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What Does 'Non-Inferior to' Really Mean?

A Clinician Thinking Out Loud

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Clinical trials · Non-inferiority trials · Treatment comparison

Abstract
As clinicians, we are frequently faced with papers stating that something is 'non-inferior' to something else. By definition, a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a small pre-specified amount. This amount is known as the non-inferiority margin, or delta. Clinicians must know who has chosen the margin, and why. Only when the advantages of the trial treatment clearly overcome the amount of 'worsening' which is implicit in the concept of non-inferiority and delta can we recommend this new 'non-inferior' (or, rather, 'just a little bit worse') treatment to our patients.

Would you buy a car which is definitely less good in terms of safety and durability than the model you had set out to buy, just because the first vehicle is a bit less expensive? The answer to this question obviously depends on the degree of both these differences. If the safety is just 0.05% inferior and the cost is 20% less, I – and, I expect, most of you – would probably say 'Yes OK,' but if the percentages were inverted we all would say 'No thanks'. This example describes, believe or not, the problem of non-inferiority studies, from the (admittedly) simple and practical point of view of us clinicians and – more importantly – our patients.

We are frequently faced with papers and protocols stating that something is, or should be, 'non-inferior' to something else. Is this just statistical stuff we need not care about that much, or is it a useful way to compare treatments which may affect our clinical practice? In other words, should we carefully read the methodological part of the paper or protocol in order to understand what 'non-inferior' means in each individual case, or should we simply accept the fact (or the hypothesis) that the new treatment is or might be not too much worse than the old one?

By definition, a non-inferiority trial aims to demonstrate that the test product is not worse than the comparator by more than a small pre-specified amount. This amount is known as the non-inferiority margin, or delta. If we are to show non-inferiority, we have to specify a non-inferiority margin in the protocol of the study. After the study is completed, the lower 95% confidence interval of the difference between the test treatment and the comparator must not overcome the limit of delta; that is, we want to be 95% sure that the test treatment is not worse than the comparator by more than delta, which we have accepted on clinical grounds. Reasons to accept delta may be less toxicity, ease of administration, and/or lower cost.

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There are two important questions on this topic: who choses the margin? And why would we not perform a true superiority study, including the putative advantages in a cumulative outcome? This second question has been discussed in depth in a recent paper by Garattini and Bertelè [1], in which the authors conclude that usually, if not always, non-inferiority trials ask no relevant clinical question but just assure a place in the market for the new drug or device. However small an increase in the relative risk is, this unavoidably implies an absolute excess of adverse events in the population, which is unethical. In fact, as stated in the 2005 EMEA document [2], when the treatment under consideration is used for the prevention of death, it can be very difficult to justify a non-inferiority margin of any size, because discussion of the number of extra deaths that are acceptable is ethically very difficult. I imagine that it would be hard to find a patient who, if correctly informed, would give consent for being treated with a drug which, although easier to take, may pose a higher risk of death, even if the risk is just 1% higher.

Anyway, in the clinical scenario, we are frequently faced with situations in which some sort of non-inferiority might be accepted. Just suppose you have a new formulation of acetylsalicylic acid that almost completely eliminates gastric side effects. Obviously, were we to show that it is non-inferior to traditional acetylsalicylic acid in terms of prevention of strokes, myocardial infarctions and deaths, then we could give it to our patients, who would receive an important advantage from this knowledge.

So the problem is not the philosophy of non-inferiority trials per se, but who actually chooses the non-inferiority limit, and why. In the above example, the following could be a reasonable line of thinking: since the positive effect of the old drug is 20%, but the risk is 5%, I can accept the new drug (which I already know has a 2.5% risk) if it is not more than 2% less effective. This kind of 'common sense' calculation has nothing to do with the complex (and sometimes hardly understandable) sample size determination written in many commercially driven non-inferiority protocols.

Another point which must be clearly stated is that the new treatment must be superior to placebo. We can usually make an inference on that by looking at previous studies on that topic. However, delta should be small enough to clearly exclude an effect 'not superior' to placebo. For instance, if we know from previous studies that drug A can be 5–10% superior to placebo, when wishing to compare drug B to A in a non-inferiority trial, we must choose a delta whose lower confidence interval is higher than 5% (that is, the new drug can be proven to be superior to placebo). As everyone can see, this is not just a mere statistical problem, but a clinically important one, and we clinicians must be involved in the discussion and decision about the choice of delta [3–5].

When faced with non-inferiority studies, we clinicians also have to bear in mind that these studies have some inherent weaknesses that usually are not present in superiority trials. For instance, the simple fact that the aim of the study is not to show an important difference between the two treatments means that a moderately large rate of discontinuation from the study drug can obscure the true treatment effect, facilitating the finding of 'no difference'. For the same reason, the usual intention-to-treat analysis can bias the result in favor of non-inferiority, and usually in this kind of study both intention-to-treat and per protocol analyses are requested, and obviously the results must go in the same direction in both arms. There are also other statistical problems (i.e. sample size calculation), which I will not discuss in detail here.

The main problem with non-inferiority studies is always how to specify an appropriate non-inferiority margin. Thus, when reading papers or protocols based on non-inferiority, the right question we have to ask is 'How much worse is it?' This should be immediately followed by another question: 'Are my patients keen to be offered a less effective treatment if it carries a different, clear-cut advantage?' If the answer to the first question is a very low figure, and the answer to the second question is definitely yes, than I would recommend this new, non-inferior (or rather, 'just a little bit worse') treatment to my patients. Would you?

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