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

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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, $\alpha$
- 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 $\mu_i$

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 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

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

$N$ large $\Rightarrow$ $n_i$ large $\Rightarrow$ $g(\mu_i) \mid Y \sim \text{Normal}$

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

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. $E(\text{total no. successes})$)

$N = 100$
Example: single arm binary trial

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\( N = 100 \)