Uptake of adaptive and Bayesian methods in the design of early phase trials within CTUs

Thomas Jaki

Department of Mathematics and Statistics,
Lancaster University, Lancaster, United Kingdom

Drug development

Development of a novel medicinal product

- takes 10-15 years
- costs several hundred million pound on average
  - largest contributors are confirmatory (Phase III) clinical trials
  - often involve thousands of patients with follow-up period frequently lasting years

Success rates

In recent years

- 45% of confirmatory clinical trials overall and
- even 59% of confirmatory trials in oncology

have been unsuccessful (Kola & Landis, 2004).

Reasons for failed confirmatory trials

Reasons for failed confirmatory trials are thought to be:

- taking forward treatments that should have been abandoned during early efficacy studies;
- studying the wrong patient population;
- insufficient precision when
  - determining the maximum tolerated dose;
  - assessing safety;
  - determining the optimal dose.

The successes

Between 1980-1999

- 21% of new molecule entities required dose change after registration
- 79% are safety related dose reductions
- Median time to change is 2.0 years (1995-1999)

according to Cross et al (2002).

Pharmaceutical industry

Within the pharmaceutical industry there is

- great interest and
- increasing use

of adaptive designs and Bayesian methods (eg Krams et al., 2007).

Personal impressions

- Good take up within the UK public sector of new statistical methods for the design of phase III clinical trials;
- Many early phase trials are based on
  - Gehan (1960)
  - Carter (1973) - 3+3 design
  - Simon (1989) - Simon's design
- More recent innovations appear to be less common.

Questionnaire

Questionnaire designed to find out

- if a CTU was involved in early phase trials;
- which early phase trial designs are used;
- if some specific methods are known (eg Simon's 2-stage design, continual reassessment method).

Results

- 35 out of 39 CTUs responded;
- 8 are involved in Phase I trials;
- 23 are involved in Phase II trials.

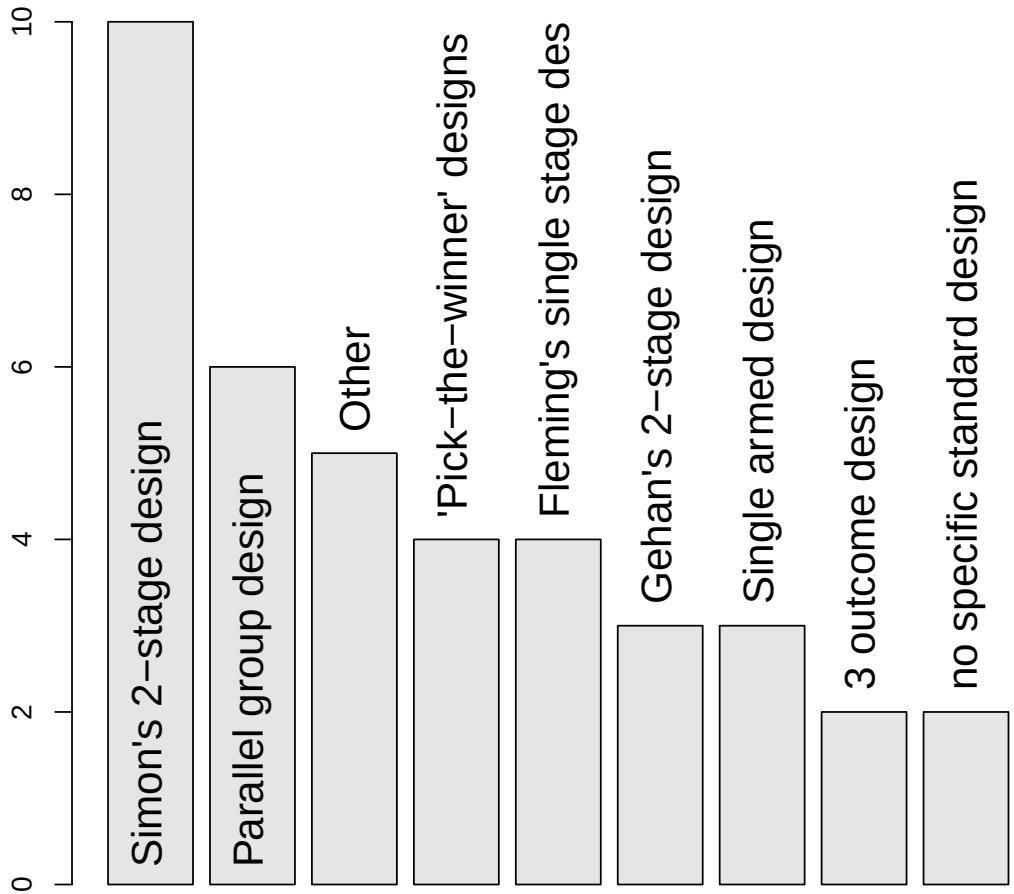
Phase I

- Phase I designs used

3+3 design	A + B design with/without de-escalation	standard off the shelf designs
7	1	1

- 1 trial using continual reassessment method planned.

Phase II


0
2
4
6
8
10
Simon's 2−stage design
Parallel group design
Other
'Pick−the−winner' designs
Fleming's single stage des
Gehan's 2−stage design
Single armed design
3 outcome design
no specific standard design

Known designs

Of the 23 CTUs that are involved in early phase studies

- 22 were familiar with Simon's 2-stage design;
- 7 were unfamiliar with CRM;
- 5 were unfamiliar with seamless Phase I/II and II/III trials.

Follow up visits

- Visited 13 CTUs
- Presentation on questionnaire and “newer” designs
- Informal discussion on design issues

How a design is chosen

1. CTU member designs study - no other input
2. Investigator insists on design
3. CTU member designs study - input from external experts
4. CTU discusses design

Key issues

- Time
  - until design needs to be finalized
  - competing demands on time
  - it takes to design an adaptive study
- Expertise
- Investigators drive design choice

Some facts

- Literature evolves quickly
  - 96.7% of published Phase I trials used 3+3 design between 01/2007 and 12/2008 (Le Tourneau et al, 2009)
- Funding structures do not support adaptations
- CTU structure does not support adaptations

Some positive developments

- Development courses are being offered
- A practical guide to designing early phase trials is being developed
- Some funders start to encourage adaptive designs
- Regulators have voiced an opinion about adaptive designs

References

Carter, S. K. (1973). Study design principles for the clinical evaluation of new drugs as developed by the chemotherapy programme of the National Cancer Institute. In: Staquet, M.J. (Ed.) The Design of clinical trials in Cancer Therapy. Brussels: Editions Scient. Europ. 242-289.

Cross, J., Lee, H., Westelinck, A., Nelson, J., Grudzinskas, C. & Peck C. (2002). Postmarketing drug dosage changes of 499 FDA-approved new molecular entities. *Pharmacoepidemiology and Drug Safety* 11(6):439-446.

Gehan, E. A. (1960). The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *Journal of Chronic Diseases*, 13:346-353.

Kola, I. & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3(8):711-715.

Krams, M., Burman, C-F., Dragalin, V., Gaydos, V., Grieve, A. P., Pinheiro, J. and Maurer, W. (2007). Adaptive Designs in Clinical Drug Development: Opportunities, Challenges, and Scope Reflections Following PhRMA's November 2006 Workshop. *Journal of Biopharmaceutical Statistics*, 17, 957-964.

O'Quigley, J., Pepe, M. & Fisher L. (1990). Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer. *Biometrics*, 46(1):33-48.

Simon, R. (1989). Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials*, 10:1-10

Le Tourneau C., Lee J. J. & Siu L. L. (2009). Dose escalation methods in phase I cancer trials. *Journal of the National Cancer Institute*, 101:708-720.

LANCASTER UNIVERSITY