Breaking the blind: trade-off between patients' safety and impact on data integrity

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Why to blind?

- Used to reduce the risk of bias in clinical trials with two or more study groups.
- Awareness of the intervention assigned to participants can introduce
  - **ascertainment bias** in the measurement of outcomes, particularly subjective ones (eg, quality of life)
  - **performance bias** in the decision to discontinue or modify study interventions (eg, dosing changes), concomitant interventions, or other aspects of care
  - **exclusion/attrition bias** in the decision to withdraw from the trial or to exclude a participant from the analysis.

What are the potential groups that can be blinded?

- trial participants
- care providers
- data collectors
- outcome assessors or committees
  - NB: blinding of data monitoring committees is generally discouraged.
- data analysts and manuscript writers

Types of blinding

Type	Description
Unblinded	**All are aware of the treatment the participant receives**
Single blind	**Only the participant is unaware of the treatment they receive**
Double blind	**The participant and the clinicians / data collectors are unaware of the treatment the participant receives**
Triple blind	**Participant, clinicians / data collectors and outcome adjudicators / data analysts are all unaware of the treatment the participant receives.**

Unblinded trial

- Should be used:
  - For surgical procedures
  - When changes in lifestyle are required
  - When endpoints are objective and cannot be interpreted in different ways
  - For case studies with life-threatening situations
  - In post-marketing surveillance

When possibile, use blinding

- When blinding of trial participants and care providers is not possible because of obvious differences between the interventions, blinding of the outcome assessors can often still be implemented.
- It may also be possible to blind participants or trial personnel to the study hypothesis in terms of which intervention is considered active.
  - For example, in a trial evaluating light therapy for depression, participants were informed that the study involved testing two different forms of light therapy, whereas the true hypothesis was that bright blue light was considered potentially effective and that dim red light was considered placebo.

Testing the effect of inadequate blinding

Feys *et al. Systematic Reviews* 2014, **3**:14
http://www.systematicreviewsjournal.com/content/3/1/14

SYSTEMATIC REVIEWS

RESEARCH **Open Access**

Do randomized clinical trials with inadequate blinding report enhanced placebo effects for intervention groups and nocebo effects for placebo groups?

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Available online at www.sciencedirect.com

SCIENCE DIRECT

Contemporary Clinical Trials 26 (2005) 459–468

Contemporary Clinical Trials

www.elsevier.com/locate/conclintrial

Pre-trial evaluation of the potential for unblinding in drug trials: A prototype example

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Received 2 March 2004; accepted 7 February 2005

Published by Oxford University Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology 2007;36:654–663
doi:10.1093/ije/dym020

Blinded trials taken to the test: an analysis of randomized clinical trials that report tests for the success of blinding

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Blinding is rarely tested. Test methods vary, and the reporting of tests, and test results, is incomplete. There is a considerable methodological uncertainty how best to assess blinding, and an urgent need for improved methodology and improved reporting.

Defining blinding/unblinding procedures

- A clear protocol description of the conditions and procedures for emergency unblinding
  - helps to prevent unnecessary unblinding;
  - facilitates implementation by trial personnel when indicated;
  - enables evaluation of the appropriateness of the planned procedures.

Steps for avoiding unblinding

- Provide information about the adverse events
- Define who can be unblinded
- Increase Numbers

Unnecessary code-breaking: an example

Situations that might warrant breaking the code are usually defined in the protocol. Still, some investigators understand breaking the blind as a compulsory step to be followed with any serious adverse event, even if knowledge of the study drug is not relevant to the treatment of the adverse event.

An investigator phoned the sponsor asking to open a subject's blinding code. The subject was in a double-blind Phase 2 study for the treatment of benign prostatic hyperplasia. The therapies being compared were two different doses of a new alpha blocker, a marketed alpha blocker, and placebo.

Dr. "X," who sounded as though he were in a state of great panic.

"Subject MJO received the first dose four hours ago, and now he is having postural hypotension," said Dr. X. "His blood pressure is dropping every second, and now it is 101/65. I need to know immediately what drug he is taking," he demanded.

Ayala E: Applied Clinical Trials 2001

Unnecessary code-breaking: an example

"Is there any particular treatment for this event?"

"The standard treatment as for any postural hypotension," I said. "There is no need to open the blind."

The response did not calm the doctor's anxious demands.

"Well, I need to know the drug anyway. In the event of a cardiac arrest, the emergency personnel will need to know all the medications he was taking. And even if there's no emergency, I'd like to tell the subject what he was taking," he said firmly.

"I will need to discuss this with the project manager in charge of the study," I said,

but Dr. X was not to be delayed. "Look, his blood pressure is dropping to 91/60!" he said. "He is sick and dizzy. There is no time for discussion—I'm opening the code."

I did not argue further. The blinding code was opened, and revealed the standard treatment.

Dr. X administered intravenous fluids, as for any postural hypotension.

One hour later, the subject had recovered.

Ayala E: Applied Clinical Trials 2001

Searching the trade-off between patients' safety and impact on data integrity

Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study *Lancet* 2011; 377: 914-23

ITT

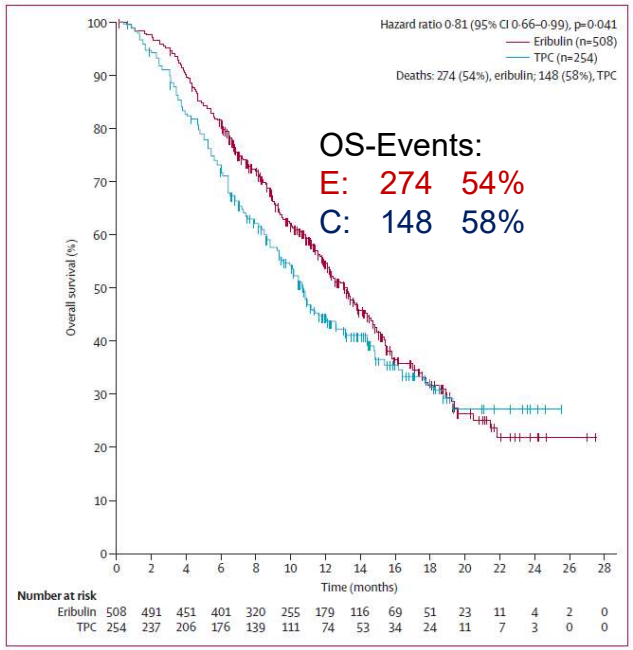

Figure 2: Kaplan-Meier graph of overall survival
Analysis was protocol prespecified and included the intention-to-treat population. Tickmarks show censored data. TPC=treatment of physician's choice.

IRB Invest

ITT

PP

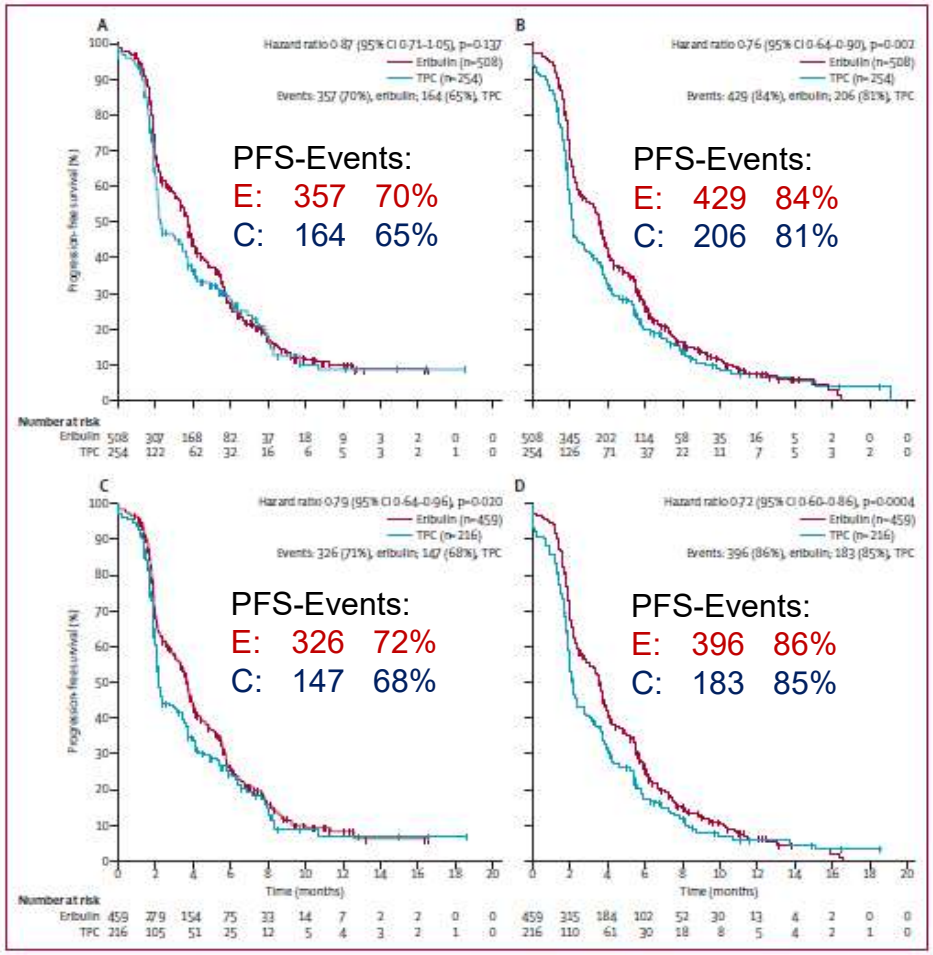

Figure 4: Kaplan-Meier graphs of progression-free survival by (A) independent review and (B) investigator review of the intention-to-treat population, and (C) independent review and (D) investigator review of the per-protocol population
All analyses were protocol prespecified. Tickmarks show censored data. TPC=treatment of physician's choice.

Searching the trade-off between patients' safety and impact on data integrity

- Co-primary endpoints: OS and PFS
  - **Analyze PFS at IA only if OS positive;** at final analyses either endpoint can also be tested independently
- OS (one interim for efficacy and final analysis)
  - Median control group: 18 months - Target HR: 0.70 (median survival improvement ~7.7 months)
  - Type 1 error (alpha): 0.04 two-sided (spent over IA and FA, OBF boundaries); Power: at FA 83%, (64% at IA)
  - **326 death events required for FA** (IA planned at ~80% of events, i.e. 260/326 events, ~ 37 mos into the study)
- PFS (analyzed at IA only if OS IA positive; else analyzed at the final OS)
  - Median control arm: 10 months
  - Target HR: 0.70 (median PFS improvement ~4.3 months) - Type 1 error (alpha): 0.01 two-sided; Power: 80
  - **413 PFS events required** (if OS IA positive, then PFS analyzed earlier ~ 37 months, at 5% alpha two-sided; 353 events power ~88%)
- Accrual 24 months; follow-up of 24 months; **550 patients planned** (incl ~ 10% dropouts)

Conclusive remarks

- Randomization, avoidance of exclusions after trial entry, and double blinding (or masking) may represent the most important methodological components for reducing bias in controlled trials.
- Patients safety has to be of primary importance for investigator and this may explain why investigators are sometimes eager to open a subject's blinding code when they perceive a medical emergency.
- Situations that might warrant breaking the code have to be defined in the protocol.
- Still, there are situations other than safety that may affect the blinding, that not always can be anticipated.
  Ad hoc committee should be in charge for dealing with these issues.