Optimising the design of thorough QT/QTc studies

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Statistical Aspects of Safety Data

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Agenda

- Introduction
- Study design
- Design optimisation
- Summary

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Introduction

- Motivation
- Objective of this presentation
- ICH E14
- Analysis

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Regulatory guidance: ICH E14

"The effect of an investigational drug on the QT/QTc interval is most commonly analyzed

using the largest time-matched mean difference between the drug and placebo (baseline adjusted) over the collection period ."

"a negative 'thorough QT/QTc study' is one in which

the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10ms".

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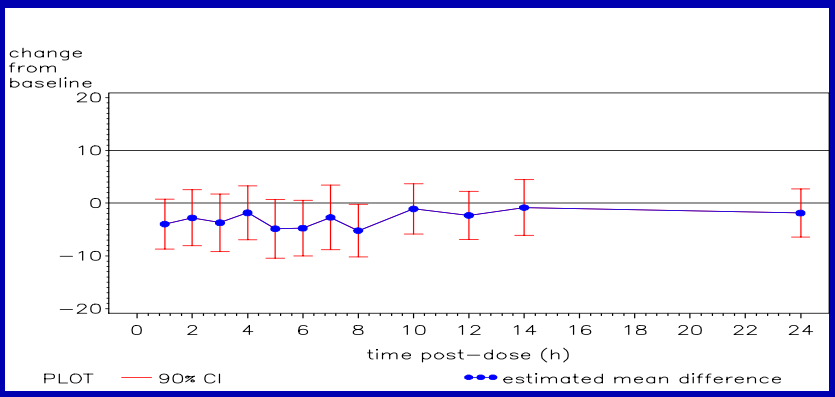
Data analysis: ICH E14

“change from mean baseline in QTc (msec)”



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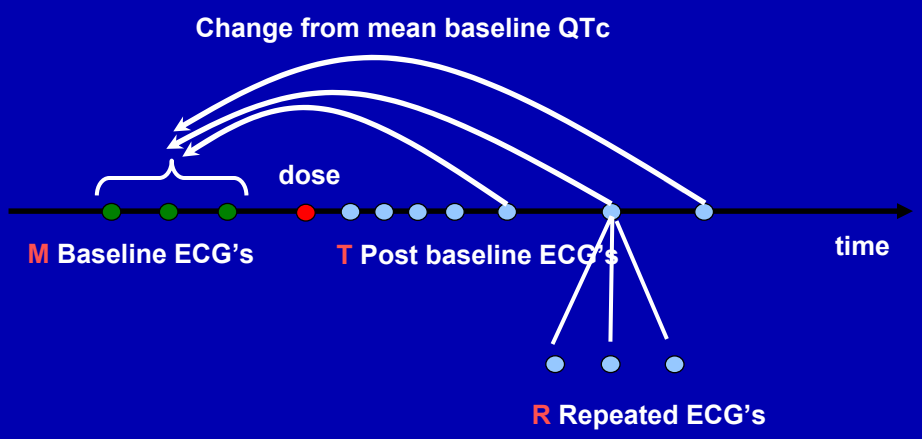
Design



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Key Design decisions

- Cross-over or parallel design
- Number of ECG's at baseline
- Number of ECG's post baseline
- Number of repeated ECG's at each time point

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"Optimising" the design

Utility function

- Ethical/operational: Number of subjects (n)
- Economic: Cost of the trial (C)

Objective

- Minimise (n)
- Minimise (C)

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Utility: number of subjects

From medical colleagues

$$n = 2\frac{M+1}{M}s^2(R)\left(\frac{\mu_\alpha + \mu_\beta}{\frac{T_r}{\delta - d}}\right)^2$$

$$\mu_\alpha = \Phi^{-1}(1-\alpha)$$

Dependent on R (no. repeated ECG's)

n – number of subjects per treatment arm
δ = 10 msec
T_r – number of relevant time points
d – expected treatment difference

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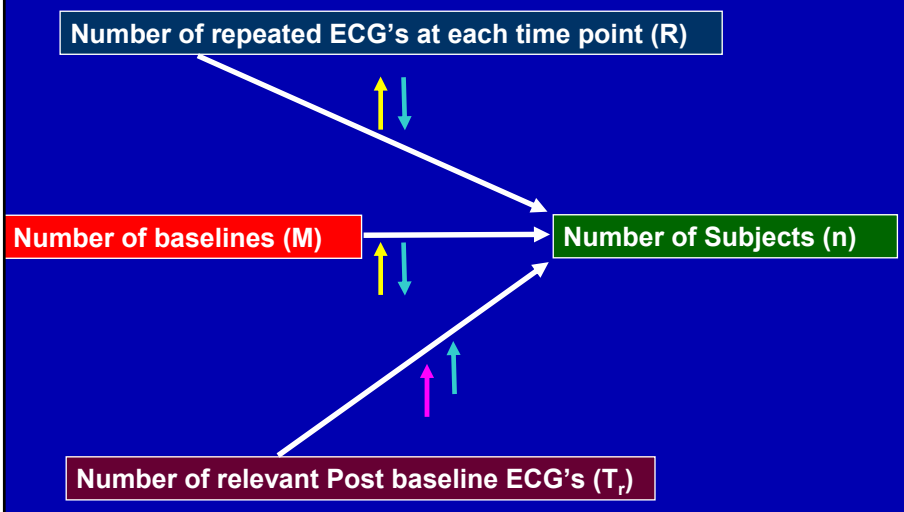
Number of subjects



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Utility: cost

- Assumptions
  - Cost per patient: USD 2000
  - Cost per QT measurement: USD 80

Total cost (C):

$$C = G*n*(2000+R*(M+T)*80)$$

G – no of treatment groups

n – no of subjects per group

R– no of repeated ECG's

T – no of post baseline time points

M – no of baseline time points

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Optimisation variables

- Fixed variables:
  - G = 3 (no. of treatment groups)
  - T_r = 4 (no of relevant post baseline time points)
  - T = 10 (total no. of post baselines)
  - d = 5 msec (estimated treatment diff to placebo)

- Freely varying:
  - R : no. of repeated ECG's
  - M : no. of baseline time-points

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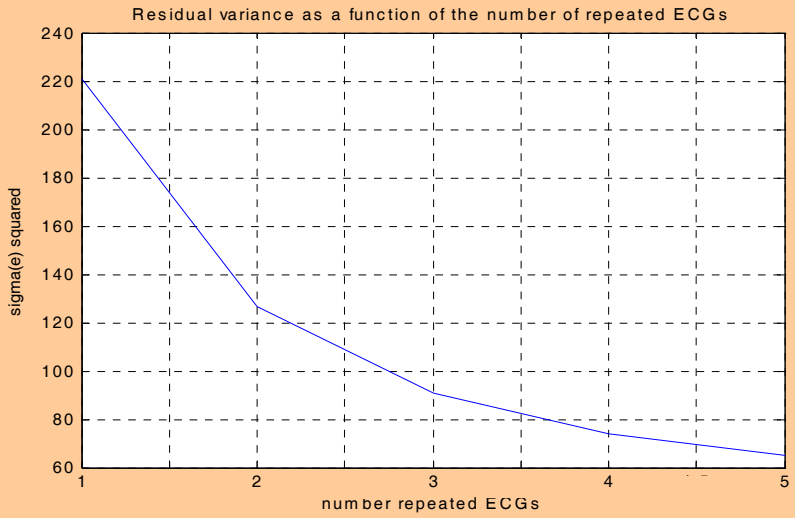
Residual variance vs no of repeats



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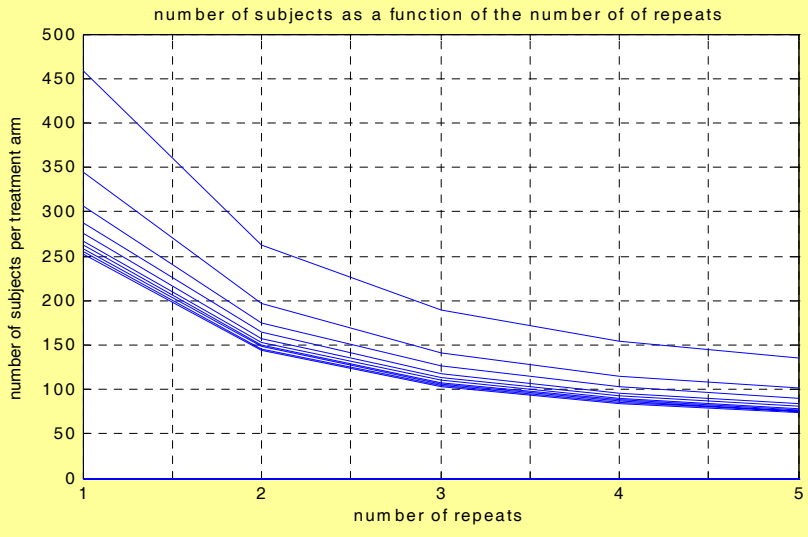
No. of subjects vs no. of repeated ECG's



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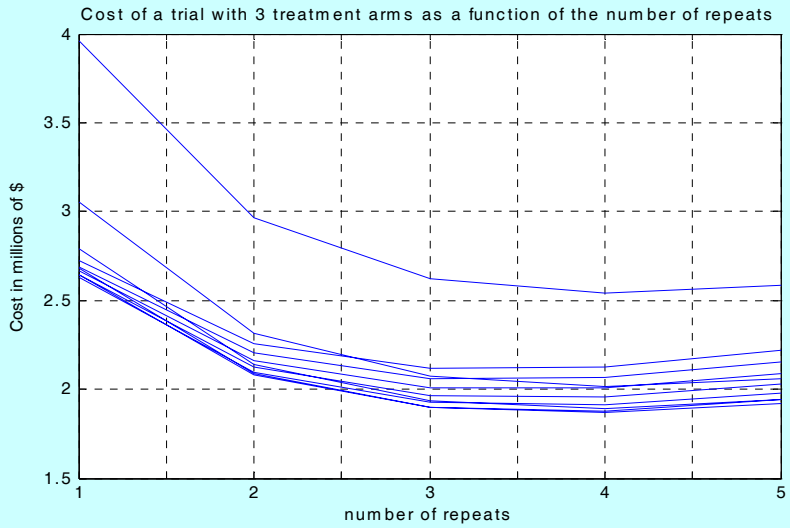
Cost vs no. of repeated ECG's



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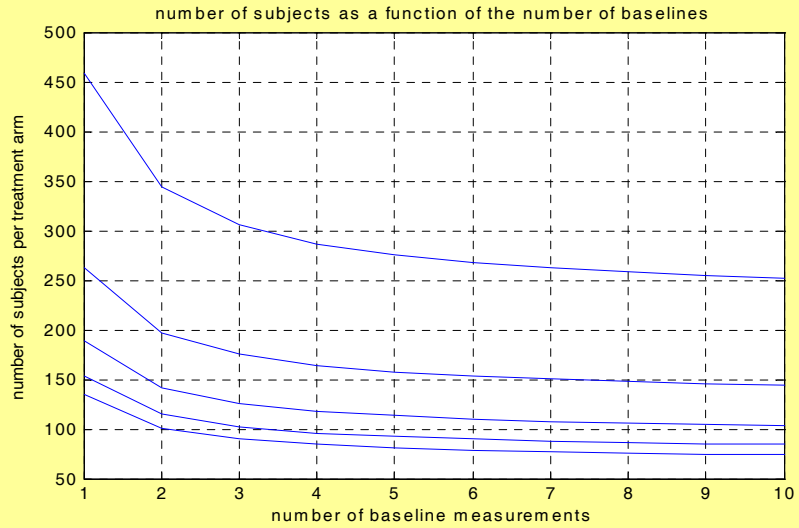
No. of subjects vs no. of baseline timepoints



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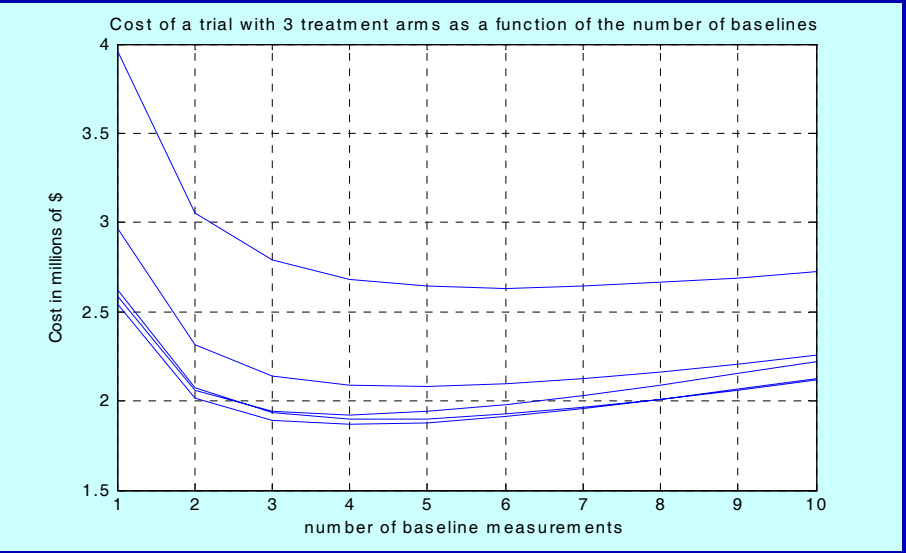
Cost vs no of baseline time-points



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Optimal design

- **Minimum Cost C = $1.87 million**
  - **R = 4 (no. of repeated ECG's)**
  - **M = 4 (no. of baseline time points)**
  - **n = 96 (no of subjects per treatment group)**
- **Fixed variables:**
  - **G = 3 (no. of treatment groups)**
  - **T_r = 4 (no of relevant post baseline time points)**
  - **T = 10 (total no. of post baselines)**
  - **d = 5msec (estimated treatment diff to placebo)**

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Summary

Design issues

Design optimisation

Simple objective method

Support decision making

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Thank you.

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Data analysis: ICH E14

Test $H_0^t : \Delta(t) \geq 10ms$ versus $H_1^t : \Delta(t) < 10msc$

for each time point *(t)* separately.

$\Delta(t)$ - mean difference between QTc for the two treatments at time *t*

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