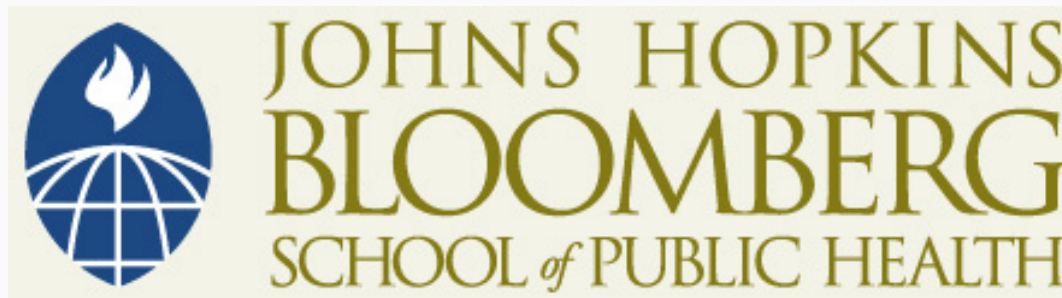


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JOHNS HOPKINS
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A Course Summary and Review

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History and Purpose of Regulation

- 1906: Food and Drugs Act
- 1962: Kefauver-Harris Amendments
- Early 1960s: Thalidamide
- 1968: UK Medicines Act
- 1990: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- “Promoting and protecting public health”

QuickTime™ and a
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are needed to see this picture.

Study Designs

- Types of design:
 - Parallel, cross-over, factorial, cluster
- Phases and purposes of trials
 - Control groups, chronic vs. acute, exploratory vs. confirmatory, etc.
- What are the objectives?

Objectives and Hypotheses

- Hierarchy of strength of evidence
- Phases of studies and different objectives

Study Population

- Eligibility criteria
 - Who is **included**; who is **excluded**
 - Feasibility, generalizability, enrichment designs
- From population down to study sample
- We must ask:
 - “To whom do the results apply?”

Study Designs

- Treatment allocation, blinding, and randomisation
- Stratification, blocking, clustering (adaptive methods)
- Open label, single-blind, double-blind
- Methods with problems
- Practical management problems

Control Groups

- “Adequate and well-controlled studies”
- Types of control:
 - Placebo, no treatment, active control (historical controls)
- ICH E10 (Choice of Control Group in Clinical Trials)

Placebos

- Reasons and justifications
- The “placebo effect”
- Placebo or “no treatment” control
- Ethics of placebo control

Outcomes and Endpoints

- Definitions
 - Endpoints are not the same as objectives
- What's in a "good" endpoint?
- Clinical endpoints, surrogate endpoints, objective endpoints, subjective endpoints . . .
- Primary, co-primary, composite endpoints

Surrogate Endpoints

- Why? What's the justification?
- Surrogates and biomarkers
- "Validation"
- Limitations
- Risks and benefits in public health
- Risks and benefits in licensing decisions

Analysis Issues

- Intention to treat
- What question are we asking?
- Who wants to know the answer?
 - And what question do they want answered?
- Dangers of not including all the subjects in the analysis (sub-group if compliers/non-compliers)
- Comment from various regulatory guidelines

Analysis Issues

- Subgroups and post-hoc analyses
- Dangers of multiple analyses
- Pre-specification of analysis plan
- “Post-hoc” analysis (“fishing expeditions”)
- Too many and too few(!) statistically significant differences

Missing Data

- Causes
- Relationship to reason for missing data
- Problems of bias
- Imputation methods
- Assumptions to make for analyses
- Prevention always better than cure

Multiplicity

- Sources:
 - Multiple treatment arms, controls, sub-groups
- Various approaches (“solutions”):
 - Bonferroni method, multivariate statistical methods
- “Lumping” and “splitting” approaches

Non-Inferiority

- ICH E9 and ICH E10 guidelines
- Meaning of “non-inferiority”
- Choice of control group
- Purposes of non-inferiority trials
- Problems of “bio-creep”
- Choice of non-inferiority margin

Multi-Regional Studies and Bridging Studies

- ICH E5
- Ethnic sensitivity
- Intrinsic and extrinsic factors
- Bridging studies to “fill a hole”
 - When are they needed?
- What to consider about the need and acceptability of bridging studies

Interim Monitoring

- Some history and regulatory status of data monitoring committees (DMCs)
- Food and Drug Administration (FDA) guidance
- Committee for Medicinal Products for Human Use (CHMP) guidance
- World Health Organization (WHO) guidance
- Who sits on a DMC and what do they do?

Operational Aspects of DMCs

- Statistical considerations
- Confidentiality of discussion and results
 - Closed session and open sessions
- Stand operating procedures
- Decision making and reporting
- DMC responsibilities
- Sponsor access to interim data
- Government vs. industry sponsored trials