Westfälische Wilhelms-Universität Münster

medizinische fakultät
Westfälische Wilhelms-Universität Münster

Ein universelles Bayes-Design für einarmige Phase II-Studien mit binärem zeitlich erfasstem Endpunkt

Joachim Gerß

joachim.gerss@ukmuenster.de

Institute of Biostatistics and Clinical Research

IBKF
Institut für Biometrie und Klinische Forschung

wissen.leben
WWU Münster

Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

1. The Retinoblastoma Trial

- Retinoblastoma:
  rare, rapidly developing malignant tumor of the eye in children
- 10 patients per year
- Single-arm Phase II trial:
  Efficacy of intra-arterial chemotherapy with carboplatin
- Primary outcome: 6 months event-free eye survival (EFES)
- H_0: unacceptable response
  EFES ≤ 0.4
  event rate p≥0.6

  versus

  H_1: desirable response
  EFES ≥ 0.6
  event rate p≤0.4
- $\alpha = \beta = 0.1$
- Interim analysis with futility stop

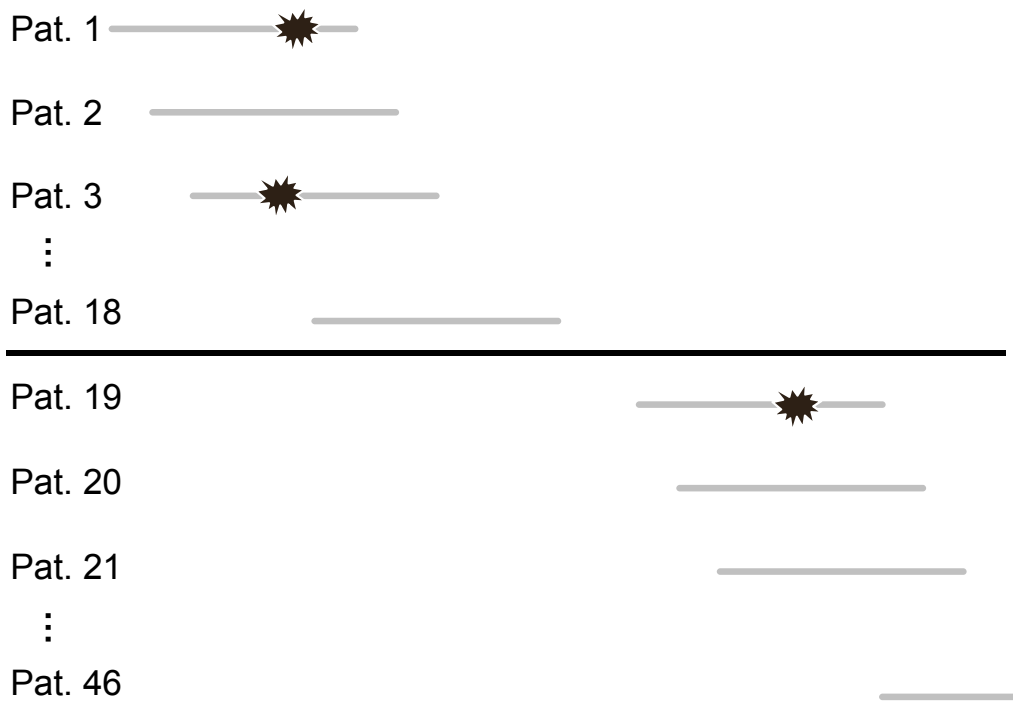
Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

H_0: unacceptable response
EFES ≤ 0.4
event rate p≥0.6

H_1: desirable response
EFES ≥ 0.6
event rate p≤0.4

2. Long-Term Binary Endpoint
a. Suspend Recruitment: Simon Design



Simon Optimal Design

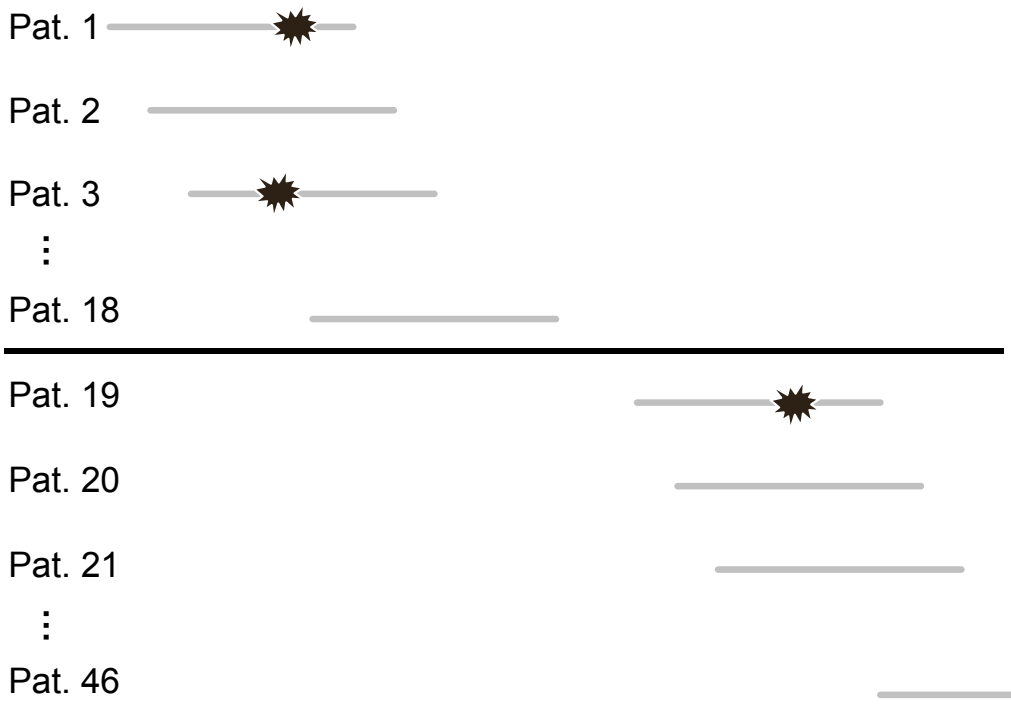
1st stage: 18 patients

- If ≥11/18 events => Futility stop,
  Reject drug
- If ≤10/18 events => Continue to 2nd stage

2nd stage: +28 patients (=> Σ=46 patients)

- If ≥24/46 events => Reject drug
- If ≤23/46 events => Accept drug,
  Reject H_0

2. Long-Term Binary Endpoint
a. Suspend Recruitment: Bayesian Approach



Bayesian Beta-Binomial Model

Interim analysis: n = 18 patients

$x_i \in \{0,1\}$ event indicator

Data model: $\text{Prob}(X_i=1|p) = p$

$\text{Prob}(X_i=0|p) = 1-p$

Noninformative prior: $f(p) = I_{[0,1]}(p)$

$\Rightarrow$ Posterior $f(p|x_1,\ldots,x_n) =$

$= f(x_1,\ldots,x_n,p) \,/\, f(x_1,\ldots,x_n)$

$= f(x_1,\ldots,x_n|p) \cdot f(p) \,/\, f(x)$

$\propto \prod \text{Prob}(X_i=x_i|p) \cdot I_{[0,1]}(p)$

$= \prod \text{Prob}(X_i=1|p) \cdot \prod \text{Prob}(X_i=0|p) \cdot I_{[0,1]}(p)$

Patients i with event

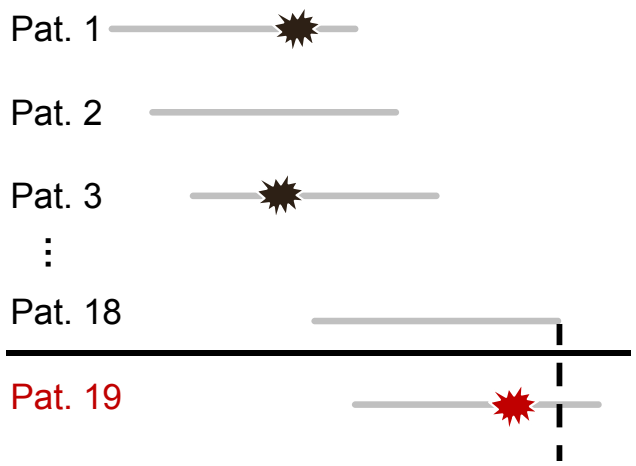
Patients i without event during 6 mo follow-up

$= p^{\Sigma xi} \cdot (1-p)^{n-\Sigma xi} \cdot I_{[0,1]}(p)$

Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

2. Long-Term Binary Endpoint
b. Continue Recruitment: Bayesian Approach…



Bayesian Model

Interim analysis: n = ~~18~~ 19 patients

$x_i \in \{0,1\}$ event indicator

Patients i with event: $\text{Prob}(X_i=1|p) = p$

Pat w/o event during 6 mo follow-up: $\text{Prob}(X_i=0|p) = 1-p$

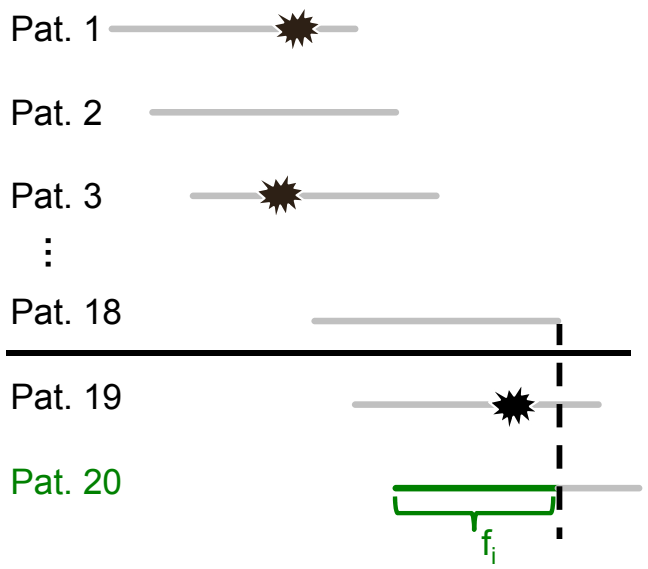
Noninformative prior: $f(p) = I_{[0,1]}(p)$

$$\Rightarrow \text{Posterior } f(p|x_1,\ldots,x_n) \propto \prod \text{Prob}(X_i=x_i|p) \cdot I_{[0,1]}(p)$$

$$= \prod_{\text{Patients i with event}} \text{Prob}(X_i=1|p) \cdot \prod_{\substack{\text{Patients i without event} \\ \text{during 6 mo follow-up}}} \text{Prob}(X_i=0|p) \cdot I_{[0,1]}(p)$$

$$= p^{\Sigma xi} \cdot (1-p)^{n-\Sigma xi} \cdot I_{[0,1]}(p)$$

2. Long-Term Binary Endpoint
b. Continue Recruitment: Bayesian Approach…



Bayesian Model

Interim analysis: n = ~~18~~ ~~19~~ 20 patients

$x_i \in \{0,1\}$ event indicator

Patients i with event:	$Prob(X_i=1\|p) = p$
Pat w/o event during 6 mo follow-up:	$Prob(X_i=0\|p) = 1-p$
Pat w/o event, follow-up f_i < 6mo:	$Prob(X_i=0\|p) = 1 - p \cdot f_i/6$

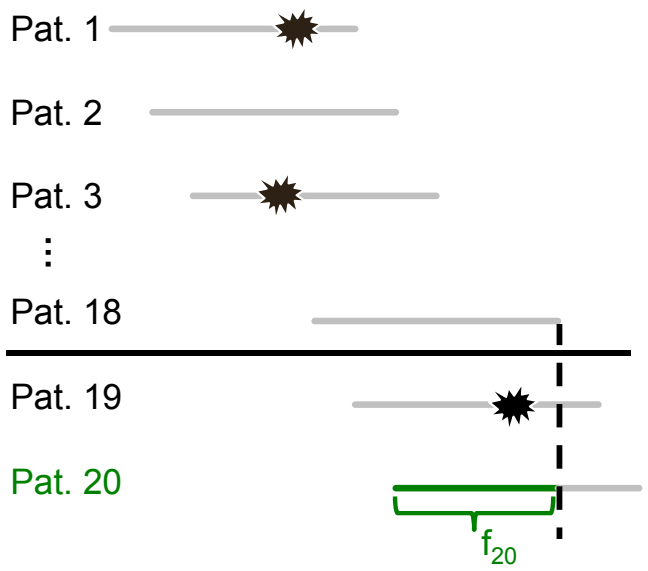
Noninformative prior: $f(p) = I_{[0,1]}(p)$

$$\Rightarrow \text{Posterior } f(p|x_1,\ldots,x_n) \propto \prod Prob(X_i=x_i|p) \cdot I_{[0,1]}(p)$$

$$= \prod_{\substack{\text{Patients i}\\ \text{with event}}} Prob(X_i=1|p) \cdot \prod_{\substack{\text{Patients i}\\ \text{without event}\\ \text{during 6 mo follow-up}}} Prob(X_i=0|p) \cdot \prod_{\substack{\text{Patients i}\\ \text{without event}\\ \text{during follow-up } f_i < 6\text{mo}}} Prob(X_i=0|p) \cdot I_{[0,1]}(p)$$

$$= p^{\Sigma x_i} \cdot (1-p)^{\#\text{no event in 6mo fu}} \cdot \prod_{\substack{\text{Patients i}\\ \text{without event}\\ \text{during follow-up } f_i < 6\text{mo}}} (1 - p \cdot f_i/6) \cdot I_{[0,1]}(p)$$

2. Long-Term Binary Endpoint
b. Continue Recruitment: Bayesian Approach (!)



Bayesian Model

Interim analysis: n = ~~18~~ ~~19~~ 20 patients

$x_i \in \{0,1\}$ event indicator

Patients i with event:	$Prob(X_i=1\|p,p_{20}) = p$
Pat w/o event during 6 mo follow-up:	$Prob(X_i=0\|p,p_{20}) = 1-p$
Pat w/o event, follow-up $f_{20} < 6mo$:	$Prob(X_{20}=0\|p,p_{20}) = 1-p_{20}$
Noninf. prior: $f(p,p_{20}) = f(p_{20}\|p) \cdot f(p) =$	$1/p \cdot I_{[0,p]}(p_{20}) \cdot I_{[0,1]}(p)$

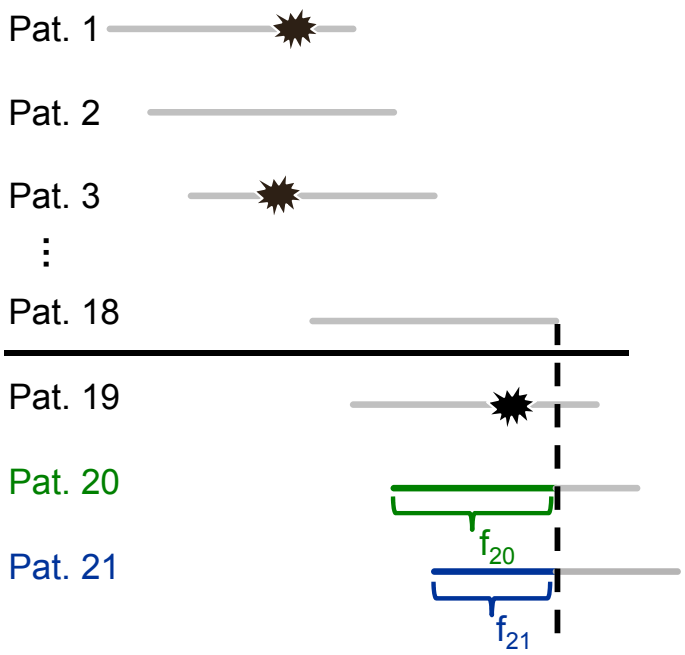
$\Rightarrow$ Posterior $f(p,p_{20}|x_1,\ldots,x_n) \propto \prod Prob(X_i=x_i|p,p_{20}) \cdot f(p,p_{20})$

$= \prod_{\text{Patients i with event}} Prob(X_i=1|p) \cdot \prod_{\text{Patients i without event during 6 mo follow-up}} Prob(X_i=0|p) \cdot Prob(X_{20}=0|p_{20}) \cdot f(p,p_{20})$

$= p^{\Sigma xi} \cdot (1-p)^{n-\Sigma xi-1} \cdot (1-p_{20}) \cdot 1/p \cdot I_{[0,p]}(p_{20}) \cdot I_{[0,1]}(p)$

$\Rightarrow$ Posterior $f(p|x_1,\ldots,x_n) = \int f(p,p_{20}|x_1,\ldots,x_n)\, dp_{20}$

2. Long-Term Binary Endpoint
b. Continue Recruitment: Bayesian Approach (!)



Bayesian Model

Interim analysis: n = ~~18~~ ~~19~~ ~~20~~ ~~21~~ patients

$x_i \in \{0,1\}$ event indicator

Patients i with event: $Prb(X_i=1|p,p_{20},p_{21}) = p$

Pat w/o event during 6 mo foll-up: $Prb(X_i=0|p,p_{20},p_{21}) = 1-p$

Pat w/o event, follow-up f_{20} < 6mo: $Prb(X_{20}=0|p,p_{20},p_{21}) = 1-p_{20}$

Pat w/o event, follow-up f_{21} < 6mo: $Prb(X_{21}=0|p,p_{20},p_{21}) = 1-p_{21}$

Prior: $f(p,p_{20},p_{21}) = f(p_{21}|p_{20},p) \cdot f(p_{20}|p) \cdot f(p)$

$= 1/p_{20} \cdot I_{[0,p20]}(p_{21}) \cdot 1/p \cdot I_{[0,p]}(p_{20}) \cdot I_{[0,1]}(p)$

=> Posterior $f(p,p_{20},p_{21}|x_1,\ldots,x_n) \propto$

$\propto \Pi\, Prob(X_i=x_i|p,p_{20},p_{21}) \cdot f(p,p_{20},p_{21})$

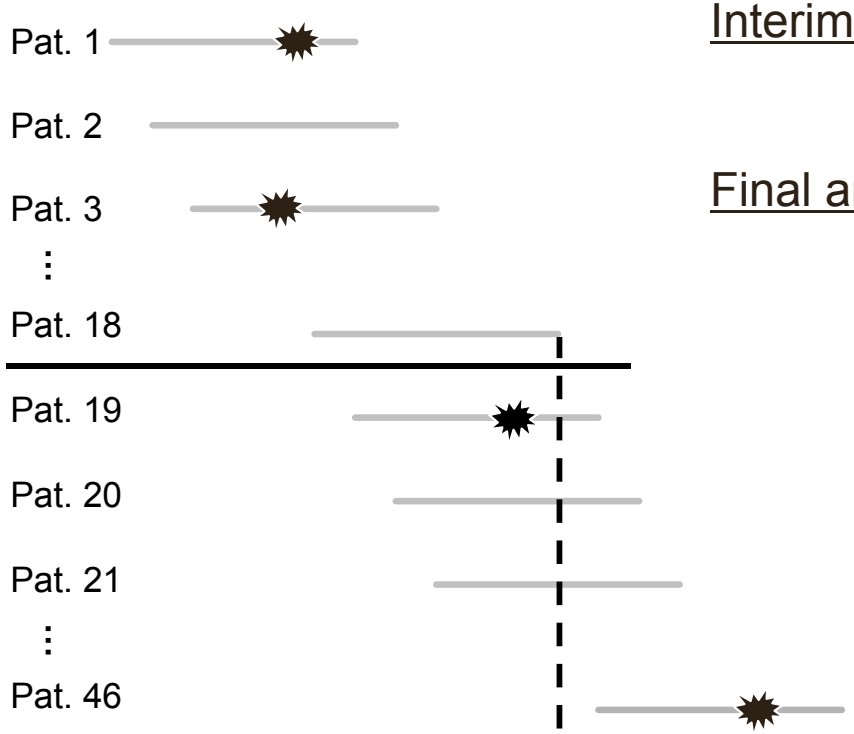
$=p^{\Sigma xi} \cdot (1-p)^{n-\Sigma xi-2} \cdot (1-p_{20}) \cdot (1-p_{21}) \cdot 1/p_{20} I_{[0,p20]}(p_{21}) \cdot 1/p I_{[0,p]}(p_{20}) \cdot I_{[0,1]}(p$

=> Posterior $f(p|x_1,\ldots,x_n) = \int\int f(p,p_{20},p_{21}|x_1,\ldots,x_n)\, dp_{21}\, dp_{20}$

H_0: unacceptable response
EFES ≤ 0.4
event rate p≥0.6

H_1: desirable response
EFES ≥ 0.6
event rate p≤0.4

2. Long-Term Binary Endpoint
b. Continue Recruitment: Bayesian Approach (!)



Bayesian Model

Interim analysis: $\propto f_{interim}(p|x_1,\ldots,x_n)$

If $Prob_{interim}(EFES \geq 0.6) \leq 0.025$ => Futility Stop

Final analysis: $\propto f_{final}(p|x_1,\ldots,x_n)$

If $Prob_{final}(EFES \leq 0.4) < 0.1$ => Reject H_0, Accept drug

If $Prob_{final}(EFES \leq 0.4) \geq 0.1$ => Reject drug

Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

H_0: unacceptable response
EFES ≤ 0.4
event rate p≥0.6

H_1: desirable response
EFES ≥ 0.6
event rate p≤0.4

3. Simulation (1)

- 100.000 runs

	Design	Futility Stop		Prob(Reject H_0)	
		H_0	H_1	H_0	H_1
Suspend Recruitment	Simon	0.565	0.058	0.094	0.901
	Bayes	0.373	0.020	0.104	0.927
Continue Recruitment	Bayes	0.486	0.033	0.100	0.919

H_0: unacceptable response	H_1: desirable response
EFES ≤ 0.4	EFES ≥ 0.6
event rate p≥0.6	event rate p≤0.4

Case and Morgan 2003

- Case and Morgan. Design of Phase II cancer trials evaluating survival probabilities. *BMC Medical Research Methodology* 2003, **3**:6.
- Straightforward extension of Simon's Design to time-to-event data
- Test statistics based on the Nelson-Aalen estimate of the cumulative hazard function evaluated at the interim (Z_1) and final analysis (Z_2)
- Assumptions regarding the expected survival distribution and accrual rate

➢ (Z_1,Z_2) ~ multivariate normal with correlation ρ

➢ Determine critical values of futility stop (C_1) and final analysis (C_2), satisfying type I and type II error constraints

➢ Choose design with either minimal sample size or minimal expected total study length under H_0

H_0: unacceptable response
EFES ≤ 0.4
event rate p≥0.6

H_1: desirable response
EFES ≥ 0.6
event rate p≤0.4

3. Simulation (2)

- Exponential survival, 100.000 runs

Design	Futility Stop		Prob(Reject H_0)	
	H_0	H_1	H_0	H_1
Case and Morgan 2003, assuming exponential survival	0.479	0.060	0.096	0.895
Bayes	0.409	0.039	0.100	0.911

- Weibull survival, 100.000 runs

Design	Futility Stop		Prob(Reject H_0)	
	H_0	H_1	H_0	H_1
Case and Morgan 2003, assuming exponential survival	0.478	0.063	0.096	0.892
Bayes	0.339	0.028	0.103	0.919

Overview

1. The Retinoblastoma Trial
2. Long-Term Binary Endpoints
   a. Suspend Recruitment: Simon Design
   b. Continue Recruitment: Bayesian Approach
3. Simulation
4. Summary and Conclusion

4. Summary and Conclusion

The presented Bayesian approach

- … is at least as good as other existing approaches
- … does not require parametric model assumptions
- … has transparent decision rules