Session 4: Statistical considerations in confirmatory clinical trials II
Agenda

• Interim analysis
  – data monitoring committees
  – group sequential designs

• Adaptive designs
  – sample size re-estimation
  – Phase II/III trials

• Subgroup analyses
  – exploratory and confirmatory

• Missing data
Interim Analysis
• Unblinded interim analysis: Any review of data requiring patients to be *grouped according to the randomisation* before the database is frozen

• Unblinded interim analysis conducted to:
  – Assess whether to stop study early due to…
    • Safety concerns
    • Efficacy (overwhelmingly positive results)
    • Futility
  – Adapt the study design (e.g. choose between doses)
  – Planning other studies (not recommended for confirmatory studies)

• Blinded interim analysis: no grouping of treatments according to randomisation
  – Monitor total number of clinical events
  – Review ongoing safety data
Maintain study blind

- Need to maintain blind among people directly involved in the study
  - Study staff
  - Investigators
  - Sponsor staff directly involved in the trial

- May require evaluation of interim analysis by independent data monitoring committee (IDMC)
IDMC for confirmatory trials

- Independent of investigators, sponsor involvement discouraged
- Includes clinical experts in the therapeutic area and a statistician
- Safety monitoring primary responsibility, may monitor efficacy
- Makes recommendations that impact the future conduct of the trial,
  - include continuing, terminating or modifications to the trial
- Implementation of IDMC recommendation is responsibility of the sponsor
  - Possible to ignore recommendations
Committees for a large trial

Steering Committee:
- Makes important decisions regarding the trial
- Responsible for trial integrity

Sponsor
- Designs the trial with steering committee
- Interactions with regulators
- Ensures flow of high quality data

Independent Data Monitoring Committee:
- Reviews interim analysis and makes recommendation to SC

Statistical Data Analysis Centre
- Performs interim analyses
Interim analysis for efficacy

• Allows trial to stop early for overwhelming efficacy
  – May be necessary for serious outcomes to avoid unnecessary placebo exposure
  – Can mean medicine available to patients earlier

• Risks with stopping early include:
  – Reduction in available safety database.
  – Increased variability in estimates of treatment effects.
  – Reduced information on secondary endpoints
  – Acceptance of study results is not only based on a statistically significant primary result
  – May need sufficient data to explore important subgroups
Consistency of results

- Regulators interested in assessing results before and after interim analysis
  - Substantial discrepancies with respect to the types of patients recruited and / or results obtained will raise concern
  - Difficult to interpret conclusions if it is suspected that the observed discrepancies are a consequence of dissemination of the interim results.
  - Difficult to convincingly demonstrate that no unblinded interim results have been released.
  - Differences between stages can occur by chance so Interim analyses always introduce this risk.
P-value adjustment

- If the interim analysis can only stop the trial for safety or futility, no p-value adjustment required
  - Need to make this clear in the protocol

- If interim analysis can stop for efficacy, then need to adjust for more than one look at the data
  - If there is truly no difference between treatments, have more than one chance a false positive
  - Need to control overall probability of a false positive

- If study stops for efficacy at interim there is a sample size saving compared to a fixed sample size study
  - But if the trial continues to completion, sample size is larger because of p-value adjustment
Group-sequential design

• Conduct one or more interim analyses during the course of a study.

• Two possible decisions after each interim analysis:
  – Continue the trial as planned.
  – Terminate the trial

• Control overall Type I error rate.
  – Construct stopping boundaries that enable the trial to stop early if there is overwhelming evidence of efficacy,
  – Maximum sample size (sponsor commitment) is known up front
  – O’Brien/Fleming approach typical option as the penalty for conducting interim analyses is small.

• Generally well accepted by Regulatory authorities.
Benefits & limitations of group sequential

• Benefits
  – Very well established methodology.
  – Understood and accepted by regulators (ICH-E9).
  – Allows the flexibility to stop early for efficacy
  – Can vary timing and number of interim analyses

• Limitations
  – Interim analysis performed on the same endpoint at interim and final
  – Design focus is on maximum sample size, fixed in advance
  – Can’t amend the design e.g. to drop treatments or doses
Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease

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TORCH trial

- Trial comparing mortality in COPD
- Independent IDMC
  - Interim analysis for safety every 6 months
  - Two formal efficacy interim analyses
- Final analysis
  - Unadjusted p-value 0.041
  - Adjusted p-value 0.052
Adaptive Designs
Definition

• **Adaptive Design** – any design which uses an interim analysis to modify aspects of the design (e.g. sample-size, number of treatment arms)
  – Type of design modification has to be pre-specified in the protocol

• Requires control of the type I error for regulatory purposes

• Requires assessment of homogeneity of results from different stages
  – Need to justify combining results from different stages
Sample size re-estimation

- Uncertainty about sample size assumptions. E.g. size of placebo effect
- Whenever possible, use blinded sample size reassessment e.g. total number of events
- Need to pre-specify size of treatment effect to be detected
- If based on unblinded analysis, need to show control of type I error
Sample size re-estimation

- Active
- Control
- Interim Analysis
- Sample size Re-estimation
- Final sample size
Group sequential vs. adaptive

- Group sequential design: focus is on maximum sample size
  - Plan larger trial, stop early if unexpected large efficacy
  - More statistically efficient

- Adaptive design: focus is on initial sample size
  - Start smaller, expand if need to
  - More complex analysis may be required
Phase II / III trials

Standard
2 phases

Learning

Confirming

Plan & Design
Phase IIb

A
B
C
D
Control

Plan & Design
Phase III

A
B
C
D
Control

Adaptive
Seamless
Design

Plan & Design
Phase IIb and III

Learning, Selecting and Confirming

Dose Selection

Plan & Design
Phase IIb

A
B
C
D
Control
Phase II / III trials

- Initially investigate multiple doses of experimental treatment
- Select dose to take forward based on interim analysis
- Only continue this dose and placebo for rest of study
- Requires careful control of type I error
- Can use short term endpoint for dose selection, longer term endpoint for confirmatory part of the trial
Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design

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Indacaterol trial

- Stage I (N = 115 per group, 7 groups)
  - 75, 150, 300, 600 mg indacaterol
    - vs placebo vs formoterol vs tiotropium
- Interim based on 2 week efficacy outcome
- two doses selected for to Stage 2
  - lowest dose meeting pre-defined efficacy criterion + next dose
- Final analysis performed after 26 weeks
- Careful control of type I error
- Second conventional phase III trial started in parallel after interim analysis
Phase II / III trials

• Other option, “non-inferentially seamless”
  – Two part protocol, Part A decides dose
  – Part B is confirmatory study but doesn’t use data from Part A in analysis
  – Avoids need for unblinded interim and alpha adjustment
Phase II/III trials

- Advantages of adaptive seamless designs
  - Increase of information value per patient
  - Shorter overall development time

- Issues
  - Number of treatment groups can change during trial with resulting implications in drug supply
  - Careful consideration of trial integrity issues (unblinding, consistency between stages)
  - Use of phase II/III designs misses opportunity to discuss/agree dose with regulatory authorities e.g. end-of-phase II or CHMP advice
Subgroup Analysis
Confirmatory subgroup analysis

- Generally requires pre-specification that a subgroup is expected to have larger effect
- Usually expected in the context of an overall positive trial
- Not usually possible to rescue a trial with overall non-positive result
Subgroup analysis

• Overall concern that the response of the “average” patient may not be the response of the all patients in the study

• Routine requirement for analysis by subgroup

• Aim
  • Identify patient groups with differential treatment effects
  • Assessment of internal consistency
  • Licence can be restricted if not sufficient evidence of a positive risk-benefit in the subgroup
Typical list of subgroups for analysis

- Sex
- Age
- Race
- Region
- Baseline severity measure 1
- Baseline severity measure 2
- Clinical events in the previous year
- Baseline medication
- Baseline blood biomarker
Multiplicity

- Results from analyses are interpreted as the true results for that group of patients.
- Subgroup differences in treatment effect can arise by chance.
  - Hard to identify what is a true difference.
- Single subgroup with 5 levels, equal n, 90% power to detect overall effect*
- No true difference among subgroups.
- Probability of observing at least one negative subgroup result = 32%.

Classic example of dangers

- ISIS-2 trial aspirin vs placebo for vascular deaths
- Overall trial extremely positive for reduction in mortality
- Subgroup analysis by star sign
  - Gemini or Libra: adverse effect of aspirin on mortality
  - Remaining star signs: highly significant effect of aspirin on mortality

Multiplicity: is the difference real?

- Biological plausibility
  - Pre-definition
    - Differential effect anticipated
    - Plausible but not anticipated
    - Not plausible, hypothesis generating
- Consistency across endpoints
- Replication across two trials
  - But meta-analysis can still have subgroup problems
Design assumption

• Frequent assumption (by sponsors): patient population is homogeneous
  – Pragmatic approach for sample size determination
  – Should expect a consistent treatment effect
  – Anything else due to chance

• Alternative assumption (by regulators): treatment effect will vary between subgroups
  – Burden of proof to establish an effect in each heterogeneous subgroup is with the trial sponsor
Can we limit the number of subgroups?

- **Design stage, pre-specification**
  - Scientific rationale for heterogeneous effects?
  - Should separate trials be performed?
  - Pre-agreement with regulatory authorities on important subgroups may be helpful

- **Need for subgroup analysis is related to the overall patient population**
  - Sponsors may identify targeted populations
  - The more homogeneous the population studied, the fewer requirements there should be for subgroup analyses
How to assess results?

• Tests for interaction of limited value when investigating subgroup differences
  – Low power to detect heterogeneity
  – Still have 5% or 10% false positive rate
  – Hypothesis testing not appropriate
• Estimates and CI of size of interaction can be helpful to show what differences a trial can reliably estimate
Consistency of effect

• Alternative to interaction tests is to look at effect size in each subgroup

• Formal requirements have been proposed
  • e.g. that effect size in each subgroup must at least be positive

• All requirements are problematic
Subgroup analysis - summary

• Subgroup analysis is major statistical challenge
  – Hard to identify true effects versus false positives

• Pre-identification of important subgroups helpful for interpretation

• Subgroup analysis should depend on heterogeneity of the population
  – Less requirement when population is targeted

• Difficult to define consistency of effect
  – Interaction tests are of limited value
  – Requirement for each subgroup to show given level of effect is problematic
• “The appropriate interpretation of apparently different results in different subgroups of trial results is still one of the most difficult matters of judgement in the interpretation of randomised evidence”
• At present, many clinicians and regulatory agencies pay far too much attention to irregularities between the apparent effects in different subgroups
Missing Data
Missing data analysis

- Increased regulatory focus on missing data
- All statistical analyses where data is missing rely on untestable assumptions about unobserved data
  - Best strategy is avoidance
- Missing data more problematic if imbalance in withdrawal rates across treatment arms or characteristics of withdrawals different to completers
ITT analysis (De Facto estimands)

Two separate aspects:

- Including all randomised patients and all available on-treatment data (ITT Population)
- Assessing outcome regardless of whether the patient remained on the assigned treatment

First principle almost universally agreed

Second principle less well-understood,

- either requires follow-up off treatment
- or an assumption regarding missing data
Collection of data after treatment discontinuation

- Treatment discontinuation should not necessarily mean withdrawal from study
  - May need to follow-up subjects post-withdrawal from study drug for safety and key efficacy
- Academic consensus is strongly in favour of continued data collection
- CHMP missing data guideline
  - “Continued collection of data after the patient’s cessation of study treatment is strongly encouraged, in particular data on clinical outcome”
- FDA and Europe now often request this
  - Ongoing debate whether required in all cases e.g. for symptomatic endpoints where effective medication is available to those discontinuing randomised treatment
Why is subject retention so important

- Missing clinical trial data is a key focus for regulatory authorities
- High levels of missing data can raise questions about integrity of a trial in general
- May negatively impact interpretation of efficacy and safety data
- Multiple analysis typically required, may show sensitivity of conclusion to missing data assumptions
- Requires a particular focus in long term or outcome studies
Prevention of missing data

- Focus on efforts to retain patients in trials
- Informed consent can allow for further follow-up contact off randomised treatment
- Designs can allow for multiple types of follow up, even if a subject no longer wishes to take IP
  - Contingency plans for collecting data for patients not attending visits
- Avoid withdrawal criteria where possible
  - Not all protocol deviations warrant exclusion from treatment or from the study.
  - Subjects should remain in the study unless there is a safety concern (even if the deviation is considered to impact efficacy)
- Monitoring sites for level of missing data
ITT analysis for normal data

- Historically analysis performed using LOCF (last observation carried forward)
- May not be a reasonable assumption for what happens when a patient discontinues
- Artificially increases sample size, does not reflect true variability of the trial
- Now discouraged by academics, less favoured by regulators
ITT analysis for normal data

- De jure analysis estimates what would happen if patient continued treatment
- Alternative approaches (de facto analyses) make assumptions about what happens to withdrawals e.g.
  - Active treatment withdrawals have similar future changes to placebo
  - Active treatment withdrawals jump to placebo mean

Some less obvious consequences…

- Apparent efficacy of a treatment will tend to reduce over time as withdrawals only increase, regardless of pharmacological effect
- Apparent efficacy in a subgroup will depend on withdrawals rates in the subgroup
Missing data

• De facto analysis often now required for both FDA and Europe
  – Alternative ideas exist, no standard analysis approach yet
  – Lack of robustness may mean the trial is not viewed as positive
  – Methods for some types of data not well developed
• Field is moving quickly, advisable to proactively address the issue in regulatory advice
• Best solution is to minimise missing data as far as possible