Design of clinical studies with "time-to-event" end points subject to random censoring

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Overview

- Standard Steps for Optimal Design
- Review of Enrollment, randomization and clinical trials with time to event endpoints
- Model, information matrix,
- Optimization problems
- Examples

Abstract

Additionally to observational uncertainties generated by randomness of treatment outcomes, observational errors or by variability between units/subjects that are typical in the traditional clinical trials we face uncertainties caused by enrollment process that often can be viewed as a stochastic processes. The latter makes the amount of information that can be gained during experimentation uncertain at the design stage. To address the problem we modify the concept of "optimal design" and develop methods that guarantee that the information metrics either will be greater than a predefined levels with the smallest probability or the average information will be maximized. We illustrate the approach using proportional hazard models with censored observations and enrollment described by the Poisson process.

Standard steps in optimal design

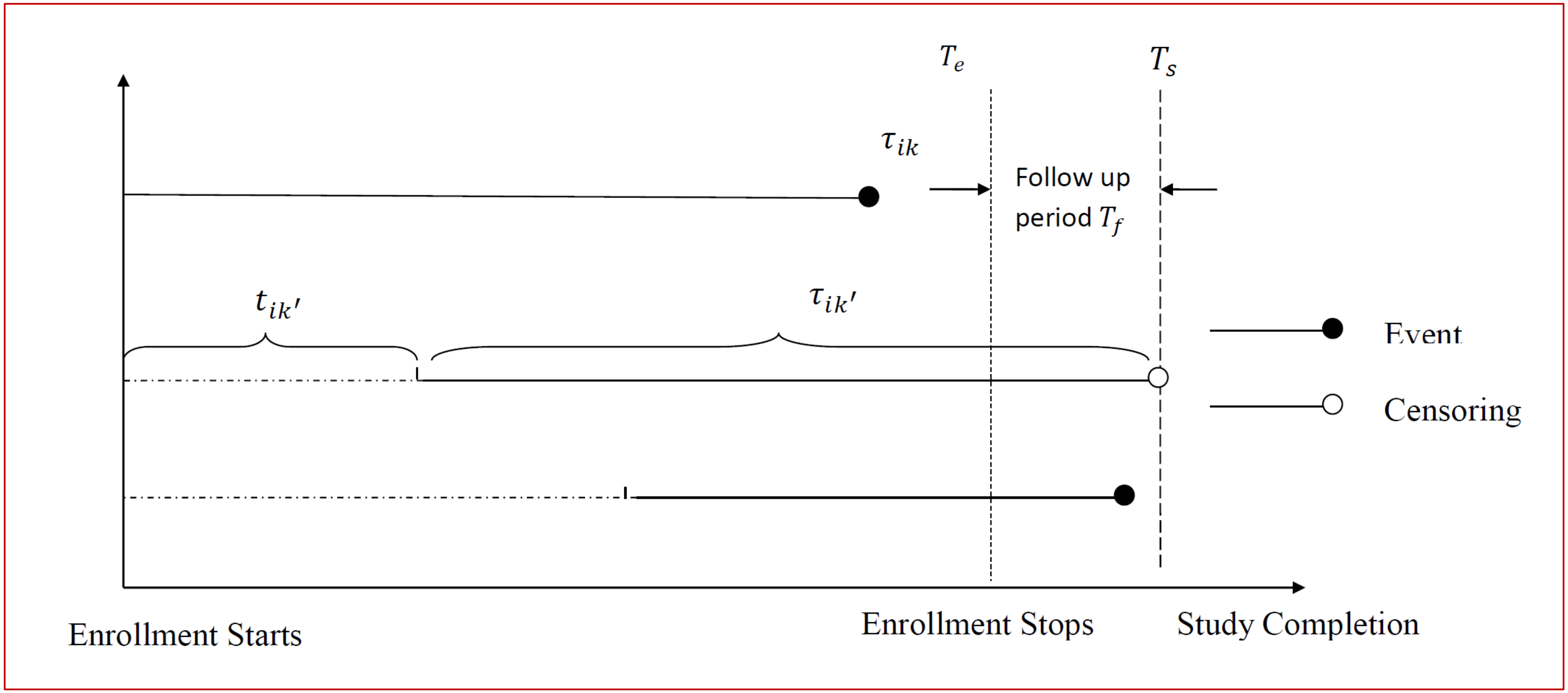
- Model: $$Y \sim p(y|\eta) \qquad \eta = \eta(x, \theta)$$
- Elemental IM: $$\nu(\eta) = \mathrm{Var}\left[\frac{\partial}{\partial \eta} \ln p(y|\eta)\right]$$
- IM of a single observatic
$$\mu(x,\theta) = F(x,\theta)\nu(\eta)F^T(x,\theta)$$
$$F(x,\theta) = \frac{\partial \eta^T(x,\theta)}{\partial \theta}$$
- Information matrix:
$$M(\theta, \{x_i\}_1^n) = \sum_{i=1}^{n} \mu(x_i, \theta)$$

Standard steps in optimal design II

- Design and controls: $\xi = \{w_i, x_i\}_1^n \qquad x \in \mathscr{X}$
- Normalized IM: $$M(\theta, \xi) = \sum_{i=1}^{n} w_i \mu(x_i, \theta)$$
- Criteria of optimality: *Convex, homogeneous, monotonous functional* $$\Psi\left[M(\xi, \theta)\right]$$
- Optimization problem: $$\xi^* = \arg\min_{\xi \in \Xi} \Psi\left[M(\xi, \theta)\right]$$
- Sample size evaluation: $$n_\bullet^* \Psi(M(\xi^*, \theta) \le \Psi^*, \quad n_i^* = w_i^* n_\bullet^*$$
- Missing: Quantitative analysis of operational costs

Enrollment, randomization and design of clinical studies with "time-to-event" end points

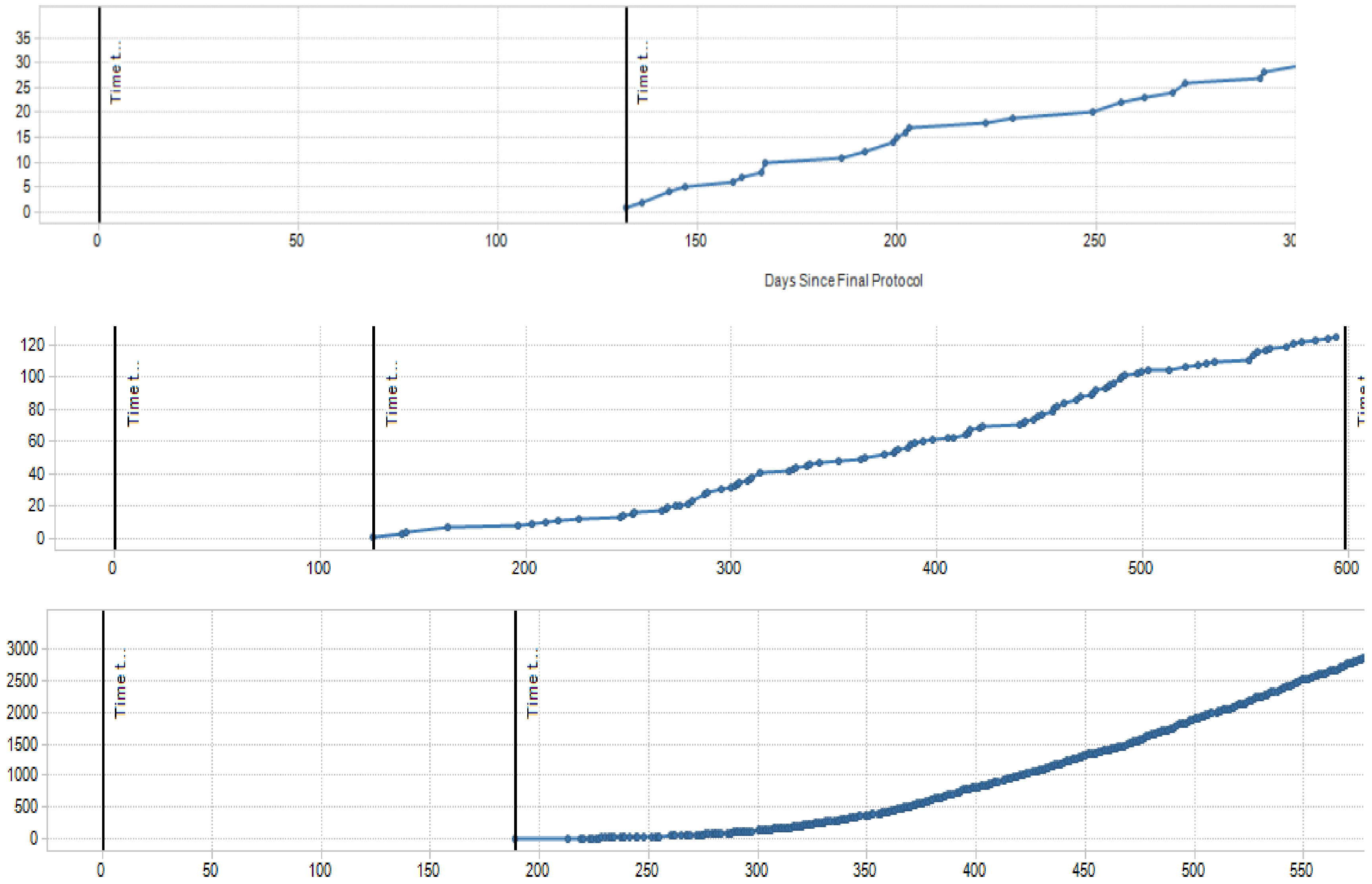
Setting the clinical trial design problem



When a study is completed we know:

- Number of subjects n_i assigned to dose x_i and all times t_{ij} these values are completely defined by and enrollment process and randomization rule.
- The outcomes $\{y_{ij}\}_1^{n_i} = \{\tau_{ij}, \delta_{ij}\}_1^{n_i}$, where $\delta_{ij} = 1$ if $\tau_{ij} \le T_s - t_{ij}$ and $\delta_{ij} = 0$ otherwise.

Typical enrollment curves



Enrollment

- We assume that enrollment follows a Poisson process with intensity $\lambda(t)$. Total enrollment $n(t)$ is Poisson distributed with parameter $\Lambda(t) = \int \lambda(t)\,dt$
- On arrival subjects are randomized across N doses $\{x_i\}$ with probabilities $\{p_i\}, \Sigma p_i = 1$
- Enrollment stops:
  - ⊗ At the pre-fixed time T_e
  - ⊗ Required number of subjects $n\bullet$ are enrolled
  - ⊗ Needed number of events $r\bullet$ have occurred
  - ⊗ Hybrid stopping rules

Notations

- Distribution function: $$\Phi(\tau,\eta) = \int_0^\tau \varphi(t,\eta)dt$$
- Survival function: $$S(\tau,\eta) = 1 - \Phi(\tau,\eta)$$
- Hazard function: $$h(\tau,\eta) = \frac{\varphi(\tau,\eta)}{S(\tau,\eta)} = -\frac{\partial \ln S(\tau,\eta)}{\partial \tau}$$
- Integrated hazard: $$H(\tau,\eta) = \int_0^\tau h(t,\eta)dt$$

Observations and Model

- Outcomes at x_i - s:

$$\left\{ y_{ij} \right\}_1^{n_i} = \left\{ \tau_{ij}, \delta_{ij} \right\}_{1,}^{n_i}$$

$$\delta_{ij} = 1 \text{ if } \tau_{ij} \le T_s - t_{ij} \text{ and}$$

$$\delta_{ij} = 0 \text{ otherwise.}$$

- Model:

$$\tau \sim \varphi(\tau, \eta), \qquad \eta = \eta(x, \theta)$$

- Log-likelihood:

$$L = \sum_i \sum_j \ln h(\tau_{ij}, \eta(x_i, \theta))\delta_{ij} - \sum_i \sum_j \mathrm{H}(\tau_{ij}, \eta(x_i, \theta))(1 - \delta_{ij})$$

Fisher Information Matrix

- Elemental FIM:

$$\nu(\tau,\eta) = \int_0^\tau \frac{\partial \ln \varphi(t,\eta)}{\partial \eta} \frac{\partial \ln \varphi(t,\eta)}{\partial \eta^\top} \varphi(t,\eta) dt + S(\tau,\eta) \frac{\partial \ln \Phi(\tau,\eta)}{\partial \eta} \frac{\partial \ln \Phi(\tau,\eta)}{\partial \eta^\top}$$

or

$$\nu(\tau,\eta) = \int_0^\tau \frac{\partial \ln h(t,\eta)}{\partial \eta} \frac{\partial \ln h(t,\eta)}{\partial \eta^\top} \varphi(t,\eta) dt$$

- FIM of a single observation:

$$\mu(x,\tau,\theta) = F(x,\theta)\nu(\tau,\eta(x,\theta))F^\top(x,\theta)$$

$$\tau = T_s - t, \quad F(x,\theta) = \partial \eta^\top(x,\theta)/\partial \theta$$

- Total FIM:

$$\underline{M}(\{t_{ij}\}, T_s, \theta) = \sum_{i=1}^{N} \sum_{j=1}^{n_i} \mu(x_i, \tau_{ij}, \theta) = \sum_{i=1}^{N} F^\top(x_i,\theta) \left[\sum_{j=1}^{n_i} \nu(\tau_{ij}, \eta(x_i,\theta)) \right] F(x_i,\theta)$$

Only known after enrollment completion

$$n_i \overline{\nu}(x_i,\theta), \quad \overline{\nu}(x_i,\theta) = n_i^{-1} \sum_{j=1}^{n_i} \nu(\tau_{ij}, \eta(x_i,\theta))$$

Elemental information matrices

Distribution	Density	Hazard Function Quantiles	Elemental Information
Exponential(η) $\eta > 0$	$\frac{1}{\eta}\, e^{-\frac{\tau}{\eta}}$	$\frac{1}{\eta}$, $-\eta \ln(1-P)$	$\frac{1}{\eta^2}\left(1 - e^{-\frac{T}{\eta}}\right)$
Weibull(α, η) $\alpha > 0$, $\eta > 0$	$\frac{\alpha}{\eta}\left(\frac{\tau}{\eta}\right)^{\alpha-1} e^{-(\tau/\eta)^{\alpha}}$	$\frac{\alpha}{\eta}\left(\frac{\tau}{\eta}\right)^{\alpha-1}$, $\eta\left(-\ln(1-P)\right)^{1/\alpha}$	$\nu_{\alpha\alpha} = \frac{1}{\alpha^2}\int_0^{-\ln(1-\omega)} \left[1+\ln u\right]^2 e^{-u} du,$ $\nu_{\alpha\eta} = \nu_{\eta\alpha} = \frac{1}{\eta}\int_0^{-\ln(1-\omega)} \left[1+\ln u\right] e^{-u} du,$ $\nu_{\eta\eta} = \frac{\alpha^2}{\eta^2}\omega,$ $\omega = 1 - e^{-(T/\eta)^{\alpha}}$
GE(α, η) $\alpha > 0$, $\eta > 0$	$\frac{\alpha}{\eta} e^{-\frac{\tau}{\eta}}\left(1 - e^{-\frac{\tau}{\eta}}\right)^{\alpha-1}$	$\frac{\frac{\alpha}{\eta} e^{-\frac{\tau}{\eta}}\left(1-e^{-\frac{\tau}{\eta}}\right)^{\alpha-1}}{1-\left(1-e^{-\frac{\tau}{\eta}}\right)^{\alpha}}$, $-\eta \ln\left(1 - P^{1/\alpha}\right)$	$\nu_{\alpha\alpha} = \frac{1}{\alpha^2}\left[\overline{\omega} + \frac{\overline{\omega}}{1-\overline{\omega}}(\ln \overline{\omega})^2\right],$ $\nu_{\alpha\eta} = \nu_{\eta\alpha} = -\frac{\alpha}{\eta}\int_0^{\overline{\omega}^{1/\alpha}} \left[\frac{1}{\alpha} + \frac{\ln u}{1-u^{\alpha}}\right],$ $\times\left[1 + \frac{\ln(1-u)}{u} - \frac{\alpha(1-u)\ln(1-u)}{u(1-u^{\alpha})} u^{\alpha-1} du\right]$ $\nu_{\eta\eta} = \frac{\alpha}{\eta^2}\int_0^{\overline{\omega}^{1/\alpha}} \left[1 + \frac{\ln(1-u)}{u} - \frac{\alpha(1-u)\ln(1-u)}{u(1-u^{\alpha})}\right]^2 u^{\alpha-1} du,$ $\overline{\omega} = \left(1 - e^{-(T/\eta)}\right)^{\alpha}$
Log-Logistic(α, η) $\alpha > 0$, $\eta > 0$	$\frac{\frac{\eta}{\alpha}\left(\frac{\tau}{\alpha}\right)^{\eta-1}}{\left(1+\left(\frac{\tau}{\alpha}\right)^{\eta}\right)^2}$	$\frac{(\eta/\alpha)(\tau/\alpha)^{\eta-1}}{1+(\tau/\alpha)^{\eta}}$, $\alpha\left(\frac{P}{1-P}\right)^{1/\eta}$	$\nu_{\alpha\alpha} = \frac{1}{3}\left(\frac{\alpha}{\eta}\right)^2\left[1 - \frac{1}{\left(1+\left(\frac{T}{\alpha}\right)^{\eta}\right)^3}\right],$ $\nu_{\alpha\eta} = \nu_{\eta\alpha} = -\frac{1}{2\alpha}\left[1 - \frac{1}{\left[1+\left(\frac{T}{\alpha}\right)^{\eta}\right]^2}\right],$ $\nu_{\eta\eta} = \frac{1}{\eta^2\left[1+\left(\frac{T}{\alpha}\right)^{-\eta}\right]}$
Log-Normal(α, η) $\alpha > 0$, $\eta > 0$	$\frac{1}{\sqrt{2\pi}\tau\alpha} e^{-\frac{(\ln\tau - \ln\eta)^2}{2\alpha^2}}$	$\frac{\frac{1}{\tau\alpha}\phi\left(\frac{\ln\tau}{\eta}\right)}{\Phi\left(\frac{-\ln\tau}{\alpha}\right)}$, $\lambda e^{\alpha\Phi^{-1}(P)}$	$\nu_{\alpha\alpha} = \frac{1}{(1-\omega)\alpha}\left[\phi\left(\Phi^{-1}(\omega)\right)\right]^2\left(\Phi^{-1}(\omega)\right)^2,$ $\nu_{\alpha\eta} = \frac{1}{\eta(1-\omega)\alpha}\left[\phi\left(\Phi^{-1}(\omega)\right)\right]^2\left(\Phi^{-1}(\omega)\right),$ $\nu_{\eta\eta} = \frac{1}{\eta^2(1-\omega)\alpha}\left[\phi\left(\Phi^{-1}(\omega)\right)\right],$ $\omega = \Phi\left(\frac{\ln T - \ln\eta}{\alpha}\right)$

Standard steps in optimal design

- Derivation of normalized FIM:

$$M(\theta, \xi) = \sum_{i=1}^{N} p_i \mu(x_i, \theta)$$

- Selection of criteria of optimality (*convex, homogeneous, monotonous functional)*:

$$\Psi[M(\xi, \theta)]$$

- Solution of the optimization problem:

$$\xi^* = \arg\min_{\xi} \Psi[M(\xi, \theta)]$$

where $\xi = \{p_i, x_i\}_1^N$ ar $x \in \mathscr{X}$

- Sample size evaluation:

$$n_\bullet^* \Psi[M(\xi^*, \theta)] \leq C^*, \quad n_i^* = p_i^* n_\bullet^*$$

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Two useful results

- Coloring Theorem

> Let the probability that a point of a Poisson process of intensity $\lambda(\tau)$ receives the i-th color being p_i and colors of different points being independent. Then the colored processes are independent Poisson processes with intensities $\lambda_i(\tau) = p_i\lambda(\tau)$.

- Campbell's Theorem (sums over Poisson processes)

$$\mathrm{E}\left[\sum_{j=1}^{n} f(\tau_j)\right] = \Lambda(T)\int_0^T f(\tau)l(\tau)d\tau \quad \text{and} \quad \mathrm{Var}\left[\sum_{j=1}^{n} f(\tau_j)\right] = \Lambda(T)\int_0^T f^2(\tau)l(\tau)d\tau$$

$$l(\tau) = \lambda(\tau)/\Lambda(T), \quad \Lambda(T) = \int_0^T \lambda(\tau)d\tau$$

Kingman, J.F.C. (1993). Poisson Processes, Oxford Science Publications, New York.

Expected FIM of a single observation

Let $\Sigma_i = \sum_{j=1}^{n_i} \nu\left(T_s - t_{ij}, \eta(x_i,\theta)\right) = \sum_{j=1}^{n_i} \nu\left(T_e + T_f - t_{ij}, \eta(x_i,\theta)\right)$ and p_i be randomization rates , then $\mathrm{E}\left[\sum_{j=1}^{n_i} \nu\left(\tau_{ij}, \eta(x_i,\theta)\right)\right] = p_i \Lambda(T_e) \overline{\nu}\left(T_e, T_f, \eta(x_i,\theta)\right)$

and

$$\mathrm{Var}\left[\sum_{j=1}^{n_i} \nu^2_{\alpha,\beta}\left(\tau_{ij}, \eta(x_i,\theta)\right)\right] = p_i \Lambda(T_e) \overline{\nu^2_{\alpha,\beta}}\left(T_e, T_f, \eta(x_i,\theta)\right)$$

where $\overline{\nu}(T_e, T_f, \eta) = \int_0^{T_e} \nu(T_e + T_f - t, \eta) l(t) dt = \mathrm{E}\left[\nu(T_e + T_f - t, \eta)\right]$ and

$l(t) = \lambda(t)/\Lambda(T_e)$

$$\overline{\mu}\left(T_e, T_f, \eta(x,\theta)\right) = F(x,\theta)\overline{\nu}\left(T_e, T_f, \eta(x,\theta)\right) F^\top(x,\theta)$$

Design optimization

- Expected FIM: $\mathfrak{M}(\xi, T_e, T_f, \theta) = \mathrm{E}\left[\underline{\mathrm{M}}(\{t_{ij}\}, T_e, T_f, \theta)\right] = \Lambda(T_e) \sum_{i=1}^{N} p_i \overline{\mu}\left(T_e, T_f, \eta(x_i, \theta)\right)$
- Normalized expected FIM: $\mathrm{M}(\xi, T_e, T_f, \theta) = \sum_{i=1}^{N} p_i \overline{\mu}\left(T_e, T_f, \eta(x_i, \theta)\right)$
- Design problem given T_e, T_f, θ (almost nothing new):

$$\xi^*(T_e, T_f, \theta) = \arg\min_{\xi} \Psi\left[\Lambda(T_e)\mathrm{M}(\xi, T_e, T_f, \theta)\right] = \arg\min_{\xi} \Psi\left[\mathrm{M}(\xi, T_e, T_f, \theta)\right]$$

- Next step (challenging even for homogeneous enrollment, λ(t)=const):

$$(T_e^*, T_f^*) = \arg\min_{T_e, T_f} \Psi\left[\mathrm{M}\left(\xi^*(T_e, T_f, \theta), T_e, T_f, \theta\right)\right], \;\; C(\lambda, T_e, T_f) \le C^*$$

Proportional hazard family

- Model:

$$h(\tau,\eta)=\eta h_0(\tau),\;\; H(\tau)=\eta H_0(\tau)=\eta\int_0^\tau h_0(t)dt,$$
$$S(\tau,\eta)=e^{-\eta H_0(\tau)},\qquad \varphi(\tau,\eta)=\eta h_0(\tau)e^{-\eta H_0(\tau)}$$

- Elemental FIM:

$$\nu(\tau,\eta)=\frac{1}{\eta^2}[1-e^{-\eta H_0(\tau)}]=\frac{1}{\eta^2}\Phi(\tau,\eta)$$

- For homogeneous Poisson enrollment process:

$$\bar{\nu}(T_e,T_f,\eta)=\frac{1}{\eta^2}\int_0^{T_e}\frac{1}{T_e}\Phi(T_e+T_f-t,\eta)dt=\frac{1}{\eta^2}\bar{\Phi}(T_e+T_f,\eta)$$

- If $\eta(x,\theta)=e^{\theta^\top f(x)}$, i.e. $F(x,\theta)=\eta(x,\theta)f^\top(x)$, then

$$\mathrm{M}(\xi)=\mathrm{M}(\xi,T_e,T_f,\theta)=\sum_{i=1}^{N}p_i\omega(x_i)f(x_i)f^\top(x_i)\qquad \omega(x)=\bar{\Phi}(T_e+T_f,\eta(x,\theta))$$

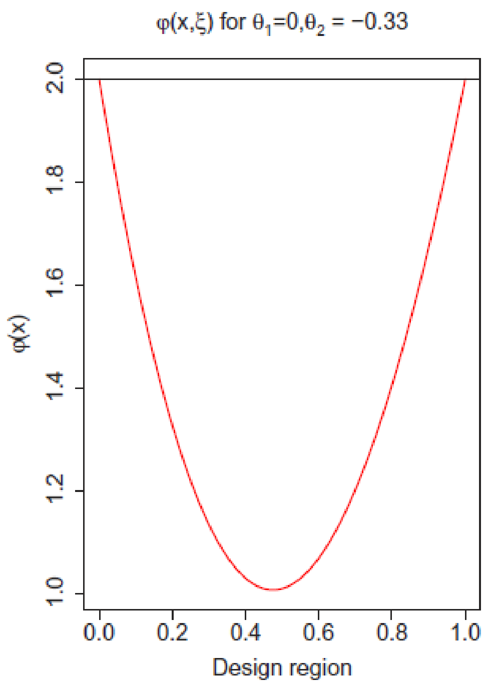
Most of cases are similar to classical Optimal Design

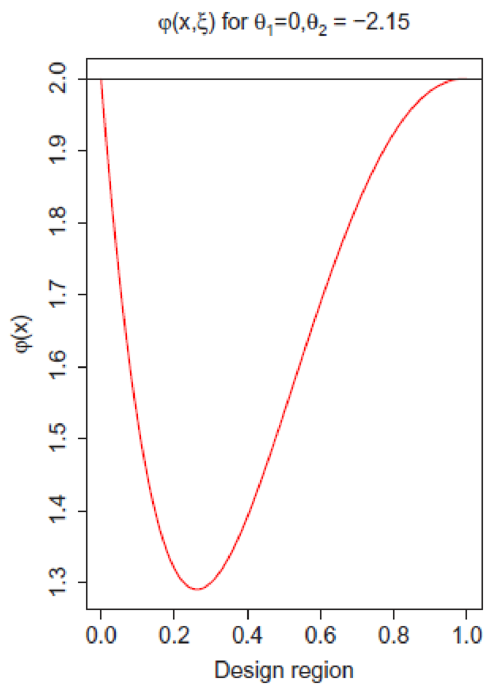
- Elemental FIM for a constant hazard /exponential model

$$\bar{v}(T_e, T_f, \eta) = \frac{1}{\eta^2}\left[1 - \frac{1}{\eta T_e}\left(e^{-T_f/\eta} - e^{-T_s/\eta}\right)\right]$$

- Stopping by $n_\bullet$ (constant cumulative enrollment rate):

$$\xi^*(n_\bullet, T_f, \theta) = \arg\min_\xi \Psi\left[n_\bullet \mathrm{M}(\xi, n_\bullet/\lambda, T_f, \theta)\right] = \arg\min_\xi \Psi\left[\mathrm{M}(\xi, n_\bullet/\lambda, T_f, \theta)\right]$$





$T_e = 6$ months

$T_f = 12$ months

left: $\theta_1 = 0, \theta_2 = -0.33$

right: $\theta_1 = 0, \theta_2 = -2.15$, which corresponds to HR=0.1

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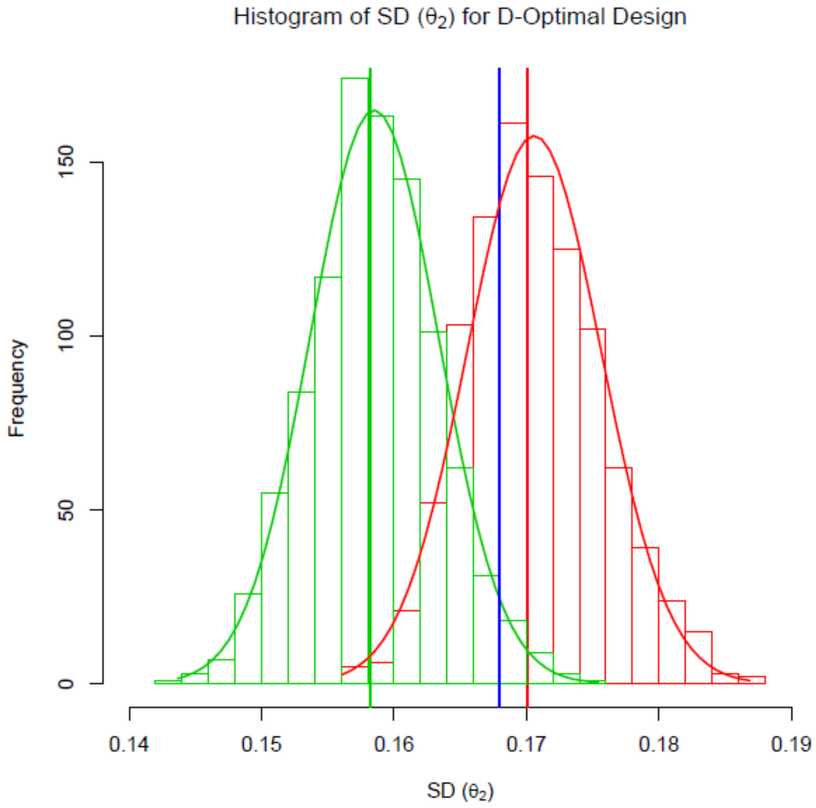
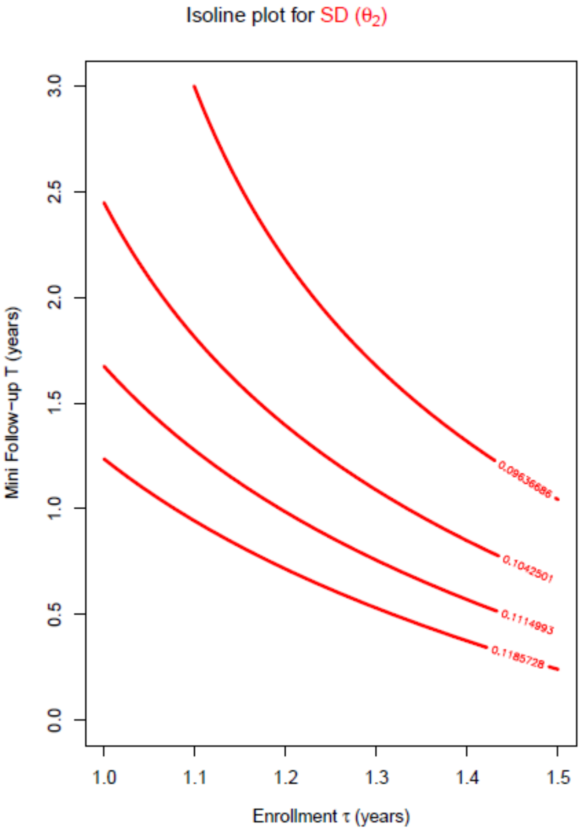
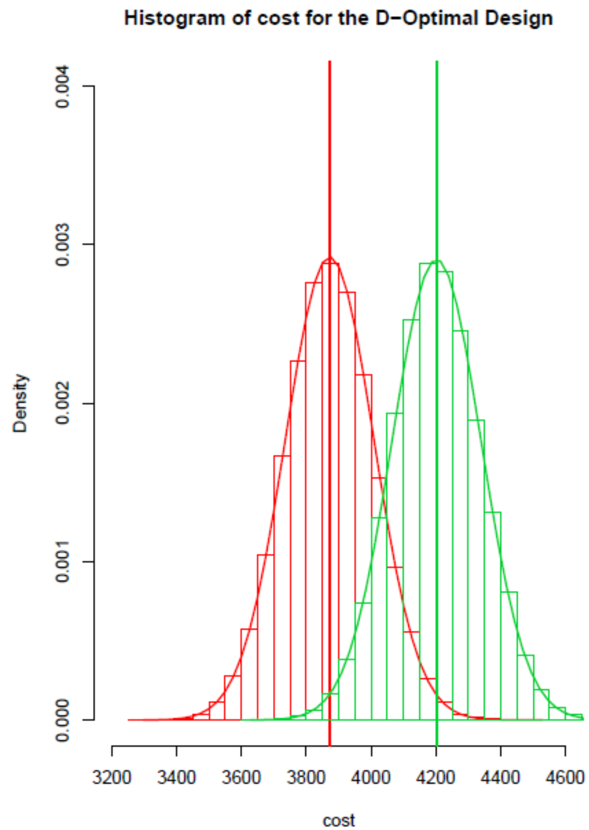
Case Studies: distributions vs expectations



	Left Scenario	Right Scenario
Enrollment	240 subjects in 6 months	300 subjects in 6 months
Minimum Follow-up	10 months	6 months
Randomization	1:1, and patient enrollment follows Poisson Process	
θ_1 (median survival time for Placebo)	0 (8.3 months)	
θ_2 *(hazard ratio)*	-1/3 (0.7165)	
StD *required to reject* $\theta_2 = 0$	0.168	
Probability to have Std≤ 0.168	>97.5%	<50%

Case studies (Cost)





c_0 = initiation cost

c_1 = cost of enrolling a single subject

c_2 = general trial maintanance

c_3 = daily expense for a patient in trial

c_4 = potential loss of revenue due to delay

c_5 = penalty not able to meet the criteria to reject H_0

10,000 simulation runs

$$C\left(\Lambda\left(T_e\right), T_e, T_f\right) = c_0 + c_1 \sum_i n_i + c_2 T_s + c_3 \sum_j \sum_i \lambda_{ij} + c_4 T_s + c_5 I\left(\text{var}\left(\hat{\theta}_2\right) > s*\right)$$

	RED Scenario	GREEN Scenario
Enrollment (Expected)	540 subjects in 18 months	432 subjects in 14.5 months
Minimum Follow-up	12 months	31 months
Randomization	1:1, and patient enrollment follows Poisson Process	
θ_1 (median survival time for Placebo)	-0.367 (12 months)	
θ_2	log(0.732)	

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Censoring Time Distribution	Density	Average Elemental Information $\overline{\nu}(\eta, T, \zeta)$
Uniform$(0, T_e)$ $T_e \leq T$	$\frac{1}{T_e}$	$\frac{1}{\eta^2}\left[1 - \frac{\eta}{T_e}\left(e^{-(T-T_e)/\eta} - e^{-T/\eta}\right)\right]$
RT Exponential(λ, T_e) $T_e \leq T$	$\frac{\frac{1}{\lambda}e^{-t/\lambda}}{1-\exp\left(-\frac{T_e}{\lambda}\right)}$	$\frac{1}{\eta^2}\left[1 - \frac{e^{-\frac{T}{y}}}{\left(1-e^{-\frac{T_e}{\lambda}}\right)\left(1-\frac{\lambda}{\eta}\right)}\left[1 - e^{-\left(\frac{1}{\lambda}-\frac{1}{\eta}\right)T_e}\right]\right]$
RT Gamma$(t; \alpha, \beta, 0, T_e)^*$ $\alpha > 0$, $\beta > 0$	$k\left(\frac{t}{\beta}\right)^{\alpha-1} e^{-t/\beta}$ $k = \frac{\alpha}{\beta\Gamma(1+\alpha,0)-\beta\Gamma(1+\alpha,\frac{T_e}{\beta})+e^{-\frac{T_e}{\beta}}\beta^{\alpha+1}}$	$\frac{k}{\eta^2}\left[\beta\widetilde{\gamma}\left(\alpha, \frac{T_e}{\beta}\right) - e^{-\frac{T}{\eta}}\beta\left(1-\frac{1}{\eta}\right)^{-\alpha}\widetilde{\gamma}\left(\frac{1}{\beta}-\frac{1}{\eta}\right)^{T_e}\right]^\star$
Beta$(t; \alpha, \beta, 0, T_e)$ $\alpha > 0$, $\beta > 0$	$B(\alpha, \beta)t^{\alpha-1}(1-t)^{\beta-1}$	$\frac{1}{\eta^2}\left[1 - \Phi\left(\beta, \alpha+\beta, -T_e\eta\right)\right]^\dagger$

$*$Note: RT Gamma=Right Truncated Gamma Distribution, $t \sim \text{Gamma}\left(\alpha, \beta\right), t_s \in (0, T_e)$

$\star$Note : $\widetilde{\gamma}\left(\alpha, z\right) = \int_0^z e^{-t}t^{t-1}dt$is an incomplete gamma function;

†Note : $\Phi\left(\alpha, \omega; z\right) = 1 + \frac{\alpha}{\omega}\frac{z}{1!} + \frac{\alpha}{\omega}\frac{(\alpha+1)}{(\omega+1)}\frac{z^2}{2!} + \frac{\alpha}{\omega}\frac{(\alpha+1)}{(\omega+1)}\frac{(\alpha+2)}{(\omega+2)}\frac{z^3}{3!} + \ldots$is called a confluent hypergeometric function.See Gradshteyn and Ryzhik (2007).

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Standard steps in optimal design III

- N&S condition for ξ^* be optimal is that $\min_{x \in \mathscr{X}} \psi(x, \xi^*) \geq 0$

$\Psi(\xi)$	$\psi(x,\xi)$
$\log \lvert D \rvert, \quad \lvert D \rvert^{1/m}, \quad \prod_{\alpha=1}^{m} \lambda_\alpha(D)$	$\operatorname{tr} \nu(x) F^T(x) D F(x) - m$
$\log \lvert A^T D A \rvert,$ $\dim A = k \times m, \ \operatorname{rank} A = k < m$	$\operatorname{tr} \nu(x) F^T(x) D A (A^T D A)^{-1} A^T D F(x) - k$
$\operatorname{tr} D, \quad \sum_{\alpha=1}^{m} \lambda_\alpha(D)$	$\operatorname{tr} \nu(x) F^T(x) D^2 F(x) - \operatorname{tr} D$
$\operatorname{tr} A^T D A, \quad A \geq 0$	$\operatorname{tr} \nu(x) \left(F^T(x) D A\right)^2 - \operatorname{tr} A^T D A$
$\operatorname{tr} D^\gamma, \quad \sum_{\alpha=1}^{m} \lambda_\alpha^\gamma(D)$	$\operatorname{tr} \nu(x) F^T(x) D^{\gamma+1} F(x) - \operatorname{tr} D^\gamma$
$\lambda_{\min} = \lambda_{\min}(M)$ $= \lambda_{\max}^{-1}(D)$	$\sum_{i=1}^{a} \pi_i P_i^T F(x) \nu(x) F(x) P_i - \lambda_{\min}$ $\lambda_{\min} P_i = M P_i,$ a is the multiplicity of $\lambda_{\min}$, $\sum_{i=1}^{a} \pi_i = 1, 0 \leq \pi_i \leq 1$

Thanks you.