

# Flexible designs for interim data review

A practical and regulatory perspective

Caroline Morgan, DPhil

Cardinal Systems, Paris  
c.morgan@cardinal-sys.com  
www.cardinal-sys.com

# Overview

- Flexible designs
- Regulatory issues
- Statistical & practical considerations
  - Practical examples
- Data Monitoring Committees (DMCs)
  - Practical examples

## What is a flexible design?

- Adaptive randomisation
- Blinded/unblinded sample size adjustment following an interim analysis (e.g. internal pilot study)
- Early stopping for efficacy/futility
- Combination phase I/II (safety/dose ranging), II/III (dose ranging/efficacy) studies

## Why so much interest?

### Getting GOOD drugs to market QUICKLY

Flexible designs can:

- Cut resources and drug-development time significantly
- Decrease overall number of patients in trial and number of patients assigned to control group (if inferior)
- Verify/modify initial design assumptions

Due to statistical and technological advancements these designs are practical as well as attractive:

- $\alpha$ -spending functions: pre-planned designs that remain flexible in terms of timing and number of interim analyses
- IVRS: Logistic management and adaptive randomisation
- EDC: Real-time access to high-quality data and strict security levels to ensure authorisation

# Regulatory issues

- Well established, statistically robust designs that control the type I error and give estimates and confidence intervals for treatment effects
- Fully pre-specify the design in protocol
- Discuss with regulatory agencies in advance
- Use an independent DMC

## ICH E9: Section IV

# Trial Conduct Considerations

- Major changes to the protocol/inclusion/exclusion criteria/endpoints should be avoided
- Preplan using sound statistical methods - avoid type I error rate inflation (false positive result)
- Ensure good ethical practice
  - Safeguard both patients in the trial and future patients with the disease (individual *versus* collective ethics)
- Use an independent DMC to review interim data

## Statistical considerations

Increasing the risk of a false positive result

Number of tests at the 5% level	Overall type I error rate ( $\alpha$ )
1	0.05
2	0.08
5	0.14
50	0.32
1000	0.53

## Practical considerations

- Unknown/variable efficacy parameters
- Better prior physiopathological understanding
- Lack of existing treatment/clinical information
- Orphan indication/small population
- Necessity for flexible number/timing of interim analyses
- Desire to obtain more advanced conclusions from exploratory (e.g. Phase II) analyses (better understanding of treatment efficacy/comparison to control treatment)

## Practical examples: $\alpha$ -spending function

- Phase III comparative study in a chronic indication with primary end-point at 2 years but a regulatory accepted surrogate at 3 months
- Hypotheses at 3 months:
  - Active treatment: 90% response rate
  - Control treatment: 65% response rate
  - Recruitment rate  $\approx$  100 patients/year
- A fixed design to test for superiority with 1:1 randomisation, power=0.9 and two-sided  $\alpha=0.05$  would require 57 patients per treatment arm
- Recruitment period  $\approx$  1.5 years

## Practical examples: $\alpha$ -spending function

- Plan two interim analyses using the Lan and DeMets (1983)  $\alpha$ -spending function
- Verify hypotheses at the first interim analysis and increase sample size if necessary
- Possibility to stop early (at either interim analysis) for futility/efficacy (recruited patients will be followed to 2 years regardless)
- Maximum sample size of 59 patients per treatment arm

## Practical examples: $\alpha$ -spending function

First interim analysis presented to the DMC after approx. 8 months of recruitment

- Surrogate endpoint at 3 months:
  - Active treatment: 19/20 (95%) response rate
  - Control treatment: 14/20 (70%) response rate
  - Z-statistic=2.2 (upper critical bound=3.7)

## Practical examples: $\alpha$ -spending function

Second interim analysis presented to the DMC after approx. 15 months of recruitment

- Surrogate endpoint at 3 months:
  - Active treatment: 38/43 (88%) response rate
  - Control treatment: 27/41 (66%) response rate
  - Z-statistic=2.6 (upper critical bound=2.5)
- Advantages:
  - Total recruitment = 84 (+ overrun)
  - Avoided further problems with recruitment
  - Study duration at least 6 months inferior to that originally planned

## Practical examples: Combination Phase II/III

- Two-stage design (Bauer and Keiser, SIM 1999) to compare 3 doses of an active treatment for severely depressed patients to placebo
- First stage – perform an unblinded interim analysis and drop one or more inefficient or less efficient doses
- Second stage – revise the sample size and continue with the most efficient dose(s) and placebo

## Practical examples: Combination Phase II/III – Stage I

Treatment	Decrease in HAM-D	Treatment effect	Standard error	P-value
Placebo (n=39)	5.26	-	-	-
Low dose (n=40)	10.03	4.77	1.74	0.0031
Medium dose (n=38)	8.78	3.52	1.73	0.021
High dose (n=46)	7.55	2.29	1.75	0.096

## Practical examples: Combination Phase II/III – Stage 2

Treatment	Decrease in HAM-D	Treatment effect	Standard error	P-value
Placebo (n=46)	6.08	-	-	-
Low dose (n=38)	10.00	3.92	1.74	0.0127
Medium dose (n=39)	14.00	7.92	1.73	<0.0001

By the Fisher combination test and the closure principle we conclude that both the low dose and the medium dose are significantly superior to placebo

# Independent Data Monitoring Committees (DMCs)

- **What is a DMC?**
  - Independent body to monitor interim safety and efficacy data (also known as a DSMB)
- **Who sits on a DMC?**
  - Size varies with trial complexity and funding
  - Usually at least 2 clinicians and a statistician (other than the statistician generating the interim results)
- **Why are DMCs necessary?**
  - Ensure an unbiased review of interim data and protect the scientific validity and integrity of the trial
  - Promote objectivity (can benefit patients and sponsor)
  - Avoid premature publication

## Guidance for DMCs

- FDA draft guidance on the establishment and operation of clinical trial DMCs
  - Issued November 2001
  - 90-day public comment period ended February 2002
  - Date of final document still unknown
- DAMOCLES study (shortly to appear in the Lancet)

DAta MOnitoring Committees: Lessons, Ethics, Statistics

## Practical examples: US ECMO trial – individual ethics

- ExtraCorporeal Membrane Oxygenation *versus* Conventional Medical Treatment in newborns with respiratory failure (Ware, Statistical Science 1989)
  - ECMO – 0/9 died
  - CMT – 4/10 died } Two-sided  $p=0.09$
- After much scientific and ethical debate, the evidence was considered insufficient to make ECMO the standard of care

## Practical examples: UK ECMO trial – collective ethics

- ExtraCorporeal Membrane Oxygenation *versus* Conventional Medical Treatment in newborns with respiratory failure (Lancet, 13th July 1996)
  - ECMO – 30/93 died
  - CMT – 54/92 died } Two-sided  $p=0.0005$
- Recruitment to the trial began in January 1993 and was stopped early (November, 1995) by the trial steering committee on the advice of the independent DMC

## CHMP guidelines

Points To Consider	Status	Member state of authorship
Switching between non-inferiority and superiority	Adopted 07/00	UK
Choice of non-inferiority margin in equivalence trials	Consultation 02/04	UK
Data Monitoring Committees	Consultation 11/04	Germany
Small populations	Consultation 03/05	UK
Methodological issues in trials with flexible design and analysis plan	Draft at EWP	Germany

## EMA Concept paper on flexible designs

- « Recently statistical methods have been developed which allow for major design modifications of ongoing clinical trials under control of the pre-specified type I error. »
- « ...it is now principally possible to stop trials early for futility or proof of efficacy while having at the same time the option to increase (or decrease) the sample size... »
- « Other options include early termination of treatment arms in multi arm clinical trials as soon as e.g. inferiority of a treatment arm has been established. »
- « In this PtC it is intended to discuss pre-requisites and conditions under which these methods could be acceptable in confirmatory phase III trials for regulatory decision making. »