Society for Clinical Trials 32nd Annual Meeting

Workshop P3
Overview of Non-Inferiority Study Designs

Sunday, May 15, 2011
8:00 AM - 12:00 PM
Plaza C

Non-Inferiority Trials

Society for Clinical Trials
Vancouver, May 15th 2011

Presenters:
Simon Day, PhD
Nicole C. Close, PhD

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Program

8:00	An overview of equivalence and non-inferiority	SD
8:30	Choice of comparator and constancy of effects	NC
9:00	Assay sensitivity and data quality	SD
9:30	Choice of margins (choice of 'delta')	NC
10:00	*Break*	
10:15	Intention-to-treat and per protocol populations	NC
10:45	Switching between non-inferiority and superiority	SD
11:15	Reporting equivalence and non-inferiority trials	SD
11:45	Wrap up and general questions	SD/NC
12:00	*Conclude*	

An Overview of Equivalence and Non-inferiority

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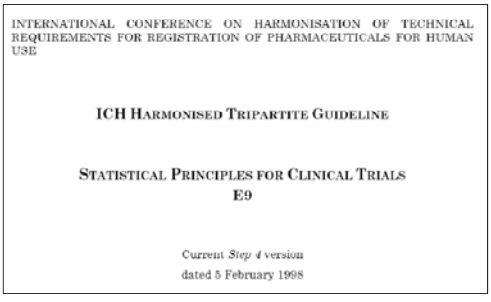
An Overview of Equivalence and Non-inferiority

- Traditionally trials have been intended to show one 'treatment' is better than another
  - Treatment is *better* than placebo
  - New treatment is *better* than old treatment
  - New treatment cures *faster* than old treatment

What Does 'Non-inferior' Mean?

- It does *not* mean 'no worse'
- It *does* mean 'worse but…'



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
E9

Current *Step 4* version
dated 5 February 1998

Statistical Principles for Clinical Trials (E9)

- **Equivalence Trial**
  A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences.
- **Non-Inferiority Trial**
  A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent (active or placebo control).

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

CHOICE OF CONTROL GROUP AND RELATED ISSUES IN CLINICAL TRIALS
E10

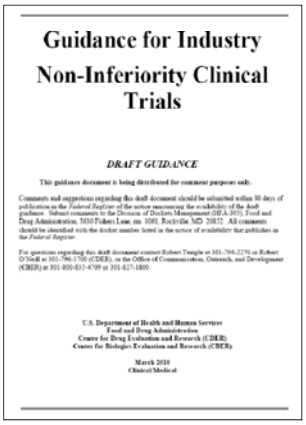
European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 27 July 2005
Doc. Ref. EMEA/CPMP/EWP/2158/99

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN

DRAFT AGREED BY THE EFFICACY WORKING PARTY	December 1999 – January 2004
ADOPTION BY COMMITTEE FOR RELEASE FOR CONSULTATION	February 2004
END OF CONSULTATION (DEADLINE FOR COMMENTS)	May 2004
AGREED BY WORKING PARTY	June 2004
ADOPTION BY COMMITTEE	July 2005
DATE FOR COMING INTO EFFECT	January 2006



Guidance for Industry

Non-Inferiority Clinical Trials

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Robert Temple at 301-796-2270 or Robert O'Neill at 301-796-1700 (CDER), or the Office of Communication, Outreach, and Development (CBER) at 301-800-833-4709 or 301-827-1800.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2010
Clinical/Medical

What Does 'Non-inferior' Mean?

- It does *not* mean 'no worse'
- It *does* mean 'worse but…'
- So why would we be interested in new treatments that are worse than existing ones?

Why Might 'Worse but…' be Acceptable?

- We all know 'statistical significance' does not imply 'clinical significance', or 'clinical relevance'
  - This is a common criticism of statistics and statisticians (although wrongly so, in my opinion!)
- So if we can define an amount of efficacy that is of no clinical relevance, can we accept 'losing' that amount of efficacy?

The 'Clinical Relevance' Argument

- What extra isn't worth having (is of 'no clinical relevance') may not be the same as what's acceptable to lose
- If there's no point in developing product *x* if it only gives a tiny extra benefit… why would we develop product *x* if it loses any benefit?

Why Might 'Worse but…' be Acceptable?

- Worse but…
  - Cheaper
  - Easier to use
  - Easier to store
  - Provides an alternative choice
  - Provides market competition
    (is this a good reason?)

Is it Only 'Worse but…'?

- Perhaps 2 distinct uses of non-inferiority
  - Show that one treatment is 'worse but not by any clinically important amount'
  - Show that a new treatment 'works' (i.e. it is better than placebo) but without using a placebo comparison
    this is called a 'putative placebo', or 'imputed placebo'

Putative Placebo
Imputed Placebo

- When a treatment already exists, perhaps for a serious condition, where use of 'true' placebo would not be acceptable
- This has impact for choosing the acceptable margin for 'loss of efficacy'

Choice of Margin
(much more in lecture 4)

- 'Worse, but not by much'
  - Margin will need to be quite small and genuinely 'of no clinical relevance'
- 'Better than placebo'
  - Margin could be quite large
  - There might be a clinically relevant loss of efficacy
  - But we can be confident of being better than placebo

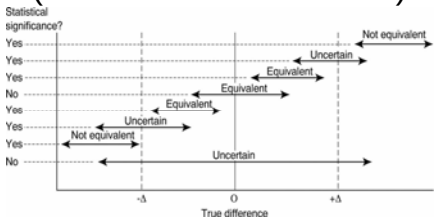
Equivalent or Non-inferior?

- These terms often get used interchangeably
- Equivalent
  - Effect must be within a given margin (plus or minus)
    (the 'plus' margin need not be the same size as the 'minus' margin)
- We would always be concerned about a loss of efficacy, but usually pleased about a gain

Equivalent or Non-inferior?

- Non-inferior
  - Not worse, but could be better
- We would often be concerned about a *loss* of efficacy with a new treatment, but if a trial showed better efficacy (even if unexpected) that would not be a problem
- Even if we plan for non-inferiority, a claim of superiority (if supported by the data) is usually acceptable (more in lecture 6)

A Variety of Trial Results (more in lectures 6 and 7)



Jones, B et al. *BMJ* 1996;**313**:36-39

What if 'No Loss of Efficacy' is Acceptable?

- Perhaps in life threatening conditions, no loss of efficacy would be acceptable
  - What are the consequences of this?
  - Can we define delta (the non-inferiority margin) as: '*x* extra deaths per 1000 patients'?

No Loss of Efficacy

- Disallowing any amount of non-inferiority is not in the interest of public health:
- Example:
  - assume delta is set at zero (i.e. non-inferiority not acceptable)
  - results: reference 1.0% event rate
    test 1.1% event rate
    95% CI (–0.4%, 0.2%)

No Loss of Efficacy

- Example:
  - assume delta is set at zero (i.e. non-inferiority not acceptable)
  - results: reference 1.0% event rate
    test 1.1% event rate
    95% CI (–0.4%, 0.2%)
  - conclude: test is 0.1% worse than reference
    DO NOT USE TEST *PRODUCT*

No Loss of Efficacy

- Example:
  - assume delta is set at zero (i.e. non-inferiority not acceptable)
  - results: reference 1.0% event rate
    test 1.1% event rate
    95% CI (–0.4%, 0.2%)
  - conclude: test *might be* 0.4% worse than reference
    DO NOT USE TEST *PRODUCT*

No Loss of Efficacy

- Example:
  - assume delta is set at zero (i.e. non-inferiority not acceptable)
  - results: reference 1.0% event rate
    test 1.1% event rate
    95% CI (–0.4%, 0.2%)
  - conclude: reference *might be* 0.2% worse than test
    DO NOT USE REFERENCE *PRODUCT*

Choice of Comparator and Constancy of Effects

Ethical Basic Premise

- No patient is denied a known effective treatment by entering a clinical trial.
- The degree of scientific rigor adopted in the evaluation of a new treatment is sufficient to prevent an ineffective, unsafe, or inferior treatment from obtaining regulatory approval or widespread use.
  - S. Pocock, 2003

Types of Controls

- ICH E10 Guidance reviews the selection of appropriate controls in clinical trials with advantages and disadvantages.
- Five types of controls:
  - Placebo
  - No treatment
  - Dose-response
  - Active
  - Historical

Comparator

- Need for a comparison in clinical trials is universally accepted.
  - Active control
- Use of an Active Control in a NI Trial
  - May be conducted even when the Sponsor thinks active control's efficacy can not be surpassed
    - Examples: safety advantages, subject adherence

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Comparator

- An established demonstrated efficacious treatment.
- Review of the Comparator also for:
  - Side effects profile
  - Cost
  - Invasiveness of procedure
  - Patient acceptability

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Ambiguous Cases

- Examples:
  - Well established active control does not exist
  - Good historical data of placebo-controlled trials for the active treatment do not exist
  - Historical data are not relevant for today

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Considerations

- Supportive evidence of efficacy with pre-existing active treatment
- Weak evidence of efficacy with pre-existing active treatment
- Prevention of type 1 error (accept "useless" treatment) and type 2 (failure to use an effective active comparator) error rates

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Comparator

- Give the comparator the best chance of success:
  - Under the same conditions which it was shown to be efficacious and in a similar population.

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Constancy Assumption

- Treatment effect from historical data is "constant" through time
  - Ex. Subjects in pre-antibiotic era more likely to be bacteremic and the outcome measure was mortality
- Statistical theory indicates that choosing a large x% protects you from violations in the constancy assumption

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Constancy Assumption

- Regulatory Concern: ineffective drug will make it to market.
- As effective as in the past-historically.
- Type 1 error rates hold if constancy assumption holds
- What to do if it does not hold?

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Major Issue?

- Rapid changes in medical practice and standard of care, so constancy assumption may be issue.
- At times, this can put an end to a discussion for a formal determination of the non-inferiority margin.

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Assay Sensitivity and Data Quality

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A Key Reference

- ICH Harmonised Tripartite Guideline Choice of Control Group and Related Issues in Clinical Trials (ICH E10)
- July 2000

‘External Validity’ of Trials

- Think about a double-blind, randomised clinical trial to compare two treatments
- The intention is to show one treatment (‘my’ treatment) is *better* than another (better than ‘your’ treatment)
- How might the trial be compromised? What could go wrong?

‘External Validity’ of Trials

- Think about a double-blind, randomised clinical trial to compare two treatments
- The intention is to show one treatment (‘my’ treatment) *is the same as* another (same as ‘your’ treatment)
- How might the trial be compromised? What could go wrong?

‘External Validity’ of Trials

Subject	Treatment	Outcome
1	?	7.2
2	?	7.7
3	?	8.0
4	?	8.1
5	?	8.3
6	?	8.4
7	?	8.4
8	?	8.5
9	?	8.6
10	?	8.7
11	?	9.1
12	?	9.1
etc.	*etc.*	*etc.*

What Helps/Hinders Detecting Treatment Differences?

- A large (mean) difference
- Small variability
  - Biological variation
  - Measurement error
  - Procedural error
  - Carelessness / poor work practices

So What is 'Assay Sensitivity'?

- It's the ability of a trial to show a treatment difference, *if there is one*
- Hard to think about
  - We're in a situation where we are thinking about treatments that may *not* differ

'Assay Sensitivity' ICH E10

'1.5 Assay sensitivity is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment.'

- Assay sensitivity is about *trials*
- Assay sensitivity is **not** about *treatments*

Good and Bad Assay Sensitivity

- Blinded assessments of objective endpoints, precisely measured
- Any open label study is prone to loss of assay sensitivity
- 'Soft' (or 'subjective') endpoints are particularly prone
- Quality of life scores (especially in open label studies)

More from ICH E10

- ICH E10 (Choice of Control Group)
  '*Assay sensitivity* is a property of a clinical trial defined as the ability to distinguish an effective treatment from a less effective or ineffective treatment. Assay sensitivity is important in any trial but has different implications for trials intended to show differences between treatments (superiority trials) and trials intended to show non-inferiority…

More from ICH E10

- ICH E10 (Choice of Control Group)
  '…When two treatments within a trial are shown to have different efficacy (i.e., when one treatment is superior), that finding itself demonstrates that the trial had assay sensitivity. In contrast, a successful non-inferiority trial (i.e., one that has shown non-inferiority), or an unsuccessful superiority trial, generally does not contain such direct evidence of assay sensitivity.'

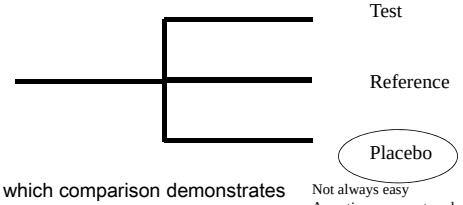
How Do We Demonstrate Assay Sensitivity?

- *BEFORE THE TRIAL*
  Historical evidence of the control treatment *consistently* showing benefit over placebo
  - A constant size of effect is not so important, but see later in next lecture
- *AFTER THE TRIAL*
  Good trial quality
  - Adherence by investigators to the protocol
  - Adherence by patients to the protocol (particularly dosing)

Assay Sensitivity: 4 steps

- Determining historical evidence of sensitivity to drug effects
  - Without this, non-inferiority is a non-starter
- Designing the trial
  - Should match conditions of historical trials
- Setting the margin
  - Clinically and statistically appropriate
- Conducting the trial
  - Should match conditions of historical trials

The Gold Standard



And which comparison demonstrates the assay sensitivity?

reference vs placebo
test vs placebo
test vs reference????

Not always easy
An active comparator already exists

Choice of Margins

ICH E-10: Choice of Control Group and Related Issues in Clinical Trials

- This guidance gives some basic information:
  - Determination of the margin in a non-inferiority trial is based on both statistical reasoning and clinical judgment, and should reflect uncertainties in the evidence on which the choice is based, and should be suitably conservative.

ICH E-10: Choice of Control Group and Related Issues in Clinical Trials (2)

  - This non-inferiority margin cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of a placebo-controlled trial.

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ADOPTION BY COMMITTEE	July 2005
DATE FOR COMING INTO EFFECT	January 2006

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Great!

- Clear as Mud on how to:
  - Define and set a non-inferiority margin
  - Analyze a non-inferiority trial

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Reminder

- Purpose:
  - Establish evidence for the efficacy of the treatment (required for drug approval)
  - Direct comparison of active comparator with treatment and historical information on the active comparator needed for assertion that treatment would have been more effective than placebo, if placebo would have been included
  - Treatment is not much less effective than active comparator by a non-inferiority margin

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Determination of NI Margin

- Three Issues and Considerations:
  - Address and/or demonstrate assay sensitivity and constancy assumption
  - Clinical relevance of margin
  - Putative placebo comparison

Test Hypotheses (1)

T represents value of the efficacy variable for the new treatment

C represents the value of the efficacy variable for the active comparator (control)

M represents the NI margin

Standard for NI trial:

H_0: C – T ≥ M (C is superior to T)

H_A: C – T < M (T is not inferior to C)

Test Hypotheses (2)

- The null hypothesis would generally be tested as a one-sided hypothesis with the 97.5% upper bound of the CI for C-T needing to be <M. If the upper bound is ≥M, all of the effect of the active comparator (C) could be lost and T might have no effect at all

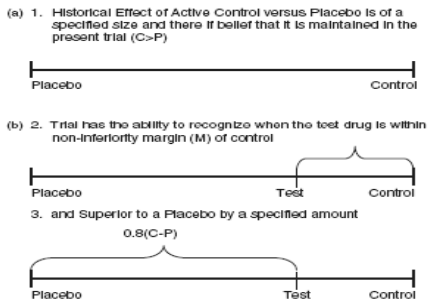
Margin Choice

- How much C can exceed T on the efficacy variable with T still being considered non-inferior to C (M>0)
- Should C and T be within a certain percentage of each other (clinical judgment/statistical discussion)

Treatment Effect

- Treatment effect generally based on placebo controlled studies of comparator
  - Ex. Summary of placebo controlled studies show that the outcome is 80% for comparator and 50% for placebo, treatment effect (M)=30%
  - Can use bound of CI to determine treatment effect as this takes into account variability of measurement

Considerations of Margin



Reference: Statistics in Medicine 2003; 22, 169-186

Also Consider

- Treatment retains at least some portion of the active comparator effect
- NI margin should preserve at least x% (*depends on therapeutic area*) of treatment effect
  - M_2=x% of M_1

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NI Margin Choice

The margin used in a trial, M, could be the entire effect of the control drug (M_1). Assuring that C-T is < M_1 will then show that the test drug is better than placebo. The M chosen could be smaller, however, M_2 (or Δ_2) if there were need to assure preservation of more than just any of the control drug effect, e.g., preservation of some fraction of the effect of the control drug. Choosing an M_2 smaller than the whole effect of the control may be important when the effect is clinically critical, e.g., mortality. M_2 might then be 50% or 25% of the entire effect of the control agent.

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M_1 and M_2 Confusion? (1)

- Some consider M_1 and M_2 separately.
  - Ok if M_1>>M_2 (e.g., many antibiotic treatments, treatment of acute leukemia) but not if M_2 is almost equal to M_1 (or larger).
  - Common in cancer trials to declare equivalence if survival inferiority of 20% was excluded. But the active control in many studies did not have a known effect as large as 20% more than no treatment (that's a 2 month survival advantage if the control is 10 months) so that successfully excluding a more than 20% difference could nonetheless represent loss of all effect or even harm. In many cases this approach was used even if no survival effect of the control was documented
- There is a certain logic to that approach regarding clinical value, but it cannot show effectiveness

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M_1 and M_2 Confusion? (2)

- The non-inferiority margin of interest in many trials of many anti-infectives is M_2. That is, there may be no doubt at all that an active agent can be distinguished from an inactive one every time, and the real interest is in assuring that a new agent is not inferior by too much.
- Examples:
  - Non-anti-infective (treatment of testicular cancer, Acute response to bronchodilators, Anesthetic agents, Thrombolytics) and Infectious disease (UTI, Meningitis)

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Choice of M_2 (1)

- How much effect needs to be retained in such situations?
- The very reason you can't do a placebo-controlled trial is a reason for assuring preservation of a good part of the active comparator drug effect. So for:

  50% thrombolytics
  75% adjuvant breast Ca

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Choice of M_2 (2)

- That is not all one hopes to retain, but sample sizes become rapidly unrealistic if greater retention is sought
- M_2/Δ_2 is discussed a lot for antibiotics

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Statistical Margin

- Clinically justified but if this can't be achieved….
- Development of a statistical margin
  - Derived from the control effect estimated using historical trial data via meta analysis.

How to Determine Margin

- What if no placebo controlled studies
- Define putative placebo effect based on historical data
  - 78% (78/100) in 1935 pre-penicillin (mortality)
  - 25.2% (25/99) in 1947 after introduction of penicillin (mortality)
  - treatment effect (pre-penicillin vs. penicillin)
  - 52.7% (95% CI: 38.9% to 63.6%)
  - NI=26.35% or 19.45%
- Are historical data relevant to studies today?
  - Different standard of care and subject population

Contributing Challenges

- Which historical trials should be selected?
- Improper handling of noncompliant subjects
- Missing data
- Analysis issues (more in next Lecture)

Intention-To-Treat and Per Protocol Populations

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Analysis Population Definitions

- Intention-to-Treat: subjects are analyzed according to the treatment to which they were assigned, regardless of whether they received the treatment or not
- Per-Protocol: includes all subjects who completed the full course of assigned treatment and had no major protocol violations

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Analysis Issues

- Superiority study
  - ITT analysis – analyze all subjects randomized to the assigned treatment assignment regardless of whether they received that assignment.
    - This is statistically conservative as it makes it more difficult to show a difference between groups (more likely to not see a difference)
- Non-inferiority study
  - ITT is too liberal.
  - ITT tends to bias towards making the two treatments look similar because those who do not take the complete treatment regimen are included in the analysis

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Per-Protocol Preferable?

- It would seem that a Per-Protocol analysis is preferable in a NI setting
- Opposition to the current thinking of ITT as the preferable analysis
- Per-Protocol analysis as preferable and the impact on randomization
- Per-Protocol is subjective in definition

FDA Regulatory Thinking

- Currently: Study objective needs to be answered by conducting both the ITT and Per-Protocol (PP) analysis, especially in the NI trial
- CPMP* 2000: "…similar conclusions from both the Intent-To-Treat and Per-Protocol are required in a non-inferiority trial."

* Committee on Proprietary Medical Products Points-to-Consider

Sample Size

- When both ITT and PP are conducted, plan for appropriate sample size.
- PP will have fewer subjects in the analysis, so that sample size calculations ensure sufficient numbers in the PP population and then increased for the ITT population

Reference: Jones et al.,British Medical Journal, 1996.

Trial Issues (1)

- Bias in outcome assessment – assign every subject a success
  - In superiority study – biases toward null (no difference between treatment groups)
  - In non-inferiority study - bias toward alternative (towards non-inferiority)
- Non-compliance and drop outs
  - Biases study towards alternative (towards non-inferiority)

Trial Issues (2)

- Severity of subjects enrolled
  - Do subjects have the disease under study and can they benefit from treatment under study
    - Will be a success and bias study towards alternative (towards non-inferiority)

Trial Issues (3)

- Use of concomitant medication that interferes with treatments or that reduces extent of potential response
  - If an effective antibiotic, subject will be a success and bias study towards alternative (towards non-inferiority)
- Missing data: can the same methods for imputation, etc be used in NI as in superiority trials (LOCF conservative in NI?)

Switching Inference Between Non-inferiority and Superiority

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Equivalent or Non-inferior?

- Equivalent
  - Effect must be *within* a given margin (plus or minus)
    (the 'plus' margin need not be the same size as the 'minus' margin)
- We would always be concerned about a *loss* of efficacy, but usually pleased about a *gain*

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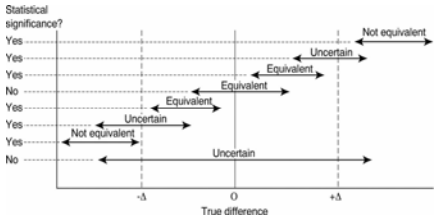
Possible Trial Results



Jones, B et al. *BMJ* 1996;**313**:36-39

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‘The’ Reference

- Committee for Proprietary Medicinal Products (CPMP)
  ‘Points to Consider on Switching Between Superiority and Non-Inferiority.’
  EMEA, London, 2000
- http://www.emea.europa.eu/pdfs/human/ewp/048299en.pdf

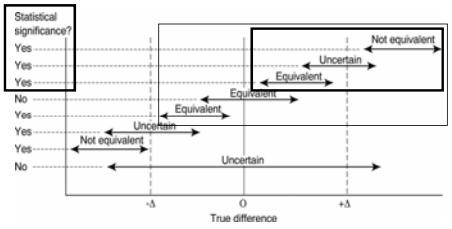
Overview of the Guidance

- II. Trial Objectives
  - II.1 superiority
  - II.2 equivalence
  - II.3 non-inferiority
- III. Relevance of pre-definition
- IV. Switching the objective of the comparison
  - IV.1 interpreting non-inferiority as superiority
  - IV.2 interpreting superiority as non-inferiority
- V. Changing the equivalence margins

Interpreting Non-inferiority as Superiority

‘If the 95% confidence interval for the treatment effect lies entirely above $-\Delta$ but also above zero then there is evidence of superiority in terms of statistical significance at the 5% level ($p<0.05$).
It is acceptable to calculate the *p*-value associated with a test of superiority and to evaluate whether this is sufficiently small to reject convincingly the hypothesis of no difference.
Usually this demonstration of a benefit is sufficient on its own…’

Switching to Superiority



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What About 'Clinical Relevance'?

'Usually this demonstration of a benefit is sufficient on its own…'

'Usually This Demonstration…'

'…provided the safety profiles of the new agent and the comparator are similar. When there is an increase in adverse events, however, it is important to estimate the size of the effect to evaluate whether it is sufficient in clinical terms to outweigh the adverse effects.'

IV.1.3 Size of Additional Clinical Benefit

'Since the comparator in a non-inferiority trial must be an effective agent, any superiority to that agent should carry the implication of acceptable superiority to no treatment (placebo). For this reason the size of the additional clinical benefit demonstrated is not likely to be relevant to a claim of efficacy except in relation to any increase in adverse effects and hence relative risk/benefit.'

Switching to Non-inferiority

- What was the comparator, and at what dose?
  - Think about the comparator being a placebo
  - A claim of superiority would be meaningful but a claim of non-inferiority would not

Switching to Non-inferiority

- Trial quality
  - Deviations from intended inclusion criteria, dosing schedules, poor measurements methods, etc., tend to reduce the sensitivity of a trial
  - Conclusions of 'no difference' are more likely with poor quality
  - If the trial's quality is 'adequate' to justify non-inferiority, then it must be good enough to justify 'superiority'

Switching to Non-inferiority

- What is the acceptable margin of non-inferiority, and when was it decided?
- It seems odd (and it's almost unseen) to specify a non-inferiority margin in a trial that aims to show superiority
- Pre-specification avoids accusations of bias
- *Post hoc* specification, after a trial has failed to show superiority is not usually acceptable

Think Strategically…

- If necessary, *plan* for non-inferiority
- Then, if the *data* warrant it, you can 'upgrade' to superiority
- Don't plan the other way round (usually!)

Reporting Equivalence and Non-inferiority trials

Empiristat

Useful references

- Le Henanffe B, Giraudeau B, Baron G, Ravaud P. Quality of reporting of equivalence and noninferiority randomized trials. *Journal of the American Medical Association* 2006; **295**:1147–1151.
- Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJW. Reporting of noninferiority and equivalence randomized trials. *Journal of the American Medical Association* 2006; **295**:1152–1160.

Building on the CONSORT Statement

- CONSORT – Consolidation of the Standards of Reporting Trials
- *Not* how to do trials
- *Not* how to write study protocols
- How to *report* trials (the good bits and the not so good bits)

What you can't say…

- 'Treatment *x* was shown to be non-inferior to treatment *y*'
- It's like saying:
  'Treatment *x* is better than treatment *y*, *P*<0.05'
  - Comment 1: by how much?
  - Comment 2: what was the criterion (the margin)?

A checklist (Piaggio *et al.*, 2006)

- Title and abstract
- Introduction
  - *why* a non-inferiority (or equivalence) study?

Methods (1)

- Participants
  - Eligibility criteria. Are participants similar to those who would be recruited into a superiority trial? Why?
- Interventions
  - Details of treatments. Is the control treatment identical to that used in other trials (to define the delta margin)?
- Objectives
  - Precise definition. Is it non-inferiority, or equivalence?

Methods (2)

- Outcomes
  - Primary and secondary. Are they the same outcomes as used in superiority trials?
- Sample size
  - How was it calculated? Assuming non-inferiority or equivalence? What was the margin? Any interim analyses?

Methods (3)

- Randomization
  - How was it generated (blocking, stratification?)
  - Implementation – who generated sequence, who recruited patients, who distributed medication???
- Blinding
  - Single? Double? Exactly who, when
- Statistical methods
  - 1 or 2 sided tests? Patient populations (ITT and per protocol)

Results (1)

- Participant flow
  - The 'CONSORT' diagram
- Recruitment
  - Dates. 1st in, last out, etc.
- Baseline data
  - Demographics, disease state
  - Comparability between groups

Results (2)

- Number analysed
  - ITT, per protocol, safety
  - Give results in absolute numbers if possible (not just relative risks, odds ratios, etc.)
- Outcomes
  - Estimates of treatment effect, confidence intervals
  - Graph with point estimate, 95% confidence interval, non-inferiority margin

Results (3)

- Ancillary analyses
  - Subgroups, multiplicity issues, etc.
- Adverse events
  - Describe and discuss all important AEs

Comment

- Interpretation
  - How do results compare with pre-specified margin? Sources of uncertainty (e.g. missing data), sources of bias and imprecision, etc.
- Generalizability
  - External validity, assay sensitivity, etc.
- Overall summary of the evidence
  - Trial results in context with what is already known

Program

8:00	An overview of equivalence and non-inferiority	SD
8:30	Choice of comparator and constancy of effects	NC
9:00	Assay sensitivity and data quality	SD
9:30	Choice of margins (choice of 'delta')	NC
10:00	*Break*	
10:15	Intention-to-treat and per protocol populations	NC
10:45	Switching between non-inferiority and superiority	SD
11:15	Reporting equivalence and non-inferiority trials	SD
11:45	Wrap up and general questions	SD/NC
12:00	*Conclude*	

Non-Inferiority Trials

Society for Clinical Trials
Vancouver, May 15th 2011

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