Multi-Regional Clinical trials (MRCT) and European Marketing Authorisation Applications

Introduction

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An evolving submission policy

Classical process

Development plan including Phase III multicenter/multinational **R**andomised **C**linical **T**rials (RCT)

→ Local submission

Additional Bridging studies (e.g. in Asia: PkPd or Ph II or III trials)

→ Submissions in other regions

More recent process

Synchronised development plan including large Phase III **M**ulti-**R**egional randomised **C**linical **T**rials (MRCT)

→ Simultaneous worldwide submissions

Regulatory experience

USA (Communication R. O'Neill, 09)

- Among1926 RCT analysed over 7 years : 41 % US-Canada, 50 % US-Canada-foreign countries other and 9% foreign countries
- 21 NDA submissions where decision depended upon MRCT

European Union (Reflection paper on extrapolation of results for CT conducted outside EU to the EU population, 10)

- Eleven products highlighted difficulties in extrapolating data for one region to EU or lack of data specific to EU patients

Japon (Basic principles of global clinical trials, 07)

- 'To synchronise drug development timings in Japan with those of other countries'

MRCT : a challenge for the Pharmaceutical Industry

Expansion of Multi-Regional Clinical Trials (MRCT) justifies

- an increased requirement for Quality and Integrity of the **Trial**
  - → **S**tatistical
  - → **C**linical
  - 5 categories **SCORE** → **O**perational
  - → **R**egulatory
  - → **E**thical
- a reconsideration of several methodological and statistical issues, particularly at the study design stage
- Scientific advice to assess acceptability by regulatory authorities

* PhRMA MRCT Cross-Functional Key Issues Team

Clinical impact on trial : Preparation

Definitions and assessments

- Region definition (country, set of countries, ...)
- Identification of (dis)similarities between regions
  - Intrinsic factors : Dose and dose regimen (safety concern)
    Pathology (definition, prevalence, severity, ..., epidemiological databases)
  - Extrinsic factors : Medical practice (health care system, procedures)
    Therapeutic treatments /compliance
  - Choice of control group : placebo, reference drug, ...
  - Judgement criteria : definition and evaluation (standardisation, centralisation)
  - Quality of trial conduct and data

Statistical impact on clinical trial : Strategy

Clinical assumptions

- Homogeneity of treatment effect across regions
  → Issue : relationship between severity and treatment effect size
- Clinically relevant treatment effect
- Non inferiority margin

Strategy of the Statistical Analysis

To predefine the primary and secondary objective(s) :

Overall treatment effect +/-

- Treatment effect in one (or several) selected region
- Consistency of treatment effect between regions
- Absence of Interaction treatment x region

→Planned strategy for hypothesis testing

Statistical impact on clinical trial : Sample size

Sample size : Power control on treatment effect

- Global treatment effect +/-
- Other objective(s)

→Statistical assumptions : relevant treatment effect, nuisance parameter (variability, incidence), number of regions and (im)balance, required proportion of treatment effect,...

Randomisation

- Stratification factors (region/country, prognostic factors, ...)

→Issue : control of the anticipated balance or imbalance between regions

Statistical impact on clinical trial : Analysis

Results on Treatment effect

- Point(s) estimate(s) and Confidence Interval(s)
- Statistical model(s) adjusting for
  - Region (random/fixed factor, "small" regions, pooling of countries)
  - Prognostic factors (intrinsic/extrinsic factors, ..)
- Test(s) of hypothesis(es) → Multiple Comparisons (hierarchy, Gatekeeping procedures, ..)
- Handling of Missing Data

Descriptive results by regions (or countries)

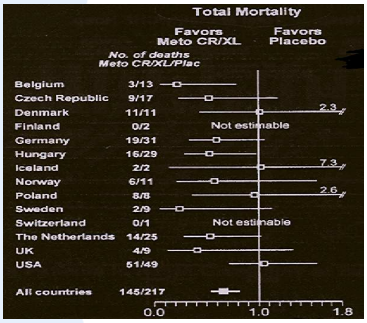
- Tables
- Forest plots
- Funnel plots

Examples of statistical results by region

Two graphical displays (meta-analysis)

- **Forest plot**

All Patients Randomized



RR and 95%CI

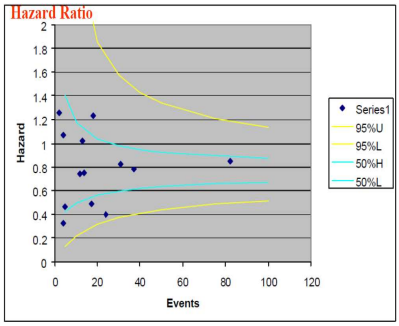
Challenges of subgroup analyses in multinational clinical trials : experience from the MERIT-HF trial

Wedel et al, Am. Heart journal, Sept. 2001

- **Funnel plot**

Hazard ratio by country (# events)

J.Hung, 2009 APEC MRCT



Clinical impact on study : Report

Interpretation - Extrapolation

Descriptive statistics overall and by region on

- Demography - Prognostic factors - Baseline variables
- Follow-up, Drop-outs, Treatment exposure, Compliance,
- Safety

An internal bridging assessment ?

Two approaches for interpretation of results

- To assess the global and more accurate effect of a drug
- To bridge
  - From the global to each local region
  - Between local regions

To summarize

- **MRCT raise extensive clinical, methodological and statistical issues at all the stages (protocol, follow-up, statistical analysis and interpretation of results) and enhance the need for a continuous collaboration between Clinicians, Statisticians and Regulators and ....**
- **Predefinition of the (statistical) objectives of a MRCT is determinant at the stage of study design**
- **Validation of the strategy with local Regulatory Agencies (Scientific Advice) must be anticipated**