Safeguarding public health

Non-inferiority trials: A regulator's perspective

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Or
Get rid of non-inferiority!!!!

The views expressed are those of the speaker and do not necessarily reflect the views of the MHRA.

Relevant guidance

ICH E10

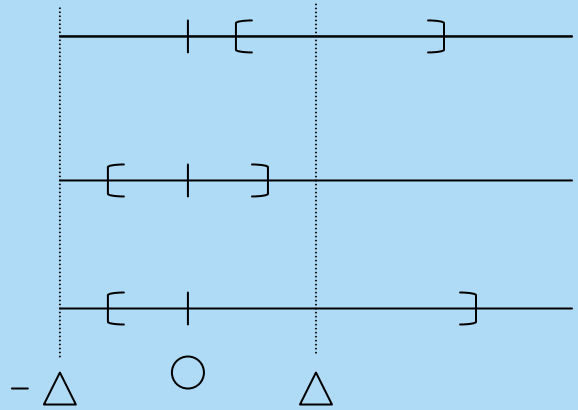
CHMP guideline on the choice of non-inferiority margin (EMEA/CPMP/EWP/2158/99)

CPMP points to consider on switching between superiority and non-inferiority

How are decisions made?

Using confidence intervals for the difference between treatments

- Superiority
- Equivalence
- Non-inferiority



Choice of margin

First principle

- To establish that the test product would have been successful if a placebo controlled trial had been possible

Second principle

- Exclude differences of clinical importance for the given situation

Both principles to be used together

Calculate margin that gives superiority over placebo

Then choose smaller margin if required for reasons of clinical importance

We've come a long way

Remember what we had before?

- non-significant p-value = no difference

So we should be very grateful for the confidence interval approach

But have we created a monster?

Most meaningless phrase in the universe…

"Non-inferiority was demonstrated…"

What does it mean?

In itself - NOTHING!!!

But dangerously people think it does…

Superiority

“Superiority” has a meaning

The 95% CI for the difference excluded 0 (or 1 for ratios).

So it is OK to say A demonstrated superiority over B

OK to say

A was non-inferior to B without any further clarification???

Non-inferiority

The phrase is problematic straight away

“Not-inferior” = “superior” in common English (assuming that no two things are ever *exactly* the same.

So only a “superiority trial” can show this.

Non-inferiority really means “at most a small amount worse”

Non-inferiority trial

Any conclusion that “non-inferiority was demonstrated” is not complete without a full description of the trial objectives.

These objectives are not to demonstrate “non-inferiority” but:

- Indirect superiority over placebo
- Not worse than X by more than some pre-specified amount
- etc, etc

This true objective is what should have been used to define the margin

CHMP guideline

“It is important to define objectives before starting the trial…

“demonstrating non-inferiority is not considered to be a sufficiently detailed objective for a trial…

Query

Someone asked me once…

This product is clearly superior – but is it non-inferior?

This was a scenario where equivalence was clearly required (a generic) so the large superiority was a problem. Applicant was disguising this by presenting their significant result for non-inferiority hoping we would assume this meant similarity.

Trying to use our “reductive” one sentence approach to such trials to their advantage.

The question illustrates the extent of this problem and how thought has been taken out of interpretation (especially in journals)

Proposal

Let’s get rid of the phrase

“non-inferiority trial”

“non-inferiority margin”

“non-inferiority”

Non-inferiority trial

This seems to have come to mean “an active control trial where the aim is not to show superiority over the reference”.

(perhaps should be called “non-superiority trial” – not such an attractive conclusion!)

What’s wrong with the phrase “active control trial”

CHMP guideline

"Many clinical trials comparing a test product with an active comparator are designed as non-inferiority trials"

Is it now all active control trials? We are asked about "non-inferiority margins" when the objective is not to show that the product is not substantially worse.

(Guideline is also guilty)

Non-inferiority trial – indirect superiority

Active control trial (no placebo) where the objective is to show indirect superiority over placebo.

We'll assume this is sufficient for a license.

Historically, active beat placebo by 50 points (95% CI lower bound 45 points)

Say margin set at 20 – this would make us confident of superiority over placebo

In new trial (everything fine) new drug 15 points worst, lower bound 19.

Non-inferiority trial – indirect superiority

Clear that new drug is superior to placebo – could calculate indirect confidence interval.

Sufficient for a license – NICE, prescribers can decide where it fits in.

But I don't want to hear that this drug is "non-inferior" to the other one!!!

Even though the "non-inferiority margin" has been satisfied

Non-inferiority trial – indirect superiority

Any conclusion that non-inferiority has been shown is potentially misleading

The trial was a success, the objectives have been met, the margin has been satisfied –

But the conclusion should be “the new drug successfully demonstrated superiority over placebo (indirectly)”

Nothing should be said in relation to the reference, unless we wish present more information and note that it was inferior.

Non-inferiority trials

We are guilty as a community of allowing any active controlled trial to be labelled as a non-inferiority trial

And then allowing (potentially misleading) conclusions that the products are non-inferior

Because we don't look closely at the precise objectives (or don't even get to see them in some publications) we take this conclusion as some sort of stamp that the products are similar.

Non-inferiority trials – not much worse

In this setting a conclusion of non-inferiority is more defensible.

But we still shouldn't allow the blanket conclusion.

We should say "X was found at most to be z points worse than y". After that we can decide whether that makes the products similar or not.

Non-inferiority trials – not much worse

Triallists will want to have some idea what kind of margin will allow them to make a similarity claim (before they begin the trial)

Regulatory agencies will need some idea when they assess

More factors than just the primary endpoint

But conclusions should not be presented as “non-inferiority”

Just present the facts!

Non-inferiority margin

Apart from planning is there a need to pre-specify the margin?

The confidence intervals do not changed based on the pre-specified margin

There is no multiplicity – only one interval exists

Precision

Once we start thinking like this a lot of problems go away

Perhaps we can start thinking about precision rather than margins

Perhaps we can stop thinking of active controlled trials as a completely difference species (although there are some differences).

Main difference

Assay sensitivity (except in 3 arm trial)

Reliable demonstration of superiority over placebo

Active control trials are NOT bad

Comparison of the treatment to a relevant comparator

Information on how the treatments compare

How is this not relevant information?

The fault lies in the reductive way we have come to present them as “non-inferiority” trials.

Precision

A helpful way of thinking sometimes is:

If the confidence interval for the difference between treatments has a width of at most x%, that will give us useful information about the relative efficacy.

We can make decisions from there – no need for a reductive label on the results.

The trial is successful if it gives us the desired precision.

Whether the drug is successful is another issue.

Conclusion

GET RID OF NON-INFERIORITY TRIALS

And bring back active control trials.

A wasn’t non-inferior to B.

The difference between A and B was x, with a 95% confidence interval. (Thus A is likely to be superior to placebo, with difference z etc)

Now make your judgements…