Approaches to sample size calculation for clinical trials in small populations

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Joint work

- This talk is based on a joint work
  - together with Simon Day, Siew Wan Hee, Jason Madan, Martin Posch, Nigel Stallard, Mårten Vågerö and Sarah Zohar
  - for the InSPiRe project, a project which has received funding from the European Union's Seventh Framework Programme under grant agreement no 602144.

Outline

- Example of a rare disease: Lyell's syndrome
- Methods for sample size calculation
  - Traditional
  - Assurance
  - Decision-theoretic
- Sample size for Lyell's case study
- Example 2: Adult-Onset Still's Disease
- Theoretical results

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
- Effect of new therapy measured by following "primary endpoint":
  - Is at least 90% of body surface area skin detachment completely healed at Day 10 of therapy?
- Anticipated based on experience:
  - Without new cellular therapy, positive primary endpoint for 50% of patients: $p_0=0.5$

Lyell's syndrome

- L'Assistance Publique-Hôpitaux de Paris sponsors a clinical study with n patients receiving new therapy
- Objective: Show that proportion of patients fulfilling primary endpoint is larger than 0.5

- How many patients (n) needed?

Methods for sample size calculation

- Traditional approach:
  - Probability to reject H_0 with a significance test of level alpha should be at least 1-β if the proportion of patients fulfilling the primary endpoint is p_1

Methods for sample size calculation

- Assurance approach (see O'Hagan et al., 2005):
  - Probability to reject H_0 with a significance test of level alpha should be at least 1-β if the proportion of patients fulfilling the primary endpoint p_1 **has a distribution F**

- E.g. p_1 assumed to have a beta-distribution Beta(a,b);
  - expected value = a/(a+b),
  - weight = a+b

Computation of sample size

- Traditional approach:

$$n = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2 p_0(1-p_0)}{(p_1 - p_0)^2}$$

- Assurance approach:

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

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

Methods for sample size calculation

- Decision-theoretic approach:
  - Decision: n
  - Each result (depending on decision and on observed random variables) has specific utility U = U(n,**X**)
  - Expected utility is (here) called gain: G=EU
  - Gain depends on unknown parameters (here p_1)
  - If we have a prior for unknown parameters, we can calculate the expected gain $\mathcal{G}$=EG
- Hee et al. (2015) review decision-theoretic designs

Decisions for Lyell's syndrome

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

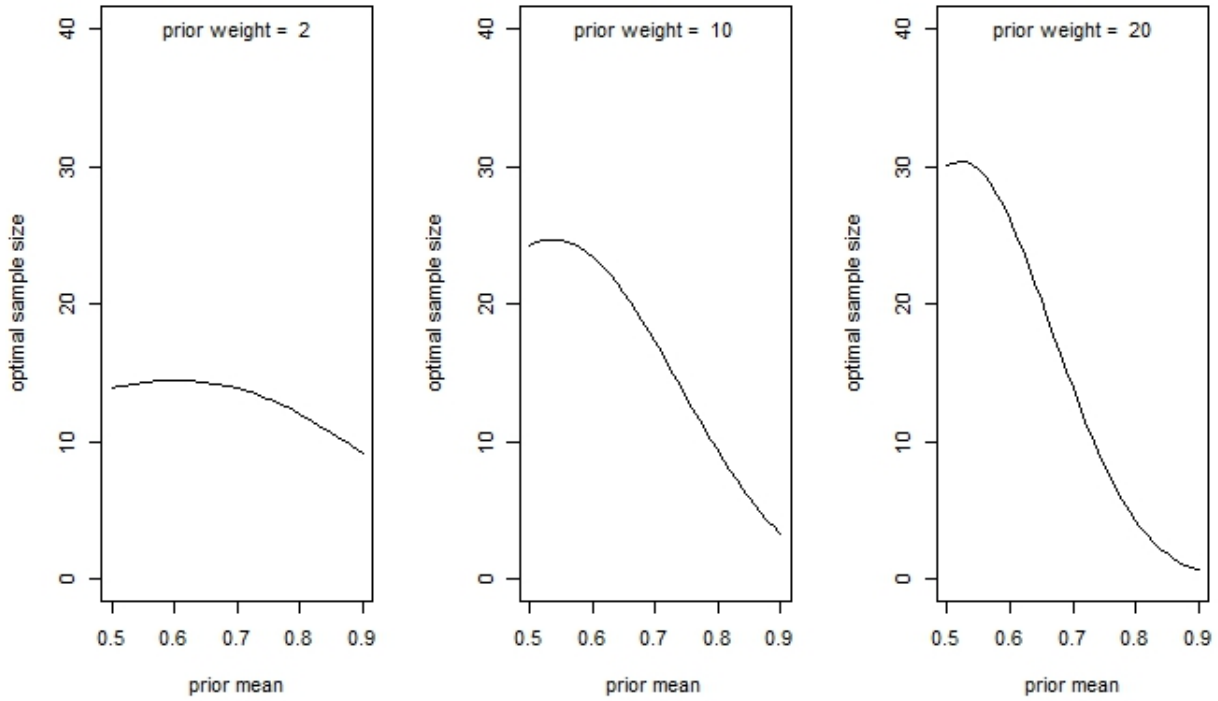
Study:	After study:
n patients treated with new cellular therapy	N-n patients (treatment depends on study result)

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 €
- X_i=1 if patient i treated successfully; X_i=0 if not
- Utility for a patient in study: $U = 100\ X_i - 25$
- Utility for a patient after study: $U = 100\ X_i - 5$

Sample size for Lyell's syndrome

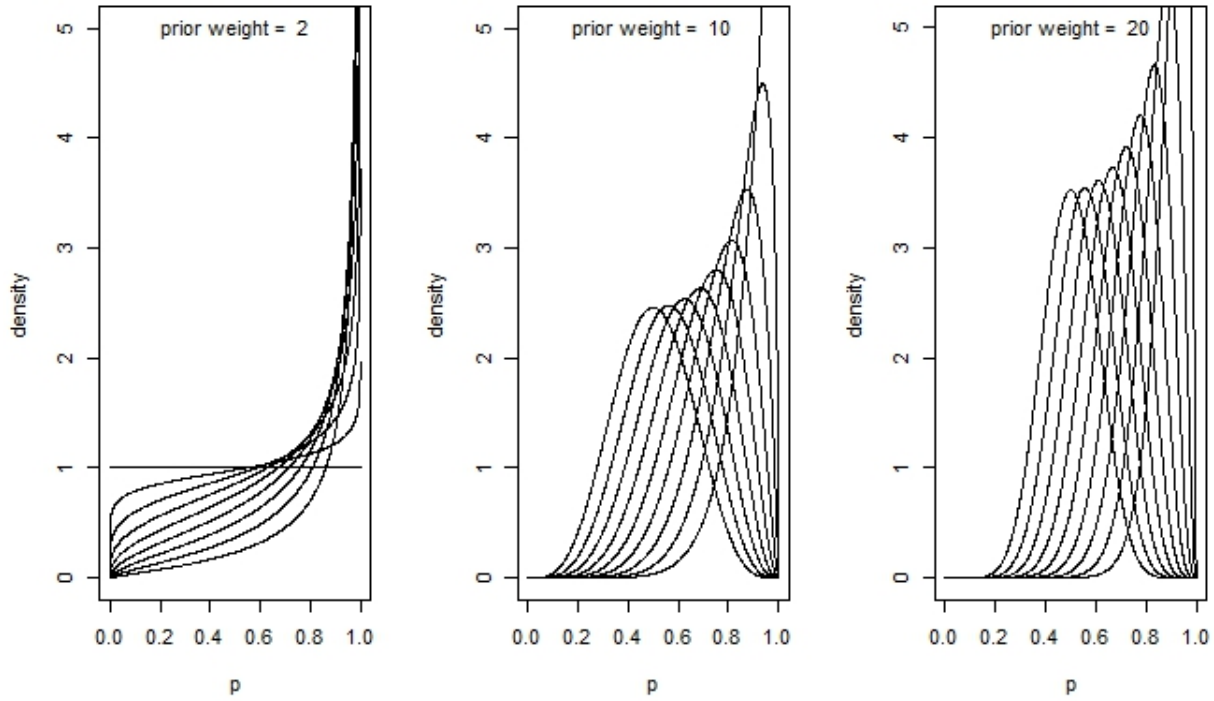
- Optimal sample size (depending on prior)



- Chosen sample size for study: n=15

Sample size for Lyell's syndrome

- Different priors



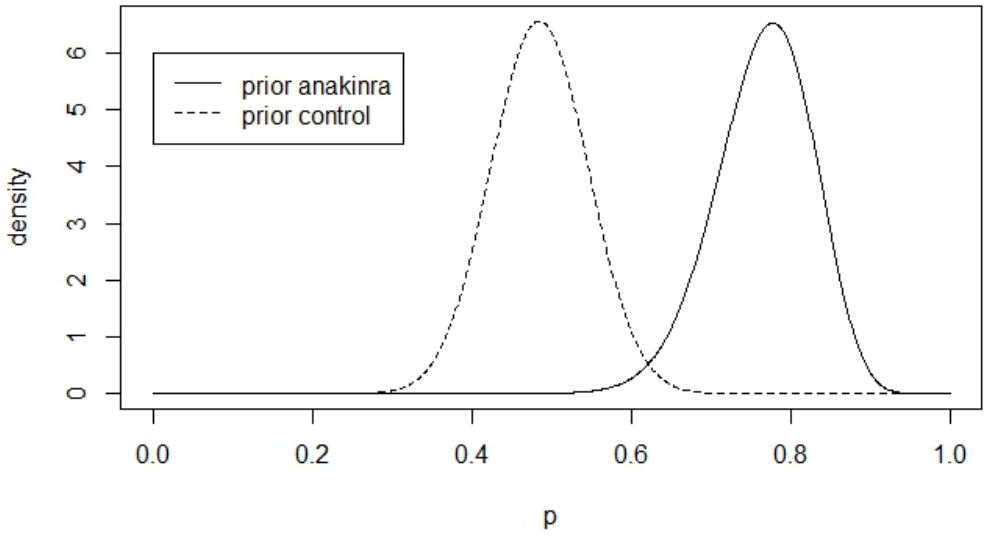
Adult-Onset Still's Disease

- 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 (n patients) with control (n patients) is planned
- Measurement of primary interest: remission (one binary variable for each patient)

Adult-Onset Still's Disease: Prior information

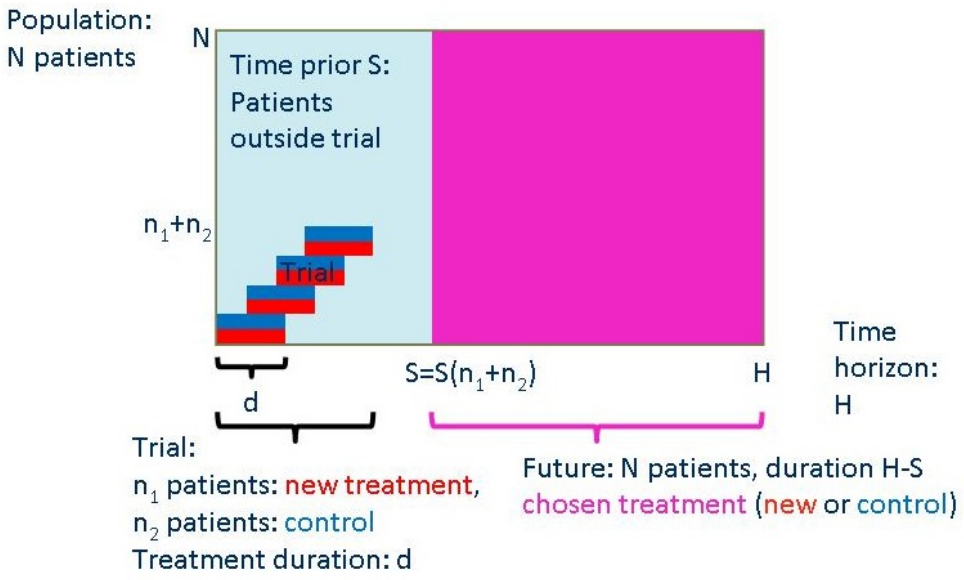
- Meta analysis based on observational remission data for anakinra-treated patients and controls available (Hong et al., 2014):
  - **36 of 47 anakinra**-treated patients and
  - **33 of 68 controls** experienced remission

Adult-Onset Still's Disease: Prior information



Adult-Onset Still's Disease: Gain function

- Gain for patients in the trial: $p - 0.05$,
  gain for patients outside-trial: $p - 0.01$,
  p = remission rate ($p=p_1$ anakinra, $p=p_2$ control)



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 (!)

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 (includes binomial and normal case)
  - 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

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

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

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

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