Identifying relevant sensitivity analyses for clinical trials

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Outline

- Rationale for sensitivity analysis in clinical trials
- Criteria for deciding whether a candidate sensitivity analysis is relevant
- Details and examples

Working definition

A sensitivity analysis addresses the **same substantive question** in a **different way**.

Why do sensitivity analysis?

In clinical trials, we have to plan our analyses in precise detail before seeing the outcome data.

Should publish the plan and stick to it on receiving the data. We cannot check assumptions when planning analyses.

Choosing an analysis based on trial data is known to lead to questionable results in several settings.

Unless you have chosen the best possible analysis, *plan SA*!

Rationale for this work

Confusion about what sensitivity analysis is. Often used to refer to any secondary analysis of primary outcome.

"*That would be a sensitivity analysis*" – overused

Three criteria for a relevant sensitivity analysis: A practical approach

1. The candidate sensitivity analysis addresses the **same question** as the primary analysis.

2. The proposed sensitivity analysis **can disagree** with the primary analysis.

3. If results disagree, there must be **genuine uncertainty** as to which analysis gives the more reliable result.

1. Addressing the same question

If two analyses address different questions, we are talking about secondary analyses, not sensitivity analyses. These may be useful but should be framed correctly.

When did your train get in?

What time did you get here this morning?

Would you think, "Different answers – what does it mean?"

1. Addressing the same question

Example: the Multicentre Aneurysm Screening Study (MASS) randomised 67,800 men to receive an invitation to an abdominal ultrasound or not.

20% of invited men did not accept their invites.

The primary analysis was by intention-to-treat.

Q – *What was the effect of being randomised to an invitation?*

A complier-average causal effect analysis was also performed.

Q – *What was the effect of abdominal ultrasound in patients who would have adhered to protocol however randomised?*

2. Analyses must be able to disagree

Sometimes two analyses that go by different names will *always* lead to the same result.

Such sensitivity analyses can be dangerous. It is like doing one analysis and being reassured that doing it again on the same data leads to the same results.

2. Analyses must be able to disagree

Example: Zheng et al. published a protocol for a study investigating the effect of Baduanjin exercise on health in college students. Some outcomes are anticipated to be missing, and the principal analysis involves a *t*-test in the complete records.

Multiple imputation as a sensitivity analysis?

Impute assuming outcome is normally distributed with different means and equal variances in the two treatment groups.

– Given sufficient imputations, the two results will agree!

2. Analyses must be able to disagree (a tip)

What if the answer is "I don't know"?

Your candidate sensitivity analysis should be motivated by concerns about certain features of the data. Try to construct datasets in which the sensitivity analysis disagrees with the primary analysis.

If you cannot, think about why you are considering this sensitivity analysis in the first place.

3. Genuine uncertainty about the best result

(Before seeing the data.)

For some candidate sensitivity analyses, it may be clear that you would always believe one over the other.

Example 1: Peters et al. found that for a cluster-randomised trial, analysis ignoring clustering and accounting for it led to different results.

No uncertainty as to the more reliable result. Futile to plan this as a sensitivity analysis.

Conclusions

Unless you think you have chosen the best possible analyses (regardless of what the data look like), it is advisable to plan sensitivity analyses in protocols and statistical analysis plans.

Ask yourself: *Is it asking the same question*; *can it disagree with the main analysis*; *would I be uncertain about which to believe?*

These criteria can be applied to study designs beyond randomised trials.

Criteria ensure only relevant sensitivity analyses get planned. You will be pleasantly surprised at how few you come up with, and it may help to improve your principal analysis.

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A tutorial on sensitivity analyses in clinical trials: the what, why, when and how

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Choosing sensitivity analyses for randomised trials: principles

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