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 reimbursers 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.
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
- Equipoise - 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’.

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

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.

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.

Anne Whitehead
Deputy Director, Medical and Pharmaceutical Statistics Research Unit
The University of Reading
REGISTRATION FORM

Coping with the Conflicting Requirements for Control

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

To: The Registrar, Henry Stewart Conference Studies, Russell House, 28/30 Little Russell Street, London WC1A 2HN, UK.
Tel: +44 (0)20 7404 3040. Fax: +44 (0)20 7404 2081.

Please tick the following box(es) for the above conference:

[ ] £581.62 per person inclusive of VAT at 17.5% (Group Bookings at £523.46 per person inclusive of VAT at 17.5%)

BLOCK CAPITALS PLEASE

M/Hrs/Miss/Ms/Dr First Name Last Name

POSITION

Mr/Mrs/Miss/Ms/Dr First Name Last Name

Please tick appropriate box:

[ ] Cheque enclosed for £ ___________________ (made payable to Henry Stewart Conference Studies)
[ ] I am unable to attend this conference but please reserve me . . . . sets of conference documentation at £125.00 each including postage and packaging.

Valid from _____ / _____ Expiry date _____ / _____

Name of Cardholder

Signature of Cardholder

Please provide card billing address if different from the firm/organisation (if it is the same, please write "same"):

Address

Postcode

Country

Please charge £ ___________________ to my credit card

Card No:

Type of Firm/Organisation

Vegetarian lunch required: YES/NO (please circle). Other special dietary requirements, please give details:

Duplicated Mailings and Corrections:

If you are interested in:

[ ] Business Opportunities:
[ ] Advertising in the documentation pack
[ ] Sponsorship opportunities
[ ] Group delegate bookings at discounted rates

Other Information:

[ ] I am unable to attend this conference but please reserve me . . . . sets of conference documentation at £125.00 each including postage and packaging.

[ ] I am unable to attend this conference but please send me details of any forthcoming events in this field.

ON RECEIPT OF THIS REGISTRATION FORM PLUS PAYMENT AN ADMISSION CARD WILL BE FORWARDED TO EACH DELEGATE TOGETHER WITH A VAT INVOICE RECEIPT.

HENRY STEWART CONFERENCE STUDIES

Henry Stewart Conference Studies was established in 1978 and provides vocational education and training of the highest standard. Each year we organise over 200 conferences, training courses and workshops in the UK, Europe and North America in pharmaceuticals, leisure, property, medical devices, healthcare marketing, market research, direct marketing, communications management, pensions management, financial compliance and finance law.

For further information on Henry Stewart Publications and Journals please call +44 (0)20 7323 2916 or go to: www.henrystewart.co.uk