Recent advances in methodology for clinical trials in small populations: the InSPiRe project

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InSPiRe
Innovative methodology for small populations research

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement number FP HEALTH 2013 – 602144.

Outline

The InSPiRe project

- *The challenge*
- *Progress and plans*

Sample size calculation in a small population clinical trial

- *Motivation*
- *Decision-theoretic model*
- *Optimal sample size*
- *Example*

The InSPiRe project
The challenge

EU FP7 HEALTH2013.4.2-3 call:
New methodologies for clinical trials for small population groups

> *"to develop new or improved statistical design methodologies for clinical trials aiming at the efficient assessment of . . . a treatment for small population groups in particular for rare diseases or personalised . . . medicine"*

Project funded February 2014 - May 2017

Progress and plans

WP1: Early phase dose-finding in small populations

Lead: Sarah Zohar (Paris)

- develop and evaluate innovative designs for early-phase dose-finding trials
- develop efficient model-based designs using PK/PD data

WP2: Decision-theoretic designs for small population clinical trials

Lead: Nigel Stallard (Warwick)

- optimise trial design allowing for population size
- value-of-information approach
- determine appropriate levels of evidence

WP3: Confirmatory trials for small populations and personalized medicines Lead: Martin Posch (Vienna)

- develop methods for identification and confirmation of subgroups
- develop optimized adaptive enrichment designs

WP4: Evidence synthesis in planning & interpretation of small population trials Lead: Tim Friede (Goettingen)

- assess evidence synthesis methods in small populations
- apply generalized evidence synthesis methods in paediatric studies

Sample size calculation in a small population
Motivation

Conventional method for definitive trial

- *fix error rates,* α
- *fix power,* $1-\beta$*, to detect specified effect*

Concerned about consequences of incorrect conclusion

Idea:

model decision-making at end of trial explicitly
allow for population size and obtain sample size accordingly

Decision-theoretic model

Total population size N
Two-arm trial: n_i patients in arm $i, i = 1, 2$

Observations $Y_{i1}, \ldots, Y_{in_i}$ with mean μ_i

Prior distribution with density $\pi(\mu_1, \mu_2)$

Gains:

patients in trial receiving treatment i: $n_i h(\mu_i)$
future patients receiving treatment i: $(N - n_1 - n_2)g(\mu_i)$
(if treatment i is recommended following trial)

Optimal decision at end of trial

Following observation of data Y,
choose treatment $\arg\max E(g(\mu_i) \mid Y)$

Optimal trial sample size

Choose n_1 and n_2 to maximise

$$\sum_{i=1,2} \{n_i E(h(\mu_i))\} + (N - n_1 - n_2) E(\max E(g(\mu_i) \mid Y))$$

Optimal sample size

For small N, can obtain optimal n_1, n_2 directly

For Y with exponential family form distribution with conjugate prior and g satisfying δ-method

N large $\implies$ n_i large $\implies$ $g(\mu_i) \mid Y \sim$ Normal

Optimum

$$n_i = \sqrt{\frac{N \int v(\mu)\pi(\mu,\mu)d\mu}{2\left(E(\max_j \mu_j)\right) - E(\mu_i)}}$$

where $v(\mu_i) = var(Y_{ij})$

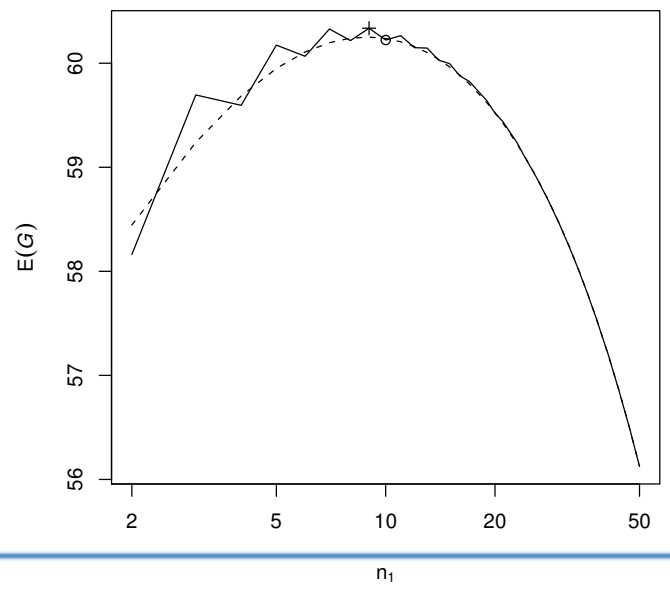
Note $n_i \sim N^{1/2}$ (extends result of Chen et al., 2003)

Example: single arm binary trial

Prior: $\mu_1 \sim \text{Beta}(1, 1)$ (prob. success for single arm)
$\mu_2 = 0.5$ (prob. success for control)

$h(\mu) = g(\mu) = \mu$ (max. E(total no. successes))

$N = 100$



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