

Trials on trial: Equivalence, ethics and evidence

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Garattini and Bertele

- ‘The scientific community should ban non-inferiority and equivalence trials’
- ‘They disregard patients’ interests in favour of commercial ones.’
- ‘It is unethical to leave to chance whether patients receive a treatment that is anticipated to provide no extra benefit’

Issues

- Is it all about commercial interest?
- What happens when we have to withdraw treatments?
- Is it OK if you set out to prove superiority but have to settle for non-inferiority?
- If no margin is ignorable what happens if the difference is in favour of the new treatment?
- Does it matter how serious the disease is?
- Is there any future for meta-analysis?

1. Commercial Interests?

Background

Patients with neutropenia and persistent fever are often treated empirically with amphotericin B or liposomal amphotericin B to prevent invasive fungal infections. Antifungal triazoles offer a potentially safer and effective alternative.

Methods

In a randomized, international, multicenter trial, we compared voriconazole, a new second-generation triazole, with liposomal amphotericin B for empirical antifungal therapy.

Results

A total of 837 patients (415 assigned to voriconazole and 422 to liposomal amphotericin B) were evaluated for success of treatment. The overall success rates were 26.0 percent with voriconazole and 30.6 percent with liposomal amphotericin B (95 percent confidence interval for the difference, -10.6 to 1.6 percentage points);

Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med.* 2002;346(4):225-234.

To the Editor:

On October 4, 2001, the Antiviral Drugs Advisory Committee of the Food and Drug Administration (FDA) discussed the results of the clinical trial reported by Walsh and colleagues in this issue of the *Journal*. The authors present the unstratified analysis in their report. The plan for the primary analysis of this trial was defined prospectively as the evaluation of the overall stratified rate of response in terms of a five-part composite end point. The stratified analysis is the appropriate primary analysis, since patients were stratified at randomization according to their degree of risk of fungal infection and their receipt or nonreceipt of antifungal prophylaxis. The planned analysis also included stratification according to the duration of neutropenia before randomization.

Powers JH, Dixon CA, Goldberger MJ. Voriconazole versus liposomal amphotericin B in patients with neutropenia and persistent fever. *N Engl J Med*. 2002;346(4):289-290.

To Summarize the Story

- Pfizer planned a non-inferiority study
- The trial failed
- Pfizer and the FDA agreed that it failed
- The academic authors changed the analysis and presented a conclusion that disagreed with the one that had been agreed with the FDA
- The FDA publishes a letter in the same issue of the New England Journal saying ‘don’t believe this paper’

The difference between the Cochrane Collaboration and me

The CC is always very concerned that you may have missed some of the evidence.

I am more concerned that you will have found some evidence that isn't there

In fact

- It is difficult to work out whether banning equivalence studies would be for or against commercial interests of pharmaceutical companies
- Harder to register, yes
- But you are safer from competition?

An example of what will be banned?

Delchier JC, Isal JP, Eriksson S, Soule JC. Double blind multicentre comparison of omeprazole 20 mg once daily versus ranitidine 150 mg twice daily in the treatment of cimetidine or ranitidine resistant duodenal ulcers. *Gut*. Sep 1989;30(9):1173-1178.

The purpose of the present study was to compare omeprazole 20 mg once daily and ranitidine 150 mg twice daily in healing duodenal ulcers unhealed by previous treatment with cimetidine greater than or equal to 0.8 g or ranitidine greater than or equal to 0.3 g daily for at least six weeks. In a double blind multicentre trial, 151 patients were randomly assigned to either omeprazole or ranitidine. Clinical assessments and endoscopies were carried out at two and four weeks. On an 'intent-to-treat' analysis (n = 151), healing was: omeprazole 46.6%, ranitidine 43.3% at day 15 and omeprazole 70.7%, ranitidine 68.4% at day 29; and among the patients who completed treatment, healing was: omeprazole 48.3%, ranitidine 46.3% at day 15 (n = 125; 95% confidence interval of the difference--17 to 21) and omeprazole 79.6%, ranitidine 75.4% at day 29 (n = 115; 95% confidence interval of the difference--13 to 21).

2. Having to withdraw Treatments

FDA Urges Early Switch to HFA-Propelled Albuterol Inhalers

Publish date: Jun 5, 2008

By: Erik Greb

Rockville, MD (May 30)—The US Food and Drug Administration advised patients, caregivers, and healthcare professionals to switch to hydrofluoroalkane (HFA)-propelled albuterol inhalers now because chlorofluorocarbon (CFC)-propelled inhalers will not be available in the US after Dec. 31, 2008. CFC-propelled albuterol inhalers are being phased out because they harm the environment by depleting the ozone layer.

FDA has approved three HFA-propelled albuterol inhalers: “Proair” HFA inhalation aerosol from Ivax (Miami, FL), “Proventil” HFA inhalation aerosol from Schering-Plough (Kenilworth, NJ), and “Ventolin” HFA inhalation aerosol from GlaxoSmithKline (London). The agency also approved Sepracor’s (Marlborough, MA) “Xopenex,” an HFA-propelled inhaler containing levalbuterol, a medicine similar to albuterol.

How was this switch achieved?

With studies like this one:

1. Lumry W, Noveck R, Weinstein S, et al. Switching from Ventolin CFC to Ventolin HFA is well tolerated and effective in patients with asthma. *Ann Allergy Asthma Immunol*. Mar 2001;86(3):297-303.

‘Both Ventolin groups had comparable pulmonary function at every visit. Predose FEV1 values were maintained or improved over time with all treatments.’

Meta-analysis

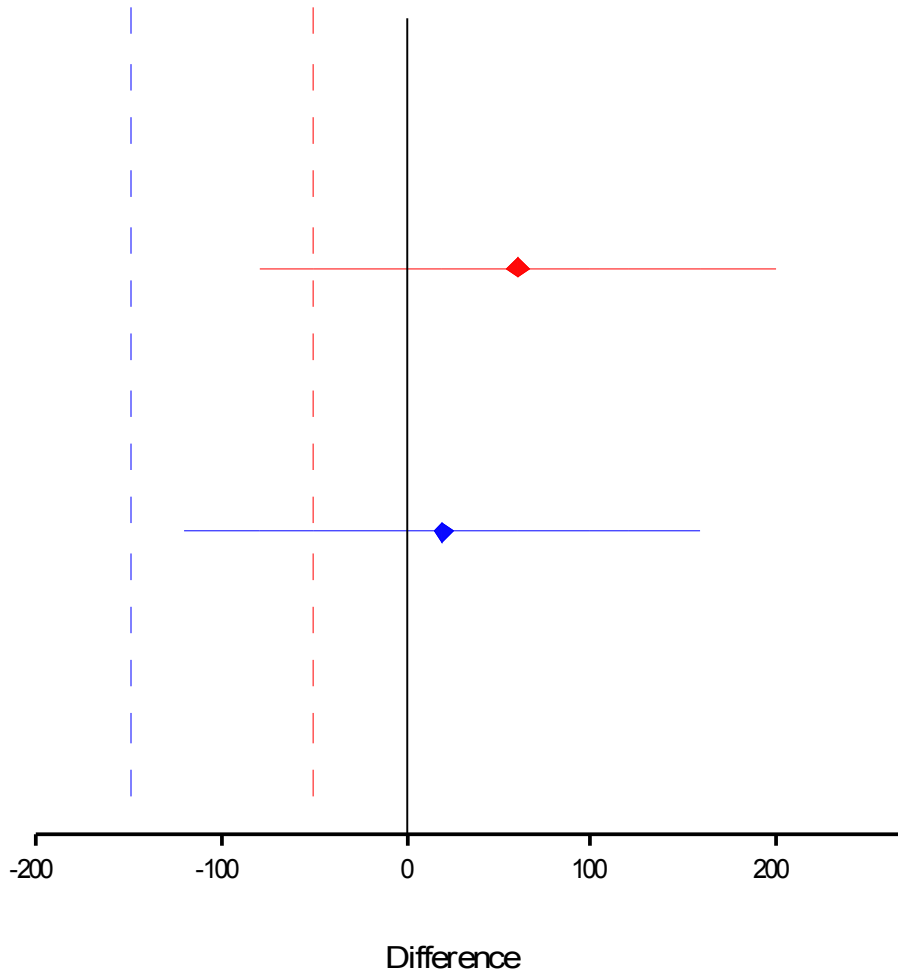
A technique for adding apples and pears together to produce turkeys.

Guernsey McPearson

3. Superiority and inferiority

- Some maintain that non-inferiority margins have to be pre-specified in order to claim equivalence
- This is nonsense and has no basis in statistical theory
- Bauer and Kiesser (1996) provide a formal proof

Two Trials of Non-inferiority

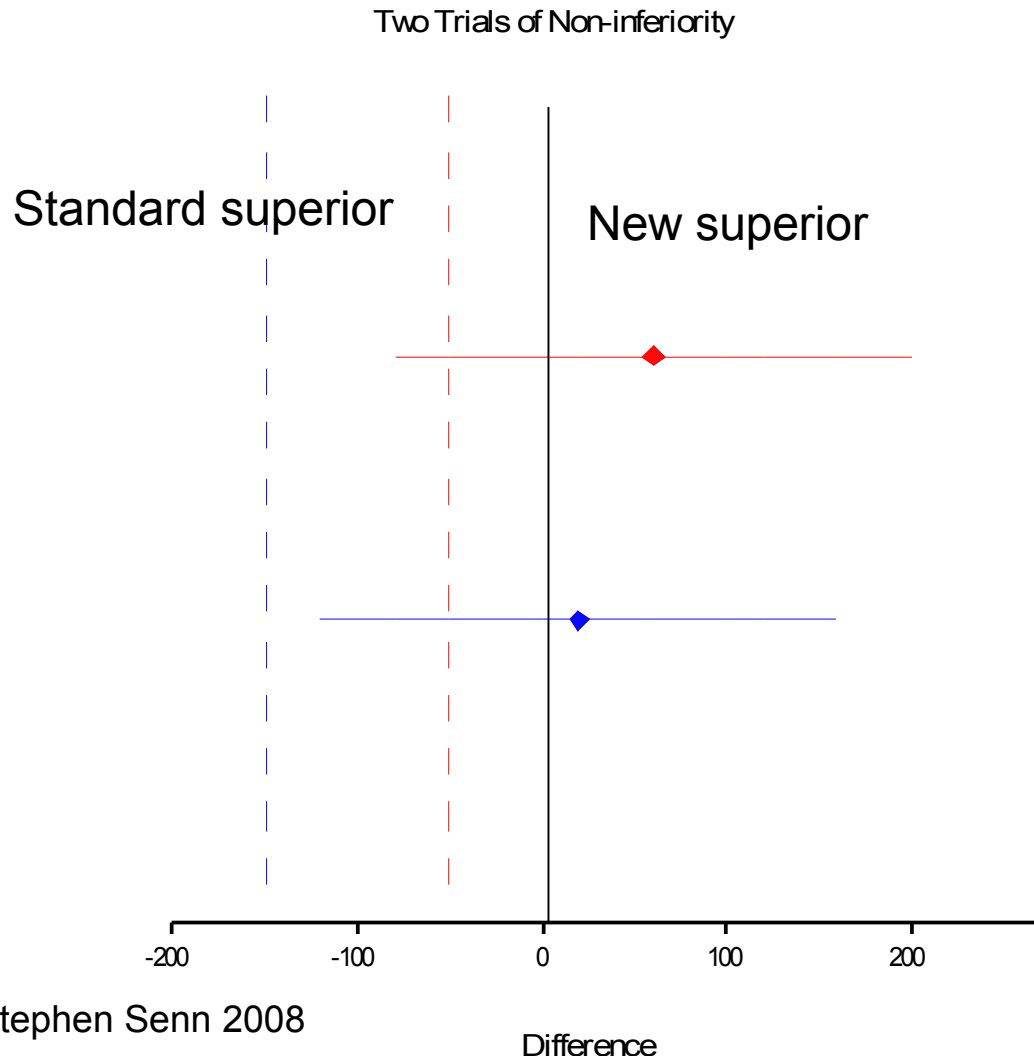


“In planning a trial it will be necessary for the sponsor to anticipate what most consumers would accept but mere pre-specification cannot pre-empt this decision. Otherwise we would have the absurdity of sponsor A (say) being able to claim efficacy because the pre-specified margin of non-inferiority in a trial in asthma was 150 ml of forced expiratory volume in one second and the lower confidence interval was at 120 ml but sponsor B not being able to do so because the margin specified was 50 ml, despite the fact that the lower confidence limit was at 80 ml.”
Biometrical Journal, 2005

Supposing I set out to prove superiority?

- Is failure unethical?
- If so how sure do I have to be before I start a trial that the new product will be superior?
 - 100%
 - why a trial at all?
 - 50% but then non-inferiority is logical
 - Some other figure?

4. No Margin Ignorable?



For both trials the new treatment is not proven superior to the standard

But the standard is not proven superior to the new treatment

And the point estimate is actually in favour of the new

So does the standard have to be abandoned?

Meta-Analyst

One who thinks that if manure is piled high enough it will smell like roses.

Guernsey McPearson

5. Does it matter how serious the disease is?

- Making it personal
- I have hayfever and would welcome alternative equally effective treatments with fewer side-effects
- In addition I tend to develop tachyphilaxis to existing treatments
- Does Dr Garratini have the right to tell me I can't participate in non-inferiority trials?

6. Is meta-analysis doomed?

- The trials we run will have to
 - Either lead to a proof of significant benefit of the new treatment
 - Or lead to the new treatment being abandoned for ever
- There will be no room for exploring degrees of equivalence
- And no need for meta-analysis

Cochrane Collaboration 1993-2008 R.I.P

So, to sum it all up, what is a meta-analysis?

Sayings of Confucius

My Point of View

- Non-inferiority trials are ethically acceptable provided
 - The condition is not life-threatening
 - Acid test might the patient be someone who could eventually benefit from the research
 - We practice true informed consent
 - There is some conceivable benefit
 - Choice
 - Side-effects
 - Formulation
- However, where these conditions are not fulfilled it is nearly always active control trials that are unethical
- Only placebo controlled trials are ethical when the disease is serious

Some Pious Nonsense

"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies *where no proven prophylactic, diagnostic or therapeutic method exists.*" (My italics.)

Declaration of Helsinki, Edinburgh Revision, 2000

A False Justification for Non-Inferiority Trials

- Typical piece of nonsense is that giving placebo implies withholding effective care
- A placebo is specific to an experimental treatments
- The issue as to what treatment is given in addition is logically independent

Alternative View

We start with standard care: the patient's entitlement.

From this position for any treatment arm for we have four possibilities

Maintenance M

Elimination E (always partial)

Augmentation A

Substitution S (always partial) $S = E + A$

Ethicist

The person you would eat first
in an Andes plane crash

Guernsey McPearson

Some Placebo-Controlled AIDS Trials

Trial	Year	Arms	Treatments
Protocol 241	1996	2	<ul style="list-style-type: none"> 1. zidovudine + didanosine + nevirapine 2. zidovudine + didanosine + nevirapine placebo
INCAS	1997	3	<ul style="list-style-type: none"> 1. zidovudine + nevirapine + didanosine placebo 2. zidovudine + didanosine + nevirapine placebo 3. zidovudine plus didanosine plus nevirapine
PENTA-ε	1998	2	<ul style="list-style-type: none"> 1. NRTI + 3TC 2. NRTI + 3TC placebo
Florida, M. et al	1999	2	<ul style="list-style-type: none"> 1. zidovudine + ddI + nevirapine 2. zidovudine + ddI + nevirapine placebo
Been-Tiktak et al	1999	4	<ul style="list-style-type: none"> 1. zidovudine + delavirdine low dose 2. zidovudine + delavirdine medium dose 3. zidovudine + delavirdine high dose 4. zidovudine + delavirdine placebo
CAESAR	1999	2	<ul style="list-style-type: none"> 1. zidovudine + lamivudine 2. zidovudine + lamivudine placebo
AVANTI 1	1999	2	<ul style="list-style-type: none"> 1. zidovudine + lamivudine + zalcitabine 2. zidovudine + lamivudine + zalcitabine placebo

To Sum Up

- We must measure the ethical scope for a clinical trial by a practical yardstick
- What is the patient entitled to if they do not enter the trial?
- How will entry to the trial affect that entitlement?
- What practical benefits to society can the trial bring?
- Have we truly practiced informed consent?