

*A Henry Stewart 2001 One-day Briefing*

# Coping with the Conflicting Requirements for Control

## *The Impact of ICH E10, the NICE Guidelines and the Revised Helsinki Declaration*

- The current regulatory requirements
- Problems with the revised Helsinki Guidelines
  - The placebo issue
  - What to do

Drug regulatory agencies dislike active-controlled studies and mistrust them. They prefer placebos. However, the revision of the **Declaration of Helsinki** (Edinburgh 2000) is making it very difficult to use placebos. Then again health care reimbursors like to see head to head comparisons with the current market leader.

The **ICH-E10 guideline** on the choice of control group in clinical trials was a long awaited document. The concept paper gave reason to hope that it would give clear and harmonised guidance to an area which has been the subject of much dispute, including the difficult issue of the role of placebo control. Most industry experts thought the final guideline though long in coming, was disappointing in content.

On another tack, **The National Institute for Clinical Excellence** (NICE) has now adopted a set of evidence based criteria for deciding what the NHS should and should not fund.

### Where does all this leave the Sponsor?

*The expert panel of speakers will examine:*

- Choice of control group - the regulators' view
- The misunderstood placebo
- Choice of control group - the view from NICE
- The impact on regulations on the large simple trial
- The regulators' interpretation of Active Equivalence Trials - Choice of control in clinical trials - issues in and implications of ICH E10 from an industry perspective
- Conflicting requirements: the impact of ICH E10, the NICE guidelines and the revised Helsinki Declaration
- Ethics of Clinical Trials
- Statistical methods for comparison with placebo in active-control trials

**Essential for all clinical trial and project managers, biostatisticians, biometricians, research scientists, clinical data managers, health economists and epidemiologists.**

Full documentation will be provided to all attendees and adequate time made available for questions.

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#### David Morgan

*Vice President of Data  
Management and  
Biostatistics*

Ingenix Pharmaceutical  
Services

&

*President of the European  
Federation of Statisticians in  
the Pharmaceutical Industry  
(EFSPi)*

### Speakers

#### David J. Brown

*Statistical Assessor*

Medicines Control Agency

#### Professor David Chadwick

*Department of Neurology  
University of Liverpool*

#### Dr Alastair Fischer

*Health Economist, Appraisals  
Team*

National Institute for Clinical  
Excellence (NICE)

#### Professor Richard Gray

*Director*

University of Birmingham  
Clinical Trials Unit

#### Dr Bernhard Huitfeldt

*Global Director of  
Biostatistics, Global Clinical  
Science*

*AstraZeneca, Sweden*

&

*Past President of the  
European Federation of  
Statisticians in the  
Pharmaceutical Industry  
(EFSPi)*

#### Professor John A. Lewis

*Consultant and Visiting*

*Professor at the University of  
Leicester.*

#### Professor Stephen Senn

*Department of Epidemiology  
and Public Health  
University College London*

#### Anne Whitehead

*Deputy Director, Medical and  
Pharmaceutical Statistics  
Research Unit*

The University of Reading

**Tuesday, 30 October 2001**  
**Radisson SAS Portman Hotel, London W1**



*A Henry Stewart 20*

# Coping with the Conflicting The Impact of ICH E10, the NICE Guidelines

PROGR

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**David Morgan**, *Vice President of Data Management and Biostatistics*, Ingenix Pharmaceutical Services

## Choice of Control Group: The Regulators' View

It is widely believed that regulators are responsible for excessive and inappropriate use of placebo controlled trials. The regulators have also attracted criticism for their requests for comparisons of new agents with active controls to evaluate comparative efficacy and safety. There are sound scientific reasons underlying these regulatory requirements. For example, the pressure to use placebo controls is strongest in those areas of medicine where comparisons with an active control alone are unreliable. Ethical considerations always define what studies are possible, but concerns about the use of placebo, as expressed in the Declaration of Helsinki, are overstated. Professor John A. Lewis, formerly of the Medicines Control Agency will discuss:

- The information sought by regulators from controlled trials
- Relevant CPMP and ICH guidelines
- The regulatory purposes of placebo and active controls
- International differences of opinion and legal framework
- The recent alarm caused by the revised Declaration of Helsinki

## Professor John A. Lewis

*Consultant and Visiting Professor at the University of Leicester*

## The Misunderstood Placebo

The recent Edinburgh revision of the Declaration of Helsinki betrays deep confusion about ethics and placebos. In this presentation, Professor Stephen Senn, Department of Epidemiology and Public Health at UCL will discuss an alternative view of placebos in clinical trials.

- Helsinki - null points
- The true purpose of placebos
- Equipose - point of departure or point of arrival?
- The myth of the two-party system
- Justice and clinical trials - a RAWLSIAN view
- Consenting adults

## Professor Stephen Senn

*Department of Epidemiology and Public Health University College London*

## NICE - The 4th Dimension

The National Institute for Clinical Excellence (NICE) takes a number of considerations into account in formulating its opinion on what technologies the NHS should fund. In this presentation, Dr Alastair Fischer, Health Economist with the Appraisals Team at NICE will give

examples from recent NICE appraisals to highlight some of the following issues:

- Guidelines laid down by the Secretary of State for Health and the National Assembly for Wales
- Clinical efficacy vs. clinical effectiveness
- Economic efficiency
- Economic and clinical efficiency compared
- Foregone opportunities
- Trade-offs between valid randomised controlled trials not comparing relevant alternatives, and modelling that is relevant but has questionable assumptions
- We are all Bayesians now, right?

## Dr Alastair Fischer

*Health Economist, Appraisals Team  
National Institute for Clinical Excellence (NICE)*

## The Impact of Regulations on the Large Simple Trial

Clinical Trials need to be large to realistically assess moderate treatment effects. To achieve large-scale recruitment at reasonable cost, trial procedures should not differ substantially from usual clinical practice. Professor Richard Gray, Director of the Clinical Trials Unit at the University of Birmingham will discuss the impact current regulations will have on a large simple trial.

- How simplification enhances statistical reliability by encouraging wider recruitment
- Eligibility - how it can be simplified through randomisation when clinicians are uncertain that new treatment provides worthwhile benefits
- Placebo controls are not excluded unless they replace an effective treatment that is already established as usual local practice
- Patients will be the victims if new regulations are over-interpreted as precluding scientifically well-designed, pragmatic, 'real life' trials

## Professor Richard Gray

*Director  
University of Birmingham Clinical Trials Unit*

## The Regulatory Interpretation of Active Equivalence Trials

As part of the process of drug registration an applicant may conduct an equivalence trial against an active comparator. Equivalence will be declared if the confidence interval for the difference between treatments excludes 'delta', a value chosen to represent a 'clinically unimportant difference'. If only it were as simple as it sounds...This presentation addresses some of the difficulties in the design, analysis and interpretation of equivalence trials, the most problematic issue being the choice of that magic number 'delta'.

## 01 One-day Briefing

# Requirements for Control. Ethics and the Revised Helsinki Declaration

### PROGRAMME

#### Chair

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- When to do an equivalence trial
- Design and analysis of equivalence trials
- Trials with an active comparator and placebo
- Choice of 'delta'
- Switching from equivalence to superiority (and *vice-versa*)
- The scientific aim of an equivalence trial: equivalence to the comparator or indirect superiority over placebo?
- How best to protect the patient – a double-edged sword

#### David J. Brown

Statistical Assessor

Medicines Control Agency

#### Choice of Control in Clinical Trials - Issues in and Implications of ICH-E10 from an Industry Perspective

The ICH-E10 guideline on the choice of control group in clinical trials did not succeed to provide harmonized guidance across regions and it is not specific enough on a number of issues leaving the drug development stakeholders uncertain about what needs to be done. The guideline does not acknowledge the gradual change of the clinical trial environment where placebo-controlled trials will be more and more difficult to conduct. This is driven by the existence of effective treatments in most therapeutic areas in combination with the new version of the Helsinki Declaration. Sooner or later efficacy for a new drug will need to be demonstrated using active-controlled non-inferiority studies for most indication areas. In order to meet this inevitable evolution, efforts must be spent to further develop the methodology for non-inferiority trials, and to ensure that published meta-analyses provide the necessary information to allow the design of high quality non-inferiority studies in the future. Dr Bernhard Huitfeldt, Global Director of Biostatistics with AstraZeneca will address some of the issues that the industry hoped would be clarified.

- The focus on individual studies rather than a whole clinical development program
- Choice of active control and the non-inferiority margin(d) in a non-inferiority trial
- Interpretation of "assay sensitivity"
- Bias in favour of placebo-control
- Failure of proposed alternative designs to resolve the unethical use of placebo

#### Dr Bernhard Huitfeldt

Global Director of Biostatistics, Global Clinical Science  
AstraZeneca, Sweden

&

Past President of the European Federation of  
Statisticians in the Pharmaceutical Industry (EFSPi)

#### Ethics of Clinical Trials

There are five major considerations of a clinical trial: Anticipation, Ethics, Inference, Organisation and Utmost faith. Ethics must form one of the cornerstones when conducting a clinical trial, but it is often overlooked. The key to a successful clinical trial is trying to balance the interests of patients against the longer term interest of obtaining reliable conclusions on sufficient data for making appropriate treatment policies for future patients. Professor David Chadwick, Department of Neurology at the University of Liverpool will discuss the ethical issues and challenges facing the clinician.

- The ethical requirements and the Helsinki Declaration
- The roles of the IRB and Ethical Committees
- Informed consent
- The protocol
- Ethical issues and future challenges

#### Professor David Chadwick

Department of Neurology

University of Liverpool

#### Statistical Methods for Comparison with Placebo in Active-control Trials

In this presentation, Anne Whitehead, Deputy Director of the Medical and Pharmaceutical Statistics Research Unit at the University of Reading, will discuss methods for designing and analysing non-inferiority trials in which the permissible non-inferiority margin has already been defined. The focus of the presentation will then be on novel methods for combining existing data from trials of the active control against placebo with new data from a trial of the new treatment against the active control. The acceptability criterion for the new treatment will be that it retain some given proportion of the effect of the active control

- Traditional approaches to testing for non-inferiority
- Determining the effect of the active control against placebo
- Setting the target effect for the new treatment against the active control
- Design issues for a trial of the new treatment against active control
- Use of meta-analysis techniques in the final analysis

#### Anne Whitehead

Deputy Director, Medical and Pharmaceutical Statistics  
Research Unit

The University of Reading

# REGISTRATION FORM N01564

## Coping with the Conflicting Requirements for Control

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