evidence.[1 2] However, blinding's illustrious reputation brings with it the danger that it is regarded as essential for a trial to be "good," especially if users place an uncritical reliance on hierarchies of evidence in which blinded evaluations are near the top.[3] Given that the number of new trials is increasing every year, with 25 000 registered since the start of 2019, we are concerned that a substantial amount of time, energy, and funding may be going into considering and implementing blinding without a sound rationale for it.[4]

Past, present, and future trials contain vast amounts of important data. If trials without blinding are inappropriately judged to be of lower quality than blinded trials then we may not be making best use of their data to improve healthcare, while blinded trials may be producing results that are more difficult to interpret than they need be. In this article, we seek to stimulate debate by challenging some of the prevailing beliefs on the benefits of blinding.

Purpose of blinding

The first recorded instance of blinding is from Paris in 1784.[5] This was a study into an unknown, mystical force called mesmerism and the claims that patients could be healed simply by encountering a "mesmeriser" or an object that had been mesmerised. People believed to have been mesmerised would sometimes show hysterical behaviour, but the French Academy of Sciences was sceptical. It assembled a distinguished scientific team, including Antoine Lavoisier and Benjamin Franklin, to conduct experiments to test mesmerism. The participants were blinded to which objects were mesmerised or whether a mesmeriser was behind a curtain and then observed for their reactions. When they were blinded, mesmerism lost its power, and the study instead established the power of blinding.

Blinding is used in trials to reduce bias by ensuring that knowledge of which intervention a given trial participant received does not influence the judgments of trial participants or investigators. This allows the identification of the "true effect" of the new intervention, as distinct from any effect arising simply from the participant's knowledge or expectation of receiving an intervention. In placebo controlled trials, any placebo effect of the new treatment would be discounted when comparing the intervention and control group to determine the effect of the active properties.

Blinding is also used to reduce bias in which the measured effect is not the true effect.[6] Blinding aims to minimise response and observer bias. Response bias occurs when participants respond inaccurately, either intentionally or unintentionally. Observer bias occurs when researchers assessing the effects of the interventions have presumptions about them and so may inaccurately measure outcomes, leading to different effect estimates. Blinding also aims to minimise co-intervention bias, in which non-trial interventions may be taken differently by the groups being compared if participants know what they have been allocated.

Evidence on the ability of blinding to minimise the "placebo effect" (which can occur regardless of whether an actual placebo is used) and reduce bias comes from comparisons between selected trials[7] and from systematic reviews of methodology research,[8-12] with lack of blinding leading to an exaggerated treatment effect of up to 68%. However, there are several negative consequences that can arise from blinding.

Negative aspects of blinding

The substantial challenges of recruitment and retention in clinical trials have been highlighted as priorities for research.[13 14] Poor recruitment leads to prolonged study times and underpowered results. These challenges are made worse by blinding, especially in trials using a placebo control. Trials with

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nested components that were blinded and unblinded found that blinded designs discouraged people from participating.[15-17] Key reasons given by patients for not wanting to enrol in these trials were that they wanted a named medication or wanted to know what was in the tablets. This suggests that achieving blinding and using a non-active comparator discourages people from joining a trial. In another study about 25% of patients expressed concerns about receiving placebos.[18]

Successful retention of patients is equally important,[19] and the use of a placebo might be damaging if patients who suspect that they have been allocated to receive it withdraw from the study. A meta-analysis investigating retention in trials of antipsychotic interventions concluded that a placebo controlled design significantly increased dropout.[20] Patient preference or resentful demoralisation can be a problem if patients in a placebo group lose motivation when they suspect or discover they are not receiving an active treatment. This could result in bias from differential loss to follow-up between groups.[21] Patients may feel frustrated because they believe they are receiving inadequate treatment and so exaggerate negative answers on questionnaires or even withdraw from the trial.[22]

The production and packaging of interventions in ways that will ensure their identity is blinded to participants, including use of placebo controls, can also cause difficulties. Not only do control interventions need to look identical to the intervention, any characteristic taste, texture, smell, colour, or viscosity of the intervention needs to be matched as well, which can be expensive.[23] Money spent on blinding has opportunity costs if it reduces funding to optimise other features that would have more influence on the trial's robustness such as the training of trial staff, boosting the sample size, and comprehensively measuring outcomes.[24] Even if the blinded control is designed to be physically identical to the intervention, any signature side effects associated with the intervention(s) may lead to unblinding.[25] Examples come from the IMOP trial of isosorbide mononitrate for cervical ripening[26] and the IMAGES trial of magnesium for acute stroke,[27] both of which had high rates of specific side effects in the intervention arms; even though no formal unblinding of researchers and patients occurred, those involved in such trials may have had a good idea about the groups that patients were in.

In addition to this passive association, others might actively look for signs that they believe to be linked to the interventions. The online community group PatientsLikeMe was set up to enable people to share information on their illnesses. Members who were enrolled in blinded clinical trials shared their outcomes, including side effects, on online platforms outside of the official protocol or any trial regulations, even before the trial's completion.[28] Their aim was to help each other deduce their allocated intervention, showing their frustration in the blinded approach. This highlights that maintaining blinding may be increasingly difficult in the age of social media and online networks.[29] Researchers have also been found to break blinding by comparing pills and searching through the restricted notes of patients.[30] Box 1 describes other problems that can arise from blinding.

Box 1: Problems associated with blinding

Emergency unblinding

If an individual's allocation has to be unblinded for clinical reasons, there is the potential that this can cascade and unblind others in the trial. A simple example would be an adverse event needing treatment that is reported by blinded trial staff, who then code break to identify which intervention the patient received. Although the trial staff are officially unblinded to only this single case, they might now associate this event or related symptoms with the specific intervention. Even worse, if all the interventions had been coded in the same way (such as "drug A" and "drug B") those who unblind themselves to one patient, effectively unblind themselves to all patients. Even in the absence of such coding, unblinding of patients in a trial using blocked randomisation might reveal the allocations of patients from the same block or strata.[31]

Testing for blinding

Testing for the success of blinding in trials has been reported in about 2% of trials,[32] usually by asking those blinded to guess treatment allocation.[33-36] In theory, any significant difference over chance suggests that blinding was compromised. However, measuring blinding is highly challenging. Asking people to say which treatment was allocated after outcomes have been accumulated makes them likely to base their answer on assumptions related to the effects of the intervention. This was observed in a 2x2 factorial trial of aspirin and sulfinpyrazone for stroke prevention in which blinded clinicians were asked to guess treatment groups and did significantly worse than chance.[37] Their guesses seemed to be influenced by their prior assumptions that sulfinpyrazone was more effective than aspirin and that patients who did well must have been on sulfinpyrazone, when in fact the trial showed the opposite.[38] This essentially confounds testing for the success of blinding with expectations about treatment efficacy.

Blinding and risks to patient safety

When blinding might compromise patient safety, it is paramount to consider whether it is necessary. For example, a placebo controlled trial of fibrinogen for postpartum haemorrhage required a moratorium on the use of any new treatments for 15 minutes after the randomly allocated treatment was given, with the sole purpose of maintaining the blind, potentially creating an unacceptable risk for the women.[39] Similarly, adjusting doses creates problems in blinded trials and in such situations, using a fixed dose of a drug with a narrow and volatile therapeutic range could compromise patient safety. Clinical trials with anticoagulants[40] and antipsychotics have been historically difficult to blind because of the need for dose adjustments.[25]

Use of a placebo or other sham therapy might lead to adverse effects that would not have happened if an open control group had been used. These could be direct harms from the procedures intended to ensure blinding, such as infection from piercing the skin to give a placebo injection or muscular problems from sham physiotherapy.

In considering these concerns about patient safety, Franklin G Miller outlined key questions that might help when deciding whether to use placebos in surgical trials.[41 42] It seems reasonable to apply a similar but expanded set of questions, as listed in box 2, when considering using blinding in all clinical trials. These questions are context dependent and would be determined by those designing the trial; if the disadvantages outweigh the benefits in one of the questions then a blinded trial might not be appropriate.

Box 2: Questions to consider before using blinding

- Is blinding needed for a scientifically sound result? (Will the intervention have a placebo effect which needs to be separated from its true effect?)
- How likely is it that patients or clinicians will behave differently if they know the intervention and would this change in behaviour bias the results?
- Are the potential harms to patients of using blinding excessive?
- Does the anticipated social value of the study results justify any potential harms of blinding?
- Does the financial cost of blinding compromise spending on other methodological aspects of trial integrity?

Pragmatism and what happens in the real world

At its simplest, a randomised trial is a comparative effectiveness study that aims to obtain as unbiased an estimate as possible of the difference in the outcomes for patients in the treatment group compared with those in the control group. Beyond this, the ultimate aim is to generate evidence that can be used to make assumptions about what will happen to future patients who receive the treatment after the trial. Blinding might help to reduce bias but hamper the evidence generated. Minimising biases with blinding might weaken the ability to predict the future accurately, because blinding is unlikely to be used in routine practice. There is a continuum from explanatory to pragmatic trials, and blinding influences where a trial is on this continuum.[43]

Some of the types of blinding that would be contemplated only in a research setting are inconsistent with the desire for pragmatism in large, phase III pragmatic effectiveness trials. Pragmatic trials strive to generate situations that are as close as possible to routine practice, when patients and clinicians will not be blinded to the intervention. Outside trial settings the intervention is known and this will have a legitimate effect on behaviour, including use of co-interventions, concerns about side effects, and decisions about continuing or stopping the therapy. Some interventions will be marketed for over-the-counter and prescription use, and both patients and clinicians will be susceptible to brand psychology, meaning choices will be determined by facets surrounding brand loyalty.[44] Clinicians might pay particular attention to assessing patients for side effects and act if they observe them. Both patients and clinicians might choose to continue with a therapy they believe to be active and beneficial and stop taking therapies they believe to have completed their action, or switch from those that do not seem to be working. Box 3 gives some hypothetical examples.

Box 3: Examples of clinical trial research questions where blinding and placebos would damage pragmatism

Does a cream reduce facial acne?

The uncertainty faced by someone looking at the array of acne creams in a pharmacy is probably not, "Should I use one of these creams or their base material?" but, "Which one of these creams should I use?" A blinded trial of two creams to see which would cause a greater reduction in acne, with independent blinded outcome assessment, would help determine whether the ingredients have different levels of activity but would not account for what happens in the real world. Patients' and clinicians' perception of how the creams are branded and marketed affects their behaviour. The influences related to psychological attachment to a brand, combined with the patient's assessment of their acne, could produce different results from those seen in the blinded trial.

Does cognitive behaviour therapy delivered by a highly skilled and experienced therapist improve the quit rates of smokers?

When the effects of personally delivered interventions such as psychotherapy, teaching, and surgery are assessed, we might wish to compare whether there are differences between those delivered by practitioners with high levels of training or experience and those delivered by relative novices. This might have important implications for the costs of the therapy or for the rate at which patients can receive it.

A blinded trial in which the patient is not informed of the practitioner's skill and experience would remove the effect of this knowledge, but in normal practice they will be aware of this information and it may even influence their decision to seek out a particular practitioner. Having access to the information might bias the patient by having a positive effect of helping them to benefit from the therapy, or, conversely, it might have a negative effect by raising their expectations of benefit which, if not met, could worsen their outcomes. These influences are real and should be part of the pragmatic trial.

This challenge also raises the difficult question of whether therapies that the patient would pay for outside of a trial should be paid for by them in the trial, as the real world outcome could be influenced by the costs of the two procedures available, regardless of the proved efficacy of each intervention.

Does physiotherapy airway clearance reduce acute exacerbations in bronchiectasis?

Clinical trials of airway clearance are difficult to fully blind because of the physical and complex nature of the intervention. It would be hard to define exactly what the sham physiotherapy consists of and how to implement it if was to be used as a placebo control. The trial would also be at a risk of unblinding if patients who are familiar with the active airway clearance intervention were allocated to the placebo arm. Physiotherapists would probably be aware when implementing a sham procedure, further weakening the blinding.

The results of such a fully blinded trial would be unlikely to translate into the real world because biases surrounding clinician preference and co-intervention bias are neglected. Even if patients were blinded, the physiotherapists may not be confident in applying a sham procedure.

Similar problems would arise in a trial exploring a physiotherapy airway clearance regime versus a drug because, even with outcome assessors blinded, it raises additional issues with the practicality around the communication between patients and clinicians. For example, scheduling patient visits would be complex as patients could not be seen carrying trial medications. A more pragmatic approach would be to blind external outcome assessors or to use an objective primary outcome, such as number of exacerbations, for the trial along with independent blinded adjudication of outcomes (a blinded endpoint committee).

Methods that increase trial integrity

The prospective randomised open blinded endpoint evaluation (PROBE) is an established method for trials.[45-47] It emphasises randomisation (with secure concealment until the allocation is revealed) and blinded outcome assessment, two facets that protect against bias. The blinding is implemented while evaluating defined endpoints during a trial. Trials using PROBE are regarded as open label with respect to patients and clinicians but implement the blinding of outcome assessors or the blinded evaluation of the trial's endpoints. This approach of keeping outcome assessors blind to the random allocation can be used in most trials, including pragmatic effectiveness trials in which outcomes are either subjective or objective. Blinding the outcome assessors throughout a trial or using blinded evaluation of endpoints by a committee at set points, reduces the effect of observer and response bias, which can cause substantial reported differences between treatments. Such methods would increase rigour when double blinding of patients and clinicians is

dropped, might be simpler to deliver, and can avoid the many challenges we have outlined. For example, although the outcome assessor is blinded, the study replicates routine practice in that patients and clinicians know which intervention is being used for a particular participant.

If blinded outcome assessment cannot be used in a trial, bias can still be substantially reduced by using objective (eg, death) rather than subjective (eg, quality of life) outcomes. This is supported by a large meta-epidemiological study that found little evidence of bias in unblinded trials that used objective outcomes for both drug and non-drug interventions.[48] Another option to reduce bias is to modify the outcome to make it less subjective. This can include avoiding surrogate markers and limiting the size of any effect on a given clinical measure (eg, using a 5 point Likert scale rather than 10 point Likert scale).[49]

Blinding in clinical trials can increase the reliability of a trial's results but has consequences for the practicality, safety, and results of some trials. We suggest that the key elements for clinical trials seeking to minimise bias when comparing the effects of interventions should be adequate randomisation, allocation concealment, use of objective outcomes, independent blinded adjudication of outcomes, and, when possible, blinded assessment of outcomes. The traditional double blinding of participants and clinicians should not be regarded as a gold standard to strive for and should be used only if the negative effects are considered carefully and are outweighed by the potential benefits.

Key messages

- Blinding of participants, clinicians, and others avoids bias in clinical trials but can sometimes be detrimental to their integrity
- Some trials without blinding are inappropriately judged as poor quality
- Blinding participants and clinicians can affect recruitment, retention, and applicability to routine practice as well as causing potential harm to patients
- Double blinded designs are not always ideal for providing a reliable answer to the trial's research question
- People using such designs should rationalise their use of blinding
- A more nuanced approach, using blinded outcome assessment and independent blinded adjudication of outcomes, alongside adequate randomisation and objective outcome measures, should reduce the main forms of bias

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