1.1 Background and Purpose

- E9 is intended to give direction to sponsors in the design, conduct, analysis and evaluation of clinical trials in the context of overall clinical development.
- Topics covered

1.2 Scope and Direction

- Focus is on statistical principles
- A qualified statistician should be responsible
- Statistical plan should be defined in the protocol
- Adherence to the protocol plan contributes to the degree of confidence in the final results and conclusions
1.2 Scope and Direction, continued

- Protocol and amendments should be approved by a statistician
- Primary relevance is to later phase trials
- May apply to data integrated across trials
- Apply as far as possible to other trial types

1.2 Scope and Direction, continued

- Minimizing bias and maximizing precision is the key focus
- Bias: the systematic tendency of any factors associated with the design, conduct, analysis and interpretation of the results of clinical trials to make the estimate of a treatment effect deviate from its true value.

1.2 Scope and Direction, continued

- Sources of Bias
  - Design
  - Conduct
  - Analysis
- Evaluation of robustness: the sensitivity of the overall conclusions to various limitation of the data, assumptions and analytic approaches to data analysis.
1.2 Introduction: Scope and Direction, continued

- Frequentist methods vs. Bayesian methods

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Part II

CONSIDERATIONS FOR OVERALL CLINICAL DEVELOPMENT

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2.1.1 Overall Clinical Development

- The Development Plan
  - The goal is to find a dose range with adequate safety and efficacy in which the risk to benefit ratio is acceptable among particular subjects.
  - Should include a well-defined program of studies, each of which makes a contribution to meeting the goal.
2.1.1 Overall Clinical Development, continued

- The Development Plan
  - Synthesis of evidence is required for overall interpretation
  - Consistency is critical

2.1.2 Confirmatory Trial

- Adequately controlled
- Hypothesis stated in advance and evaluated
- Necessary to provide firm evidence of safety or efficacy
- An estimation of the size of the effects due to the treatment and its clinical significance is essential

2.1.2 Confirmatory Trial, continued

- Should strictly adhere to the protocol and Standard Operating Procedures
- Document and explain unavoidable changes
- Design should be justified in the protocol
- Address a limited number of questions in each trial
2.1.2 Confirmatory Trial, continued

• Firm evidence of clinical benefit is required to support a claim
• Trials must be sufficient to answer each key clinical question
• Basis for generalization to the population is necessary
• Results should be robust
• The weight of one trial may be sufficient

2.1.3 Exploratory Trial

• Should have clear and precise objectives
• May or may not test based on pre-defined hypotheses
• May require some design flexibility
• Analysis may require data exploration
• Are contributory to total body of evidence
• Trials may include exploratory and confirmatory components: protocol must clearly delineate

2.2.1 Scope of Trials: Population

• Early phases: narrow subgroup
• Confirmatory trials: mirror the target population
• Balance inclusion/exclusion criteria with homogeneity to permit precise estimate of treatment effects
• Attempt to minimize influence of geography, time conducted, and investigator practices
2.2.2 Primary variables

- The variable capable of providing the most clinically relevant and convincing evidence directly related to the primary study objective
- Only one
- Usually efficacy, may be safety, QOL
- Should reflect accepted standards and norms
- Reliable, validated and published is recommended
- Use to estimate sample size

2.2.2 Primary variables, continued

- Assessment of subject outcome must be well-defined
- Example: mortality comparison of proportion alive at fixed point in time
- Clinical relevance is critical
- Carefully and clearly define in the protocol with rationale

2.2.2 Secondary variables

- Are supportive only
- Limit the number of secondary variables
- Clearly define in the protocol
2.2.3 Composite Variables

- Integrates multiple measurements into a single variable
- Addresses multiplicity without requiring adjustment to Type I error (alpha level)
- Specify in the protocol

2.2.4 Global Assessment Variables

- Developed to measure overall safety, efficacy, or usefulness of a treatment
- Integrates objective variables with the investigator’s impression of a subject
2.2.4 Global Assessment Variables

- Usually a scale of ordered-categorical ratings, fully
detailed in the protocol
- Objective variable components should also be
considered as additional primary objectives, or
important secondary variables

2.2.4 Global Assessment Variables, continued

- Integrate benefit and risk assessment in the clinical
setting
- Two products may be declared equivalent with very
different beneficial and adverse effect profiles
- Consideration of separate risk and benefit variables
helps address this problem

2.2.5 Multiple Primary Variables

- Not too common
- Must clearly define the planned manner of
interpretation in the protocol, including statistical
inference in the protocol
2.2.5 Multiple Primary Variables

- Must consider whether an impact on any of these would be necessary to achieve the study objectives
- Clearly define the hypotheses
- Evaluate intercorrelation among the variables and impact on Type I error

2.2.6 Surrogate Variables

- A variable that provides an indirect measurement of effect when direct measurement is not possible or feasible
- Must be reliable predictors of clinical benefit
- Two concerns:
  - It may not be a true predictor of the clinical outcome of interest
  - May not be possible to quantitatively compare to adverse effects

2.2.6 Surrogate Variables, continued

- Statistical criteria for evaluation is limited
- Strength of surrogacy depends on:
  - Biological plausibility of relationship
  - Documented epidemiological evidence
  - Evidence in trials that treatment effects on the surrogate correspond to effects on the clinical outcome
2.2.6 Surrogate Variables, continued

- Relationships between a clinical and a surrogate variable for one product do not necessarily apply to another class of product for treatment of the same disease.

2.2.7 Categorized Variables

- Dichotomization or categorization of continuous or ordinal variables may be desirable
- "Success" or "Response"
- Require precise definition of terms in the protocol
- Most useful when clear clinical relevance is present

2.3 Design Techniques to Avoid Bias

- Blinding
- Randomization
- Should be normal features in most controlled trials
- Protocol should consider ways to reduce frequency and handle problems of bias that do arise in the analysis
2.3.1 Blinding

- Limits the bias due to knowledge of treatment and impact on recruitment, allocation, care, attitudes toward, handling withdrawals, of subjects and exclusion of data.
- Double blind is the optimal approach
  - Maintain the integrity of the blind is critical
  - Should have written SOPs on restricted access by persons involved in the clinical evaluation of the product

2.3.1 Blinding, continued

- Double-dummy technique
- Unblinding may occur with treatment-induced effects (e.g., lab values)

![Diagram: Investigational drug group and Active control group with Investigational drug and Placebo on one side and Placebo and Active control on the other side.]

2.3.1 Blinding, continued

- Single-blind used only if double-blind is not feasible
  - Guard against entry-bias based on knowledge of treatment
  - Use a central (e.g., telephone) randomization process
  - Clinical assessments made by one who is blinded
  - Written SOPs to control unblinding
BREAKING THE BLIND

• Should be considered only when knowledge of the treatment assignment is deemed essential by the subject’s physicians to the subject’s care.
• Fully document if broken, intentionally, or unintentionally
• Blind review refers to time period after last subject completed prior to breaking the blind

2.3.2 Randomization

• Introduces a deliberate element of chance
• Provides sound statistical basis for quantitative evaluation of the evidence of treatment effects
• Produces group comparability

2.3.2 Randomization, continued

• Randomization schedule
  – Sequential list
  – Complex, with screening phases
  – Unique, pre-planned assignment should be clear
  – Reproducible
• Unrestricted randomization
  – Blocking
2.3.2 Randomization, continued

- Multicenter trials should randomize centrally
- Separate scheme for each site with blocks
- Stratify by important prognostic factors (2-3 max)

2.3.2 Randomization, continued

- Account for stratification variables in the analysis
- Next subject receives the next free number
- Blocking factor should not be stated in the protocol
- Secure the schedule and limit access

2.3.2 Randomization, continued

- Dynamic allocation: treatment allocation is influenced by current balance of allocated treatments
- Use a randomized, rather than deterministic approach
- Retain double-blind status
- Use computer algorithms to keep central office personnel blind to treatment codes
Part III
TRIAL DESIGN CONSIDERATIONS

Design Configuration

3.1.1 Parallel Groups

- Most common
- Subjects receive investigational product at one or more doses and one or more controls, such as placebo or active comparator

3.1.2 Crossover Design

- Subjects receive a sequence of two or more treatments
- Serve as their own control
- Reduces number of subjects required
3.1.2 Crossover Design, continued

- Often reduces number of assessments needed to achieve a specific power
- 2 x 2: Bioequivalence in healthy subjects with adequate wash-out
- Disease should be chronic and stable

3.1.2 Crossover Design, continued

Problems
- Carryover effects
- Loss of subjects: use only when loss is expected to be small
- Difficulty in assessing AE effects

3.1.3 Factorial Designs

- Evaluates 2 or more treatments through varying combinations of the treatments
- 2 x 2
3.1.3 Factorial Designs, continued

- Use to establish the dose-response characteristics of two treatments, when each monotherapy has been established in a prior trial.

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3.2 Multicenter Trials

- An accepted way to evaluate new medicines
- Provides a better basis for subsequent generalization of the findings

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3.2 Multicenter Trials, continued

- Enables a broader range of clinical settings and clinical judgments
- Possible to perform in different countries
- Protocol must be clear and similar at all locations
3.2 Multicenter Trials, continued

- Sample size estimates depend on assumptions among centers
- Implement standardization among centers
- Control of variability among center enrollment is advantageous
- Define "center" in the protocol

Multicenter Trials, continued

- Define the statistical model for estimating treatment effects in the protocol
- Define centers to achieve homogeneity
- Define and justify the rules for combining centers to analyze, in the protocol
- Explore heterogeneity of treatment effect in the analysis, making appropriate assumptions

3.3.1 Trials to Show Superiority

- Efficacy of a treatment is best established with:
  - superiority over placebo in a controlled trial
  - superiority to an active control treatment
  - demonstration of a dose-response relationship
3.3.2 Trials to Show Equivalence or Non-inferiority

- Equivalence: bioequivalence trials with generic products
- Non-inferiority: no worse than an active comparator

3.3.2 Active comparator trials

- Placebo and active control allows demonstration of internal validity
- Choose comparator with care
- Define the equivalence margin(s) in the protocol
- Analysis is generally based on confidence intervals
- Non-inferiority trials use a one-sided interval

3.3.3 Trials to Show Dose-response relationship

- Beneficial to use placebo as well
- Advantages:
  - Confirm efficacy
  - Investigate shape and location of dose-response curve
  - Estimate an appropriate starting dose
  - Identify optimal strategies for dose adjustments
  - Determine maximum dose for beneficial effects
3.4 Group Sequential Designs

- Use to facilitate the conduct of interim analysis
- Allows assessment of grouped subject outcomes at periodic intervals
- Define criteria in protocol
- Define early stopping rules

3.5 Sample Size

- Large enough to answer the questions asked
- Determined by the primary objective
- Use standard methods for sample size calculations

3.5 Sample Size

- Define method in the protocol and to which analysis set it applies
- For an equivalence trial or a non-inferiority trial, base it on a confidence interval that shows the treatments differ at most by a clinically acceptable difference
3.6 Data Capture and Processing

- Multiple media are acceptable: paper, electronic
- Define methods in protocol
- Distinguish missing values from values of “zero” or “absent”

Part IV

TRIAL CONDUCT CONSIDERATIONS

4.1 Trial Monitoring and Interim Analysis

- Monitoring
- Breaking the blind to make treatment comparisons
- Interim analysis unblinding must be planned and accounted for statistically
4.2 Changes in Inclusion and Exclusion Criteria

- Inclusion and exclusion criteria should remain constant
- Make changes without breaking the blind
- Always use a protocol amendment
- Address statistical consequences in the amendment, as necessary

4.3 Accrual Rates

- Monitor the rate of accrual
- If it falls below projected level, take remedial action to protect the power of the trial

4.4 Sample Size Adjustment

- Checking assumptions can be made under blinded conditions in the trial
- Revise the sample size, as needed, documenting in a protocol amendment
- Define the potential need for re-estimation in the protocol, whenever possible
4.5 Interim Analysis and Early Stopping

- Should be planned and defined in the protocol
- Amend only via a protocol amendment
- Goal is to stop the trial early if superiority is clearly established

4.5 Interim Analysis and Early Stopping

- Usually requires more evidence to stop early for efficacy than for safety
- Evaluate the effects of stopping early on other important variables
- Maintain strict confidentiality during the interim analysis

4.5 Interim Analysis and Early Stopping

- Inform the investigators only about decisions to continue or discontinue the trial
- Stop early only for ethical or safety reasons
- It may be done to plan for other trials
4.6 Role of the IDMC

- Monitors safety and critical efficacy data during a trial to make decisions for continuation, modification or termination of a trial.
- Should include statisticians and other experts

Part V
DATA ANALYSIS CONSIDERATIONS

5.1 Prespecification of the Analysis

- Describe general features of the analysis in the protocol
- Full statistical analysis plan may be in a separate document
5.1 Prespecification of the Analysis, continued

- Maintain documentation of when the analysis plan was finalized and when the blind is broken.
- Only study results from analyses defined in the protocol or amendments can be regarded as confirmatory.

5.2 Analysis Sets

- Define sets of subjects whose data are included in the main analysis
- Define, a priori, how anticipated problems will be handled in the protocol
- Define protocol violations and when they occurred to clearly define sub-sets

5.2.1 Full Analysis Set

- Intention-to-treat implies the primary analysis should include all randomized subjects
- Justify and explain any exclusions
5.2.1 Full Analysis Set, continued

- Exclude failure to satisfy entry criteria only if:
  - the criterion was measured prior to randomization
  - detection can be made completely objectively
  - equal scrutiny for all subjects is possible
  - all detected violations of the criteria are excluded

5.2.1 Full Analysis Set, continued

- May exclude subjects who took no medication, only if the decision of whether to begin treatment could be influenced by knowledge of the assigned treatment.
- Randomize subjects who took at least one dose, but have no data
- Lost-to-follow-up problem of no data

5.2.1 Full Analysis Set, continued

- Define imputation techniques
- Make decisions on analysis sets under blinded conditions
5.2.2 Per Protocol Set

- “Valid” or “efficacy” subset
- Completed certain pre-specified minimal exposure to treatment
- Primary variable measurements are available
- No major protocol violations
- Define criteria in the protocol

5.2.3 Roles of the Different Analysis Sets

For confirmatory trials:
- Generally conduct a full analysis set and per protocol analysis.
- Compare the results of different subsets
- Caution to exclude many subjects

For superiority trials:
- Full analysis set is usually a primary analysis as it tends to avoid over-optimistic estimates of efficacy resulting from per protocol analysis.
- Risk is that it is usually not too conservative
5.3 Missing Values and Outliers

- Handle carefully
- Define in the protocol
- Assure decisions are logical and can be justified medically
- There is no universal standard

5.4 Data Transformation

- Make decisions to transform key variables during study design
- Base decisions on previously conducted research
- Specify in the protocol and provide a rationale
- Data transformation should be influenced by a scale that facilitates clinical interpretation

5.5 Estimation, Confidence Intervals and Hypothesis Testing

- Specify hypotheses and treatment effect estimates in the protocol
- Treatment effects should be accompanied by confidence intervals
- Define one-sided or two-sided tests
- Set alpha levels for one-sided test at 50% of two-sided tests
5.5 Estimation, Confidence Intervals and Hypothesis Testing

- The selected statistical model should reflect current state of statistical and medical knowledge.
- Clearly define the primary analysis on the primary variables from secondary analyses.

5.5 Estimation, Confidence Intervals and Hypothesis Testing, continued

- Modeling approaches based on known pharmacological parameters, or other biologically-based data may provide valuable insight into actual or potential efficacy.

5.6 Adjustment of Significance and Confidence Levels

- Multiplicity may require adjustments
- Interim analyses, multiple primary variables, multiple treatment comparisons
5.7 Subgroups, Interactions and Covariates

- Adjustments to the analysis may be needed when covariates or subgroup effects are present.
- If known, a priori, define in the protocol
- Treatment effect itself, may vary with subgroup or covariate

5.8 Integrity of Data and Computer Software Validity

- Credibility of numerical results depends on quality and validity of methods and software for data management: entry, storage, verification, correction and retrieval.
- Employ thorough, effective SOPs
- Use reliable statistical analysis software with documented testing procedures

Part VI

EVALUATION OF SAFETY AND TOLERABILITY
6.1 Scope of Evaluation

- Early stages of development are exploratory and are usually sensitive only to frank expression of toxicity
- Later phase trials allow full characterization of safety and efficacy

6.2 Choice of Variables and Data Collection

- Methods should include:
  - Laboratory tests (chemistry and hematology)
  - Vital signs
  - Adverse events
- Ensure a consistent, valid method is used
- Use a common dictionary of terms

6.3 Set of Subjects to be Evaluated and Presentation of Data

- Usually those who received one dose of drug
- Gather as much safety and tolerability as possible
- Define broad approach in the protocol
- All adverse events should be reported whether or not they are related to treatment
- Standardize to allow lab values with different normal ranges
6.3 Set of Subjects to be Evaluated and Presentation of Data, continued

- If using a toxicity grading scale, define in the protocol
- AE incidence reporting must clearly define the denominator
- In studies with substantial background noise of signs or symptoms, reporting only treatment emergent events may be appropriate

Statistical Evaluation

- Must be addressed carefully because safety assessment is a multidimensional problem
- Conclusive statements of safety and tolerability in a large confirmatory trial is the exception rather than the rule
- Use appropriate statistical data presentations, controlling for error, as appropriate

6.5 Integrated Summary

- Useful integrated safety assessment across trials depends on adequate and well-controlled individual trials with high data quality
Part VII

REPORTING

7.1 Evaluation and Reporting

• General analysis plan should be in the protocol
• The final, detailed analysis plan should be completed under blinded conditions

7.2 Summarizing the Clinical Database

• Integrated summaries are prepared for submissions
• Statistical attention should be given to describing the demography and clinical features of the treated population
7.2.1 Efficacy Data

- Individual trials should be large enough to satisfy their objectives
- For multiple trials addressing the same efficacy question, present the key variable results identically to allow for comparison
- Meta-analytic techniques may be useful

7.2.2 Safety Data

- Thoroughly examine the safety database for potential toxicity
- Look for patterns that support an observation
- Incidence of data from pooled studies is difficult to evaluate due to lack of a comparator