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Applied decision theory for clinical trials in small populations

Frank Miller, Department of Statistics, Stockholm University

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Joint work

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- This talk is based on joint work together with **Simon Day, Siew Wan Hee, Jason Madan, Martin Posch, Nigel Stallard, Mårten Vågerö** and **Sarah Zohar** for the **InSPiRe** project.
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InSPiRe innovative methodology for small populations research

IDeAl Integrated DEsign and AnaLysis of small population group trials

SEVENTH FRAMEWORK PROGRAMME

Case study: Lyell's syndrome

- Life-threatening syndrome
- Drug-induced severe adverse drug reaction:
  Patient looses top layer skin, over whole body
- Mortality rate 22% in Europe
- In well controlled environment (specialized clinic) lower mortality rate
- Rare: incidence $2/10^6$ inhabitants in Europe

Lyell's syndrome

- New cellular therapy:
- **N=500** patients in EU could be reached by new therapy

- Hope that complete healing achieved after ~2 weeks
- Primary endpoint: Is at least 90% of body surface area skin detachment completely healed at Day 10 of therapy?
- Without new cellular therapy: anticipated that positive primary endpoint for 50% of patients: $\mathbf{p_0=0.5}$
- With new therapy: $\mathbf{p_1=?}$

Lyell's syndrome

- L'Assistance Publique-Hôpitaux de Paris sponsors a **clinical study with n patients receiving new therapy**

n ?

- Objective: Show that proportion of patients fulfilling primary endpoint is larger than $p_0=0.5$

Computation of sample size

- Traditional approach:

$$\text{power}_{p_1} = 1 - \Phi\left(z_{1-\alpha} - (p_1 - p_0) / \sqrt{\frac{p_0(1-p_0)}{n}} \right) \quad \rightarrow \quad n = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2 p_0(1-p_0)}{(p_1 - p_0)^2}$$

- Assurance approach (see O'Hagan *et al.*, 2005):

$$\text{assurance} = \int \text{power}_{p_1} \, \pi(dp_1) = \int 1 - \Phi\left(z_{1-\alpha} - (p_1 - p_0) / \sqrt{\frac{p_0(1-p_0)}{n}} \right) \pi(dp_1)$$

Sample size for Lyell's syndrome

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- Sample size for traditional and assurance approach (depending on prior)

Target / assumed mean response rate for new treatment (control response rate = 0.5)	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90
Traditional approach	>500	197	88	50	32	22	17	13
Assurance, prior weight=20	*	>500	283	88	44	27	18	13
Assurance, prior weight=10	*	*	>500	158	59	31	20	14
Assurance, prior weight= 2	*	*	*	*	>500	79	27	18

Significance level alpha=0.05, power=1-beta=0.8, p_0=0.5, beta-distribution as prior for assurance
*for these cases, the assurance would be < 0.8 even for infinitively large sample size

In our case study, p_1 assumed to have a Beta(a,b)-distribution:

expected value = a/(a+b), weight = a+b

Lyell's syndrome

- L'Assistance Publique-Hôpitaux de Paris sponsors a **clinical study with n patients receiving new therapy**

n ?

- Objective: Show that proportion of patients fulfilling primary endpoint is larger than $p_0=0.5$??
- Objective:
  Make good treatment **decisions** for the patients

Decisions for Lyell's syndrome

- Decisions in the Lyell's syndrome case:
  - Sample size **n**
  - After study:
    Decide about **treatment for future patients**

Study:	After study:
n patients treated with new cellular therapy	N-n patients (**treatment** depends on study result)

- We have a certain utility depending on our decision

Utility for Lyell's syndrome

- Utility for the Lyell's syndrome case:
  - Patients treated successfully has utility which is valued as 100 000 €
  - Costs of a patient being in the study and for new therapy: 25 000 €
  - Costs of patient being treated with new therapy after study: 5 000 €
- Total utility:

$U(n,p_1) = n\,(100\,p_1 - 25) + (N-n)\,(100\,p_0 - 5)$

if old treatment chosen after study;

$U(n,p_1) = n\,(100\,p_1 - 25) + (N-n)\,(100\,p_1 - 5)$

if new treatment chosen after study

Decision-theoretic sample size

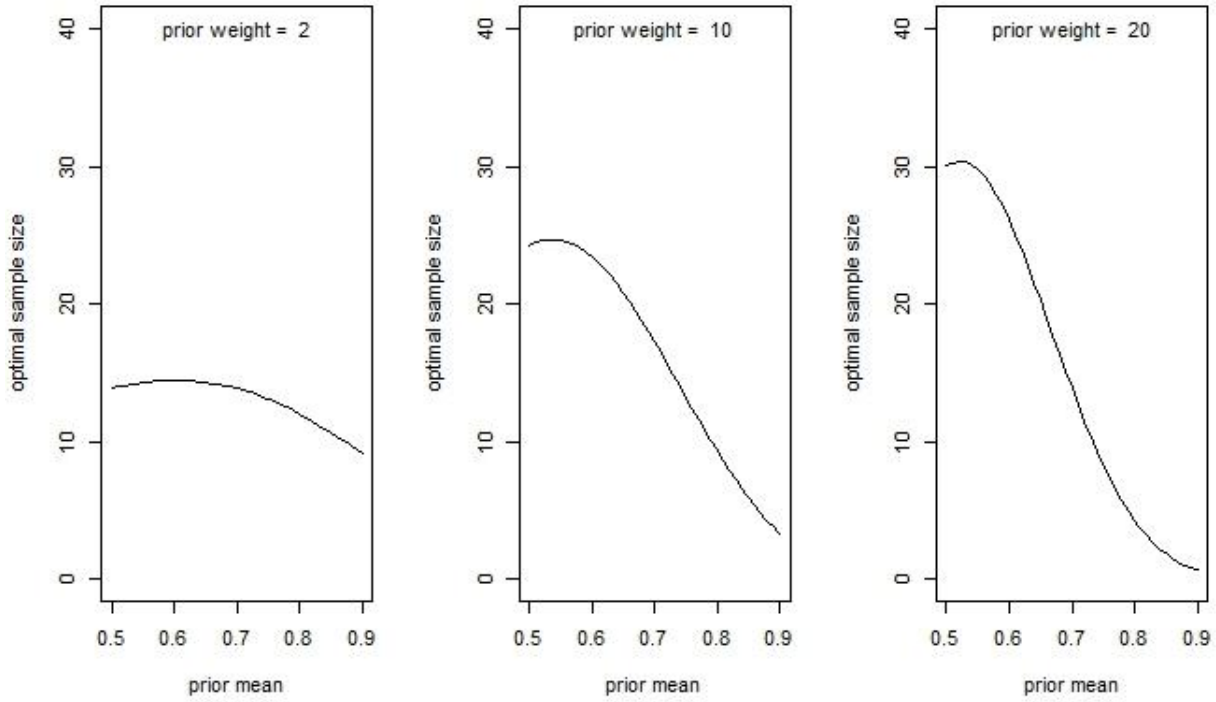
- Expected utility (gain): $G(n,p_1) = EU(n,p_1)$
  (expectation over possible study outcomes)

- Prior distribution assumed for unknown parameters (here Beta-distribution for p_1) and expected gain $\mathcal{G}(n)=EG(n,p_1)$ can be calculated
  (expectation over p_1)

- $\mathcal{G}(n)$ can be optimized over n

Sample size for Lyell's syndrome

- Optimal sample size (depending on prior)



- Chosen sample size for study: n=15

Theoretical results for optimal decision-theoretic sample size

- General context (Stallard *et al.*, 2016):
  - Clinical study: one- or two-sample case
  - Observed variable has distribution from one-parameter exponential family
  - Unknown parameter has prior distribution of conjugate form
  - Gain function in study h_i, after study g_i for treatment i=1,2
  - Size of population: N

- The optimal sample size(s) is/are of order $N^{1/2}$

Theoretical results for optimal decision-theoretic sample size

- Approximations for optimal sample sizes in the general situation (Stallard *et al.*, 2016):

$$n_1^* = \sqrt{N \frac{\int v_1 (g_1^{-1}(g_2(\xi_2)))\, g_1'(g_1^{-1}(g_2(\xi_2)))\, \pi(g_1^{-1}(g_2(\xi_2)), \xi_2)\, d\xi_2}{2(E_0(\max_{i=1,2} g_i(\xi_i)) - E_0(h_1(\xi_1)))}}$$

$$n_2^* = \sqrt{N \frac{\int v_2 (g_2^{-1}(g_1(\xi_1)))\, g_2'(g_2^{-1}(g_1(\xi_1)))\, \pi(\xi_1, g_2^{-1}(g_1(\xi_1)))\, d\xi_1}{2(E_0(\max_{i=1,2} g_i(\xi_i)) - E_0(h_2(\xi_2)))}}$$

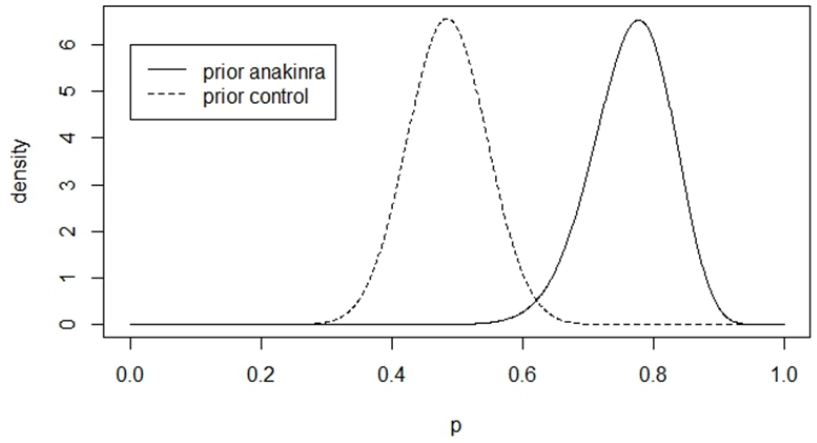
where ξ_i prior mean and v_i variance.

Case study 2: Adult-Onset Still's Disease

- Adult-Onset Still's Disease (AoSD) is a **chronic symptomatic disease** affecting around **N=1000** patients in the EU
- A randomized clinical trial comparing the treatment anakinra ($\mathbf{n_1=n}$ patients) with control ($\mathbf{n_2=n}$ patients) is planned
- Measurement of primary interest: remission (one binary variable for each patient)

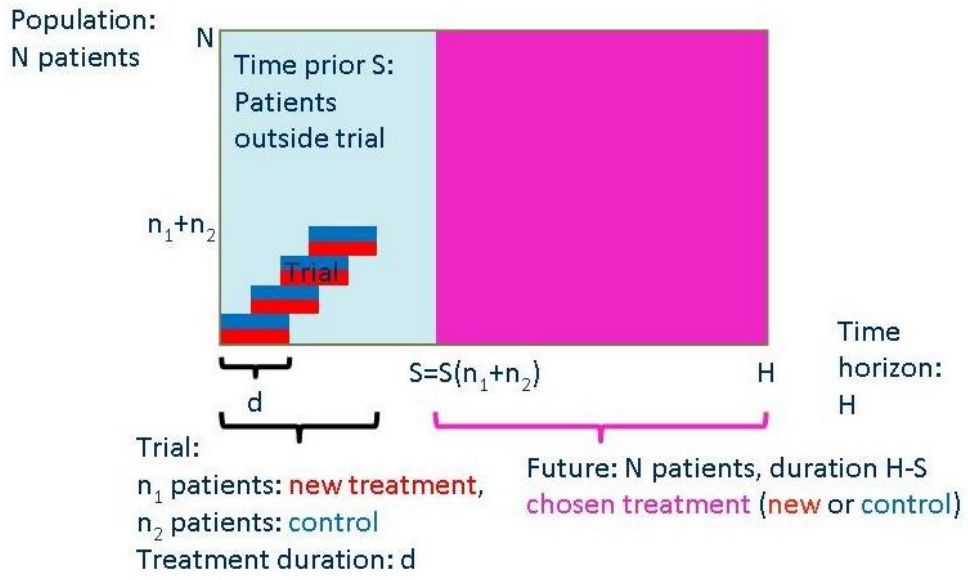
Adult-Onset Still's Disease: Prior information

- Meta analysis based on observational remission data for anakinra-treated patients and controls available (Hong *et al.*, 2014):
  - **36 of 47 anakinra**-treated patients and
  - **33 of 68 controls** experienced remission



Adult-Onset Still's Disease: Utility and gain

- For a chronic treatment, **duration of treatment in study** and **time of introduction of post-study treatment recommendation** is relevant



Adult-Onset Still's Disease: Sample sizes

- Traditional approach: n=46
- Assurance approach: n=56
  (where alpha=0.05, 1-beta=0.8)

- Decision-theoretic approach: n=0 (!)

Discussion

- Sample size justified by decision-theoretic arguments can be considerably different from traditional sample size

- Reasonable that decision-theoretic sample size n depends on population size N

- Hee *et al.* (2016) review decision-theoretic designs and distinguish “simple” and “more realistic” utility

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