ICORD 2007, Brussels

Methodological Issues on Clinical Trials with Small Sample Size

Joachim Gerß, Wolfgang Köpcke

Department of Medical Informatics and Biomathematics, Münster, Germany

joachim.gerss@ukmuenster.de

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

European Medicines Agency
Evaluation of Medicines for Human Use

INNOVATIVE DRUG DEVELOPMENT APPROACHES

FINAL REPORT FROM THE EMEA/CHMP-THINK-TANK GROUP ON INNOVATIVE DRUG DEVELOPMENT

Doc. Ref. EMEA/127318/2007

Lack of clear EU scientific position on these matters is perceived as a practical obstacle in conducting research and clinical development in Europe, particularly critical for certain types of products such as paediatric, **orphan** and other selected and innovative products.

The group was of the opinion, that especially in the areas of predictive safety testing, biomarkers, pharmacovigilance and **new statistical approaches** collaboration with DG Research and its Innovative Medicines Initiative should be highly supported and encouraged.

Statistical aspects/ study designs - Industry views

New approaches, using **more efficient clinical trial designs**, might shorten development times, while maintaining the integrity of the data.

Integral to this concept is the use of **adaptive / flexible designs**. These trials permit changes to important design characteristics based on accumulating (i.e. interim) data, thus allowing for uncertainties in factors influencing the trial design to be addressed during the trial.

There are advantages to including properly quantified existing knowledge in the design and analysis of future clinical trials. It is argued that **Bayesian methods** can provide a more natural framework for assessments of futility, selection of dose / patient population in trials with an adaptive design and in quantifying efficacy and safety in **small populations**.

Other, very specific comments, were received in the following areas: discontinue the preference for / reliance on Last Observation Carried Forward (LOCF) for imputation of **missing data**; increase the use of **longitudinal methods** rather than analyses at single time points.

Statistical aspects/study designs - Think-tank group's recommendations

The think-tank group understands the level of interest from industry in novel approaches and feel that the use of **adaptive / flexible clinical trial designs** can be supported in certain situations. However, adaptive designs are not viewed as a panacea for all ills of clinical drug development.As a general principle, it is clear that the concept of 'adaptation' fits better within the learning / exploratory phase of drug development than in the 'confirming' phase. Certain adaptations should be acceptable in confirmatory studies (for example **group-sequential methods** and blinded re-estimation of sample-size).

A third, broader, issue is whether data derived from an adaptive / flexible design is thought sufficiently reliable for approval. It is recommended that these issues be clearly addressed in the EWP reflection paper currently under development.

Bayesian methodology does have a place in drug development, for hypothesis generating in earlier phases, in the assessment of futility and potentially in '**small populations**' where there is no possibility to perform an adequately powered randomised controlled trial. However, with regards the use of 'Bayesian' methodology in confirmatory clinical trials, at present the think-tank group does not recommend the use of informative priors in Phase III trials, which should provide stand-alone, confirmatory evidence of efficacy and safety.

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Statistical hypothesis testing

Clinical trial: Comparison of two treatments

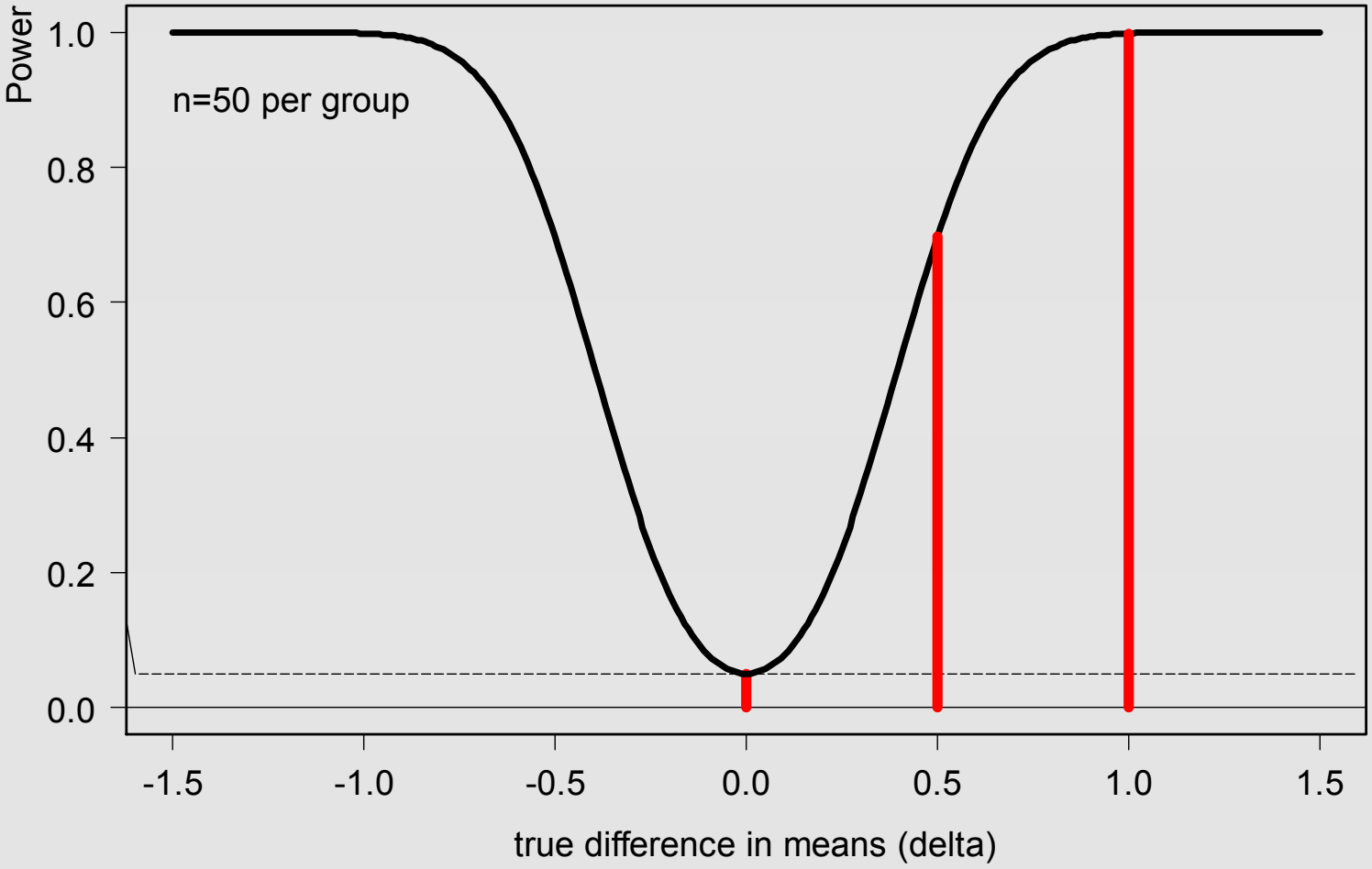
- Define the primary response variable
- Formulate the **hypotheses**
  - In case of continuous variables: $\mu_i := E(Y_i)$, i=1,2

    $H_0: \mu_1 = \mu_2$ vs. $H_1: \mu_1 \neq \mu_2$
  - In case of binary variables: $p_i := P(\text{Success in group i})$, i=1,2

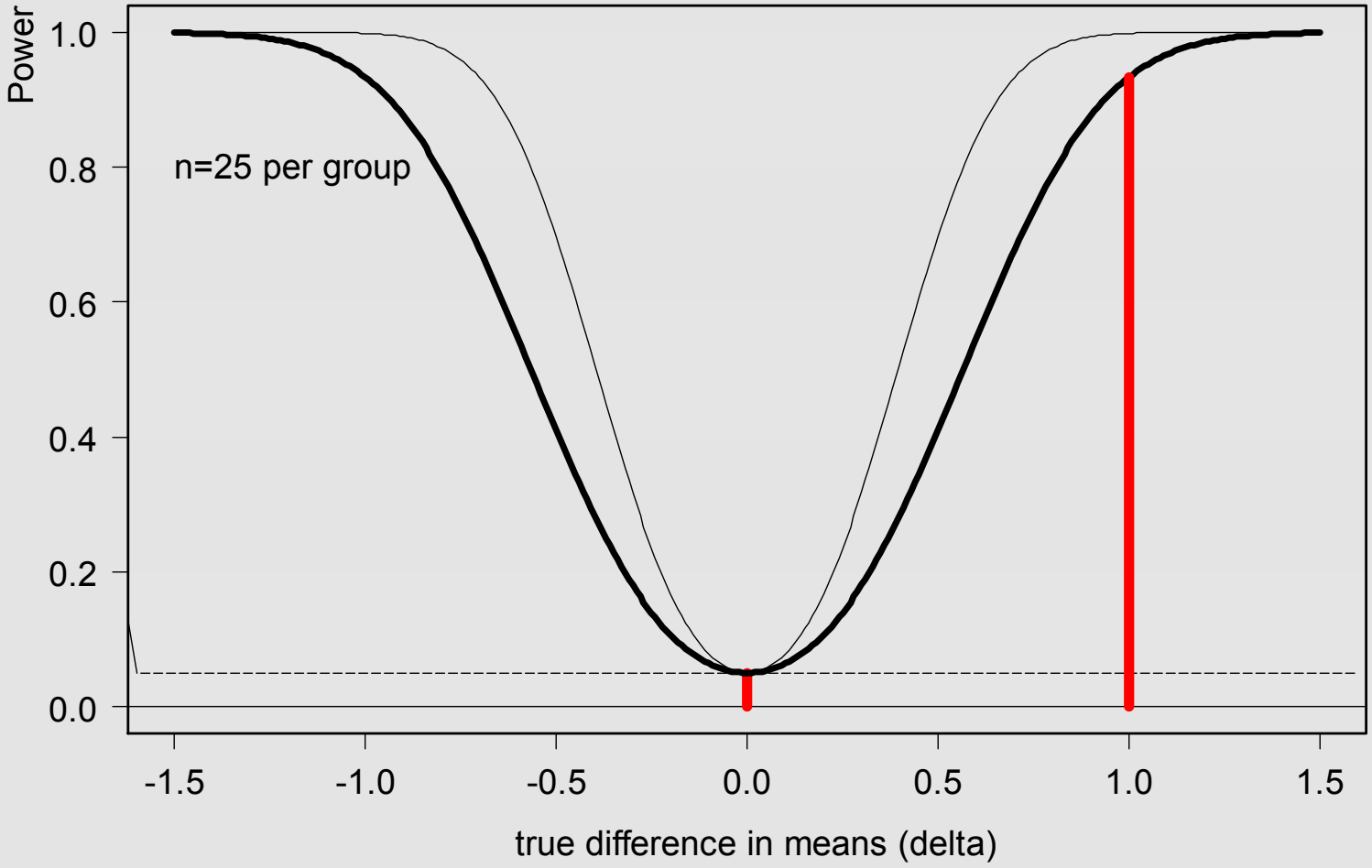
    $H_0: p_1 = p_2$ vs. $H_1: p_1 \neq p_2$
- Apply hypothesis test -> Statement in favour of H_0 or H_1
- **Measures of performance:**
  - α-***error***: Prob (Statement H_1, although H_0 holds indeed) („False alarm“)
  - ***Power***: Prob (Statement H_1, in case H_1 holds indeed) = 1 – „β-error“

    Probability of detecting an existing difference

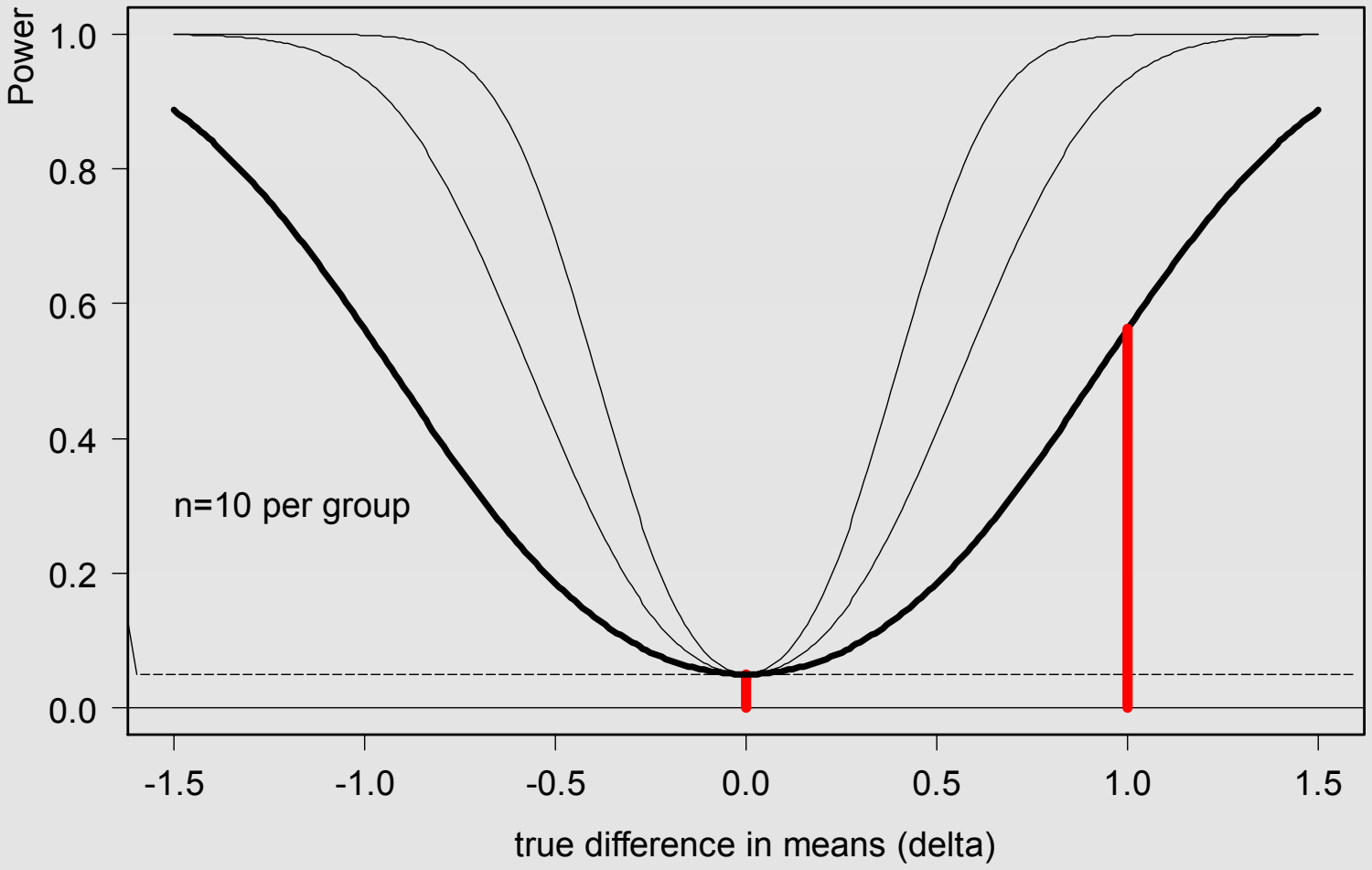
Example $H_0: \mu_1=\mu_2$ vs. $H_1: \mu_1\neq\mu_2$



Example $H_0: \mu_1=\mu_2$ vs. $H_1: \mu_1\neq\mu_2$



Example $H_0: \mu_1=\mu_2$ vs. $H_1: \mu_1\neq\mu_2$



α- and β-error in small sample trials

controlled α-error

low power (i.e. large β-error)

Consequences:

- **in case of a significant test result (p<0.05):**

  => Decision in favour of H_1

- **in case of a non-significant test result (p<0.05):**

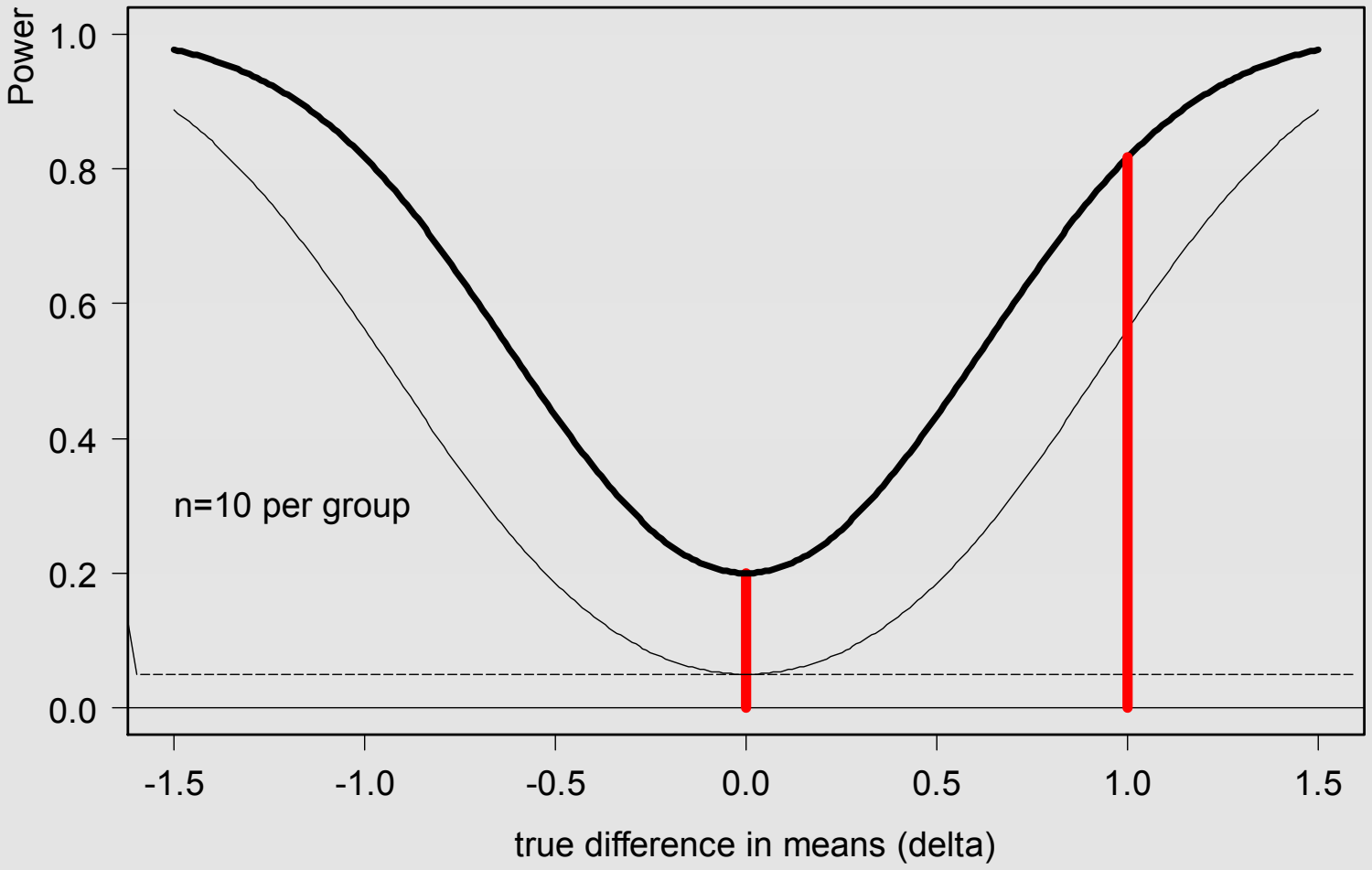
  Do not know if the test is not significant

  (a) because there *actually* is no effect (i.e. H_0 holds indeed) or

  (b) because of its *low power*
  (i.e. test is unable to detect an existing effect H_1)

?

Solution (?): Tolerate a larger α-error



Power and sample size

- **Previous calculations:**

  Given the sample size of a trial
  => Calculate the resulting power

- **Similar calculations yield:**

  Given a required power at a certain effect size
  => Calculate the required sample size of a planned trial

- **What can we do to increase the power or reduce the required sample size of a clinical trial?**

  => Increase the efficiency of statistical data analyses

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - **3.1 Overview of methodologic approaches**
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Increased efficiency of data analyses

- **Suitable choice of response variable**

  Generally metric response variables are *more powerful* than qualitative variables.

  Avoid dichotomising response variables that are observed on metric scale originally!

- **Group sequential (adaptive) designs**
- **Repeated measurement designs (Longitudinal data analysis, incl. N-of-1 designs)**
- **Adjustment for prognostic variables, Analysis of variances**
- **Nonparametric resampling methods**
- **Bayesian methods**

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation

The first recruited patients in a trial are allocated to treatments with a homogeneous 1:1 allocation ratio.

In the further course of the trial, the allocation ratio is changed based on which treatment appears to be better. New patients entering the trial are more likely to be allocated to the better treatment.

Oncology trial, Memorial Sloan-Kettering Cancer Center in New York: Applying adaptive randomisation prevented (estimated) 20% of the volunteers from getting the inferior treatment.

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation
  - Covariate-adaptive treatment allocation

Make sure that both treatment groups of a trial are balanced with respect to important covariates.

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation
  - Covariate-adaptive treatment allocation
- **Group sequential (adaptive) designs**

Group sequential designs: Perform repeated statistical analyses on accumulating data. Stop the trial as soon as the information is sufficient to conclude.

Adaptive designs: Permit changes to important design characteristics based on interim data, e.g. re-assessment of sample size, refining the definition of the patient population (?), ...

"Seamless phase II/III designs": Add phase II data to phase III data in the primary analysis of a trial.

Dose selection: Choose one of a number of doses in stage 1 of a trial, then confirming the efficacy of the chosen dose in stage 2.

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation
  - Covariate-adaptive treatment allocation
- **Group sequential (adaptive) designs**
- **Repeated measurement designs (Longitudinal data analysis, incl. N-of-1 designs)**

N-of-1 designs:

Each patient in a trial subsequently receives different treatments. The sequence of treatments is determined at random.

=> The outcome of the trial is a conclusion about the best treatment *for this particular patient*.

Results of many n-of-1 trials may be combined in a manner similar to both a cross-over study and a meta-analysis.

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation
  - Covariate-adaptive treatment allocation
- **Group sequential (adaptive) designs**
- **Repeated measurement designs (Longitudinal data analysis, incl. N-of-1 designs)**
- **Adjustment for prognostic variables**

Fact: The detection of treatment differences is hampered by random variation inherent to the response variable.

Analysis of variances: Part of the variation of the response variable is attributed to prognostic variables. Thus the remaining unexplained random variation is reduced. Reduced random variation generally leads to an increase in power.

Increased efficiency of data analyses

- **Suitable choice of response variable**
- **Adaptive randomisation**
  - Response-adaptive treatment allocation
  - Covariate-adaptive treatment allocation
- **Group sequential (adaptive) designs**
- **Repeated measurement designs (Longitudinal data analysis, incl. N-of-1 designs)**
- **Adjustment for prognostic variables**
- **Nonparametric resampling methods**
- **Bayesian methods**

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - **3.2 Resampling**
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Bootstrap

Example:

- **Comparison of two groups of patients**
- **Response measurements:**

Group 1	**4.5**	**6.4**	**5.4**	**6.9**	**8.5**
Group 2	**4.1**	**3.2**	**4.0**	**8.4**	**3.6**

Bootstrap

Example:

- **Comparison of two groups of patients**
- **Response measurements:**

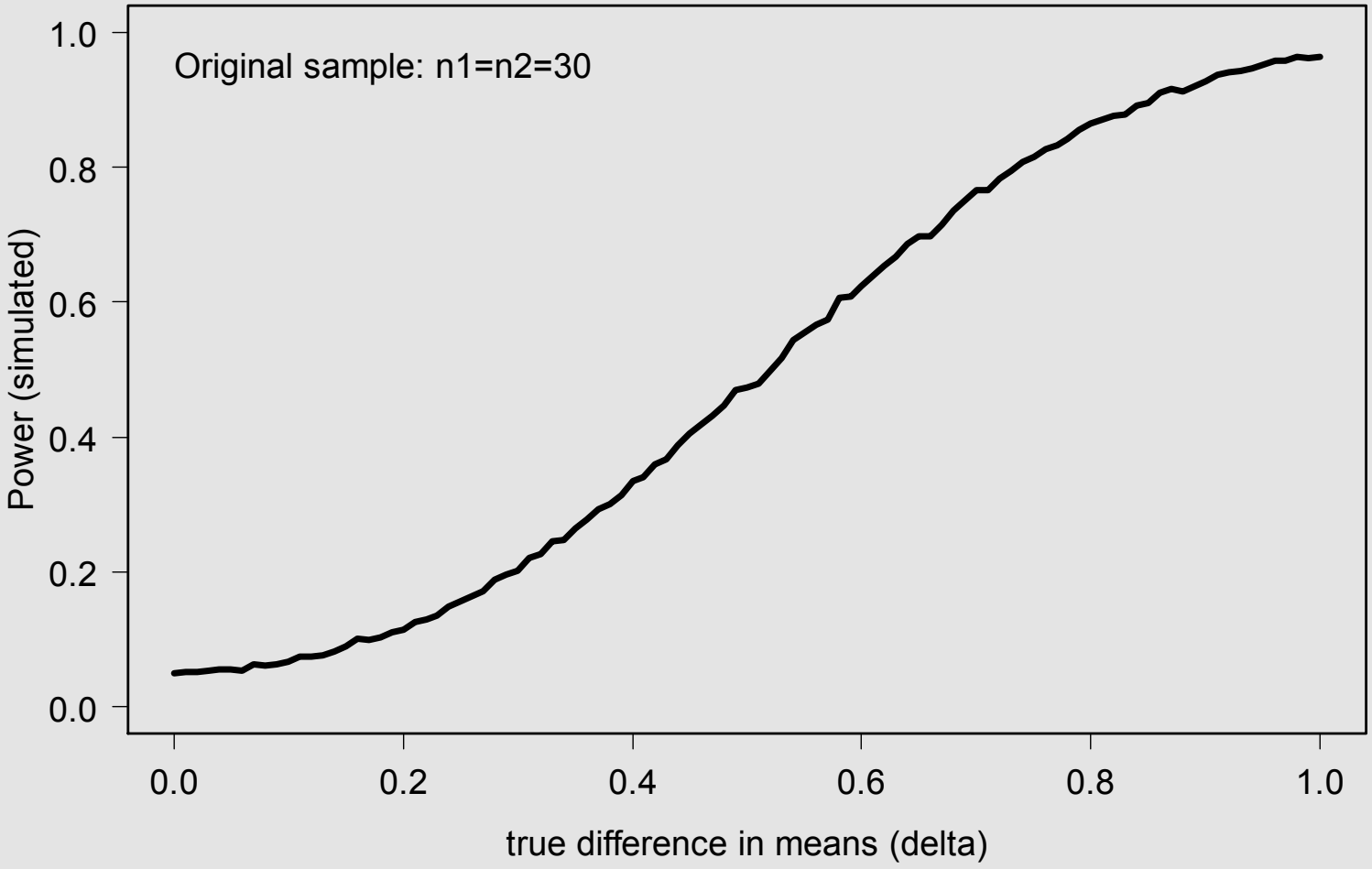
Group 1	**4.5**	**6.4**	**5.4**	**6.9**	**8.5**
Group 2	**4.1**	**3.2**	**4.0**	**8.4**	**3.6**

- **Draw a random sample *with replacement* out of the observed measurements**

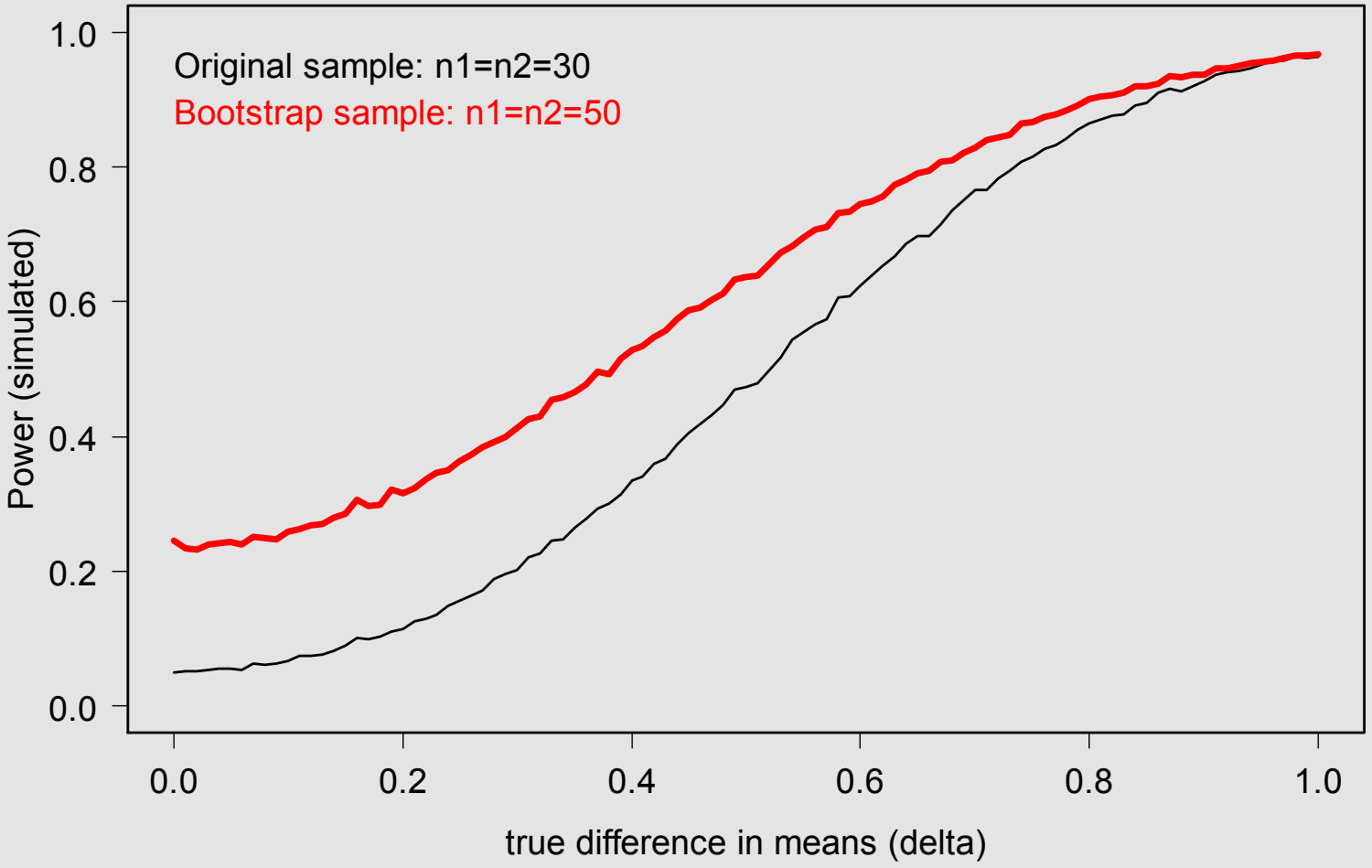
Group 1	**4.5**	**5.4**	**6.4**	**4.5**	**6.4**	**8.5**	**8.5**	**5.4**	**6.9**	**5.4**
Group 2	**8.4**	**4.0**	**4.1**	**8.4**	**3.2**	**3.2**	**4.0**	**8.4**	**4.0**	**8.4**

- **Perform the group comparison on the basis of the enlarged sample**

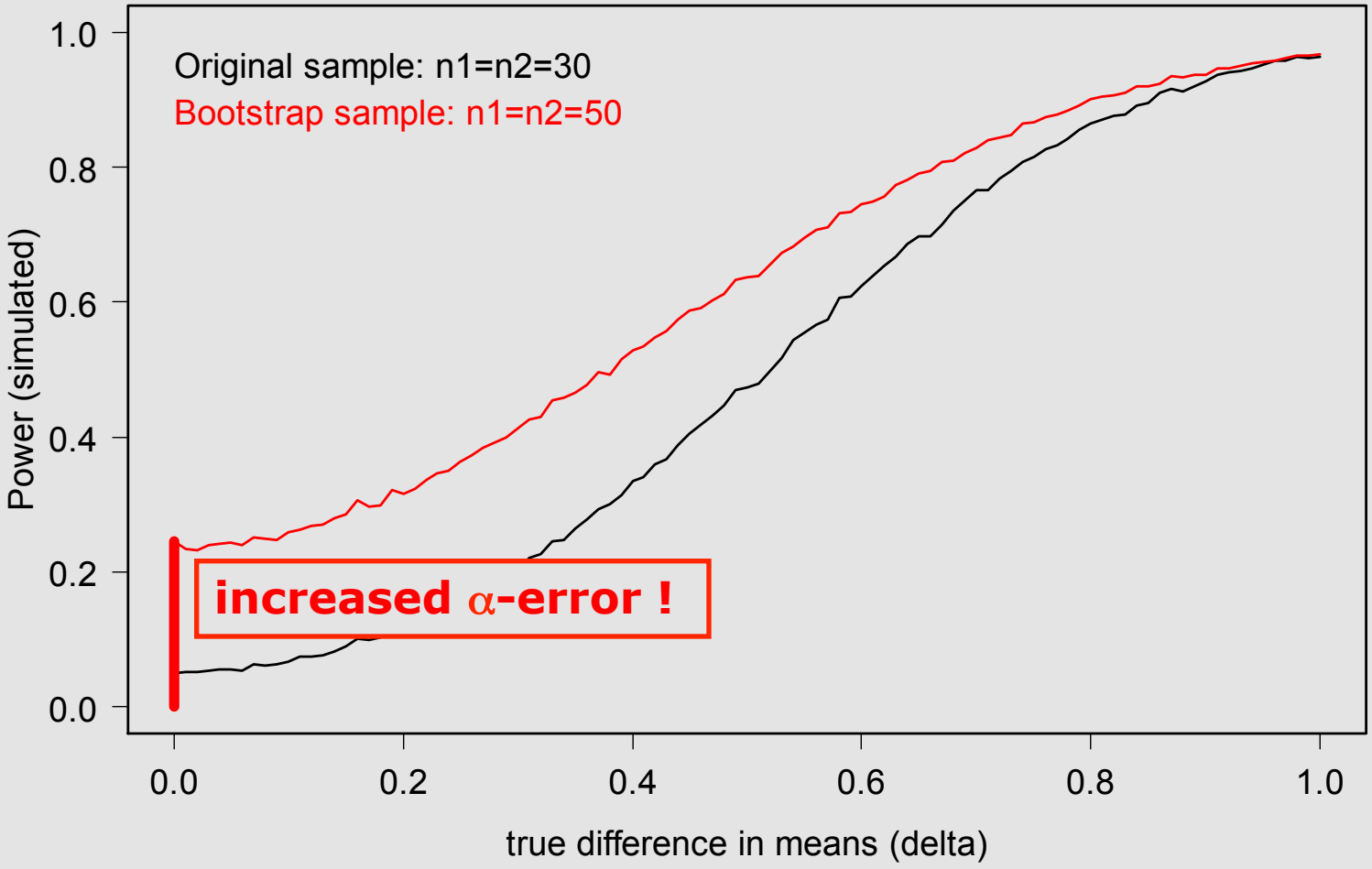
Bootstrap


Original sample: n1=n2=30
Power (simulated)
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
true difference in means (delta)

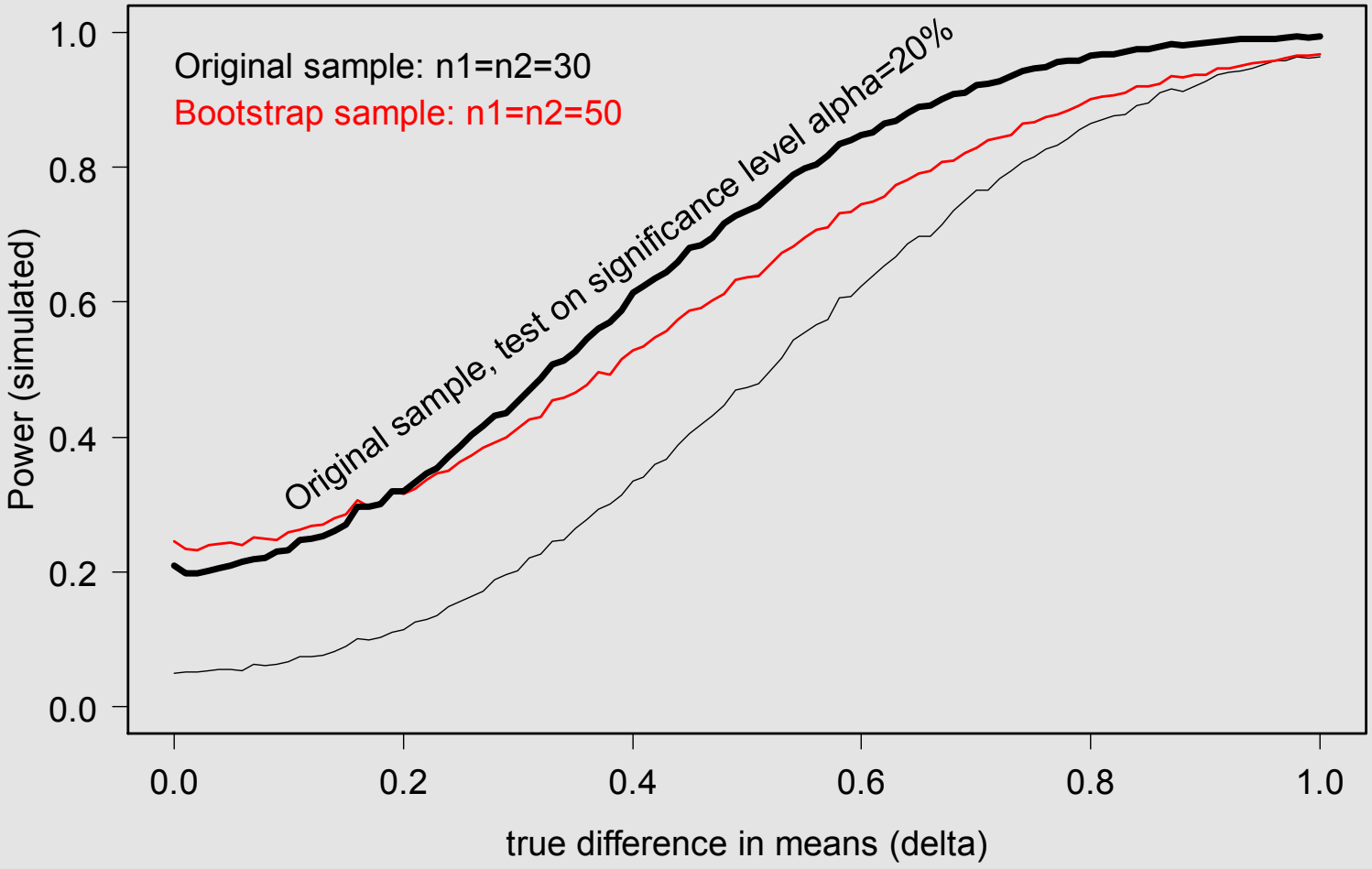
Bootstrap


Original sample: n1=n2=30
Bootstrap sample: n1=n2=50
Power (simulated)
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
true difference in means (delta)

Bootstrap


Original sample: n1=n2=30
Bootstrap sample: n1=n2=50
increased α-error !
Power (simulated)
true difference in means (delta)
0.0
0.2
0.4
0.6
0.8
1.0

Bootstrap


Original sample: n1=n2=30
Bootstrap sample: n1=n2=50
Original sample, test on significance level alpha=20%
Power (simulated)
1.0
0.8
0.6
0.4
0.2
0.0
0.0
0.2
0.4
0.6
0.8
1.0
true difference in means (delta)

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - **3.3 Repeated measurement designs**
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Example 1: Binary response variable

- Clinical trial with two parallel treatment groups and binary response variable
- Two different possible designs:

(a) (b)

- (To what extent) Is the required sample size reduced in the repeated measurement design (b) compared to the single measurement design (a)?

Example 1

- Clinical trial with two parallel treatment groups and binary response variable
- Two different possible designs:

(a)

Pat	Treat-ment	Response
1	1	$\in\{0,1\}$
2	1	$\in\{0,1\}$
...	1	$\in\{0,1\}$
4	2	$\in\{0,1\}$
5	2	$\in\{0,1\}$
...	2	$\in\{0,1\}$

(b)

- (To what extent) Is the required sample size reduced in the repeated measurement design (b) compared to the single measurement design (a)?

Example 1

- Clinical trial with two parallel treatment groups and binary response variable
- Two different possible designs:

(a)

Pat	Treat-ment	Response
1	1	$\in\{0,1\}$
2	1	$\in\{0,1\}$
...	1	$\in\{0,1\}$
4	2	$\in\{0,1\}$
5	2	$\in\{0,1\}$
...	2	$\in\{0,1\}$

(b)

Pat	Treat-ment	Response (1)	Response (2)	...
1	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
2	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
...	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
4	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
5	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
...	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$

- (To what extent) Is the required sample size reduced in the repeated measurement design (b) compared to the single measurement design (a)?

Example 1

- Clinical trial with two parallel treatment groups and binary response variable
- Two different possible designs:

(a)

Pat	Treat-ment	Response
1	1	$\in\{0,1\}$
2	1	$\in\{0,1\}$
...	1	$\in\{0,1\}$
4	2	$\in\{0,1\}$
5	2	$\in\{0,1\}$
...	2	$\in\{0,1\}$

(b)

Pat	Treat-ment	Response (1)	Response (2)	...
1	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
2	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
...	1	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
4	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
5	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$
...	2	$\in\{0,1\}$	$\in\{0,1\}$	$\in\{0,1\}$

- (To what extent) Is the required sample size reduced in the repeated measurement design (b) compared to the single measurement design (a)?

Example 1

- Expected response rates: $p_1=0.5$, $p_2=0.75$
- two-sided $\alpha=0.05$, $1-\beta=0.8$

(a) Single measurement design: $n_{total}=116$ patients

(b) Repeated measurement design (k measurements per patient):

n_{total} = ... patients

Correlation between successive measurements	k=3	k=5	k=5[1]	k=5[2]
ρ=0.5	**82**	**74**	**78**	**84**
ρ=0.6	**90**	**84**	**88**	**94**
ρ=0.7	**98**	**94**	**100**	**104**

[1] Conditional loss to follow-up rate = 5%

[2] Conditional loss to follow-up rate = 10%

Example 1

- Expected response rates: $p_1=0.5$, $p_2=0.75$
- two-sided $\alpha=0.05$, $1-\beta=0.8$

(a) Single measurement design: $n_{total}=116$ patients

(b) Repeated measurement design (k measurements per patient):

n_{total} = ... patients

Correlation bet… succe…				=5(2)
				4
		84	88	94
ρ=0.7	98	94	100	104

Statistical analyses of binary response variables in repeated measurement designs with missing data:

Generalised Estimating Equations (GEE)

(1) Conditional loss to follow-up rate = 5%

(2) Conditional loss to follow-up rate = 10%

Example 2: Metric response variable

- Clinical trial on (diastolic) blood pressure
- Two parallel treatment groups
- Baseline measurement plus 3 follow-ups at 2, 4 and 6 weeks
- Expected values:

Treatment group	Baseline	2 weeks	4 weeks	6 weeks
1	103.0 mmHg	99.6 mmHg	96.3 mmHg	92.9 mmHg
2	103.1 mmHg	98.2 mmHg	93.4 mmHg	88.5 mmHg

- Two alternative statistical approaches

  (a) Compute intra-individual changes („6 weeks" minus „Baseline")

  => unpaired t-Test, comparing treatment groups 1 versus 2

  (b) GEE: Evaluate the whole series of observed measurements

Example 2: Metric response variable

- Clinical trial on (diastolic) blood pressure
- Two parallel treatment groups
- Baseline measurement plus 3 follow-ups at 2, 4 and 6 weeks
- Expected values:

Treatment group	Baseline	2 weeks	4 weeks	6 weeks
1	103.0 mmHg	99.6 mmHg	96.3 mmHg	92.9 mmHg
2	103.1 mmHg	98.2 mmHg	93.4 mmHg	88.5 mmHg

- Two alternative statistical approaches

  (a) Compute intra-individual changes („6 weeks“ minus „Baseline“)

  => unpaired t-Test, comparing treatment groups 1 versus 2

  (b) GEE: Evaluate the whole series of observed measurements

Example 2: Metric response variable

- Clinical trial on (diastolic) blood pressure
- Two parallel treatment groups
- Baseline measurement plus 3 follow-ups at 2, 4 and 6 weeks
- Expected values:

Treatment group	Baseline	2 weeks	4 weeks	6 weeks
1	103.0 mmHg	99.6 mmHg	96.3 mmHg	92.9 mmHg
2	103.1 mmHg	98.2 mmHg	93.4 mmHg	88.5 mmHg

- Two alternative statistical approaches

  (a) Compute intra-individual changes („6 weeks“ minus „Baseline“)

  => unpaired t-Test, comparing treatment groups 1 versus 2

  (b) GEE: Evaluate the whole series of observed measurements

Example 2

- Standard deviation: σ=9.89 mmHg
- Correlation between successive measurements ρ=0.53
- two-sided α=0.05, 1-β=0.8
- Required total number of patients $\mathbf{n_{total}}$**=...**

	t-Test	GEE
No missing data	**262**	**264**
Conditional loss to follow-up rate = 5%	**306**	**288**
Conditional loss to follow-up rate = 10%	**360**	**318**

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - **3.4 Bayesian models**
4. **Software**
5. **Summary and Conclusion**

Basic paradigm

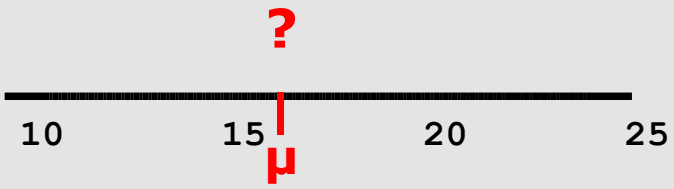
Classical / traditional: Frequentist approach

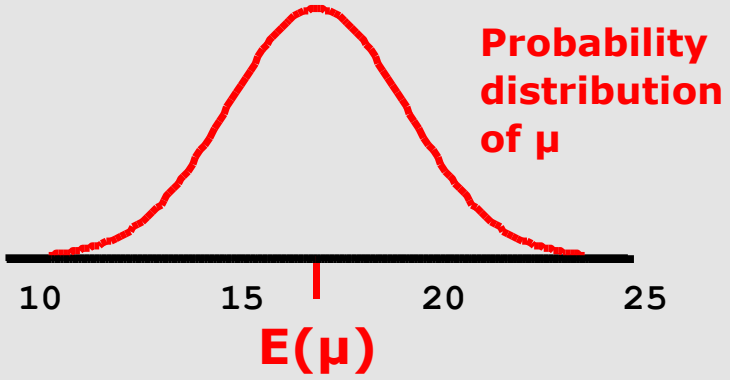
- Unknown parameters are *fixed constants*

Bayesian approach

- Unknown parameters are *random variables* with a *probability distribution*

Example: Comparison of an active treatment versus control, mean difference $\mu=\mu_1-\mu_2$ of a metric response variable





Basic paradigm

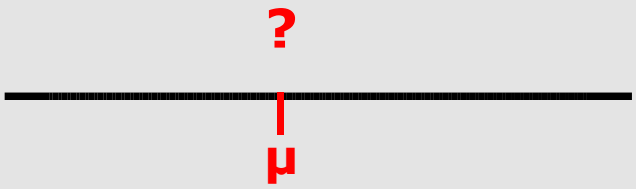
Frequentist approach

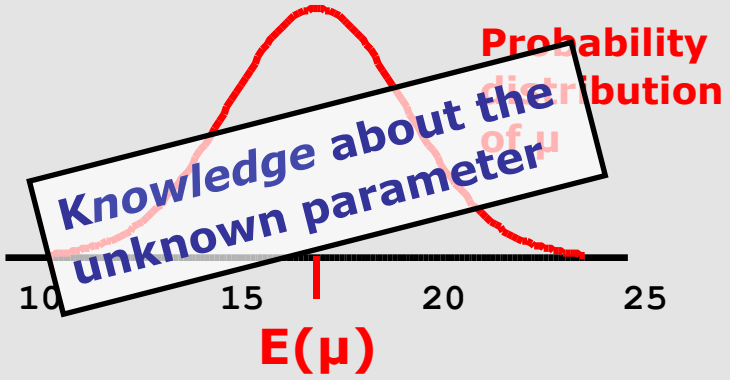
- Unknown parameters are *fixed constants*

Bayesian approach

- Unknown parameters are *random variables* with a *probability distribution*

Example: Comparison of an active treatment versus control, mean difference $\mu=\mu_1-\mu_2$ of a metric response variable





Prior and posterior distribution

Example: Mean difference of a metric response variable $\mu=\mu_1-\mu_2$

-> „To what extent is the active treatment superior to control?“

- Model the knowledge about the unknown parameter:

  1. *Before* collecting data of the present trial
     „*prior distribution p(μ)*“
  2. Collect new data and combine the prior knowledge with the information provided by newly collected data
     => *posterior distribution p(μ|data)*

- Inference is carried out on the basis of the posterior distribution of the parameter of interest.

- Bayesian data analyses are based upon a completely different paradigm compared to frequentist methods (e.g. there exist no „Bayesian p-values“).

Example: Survival Analysis

- Clinical trial with two parallel treatment groups
- Response variable: Survival of patients
- Treatment effect measured by the *hazard ratio* between both treatment groups

Hazard : $h(t) = \lim_{\Delta t \to 0} \frac{P(t < T < t + \Delta t \mid T > t)}{\Delta t}$

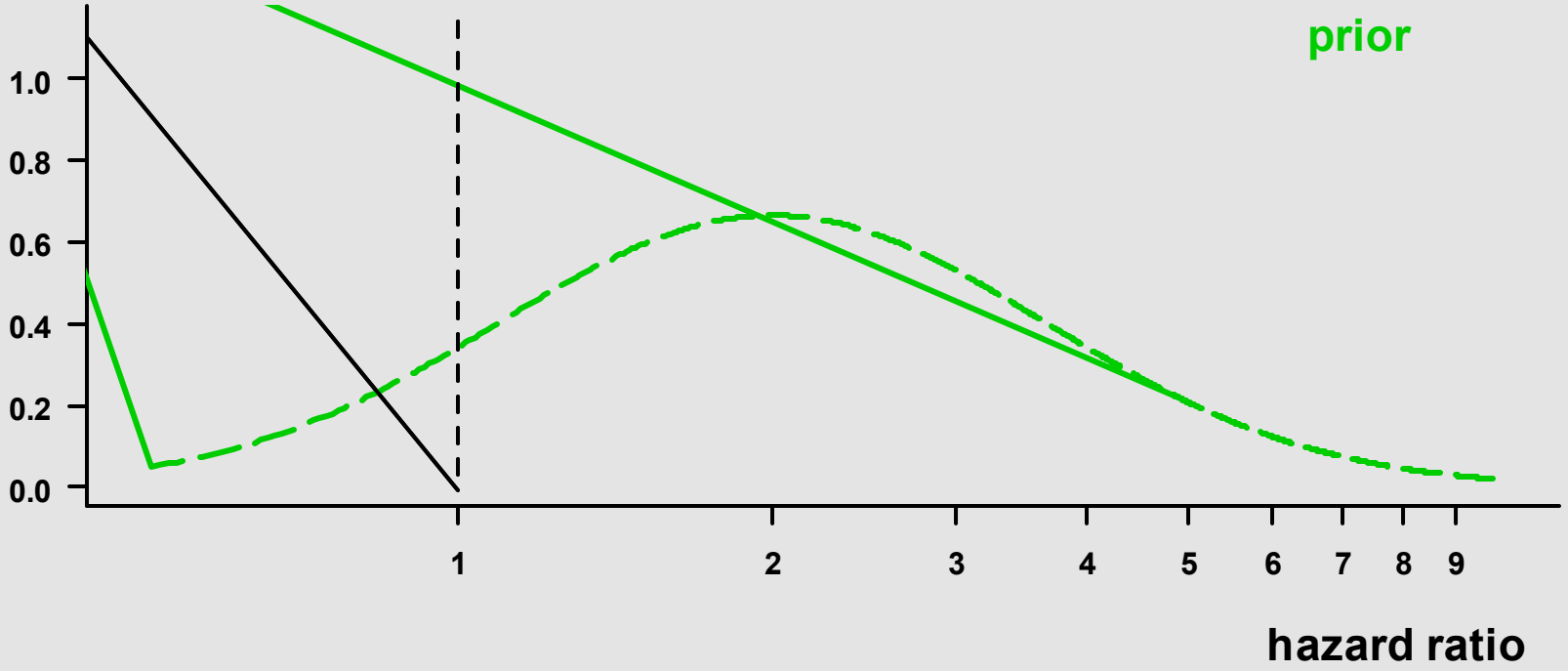
~ "Probability of death at time t – given a patient has survived so far"

Hazard ratio = Hazard in group 2 versus group 1

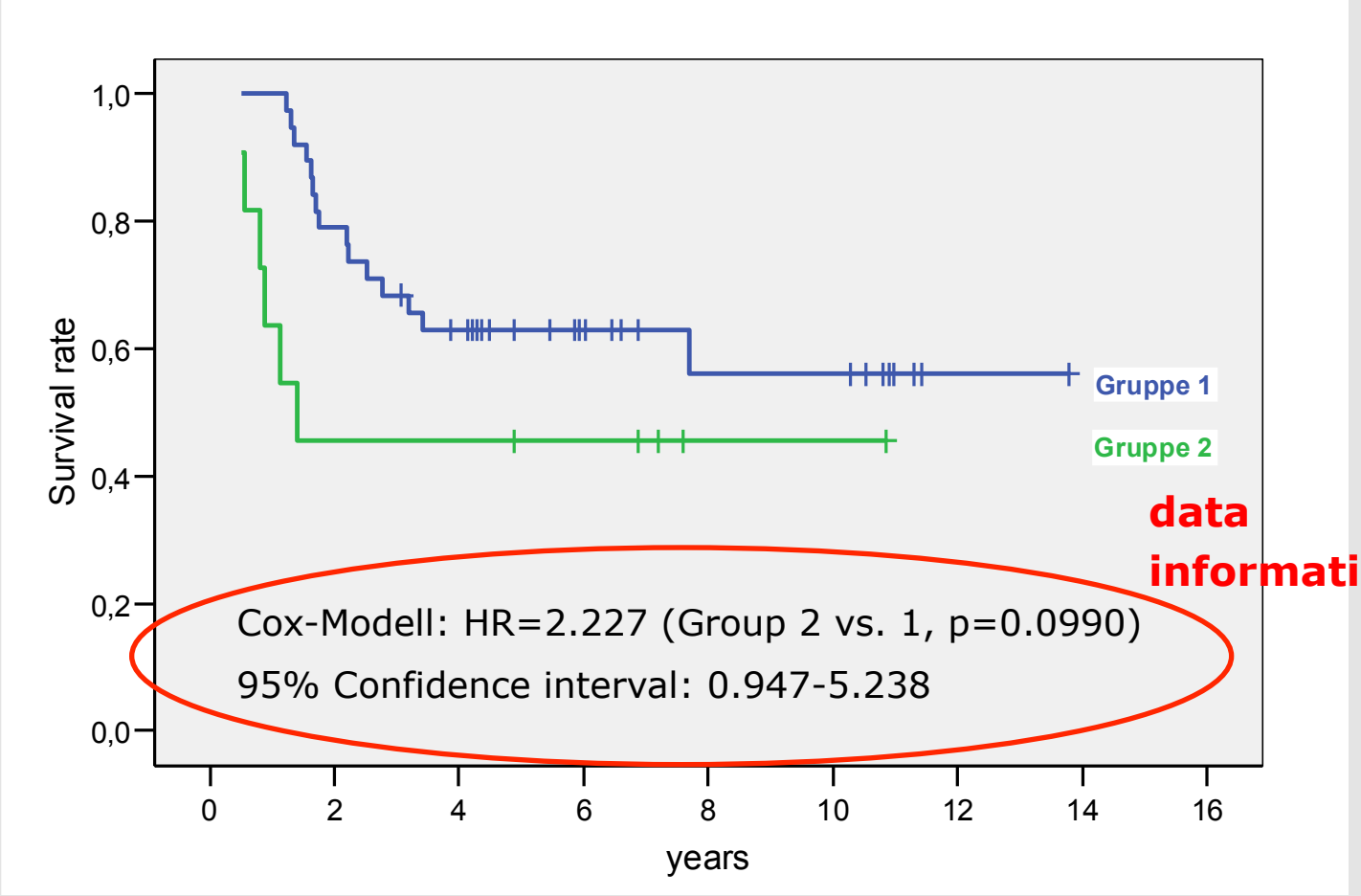
-> To what extent is the survival in group 2 inferior to group 1?

- Prior knowledge: We suppose group 2 to perform worse than group 1 (hazard ratio ≈ 2), but we are not too sure if this estimation is correct.

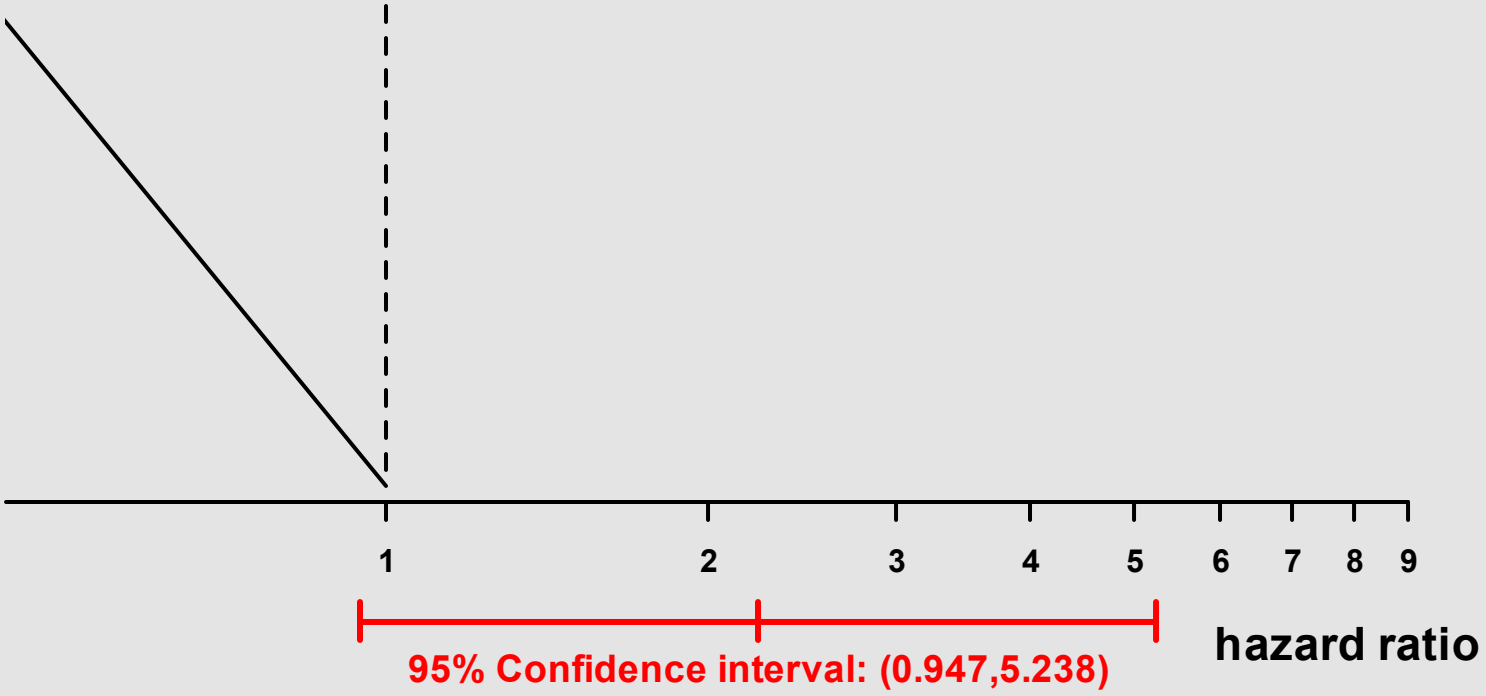
Ex. Survival: Prior distribution



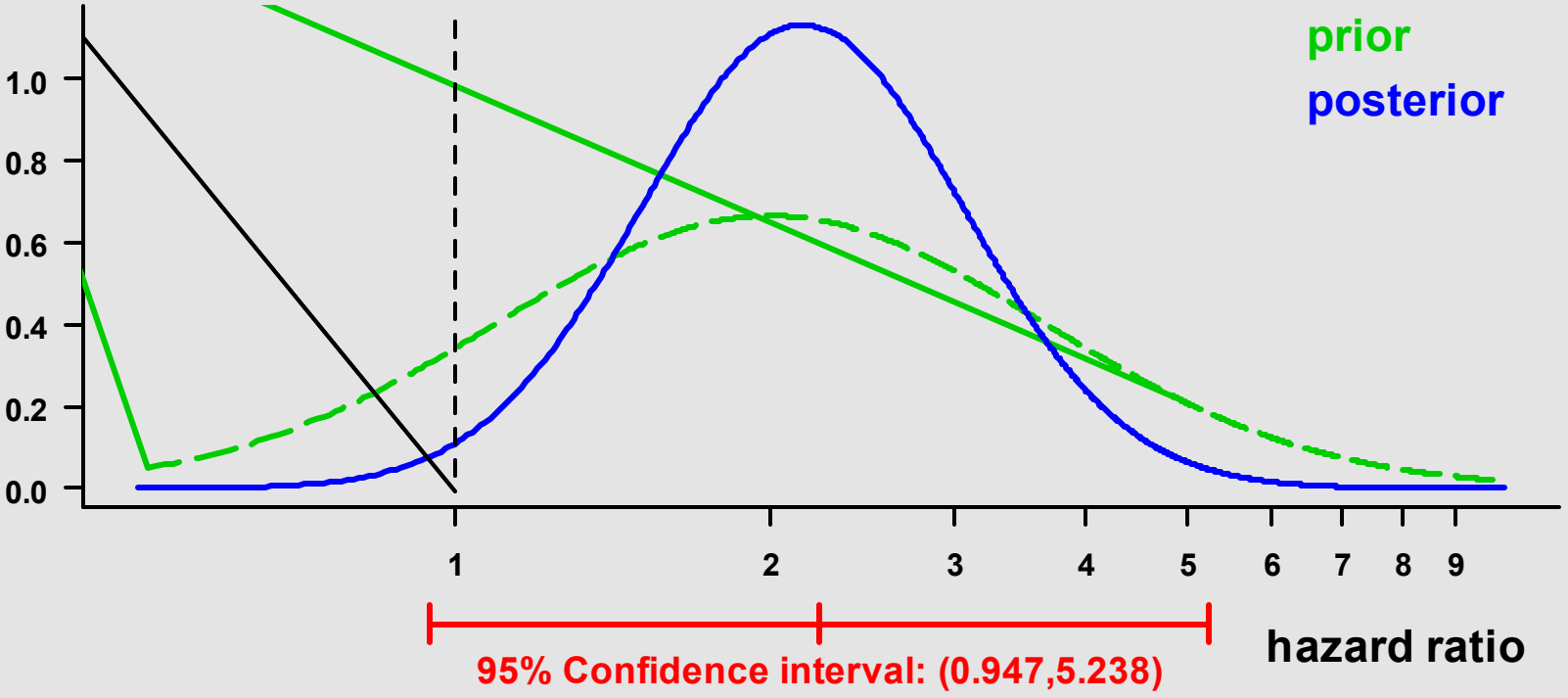
Ex. Survival: Data information



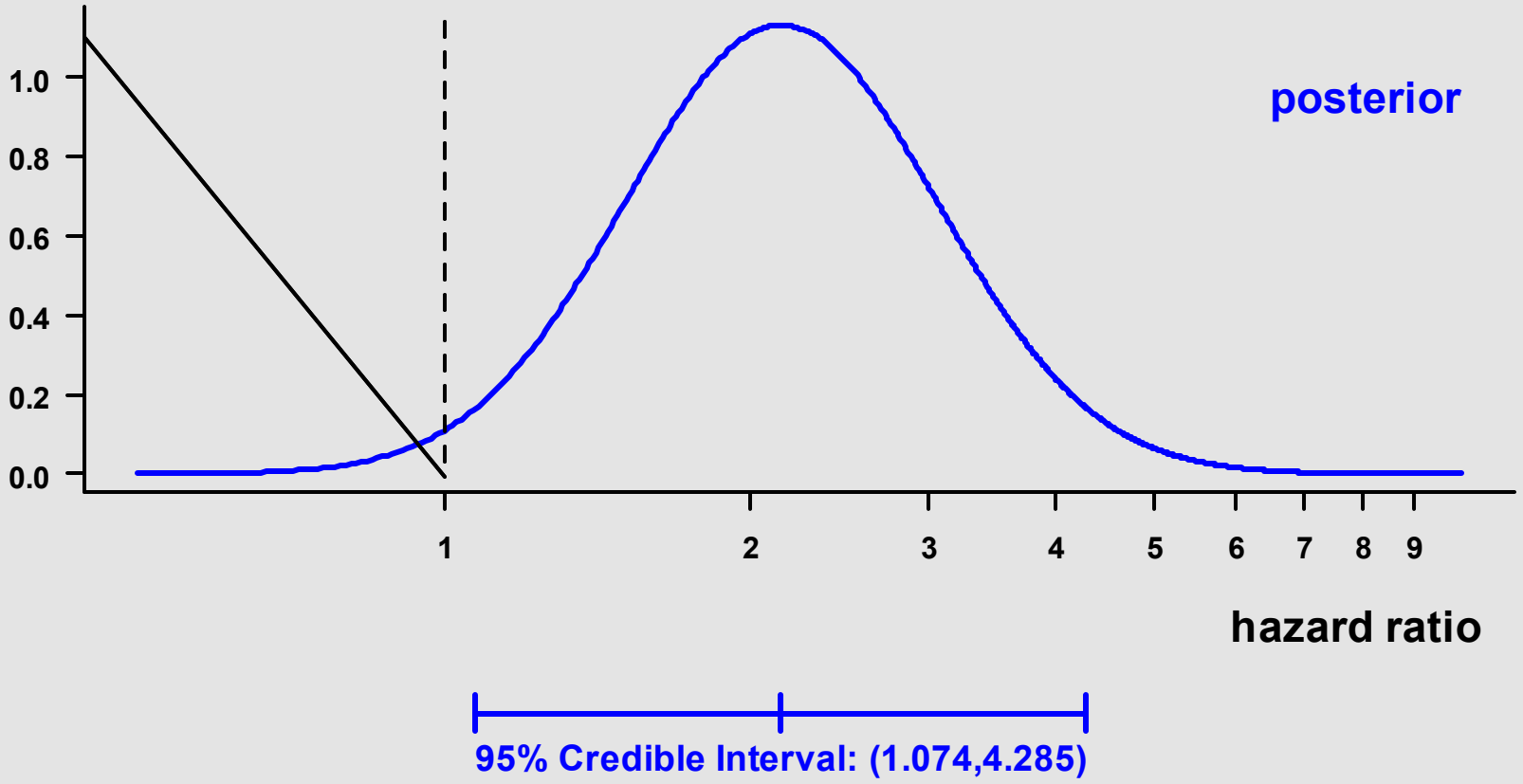
Ex. Survival: Data information



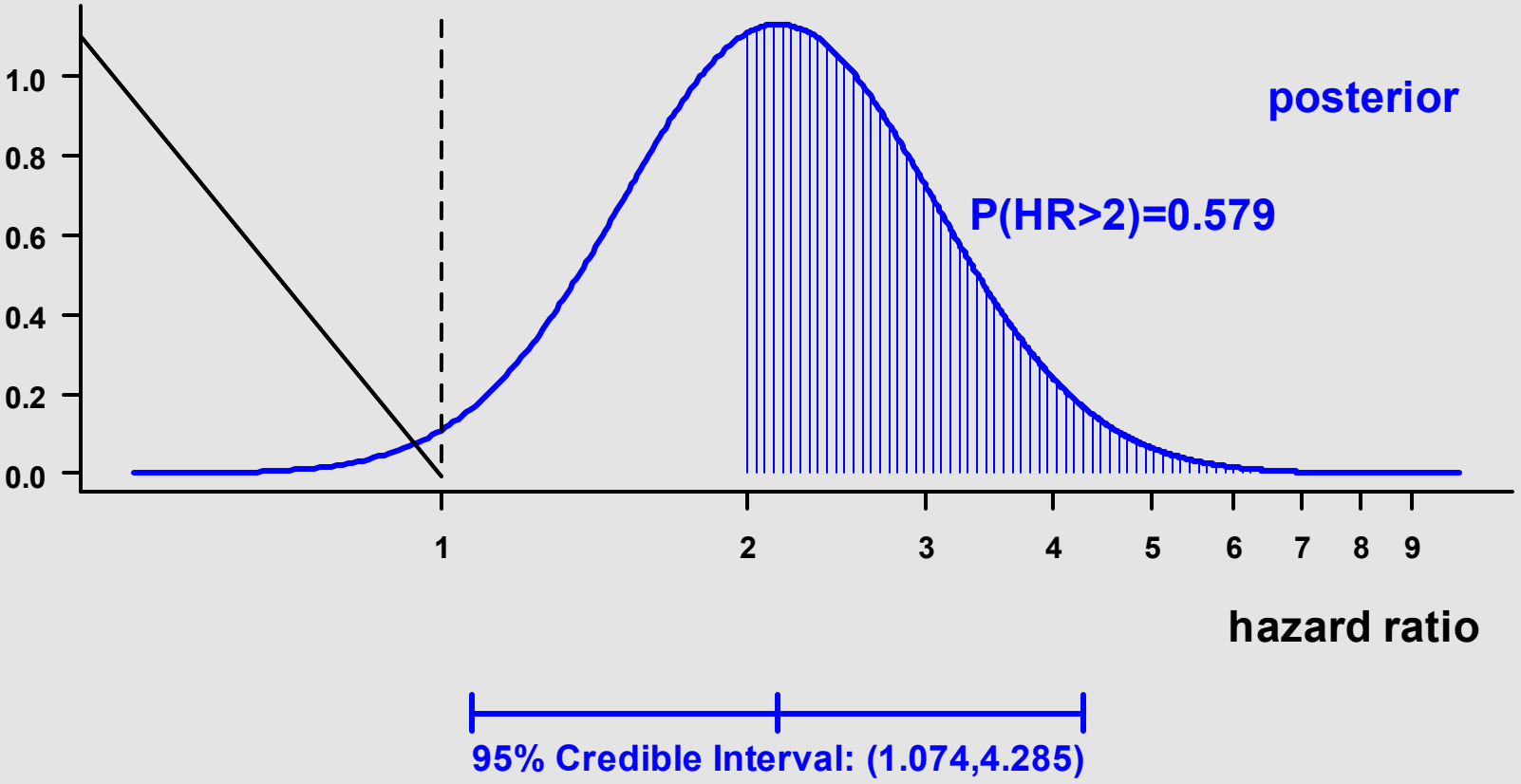
Ex. Survival: Posterior distribution



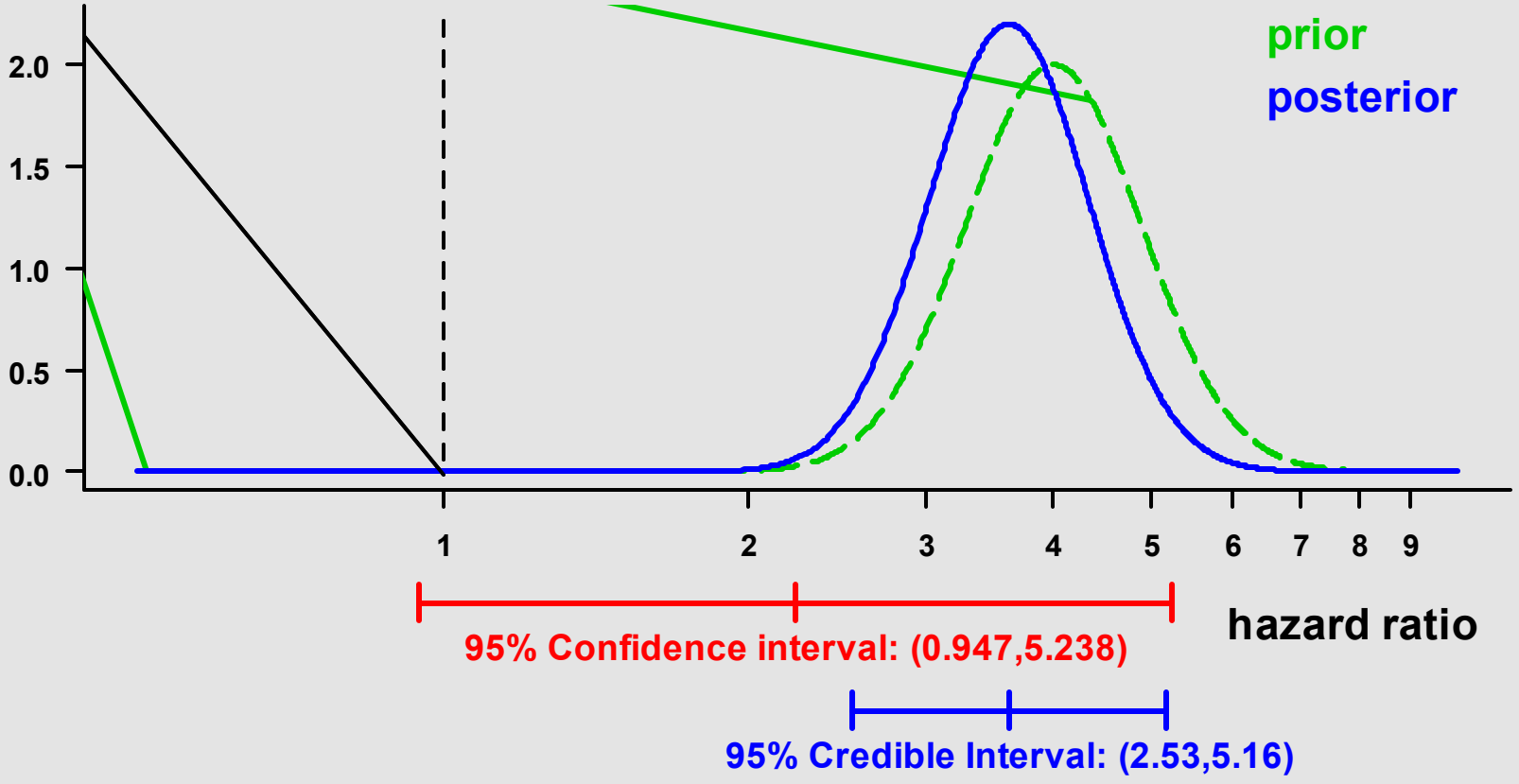
Ex. Survival: Posterior distribution



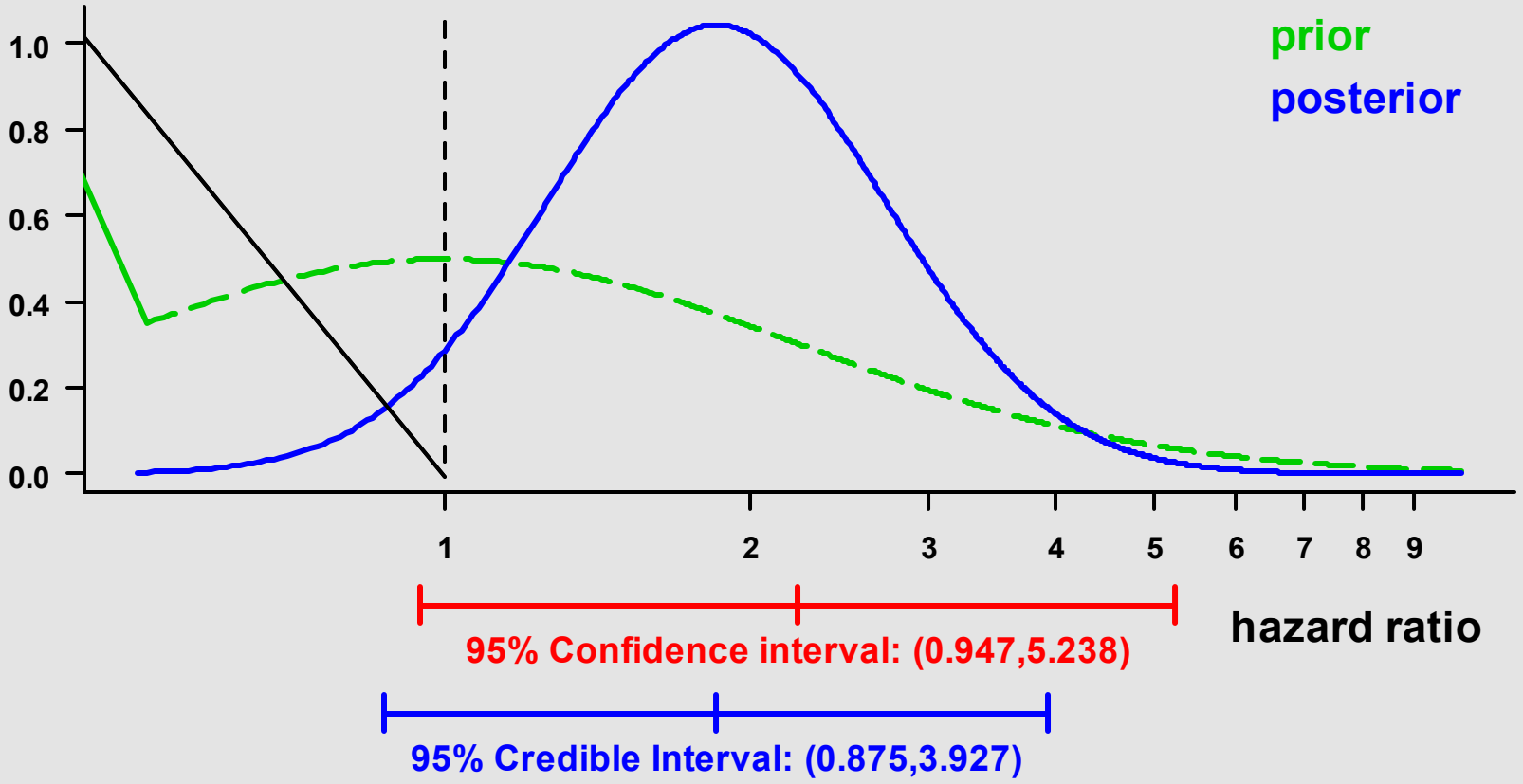
Ex. Survival: Posterior distribution



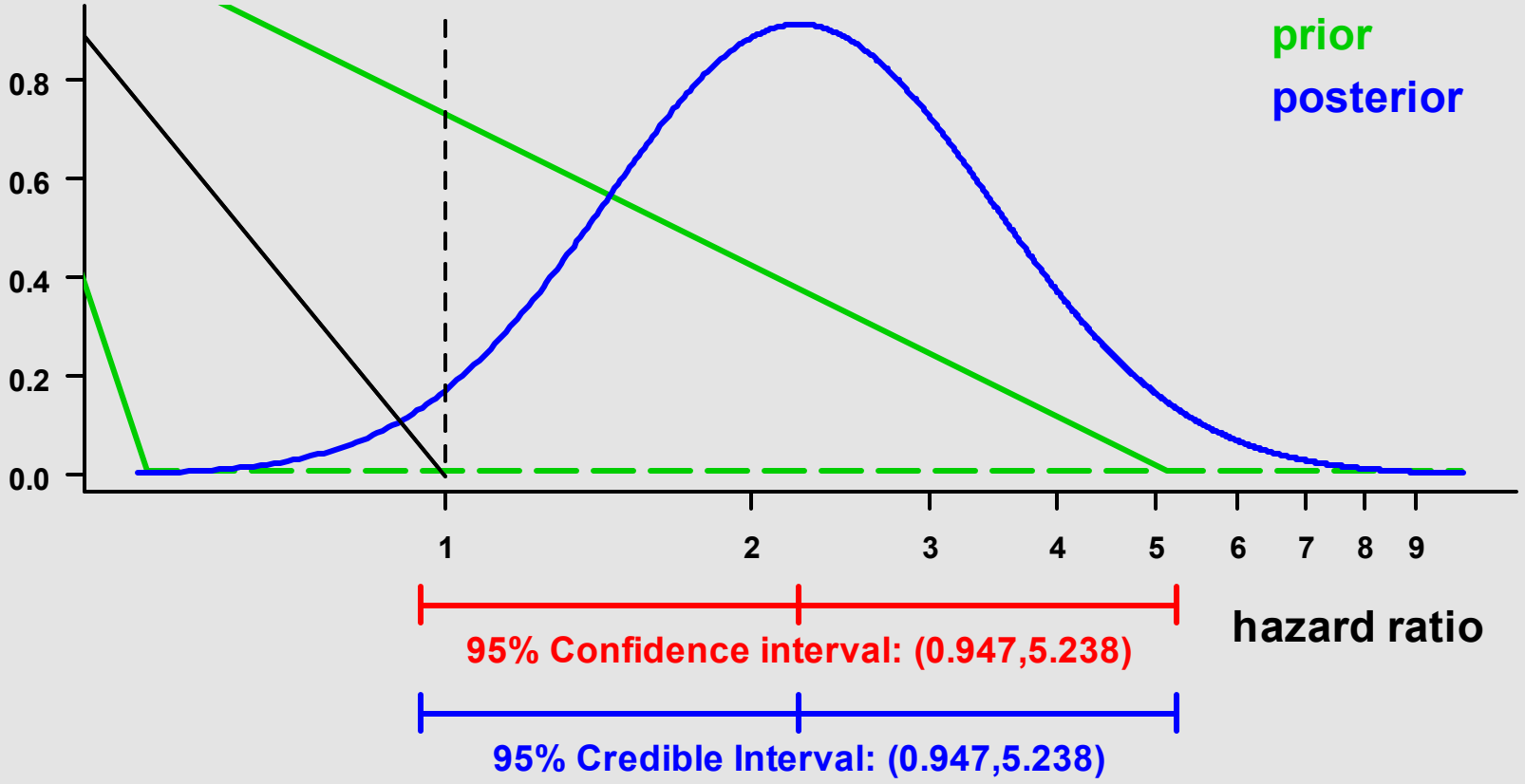
Ex. Survival: Prior and posterior distn



Ex. Survival: Prior and posterior distn



Ex. Survival: Prior and posterior distn



Pros and Cons of Bayesian methods

- **Pro**
  - Inclusion of existing knowledge in a future trial
  - Better interpretable results compared to frequentist methods
- **Contra**
  - subjective choice of prior information (no guidelines)
  - not based upon traditional and generally accepted optimality criteria
  - „Bayesian-based clinical trials require substantial planning, are often more work, and don‘t always mean you can use fewer subjects.“

Application of Bayesian methods in clinical trials

- „Bayesian methods are great – and already in use – for **exploratory studies**. But there are problems with using the methods in large confirmatory studies such as phase III trials and basing regulatory decisions on them.” R. O’Neill, FDA.
- “Innovative drug development”: **Bayesian methodology does have a place in drug development**,
  - for hypothesis generating in earlier phases,
  - in the assessment of futility and
  - **potentially in ‘small populations’** where there is no possibility to perform an adequately powered randomised controlled trial.

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Statistical software

- **Group sequential (adaptive) designs:**
  - ADDPLAN
  - EAST
  - PEST
- **Longitudinal data analysis (GEE)**
  - SAS, proc genmod
  - Sample-size calculation: Macro GEESIZE
  - R, S-PLUS
- **Adjustment for prognostic variables (Analysis of Variances):**
  - any statistical software
- **Bayesian data analysis:**
  - BUGS
  - BayesX
  - SAS, version 9

Outline

1. **The innovative drug development approaches-project**
2. **Weakness of small sample trials**
3. **Increase the efficiency of statistical data analyses**
   - 3.1 Overview of methodologic approaches
   - 3.2 Resampling
   - 3.3 Repeated measurement designs
   - 3.4 Bayesian models
4. **Software**
5. **Summary and Conclusion**

Summary and Conclusion

- There are methodological approaches that can be applied to increase the efficiency of the statistical analysis in small sample trials.
- Each single approach itself yields only a small increase in efficiency indeed. But combining the different approaches, a substantial increase in efficiency may be obtained.
- The possibilities however are not unlimited naturally. In case of a too small sample size, one has to compensate for this by „paying a price“. This price may be
  - required additional (possibly restrictive) model assumptions.
  - defeasibility and reduced acceptance of the results obtained.
- Bayesian methods represent a promising alternative to classical frequentist analyses and their application is accepted in exploratory problems. In confirmatory problems, Bayesian methods may be maintainable only in special situations (e.g. small sample trials). Otherwise a paradigm shift towards Bayesian methods is not accepted by regulatory authorities.

Literature

- **EMEA Publications**
  - Innovative Drug Development Approaches (March 2007)
  - Guideline on Clinical Trials in Small Populations (July 2006)
- **Generalised Estimating Equations (GEE)**
  - Dahmen, Rochon, König, Ziegler (2004): Sample Size Calculations for Controlled Clinical Trials Using Generalized Estimating Equations (GEE). Methods Inf Med 43: 451-6.
  - Dahmen, Ziegler (2006): Independence Estimating Equations for Controlled Clinical Trials with Small Sample Sizes. Methods Inf Med 45: 430-4.
  - Liang, Zeger (1986): Longitudinal Data Analysis Using Generalized Linear Models. Biometrika 73, 13 - 22.
- **Bayesian data analysis**
  - Spiegelhalter, Abrams, Myles (2004): Bayesian Approaches to Clinical Trials and Health-Care Evaluation, Wiley.

Thank you for your attention!