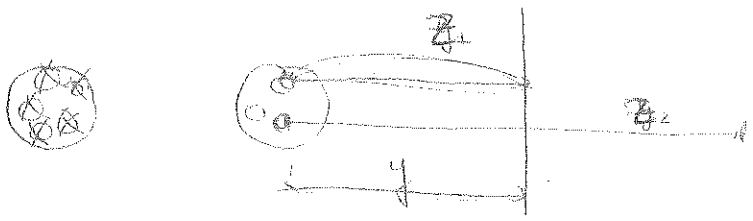

♠ Alternative: ICS 5.2 & paper by ICS (1999)

* *metastasis-competent tumor cell:* a tumor cell which has the potential of metastasizing.

○ *A natural biological motivation:* Imagine

- A patient is cured if no metastasis-competent tumor cell left after treatment.
- If N metastasis-competent cell are left, their metastasizing is independent competing risk events and the minimum of their latent times to metastasizing is observed as time to relapse.

* This can be applied for any time of survival data, such as data of time to death.

- N_i: the number of metastasis-competent tumor cells left active the initial treatment for individual i.

  - N_i: not observed $\Rightarrow$ latent variable

  - Assume $N_i \overset{iid}{\sim} \text{Poi}(\theta)$

- Z_{ij}: the random time for the j^{th} metastiatis-competent tumor cell.

  - Assume $Z_{ij} \overset{iid}{\sim} F(\cdot \mid \psi) = 1 - S(\cdot \mid \psi)$

    e.g. Weibull (fully parametric cure model, ICS 5.1), Piecewise constant hazard model (semiparametric model, ICS 5.3), Alternative semiparametric model (ICS 5.3)

  - Assume N_i and Z_{ij}'s are independent.

Given $N = 4$,

$$Y = \min(Z_1, Z_2, Z_3, Z_4)$$

$$P(Y > y) = P(Z_1 > y, Z_2 > y, Z_3 > y, Z_4 > y)$$

$$\overset{\text{indep}}{=} \prod_{j=1}^{4} P(Z_j > y)$$

$$= \left(P(Z_0 > y)\right)^4$$

$$= \left(S(y)\right)^4$$

$$= e^{s(y)\theta - \theta}\left(1 - e^{-\theta s(y)\theta}\right)$$

$$e^{-\theta} + e^{s(y)\theta-\theta} - e^{-\theta s(y) + \theta s(y) - \theta}$$

$$= e^{s(y)\theta - \theta}$$

$= e^{S(y)\theta - \theta} \cdot \left(\sum_{k=1}^{\infty} \frac{(S(y)\theta)^k e^{-S(y)\theta}}{k!} + e^{-\theta} - e^{-\theta} \right)$

$= \sum_{k=0}^{\infty} \frac{(S(y)\theta)^k e^{-S(y)\theta}}{k!}$ $\sim Poi(S(y)\theta)$ $= 1$

$\sum_{k=1}^{\infty} S(y)^k \frac{\theta^k}{k!} e^{-\theta}$

$= \sum_{k=1}^{\infty} \frac{(S(y)\theta)^k e^{-S(y)\theta} e^{+S(y)\theta - \theta}}{k!}$

- Time to relapse of a cancer (or survival time) $Y_i = \min\{Z_{ij}, 0 \le j \le N_i\}$ where $P(Z_{i0} = \infty) = 1$.
- The survival function for Y is given by

$$\begin{aligned} S_{pop}(y) &= P(\text{ no metastatic cancer by time } y) \quad \text{not cured} \\ &= P(Z_0 > y \text{ and } N = 0) + P(Z_1 > y, Z_2 > y, \ldots, Z_N > y \text{ and } N \ge 1) \\ &= \exp(-\theta) + \sum_{k=1}^{\infty} S(y)^k \frac{\theta^k}{k!} \exp(-\theta) \\ &= \exp(-\theta + \theta S(y)) \\ &= \exp(-\theta F(y)) \end{aligned}$$

$P(Z_0 > y \mid N=0) \cdot P(N=0)$; 1; $(S(y))^k \cdot P(N=k)$; $e^{S(y)\theta - \theta}\left(1 - e^{-\theta S(y)}\right)$

- a standard cure rate model with cure rate equal to $\pi = \exp(-\theta)$ and survival function for the noncured population given by $= P(N=0)$ $S^*(y) = P(Y > y \mid N \ge 1)$.
- $S_{pop}(y)$ is not a proper survival function. Why?

$e^{-\theta}$ as $y \to \infty$

- $S_{pop}(\infty) = \exp(-\theta)$: cure fraction (cure rate)

  ⋆⋆ As $\theta \to \infty$, the cure rate tends to be 0.

  ⋆⋆ As $\theta \to 0$, the cure rate tends to be 1.

- The subdensity is given by

  $$f_{pop}(y) = \theta f(y) \exp(-\theta F(y)), \text{ where } f(y) = dF(y)/dy.$$

  ⋆⋆ not a proper density since $S_{pop}(y)$ is not a proper survival function.

- $S^*(y) = P(Y > y \mid N \geq 1) = \dfrac{P(Y > y,\ N \geq 1)}{\underbrace{1 - e^{-\theta}}_{= P(N \geq 1) = 1 - P(N=0)}}$

$$= \frac{e^{-\theta F(y)} - e^{-\theta}}{1 - e^{-\theta}}$$

$$\begin{cases} S^*(0) = 1 \\ S^*(\infty) = 0 \end{cases} \quad \text{proper}$$

- $f(y) \geq 0$ for $y \geq 0$

- $f^*(y) = \dfrac{\theta f(y) e^{-\theta F(y)}}{1 - e^{-\theta}}$

- $h^* = \dfrac{f^*(y)}{S^*(y)} = \dfrac{e^{-\theta F(y)}}{e^{-\theta F(y)} - e^{-\theta}} \cdot \underbrace{\theta \times f(y)}_{= h_{pop}(y)}$

- The hazard function is given by

$$h_{pop}(y) = \theta f(y)$$

  - ⋆⋆ not a proper hazard function
  - ⋆⋆ multiplicative in θ and $f(y) \Rightarrow$ the proportional hazards model, with the covariates modeled through θ.

- For the "uncured" population,
  - ⋆⋆ survival function
  - ⋆⋆ density function
  - ⋆⋆ hazard function

- Let $\theta = \exp(\mathbf{X}'\beta)$: a canonical link in a Poisson regression model
  - ⋆⋆ For the cured group, a negative regression coefficient leads to a larger cure fraction, $\exp(-\theta)$.
  - ⋆⋆ For the non-cured group, a negative regression coefficient leads to a larger hazard, whereas a positive regression coefficient leads to a smaller hazard.

when X takes a positive value.

$X = 1$

$\beta = +2$ $\quad X\beta = 2$ $\quad \theta = e^{X\beta} = 7.389$ $\quad e^{-7.389} \wedge e^{0.0498}$

-3 $\quad -3$ $\quad = 0.0498$

- Observed data $\mathcal{D}_{obs} = (n, \mathbf{y}, \boldsymbol{\nu})$.
- Complete data $\mathcal{D} = (n, \mathbf{y}, \boldsymbol{\nu}, \mathbf{N})$.
- Assume a Weibull density for $f(y \mid \psi) = \alpha y^{\alpha-1} \exp\{\lambda - y^{\alpha} \exp(\lambda)\}$.
- The likelihood?

$$\prod_{i=1}^{n} \frac{e^{-\exp(x_i'\beta)} \left(\exp(x_i'\beta)\right)^{N_i}}{N_i!} \cdot \binom{N_i}{\nu_i} \left(S(y_i \mid \psi)\right)^{\nu_i} \left(f(y_i \mid \psi)\right)^{N_i - \nu_i} \cdot \prod_{i=1 \mid N_i \neq 0}^{n} \left(\sum_{j=1}^{N_i} S(y_i \mid \psi)\right)^{-\nu_i} \left(N_i f(y_i \mid \psi) \left(S(y_i \mid \psi)\right)^{N_i - 1}\right)^{\nu_i}$$

- Can find the MLE. But we continue...

$$N_i f(y_i \mid \psi) \; S(y_i \mid \psi)^{N_i \nu_i - \nu_i + N_i(1-\nu_i)} = \left(N_i f(y_i \mid \psi)\right)^{\nu_i} S(y_i \mid \psi)^{N_i - \nu_i}$$

- Priors
  - ⋆⋆ Prior for β

    e.g. $\pi(\beta) \propto 1$ (a uniform improper prior)
  - ⋆⋆ Prior for $\psi = (\alpha, \lambda)$

    e.g. $\pi(\psi) = \pi(\alpha \mid \delta_0, \tau_0)\pi(\lambda)$,
    where $\pi(\alpha \mid \delta_0, \tau_0) \propto \alpha^{\delta_0 - 1} \exp(-\tau_0 \alpha)$.

- What to draw?
  - ⋆⋆ Sample β
  - ⋆⋆ Sample ψ
  - ⋆⋆ Sample $\mathbf{N}$

- Parameter estimates (noninformative priors(top) vs informative priors(bottom))

Table 4. Melanoma Data: Posterior Estimates of the Model Parameters With $\alpha \sim$ gamma(1, .01) and $\lambda \sim$ N(0, 10,000)

$E(a_0 \mid \mathbf{D}_{obs}, \mathbf{D}_{0,obs})$	Variable	Posterior mean	Posterior SD	95% HPD interval
0	Intercept	.09	.11	(−.12, .30)
(With probability 1)	Age	.09	.07	(−.05, .23)
	Gender	−.12	.16	(−.44, .19)
	PS	−.23	.26	(−.73, .28)
	α	1.31	.09	(1.15, 1.48)
	λ	−1.36	.12	(−1.60, −1.11)
$E(a_0 \mid -) = .29$	Intercept	.26	.09	(.08, .43)
	Age	.13	.06	(.02, .24)
	Gender	−.24	.12	(−.48, .00)
	PS	−.01	.19	(−.38, .35)
	α	1.03	.05	(.93, 1.13)
	λ	−1.70	.11	(−1.91, −1.50)

Bayes w/o historical data info

- Recall the historical data, **E1673** can be used to have informative priors for analysis of **E1684**.
- How to incorporate? the power prior!

$$\pi(\beta, \psi \mid \mathcal{D}_0, a_0) \propto \{\mathcal{L}(\beta, \psi \mid \mathcal{D}_0)\}^{a_0} \pi_0(\beta, \psi),$$

where $\mathcal{D}_0$: complete historical data and $\pi_0(\beta, \psi)$: the initial prior

* We can consider a prior for a_0, $a_0 \sim \text{Be}(\gamma_0, \lambda_0)$.

- Cure rate estimates (**1:** MLE under the standard cure model, **2:** MLE under Model 2, **3:** Bayes under Model 2 with noninformative priors, **4:** Bayes under Model 2 with informative priors)

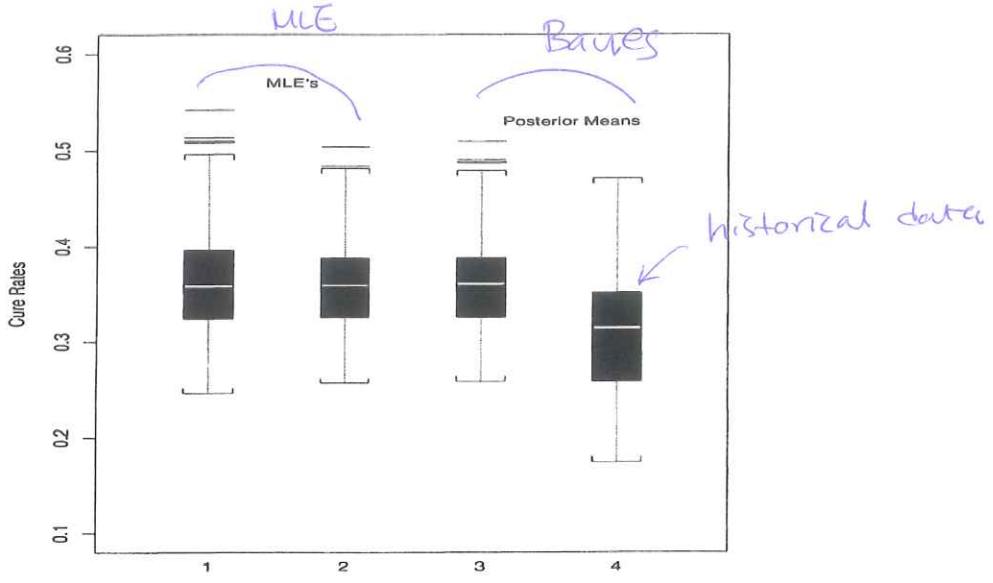

Figure 3. Boxplots of the Cure Rates for All Patients; 1, the standard cure rate model; 2, the proposed model; 3, $a_0 = 0$; and 4, $E(a_0|\mathbf{D}_0; \mathbf{D}_{0;obs}) = .29$.

- Parameter estimates (MLE(top) vs Bayes with noninformative priors(bottom))

Table 1. MLE's of the Model Parameters

	Variable	MLE	SD	P value
$\hat{\beta}$	Intercept	.09	.11	.38
	Age	.09	.07	.21
	Gender	−.12	.16	.44
	PS	−.20	.26	.44
	$\hat{\alpha}$	1.32	.09	.00
	$\hat{\lambda}$	−1.34	.12	.00

Table 4. Melanoma Data: Posterior Estimates of the Model Parameters With $\alpha \sim$ gamma(1, .01) and $\lambda \sim N(0, 10{,}000)$ $\pi(\beta) \propto 1$

$E(a_0 \mid \mathbf{D}_{obs}, \mathbf{D}_{0,obs})$	Variable	Posterior mean	Posterior SD	95% HPD interval
$a_0 = 0$	Intercept	.09	.11	(−.12, .30)
(With probability 1)	Age	.09	.07	(−.05, .23)
	Gender	−.12	.16	(−.44, .19)
	PS	−.23	.26	(−.73, .28)
	α	1.31	.09	(1.15, 1.48)
	λ	−1.36	.12	(−1.60, −1.11)

$h_0 e^{x\beta}$

AMS 276
Lecture 7: Overview of Clinical Trials

Fall 2016

- Introduction to Statistical Methods for Clinical Trials
  by CD
- Bayesian Adaptive Methods for Clinical Trials
  by B, C, L, M.

† Introduction to clinical trials (See BCLM Chapter 1 & CD Chapter 1)

- Clinical trials are **prospective studies** to evaluate **the effect of interventions** in **human** under **prespecified conditions**.
- They have become a standard and an integral part of modern medicine.
- A properly planned and executed clinical trial is the most definitive tool for evaluating the effect and applicability of new treatment modalities.
- From page 1 of BCLM.

- Clinical trials are prospective studies to evaluate the effect of interventions in human under prespecified conditions.

  - ⋆⋆ Prospective studies: Investigators conceive and design the study, recruit subjects, and collect baseline exposure data on all subjects, before any of the subjects have developed any of the outcomes of interest. The subjects are then followed into the future in order to record the development of any of the outcomes of interest.

- ⋆⋆ Intervention:

  e.g. a drug, biological agents (blood, vaccine, and tissue, or other products, derived from living sources such as humans, animals, and microorganisms), device, procedure, or genetic manipulation.

- ⋆⋆ Effect of interventions: measured by outcome or response variables.

  e.g. the occurrence of an adverse event such as death or disease recurrence.

- ⋆⋆ Human under prespecified conditions: study population.

  e.g. The Physicians Health Study investigated the potential cardiovascular benefit of aspirin and beta-carotene in *healthy men*.

potential for bias
⇒ have led to many false positive associations that could not be replicated.

ex) red meat & either breast or colon cancer

- The research process is a dynamic interaction between observation, laboratory results, and clinical trials.
- Clinical trials: experimental approach to clinical research.

  ⇒ Identify an effective and safe intervention

  ⋆⋆ The fundamental principles of clinical trials are heavily based on statistical principles related to experimental design, quality control, and sound analysis.

  ⋆⋆ No analytical methods can rescue a trial with poor experimental design.

  ⋆⋆ The conclusion from a trial with proper design can be invalid if sound analytical principles are not adhered to.

- Clinical trials are categorized into 4 phases in general (CD Table 1.6)

  - ⋆⋆ **Preclinical:** Once a risk factor identified, laboratory research is conducted to identify a means to modify the risk factor, testing it in the laboratory and often in animal models.

  - ⋆⋆ **Phase I:** With a new intervention available from laboratory research, the first step is to determine if the intervention can be given to humans, by what method, and in what dose.

    MTD

    * The goal is usually to determine the maximum dose that can be tolerated without excessive adverse effects. maximum tolerated dose

    * Typically, phase I trials are conducted either in healthy volunteers or in patients who have failed all regular treatments.

a cytotoxic agent.

- Clinical trials are categorized into 4 phases in general (CD Table 1.6)

  - ⋆⋆ **Phase II:** Trials in the second phase typically measure how active intervention is, and learn more about side effects.

    * To determine if it evokes the response that was expected and warrants further development.

  - ⋆⋆ **Phase III:** Trials in the third phase compare whether the new intervention is more effective than a standard control intervention. compare to another group of patients treated in the standard manner at the same time maybe at different medical facilities

    * According to the process by which a control arm is selected– randomized control trials, historical control, cocurrent control trial.

      compare to a group of patients previously treated w/ the current standard care

  - ⋆⋆ Trials may be single center or multiple center, and many phase III trials are multinational.

- Trial protocol: a research plan that describes all of the key design and conduct issues.
- History and Background (CD 1.1)
- **Ethics** (CD 1.2): clinical research in general and clinical trials in particular must be conducted in a manner that meets current ethical standards.
- Regulatory Issues (CD 1.9)

- The overall rationale and features of a trial are described in a trial protocol

Table 1.7 *Protocol outline.*

1. Background of the study
2. Objectives
   (a) Primary question and response variable
   (b) Secondary question and response variable
   (c) Subgroups hypotheses
   (d) Adverse effects
3. Design of the study
   (a) Study population
      i. Inclusion criteria
      ii. Exclusion criteria
   (b) Sample size assumptions and estimates
   (c) Enrollment of participants
      i. Informed consent
      ii. Assessment of eligibility
      iii. Baseline examination
      iv. Intervention allocation (e.g., randomization method)
   (d) Intervention
      i. Description and schedule
      ii. Measures of compliance