



UNIVERSITÄTS**medizin.**
MAINZ

Andreas Faldum

Privatdozent Dr. rer. nat. et med. habil.
Diplom-Mathematiker und Arzt

faldum@imbei.uni-mainz.de
06131-173938

IMBEI Institut für Medizinische Biometrie,
Epidemiologie und Informatik



UNIVERSITÄTS**medizin.**
MAINZ

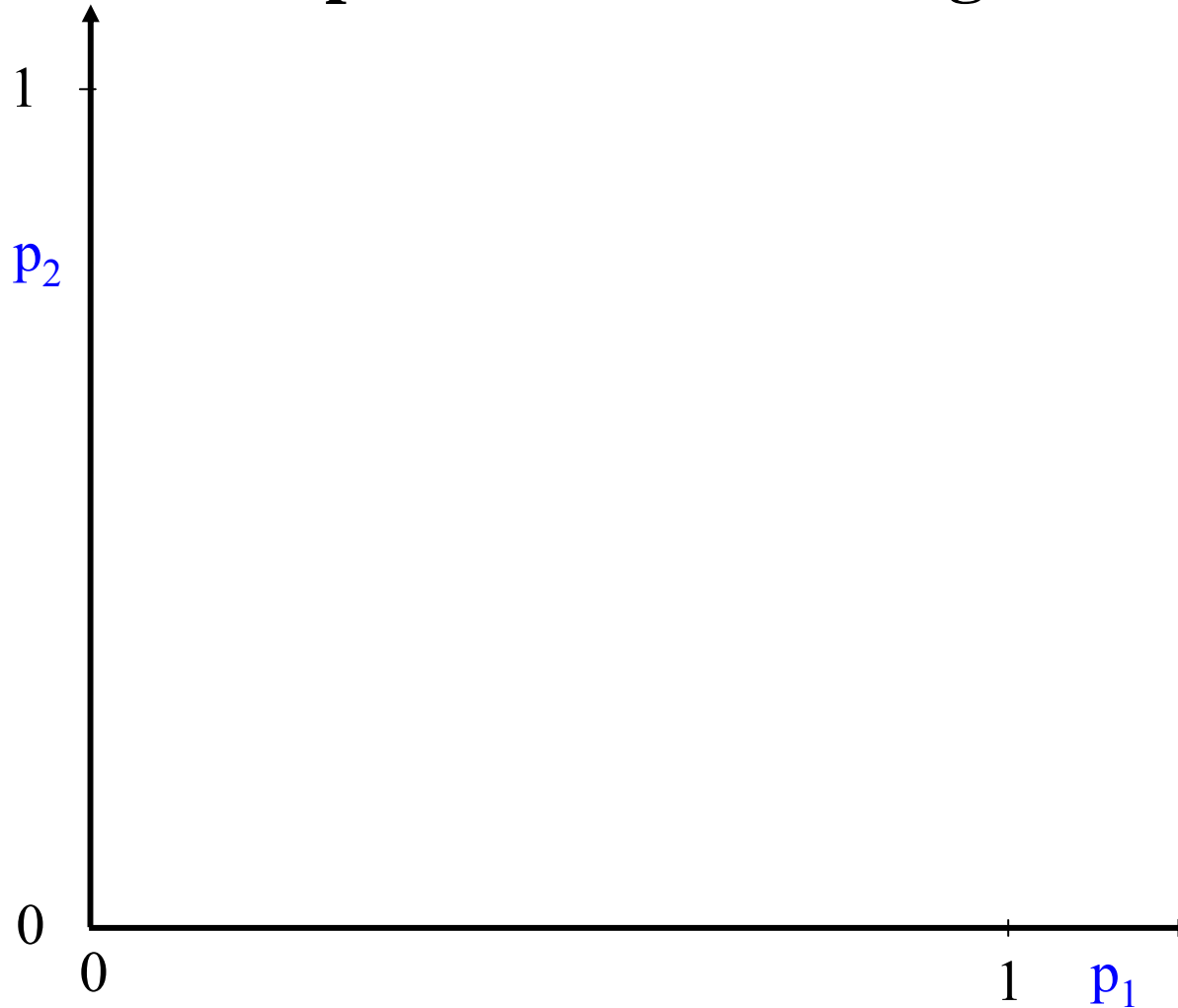
Interim Patients in Adaptive Survival Trials

ISCB 2009

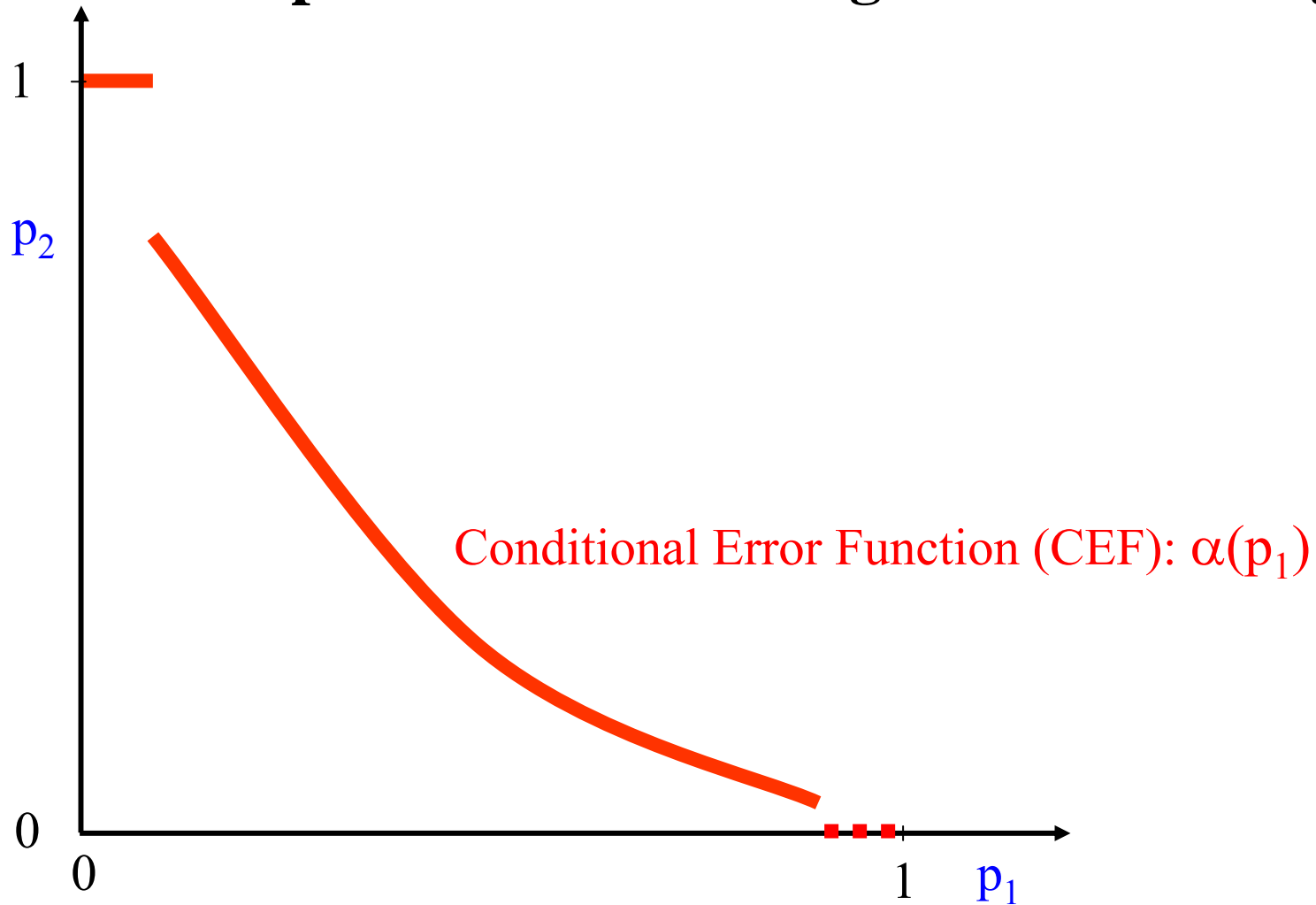
August 23rd – 27th, 2009, Prague

IMBEI Institut für Medizinische Biometrie,
Epidemiologie und Informatik

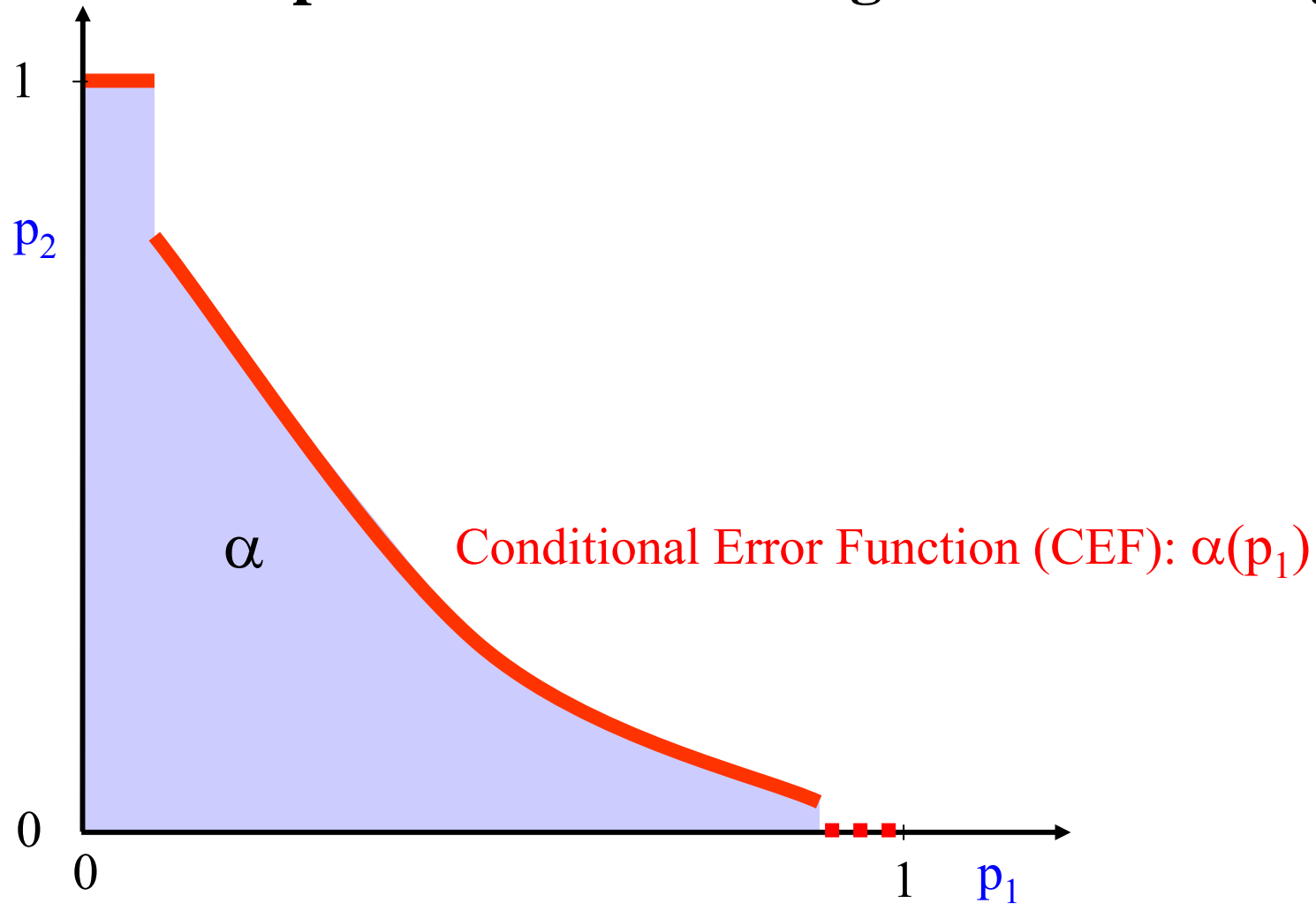
One-sided Adaptive Standard Design with Two Stages



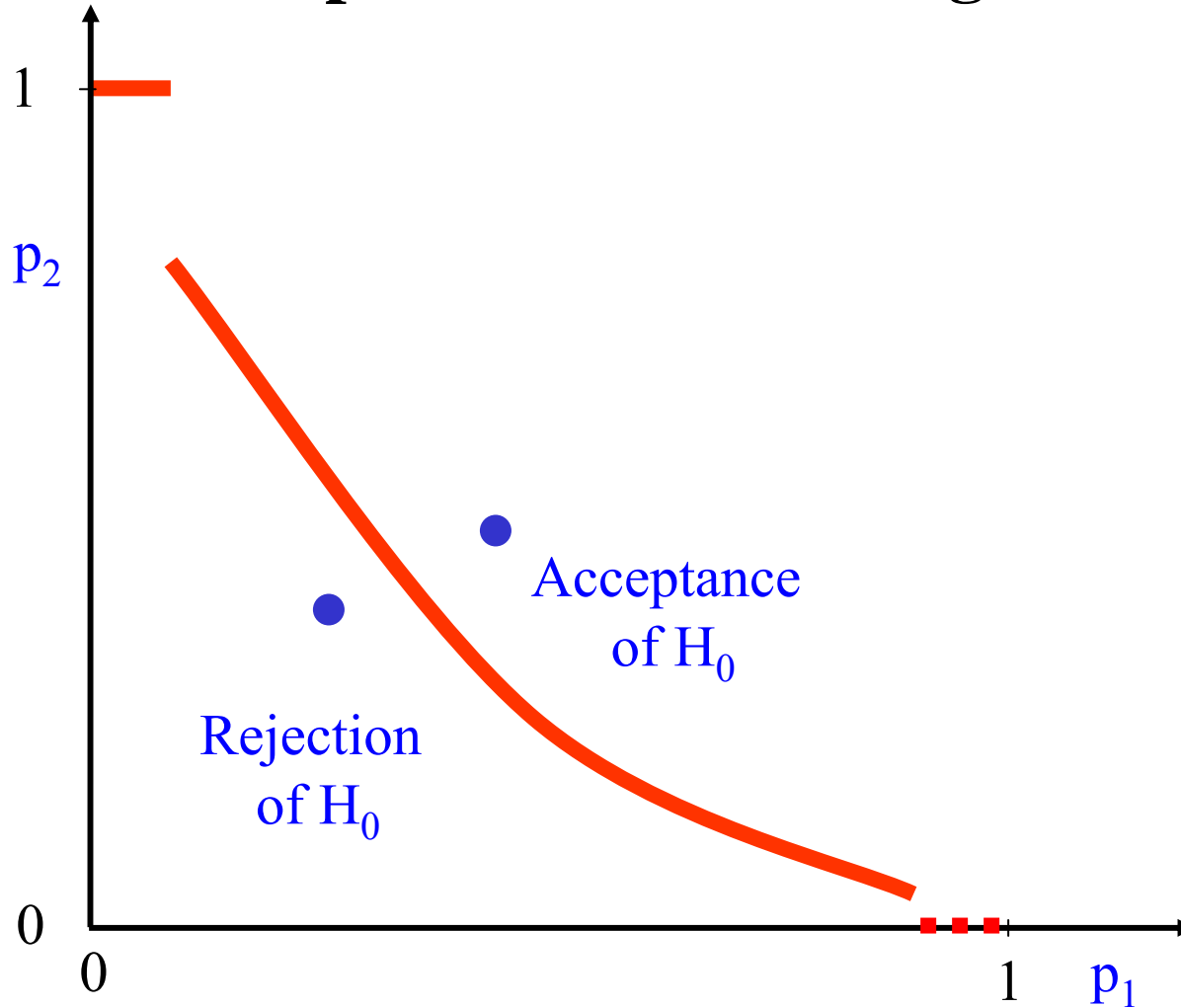
One-sided Adaptive Standard Design with Two Stages



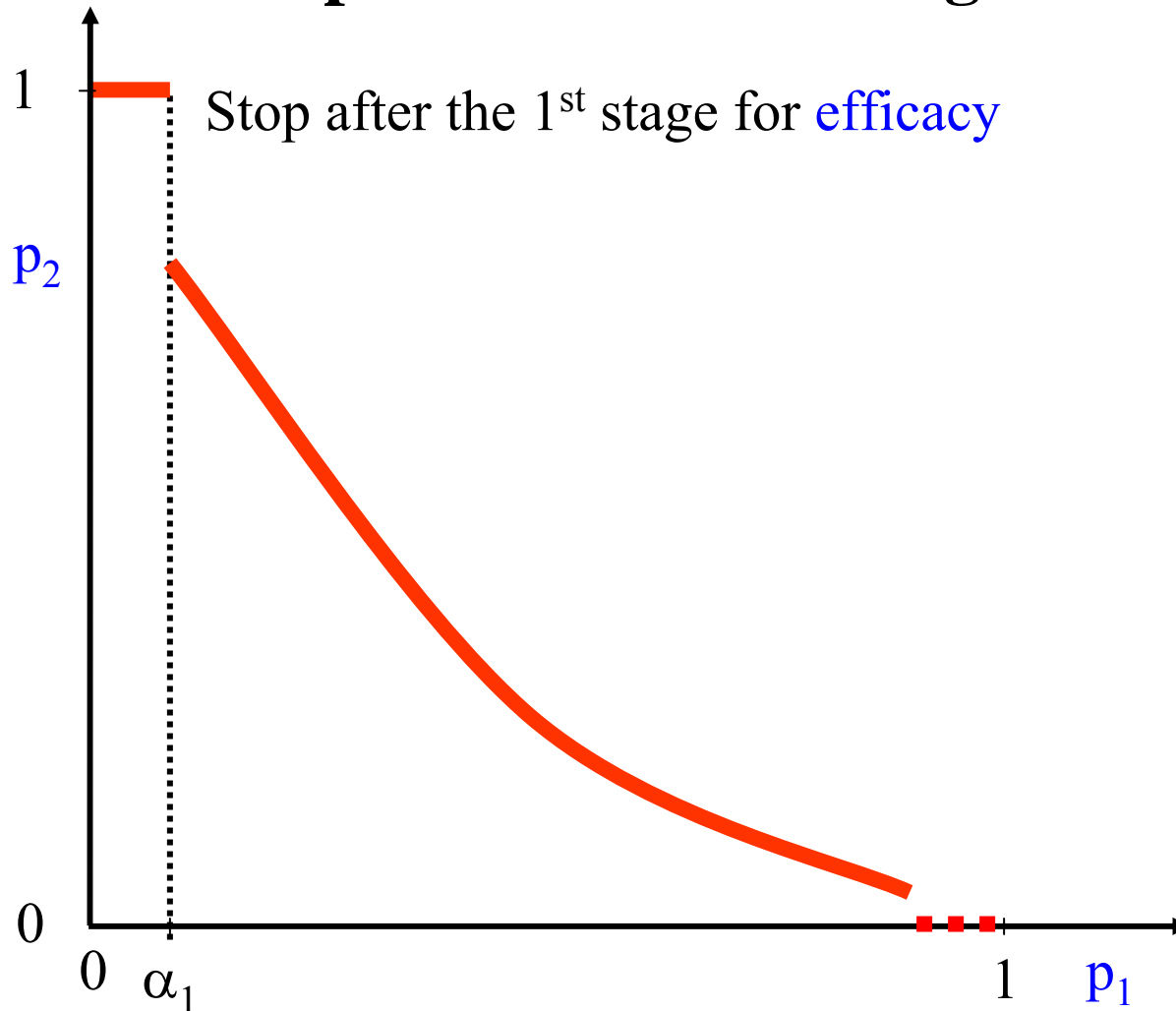
One-sided Adaptive Standard Design with Two Stages



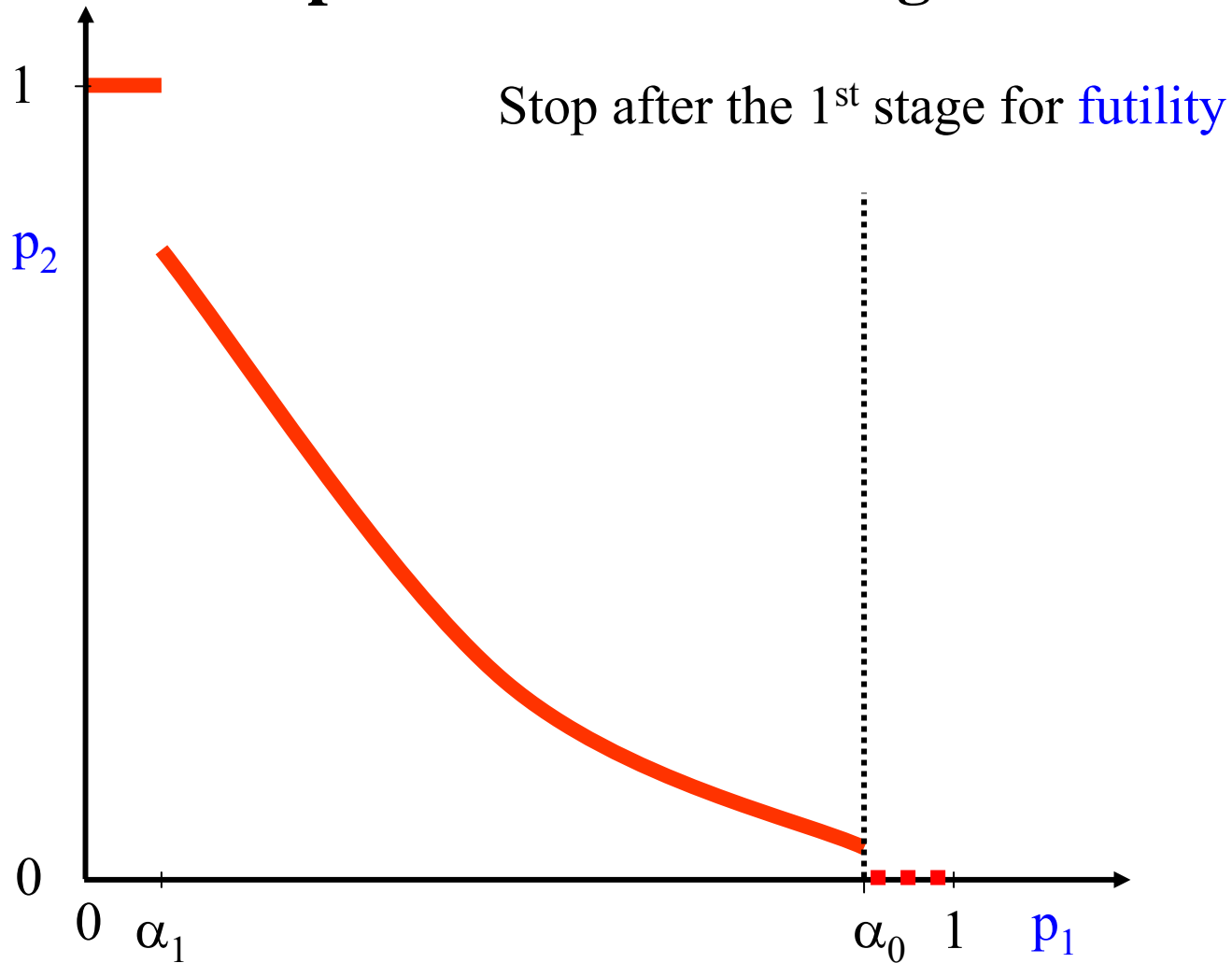
One-sided Adaptive Standard Design with Two Stages



One-sided Adaptive Standard Design with Two Stages



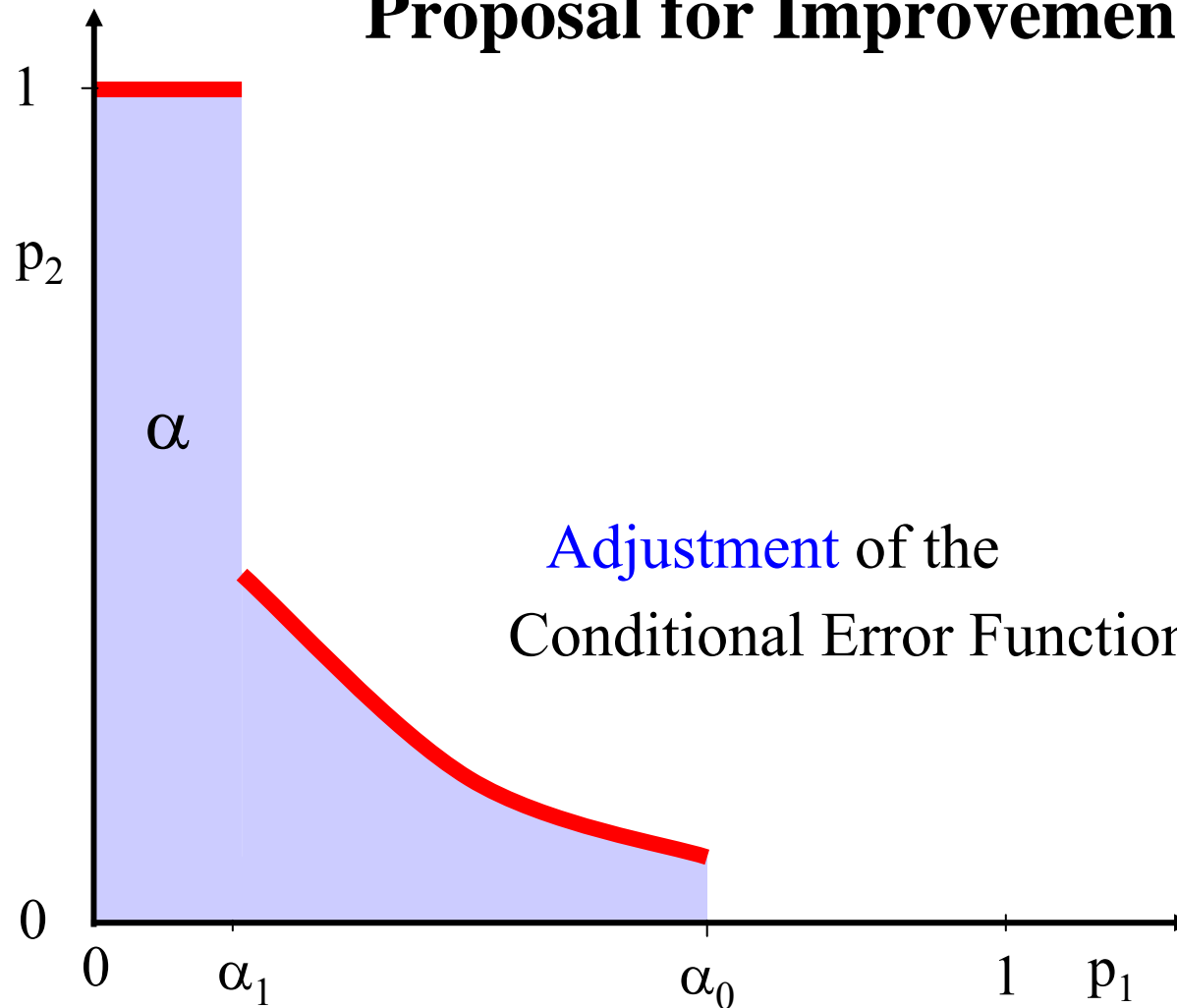
One-sided Adaptive Standard Design with Two Stages



Interim Patients: Occurrence and Problem

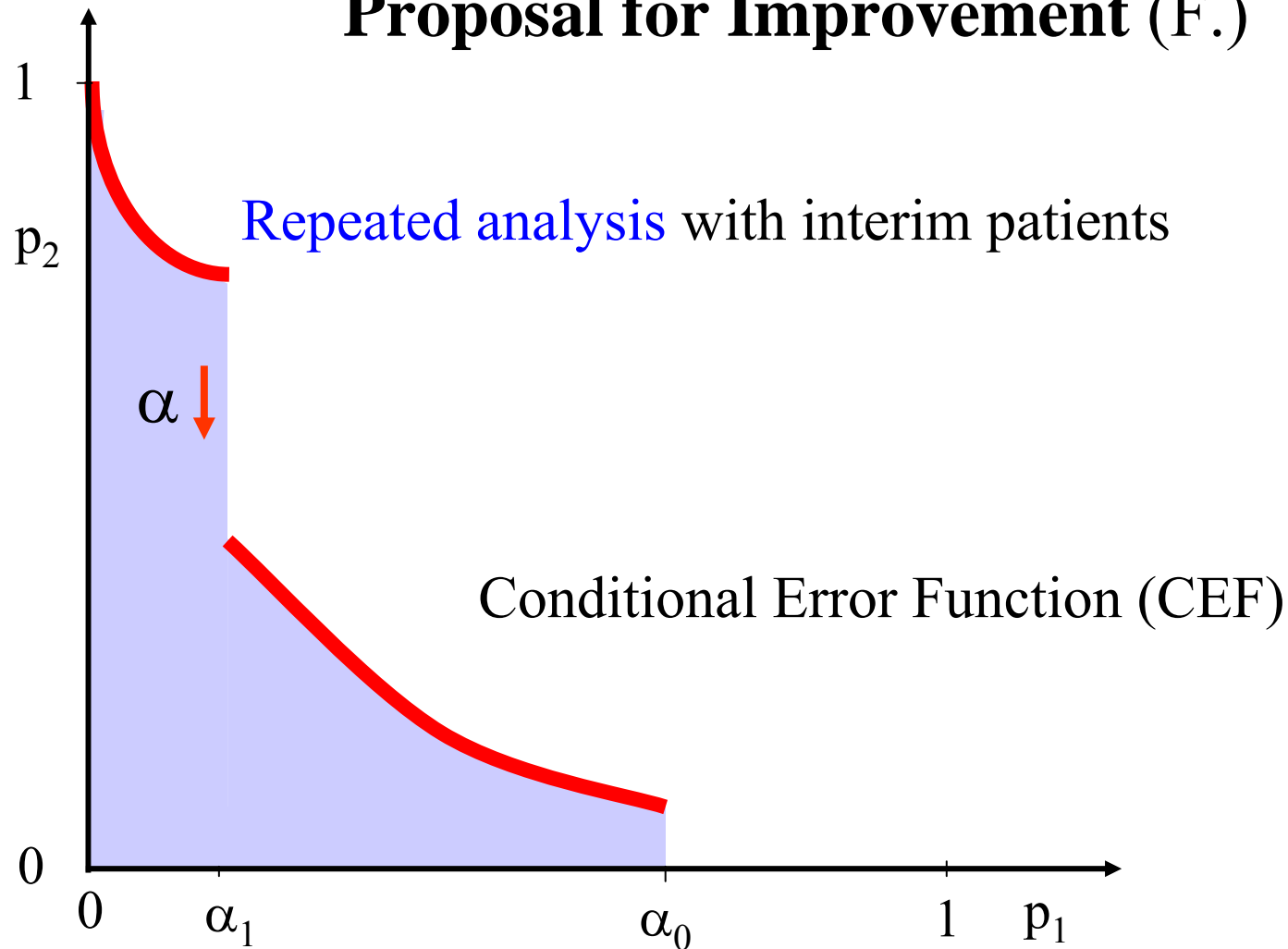
- Performance of a planned **interim analysis**
- Data collection and analysis need **time**
- Recruitment of additional patients = **interim patients**
- **Early proof of superiority** of a treatment
- **Stop** of recruitment
- Information to the relevant **office of regulatory affairs**
- Data of **interim patients not yet considered**
- **Request for all data** by the office of regulatory affairs
- **Small / contrasting effect** on the interim patients
- **Withdrawal** of the proof of superiority

Proposal for Improvement (F.)

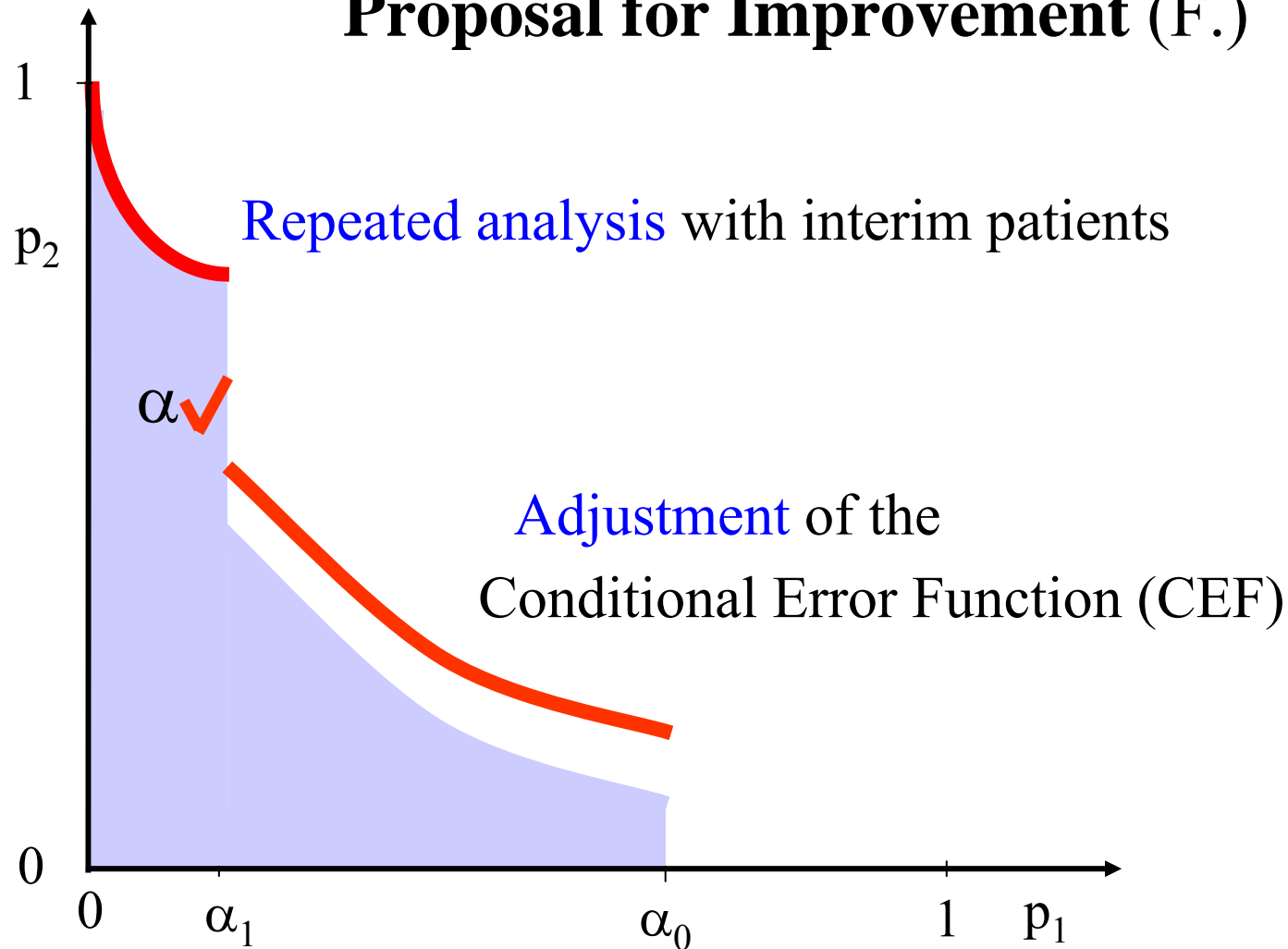


Adjustment of the
Conditional Error Function (CEF)

Proposal for Improvement (F.)



Proposal for Improvement (F.)



Proposal for Improvement

Journal of Biopharmaceutical Statistics, 17: 1211–1225, 2007
Copyright © Taylor & Francis Group, LLC
ISSN: 1054-3406 print/1520-5711 online
DOI: 10.1080/10543400701645439



STRATEGIES FOR INCLUDING PATIENTS RECRUITED DURING INTERIM ANALYSIS OF CLINICAL TRIALS

Andreas Faldum and Gerhard Hommel

*Institute of Medical Biostatistics, Epidemiology and Informatics,
University of Mainz, Germany*

Trial Investigating Liver Preservation

- Prospective **randomised** multicentre **trial**
- Comparison of aortic perfusion:
simple vs. **plus ex situ arterial flushing**
- Primary objective: **Occurrence** of **ITBL** (Ischemic Type Biliary Lesions) **within 6 months** after **liver transplantation**
- **Observation time** of each patient: **6 months**

Trial Investigating Liver Preservation

- Prospective randomised multicentre trial
- Comparison of aortic perfusion:
simple vs. plus ex situ arterial flushing
- Primary objective: Time to ITBL or death after liver transplantation
- ~~Observation time of each patient: 6 months~~
- Data acquisition, plausibility check, analysis: 3 months
- Accrual time: 21 months
- Follow-up time: 6 months
- Inverse normal logrank test

Adaptive Group Sequential Survival Trials

STATISTICS IN MEDICINE

Statist. Med. 2001; **20**:3741–3751 (DOI: 10.1002/sim.1136)

Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections[†]

Helmut Schäfer^{*,†} and Hans-Helge Müller

*Institute of Medical Biometry and Epidemiology, Philipps-University Marburg, Bunsenstraße 3,
D-35037 Marburg, Germany*

Adaptive Group Sequential Survival Trials

714

Biometrical Journal **48** (2006) 4, 714–729 DOI: 10.1002/bimj.200510190

Planning and Analyzing Adaptive Group Sequential Survival Trials

Gernot Wassmer*,¹

¹ Institute for Medical Statistics, Informatics, and Epidemiology, University of Cologne, Cologne, Germany

Received 29 June 2005, revised 26 September 2005, accepted 6 October 2005

Adaptive Group Sequential Survival Trials

STATISTICS IN MEDICINE

Conditional rejection error probability

Modification of the sample size and the schedule of interim analyses in survival trials based on data inspections[‡]

Helmut Schäfer^{*,†} and Hans-Helge Müller

Independent increments structure of the logrank test statistics

714

Biometrical Journal **48** (2006) 4, 714–729 DOI: 10.1002/bimj.200510190

Planning and Analyzing Adaptive Group Sequential Survival Trials

Gernot Wassmer^{*,1}

Inverse normal logrank statistic

Received 29 June 2005, revised 26 September 2005, accepted 6 October 2005

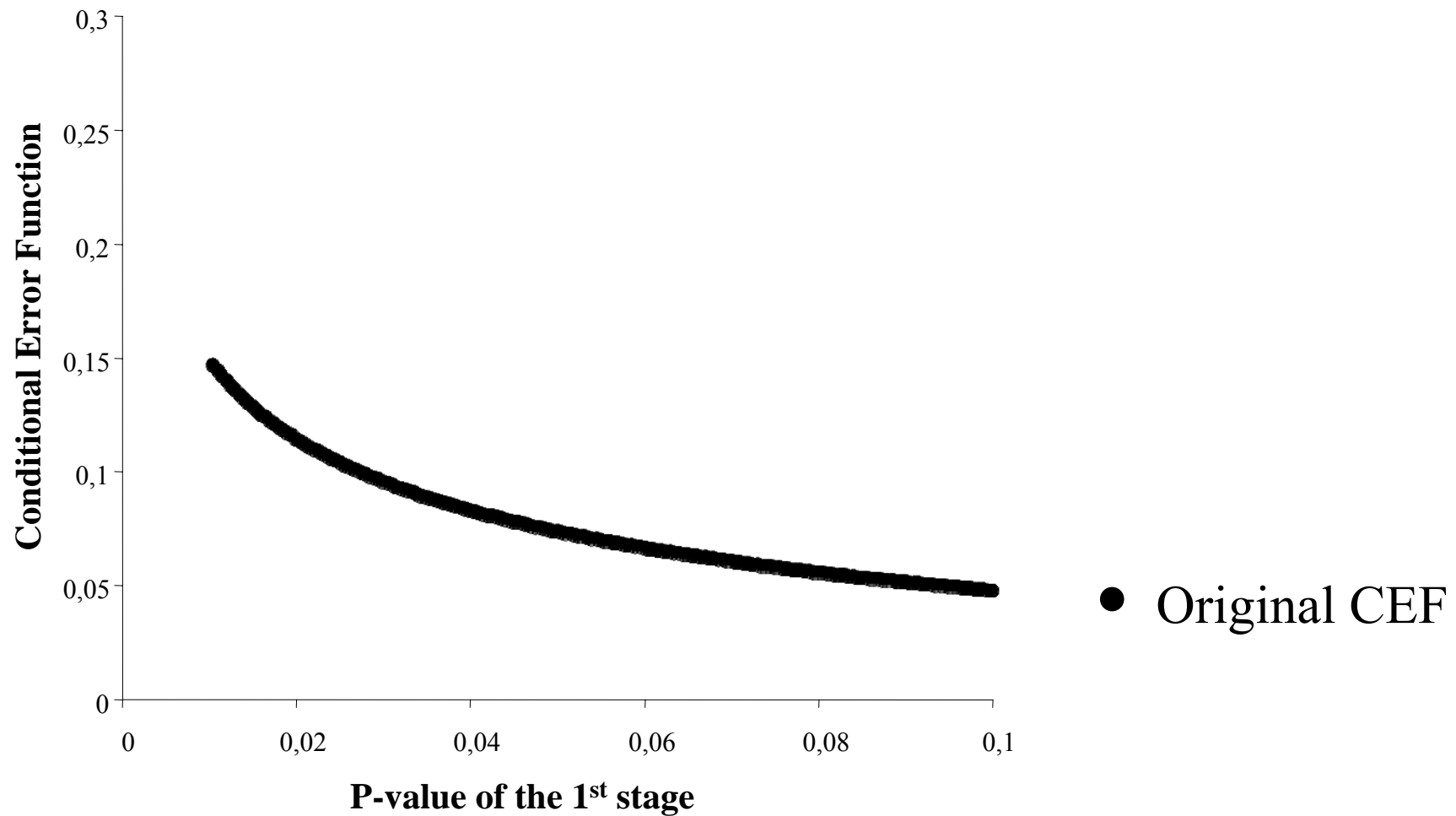
Adaptive Survival Trial: “Liver Preservation”

- One-sided adaptive design with two stages
- Interim analysis: Start after 12 months; duration 3 months
- Patients recruited by the end of the interim analysis: 150
 - 120 patients included in the interim analysis
 - 30 interim patients not included in the interim analysis
- Overall significance level: $\alpha = 0.025$
- Logrank efficacy bound of the 1st stage: $\alpha_1 = 0.010$
- Logrank futility bound of the 1st stage: $\alpha_0 = 0.500$
- Inverse normal efficacy bound of the 2nd stage: $\alpha_2 = 0.018$
- Inverse normal efficacy bound of the repeated IA: α_{IP}

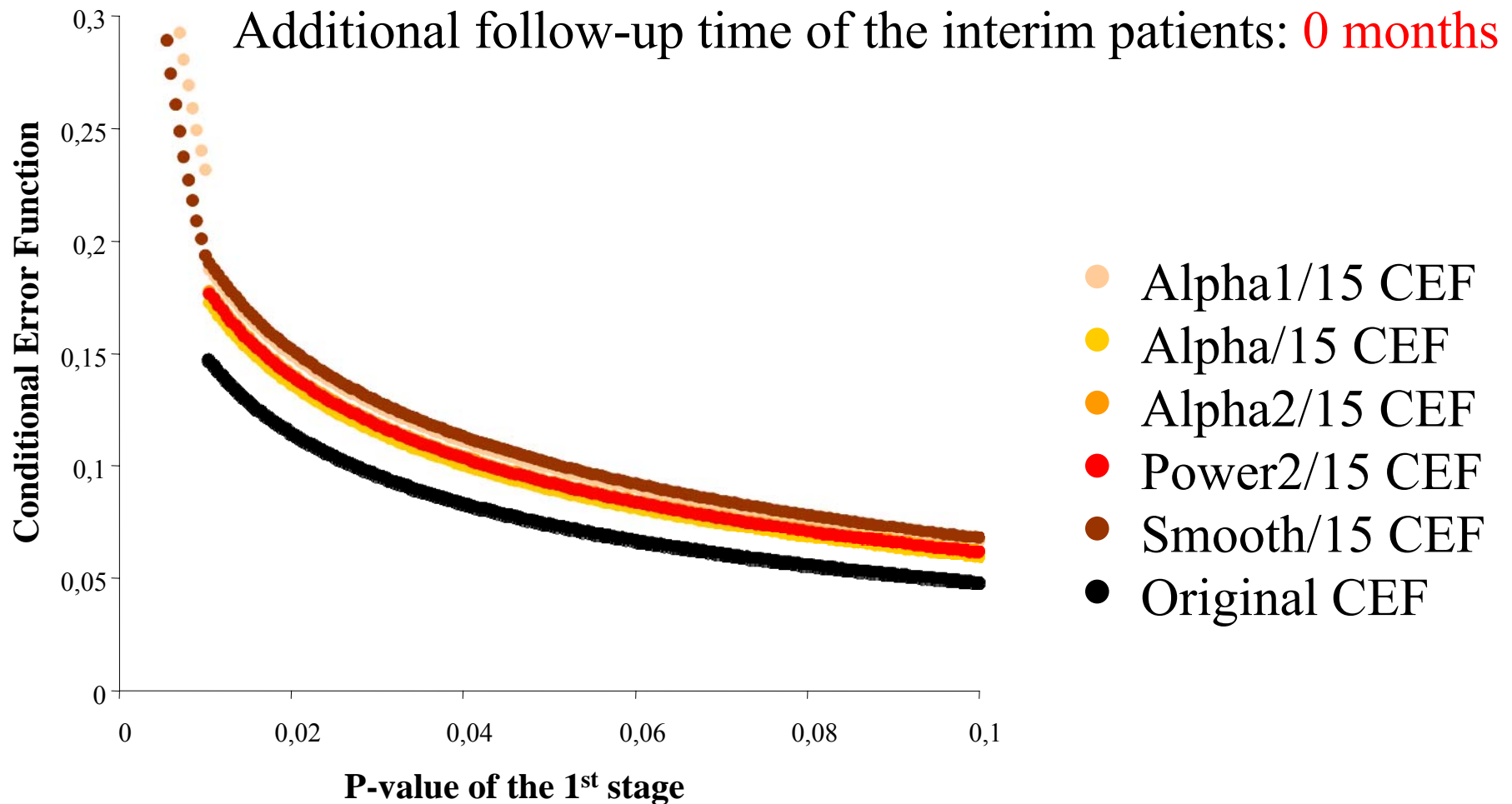
Strategies for Including Interim Patients

1. The rejection regions of the inverse normal logrank statistic:
 - a. $\alpha_{IP} = \alpha_1$:
Primary and repeated interim analysis are equal.
 - b. $\alpha_{IP} = \alpha$:
The repeated interim analysis has full level α .
 - c. $\alpha_{IP} = \alpha_2$:
Repeated interim and 2nd stage analysis are equal.
 2. Conditional power of the final analysis: $1 - \beta_{IP} \geq 1 - \beta_2 = 80\%$
Repeated interim analysis at $p_1 = \alpha_1$ equals 2nd stage analysis.
 3. Conditional Error Function: Continuous in $p_1 = \alpha_1$
Smooth change from repeated interim analysis to 2nd stage.
-

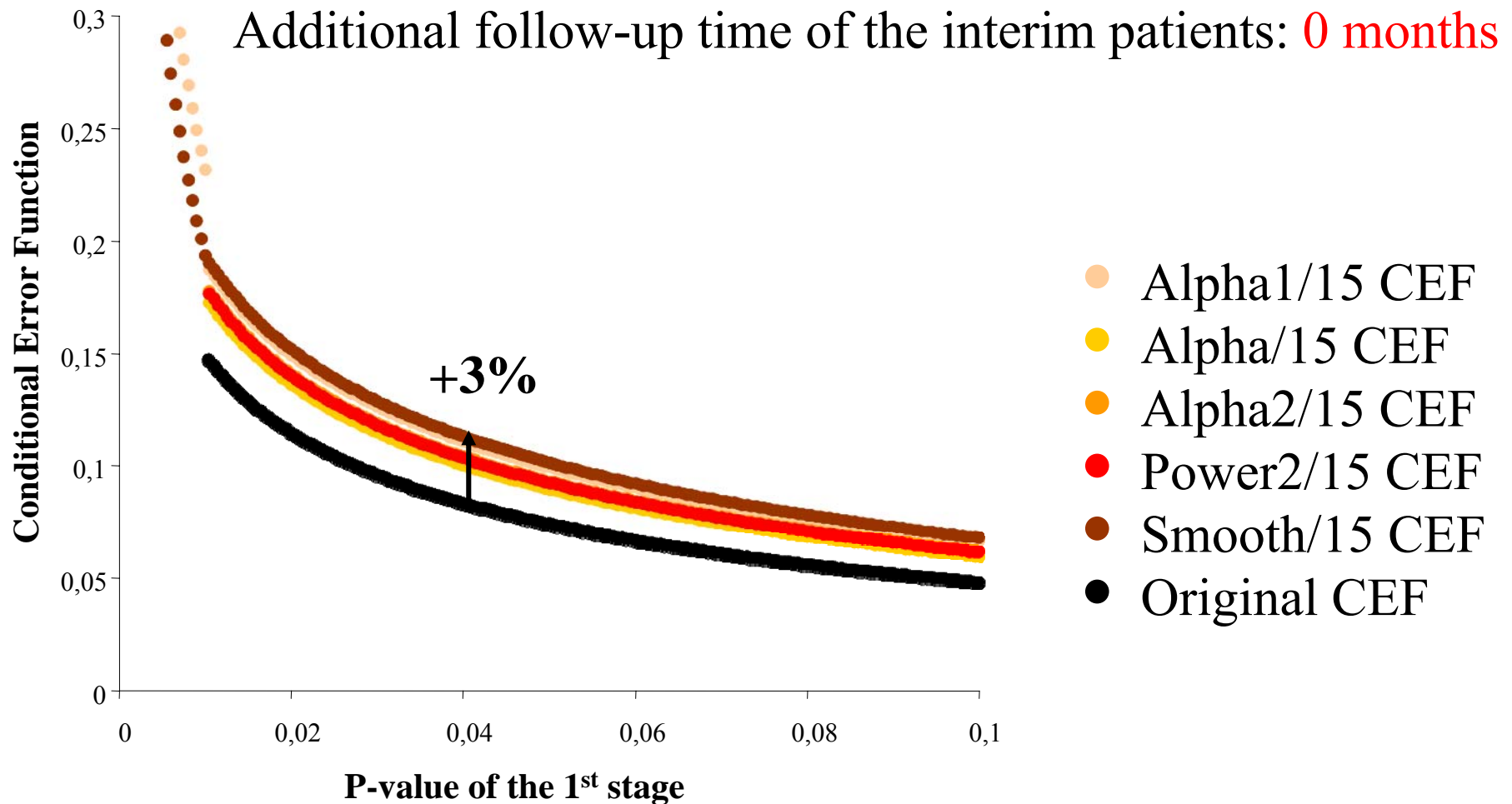
Adjustment of the Conditional Error Function



Adjustment of the Conditional Error Function

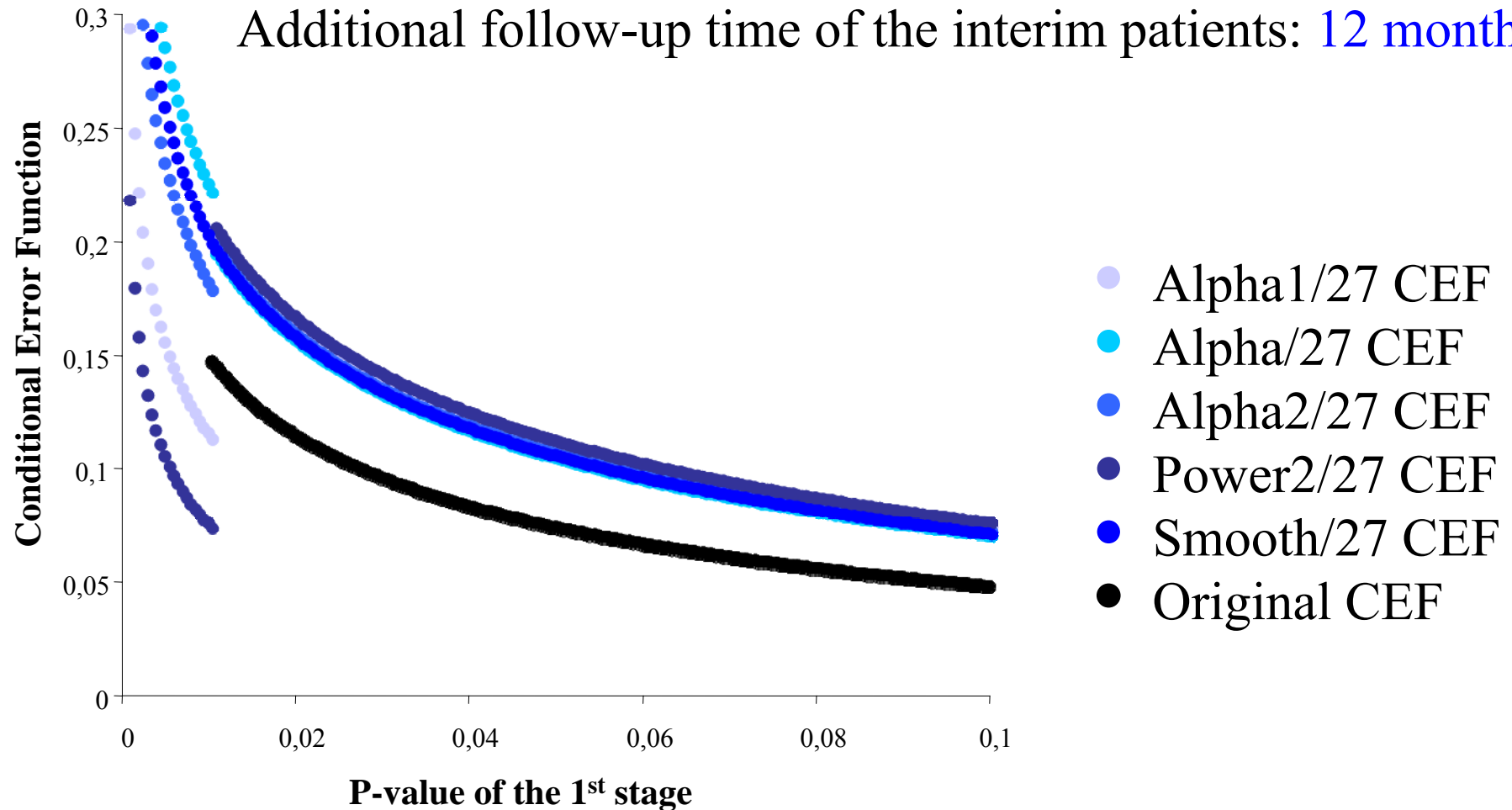


Adjustment of the Conditional Error Function



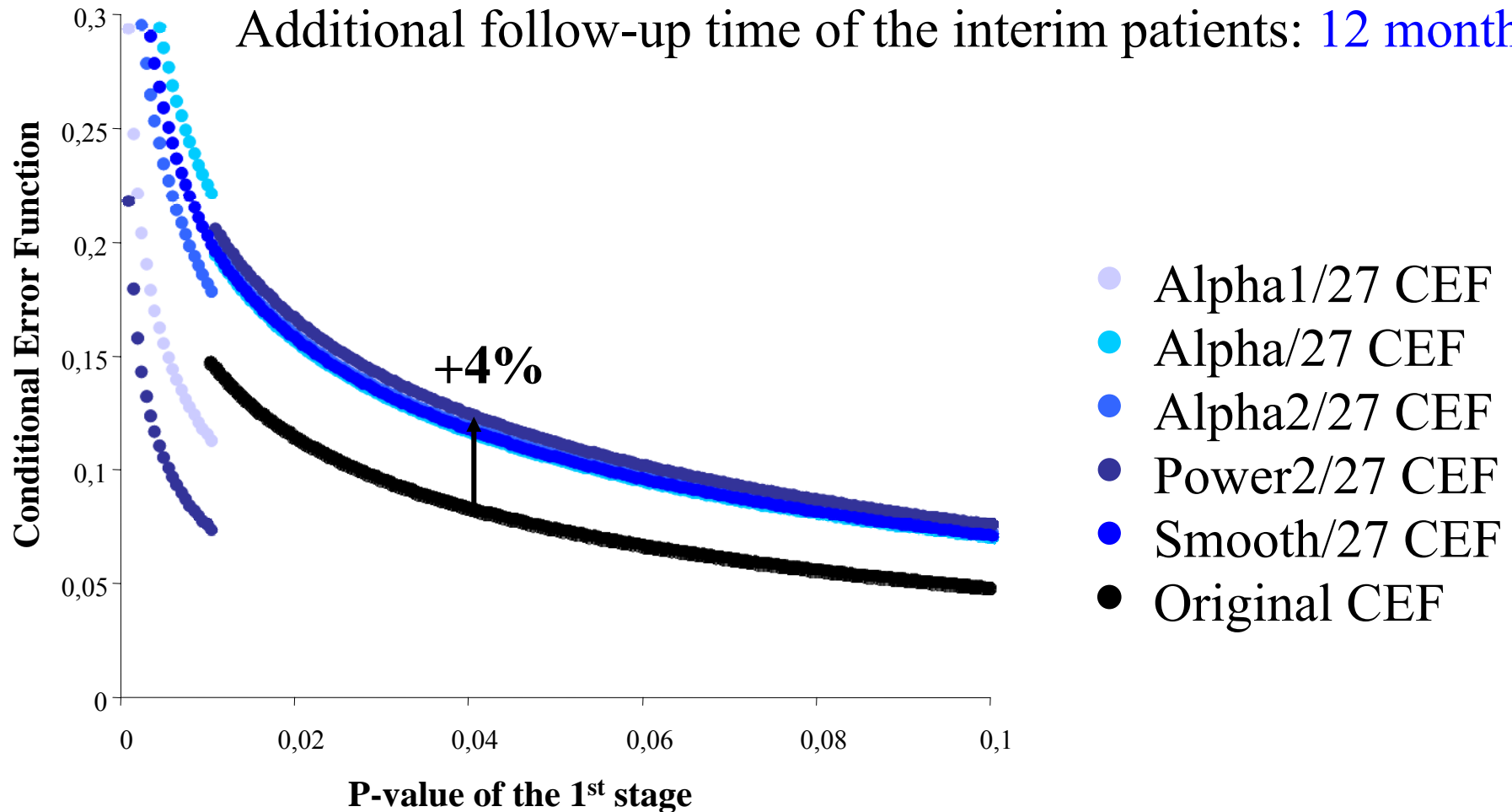
Adjustment of the Conditional Error Function

Additional follow-up time of the interim patients: 12 months



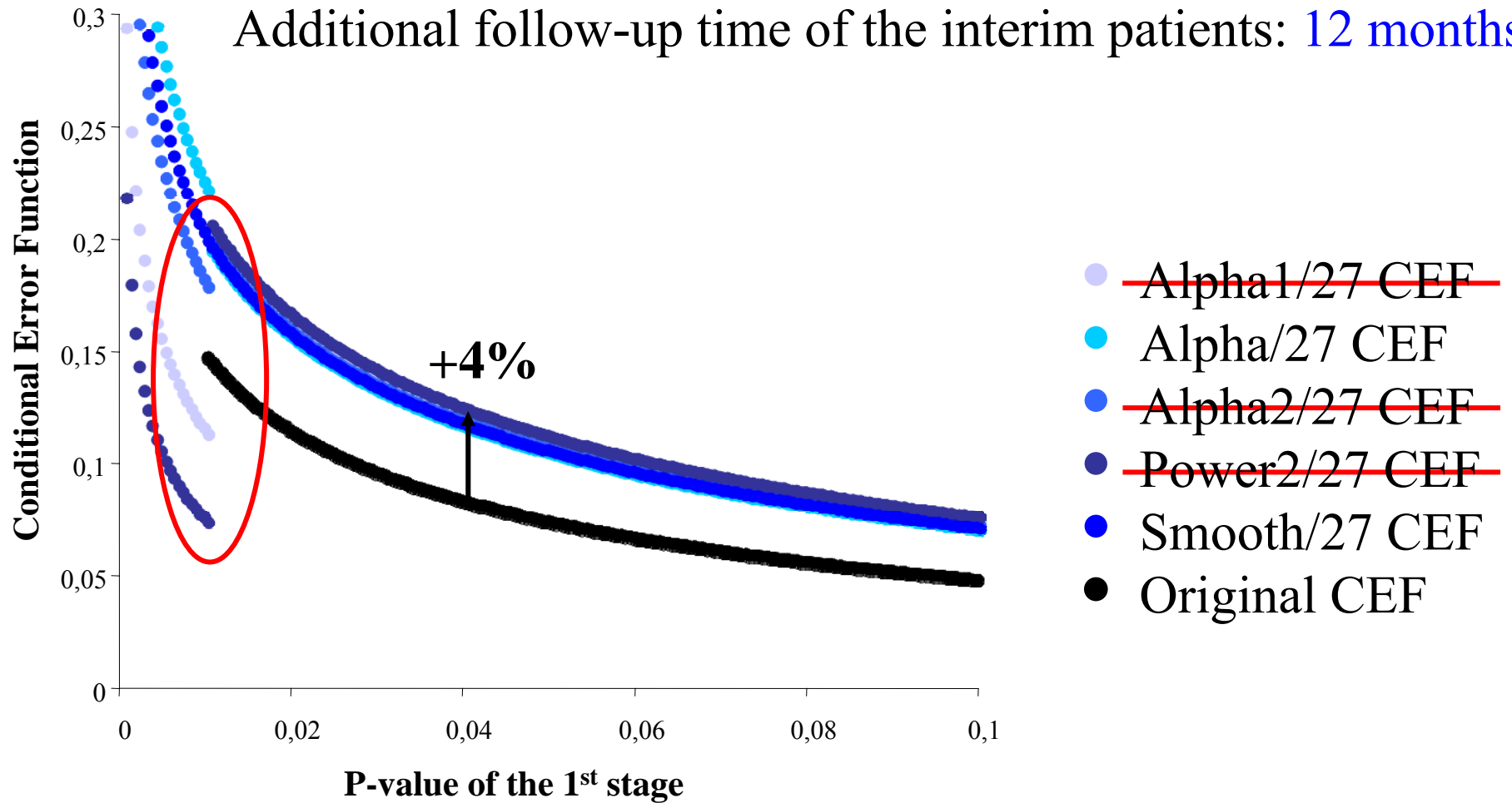
Adjustment of the Conditional Error Function

Additional follow-up time of the interim patients: 12 months

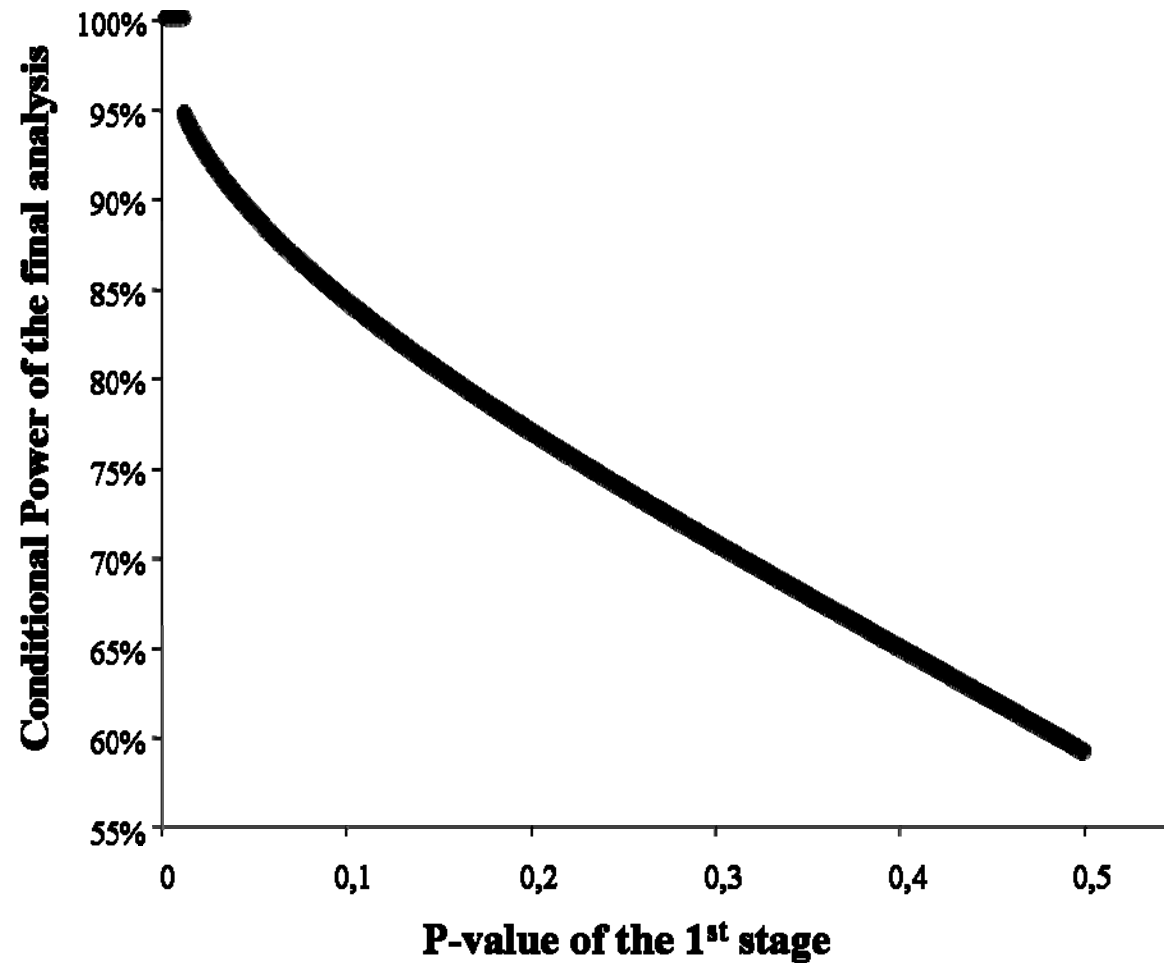


Adjustment of the Conditional Error Function

Additional follow-up time of the interim patients: 12 months

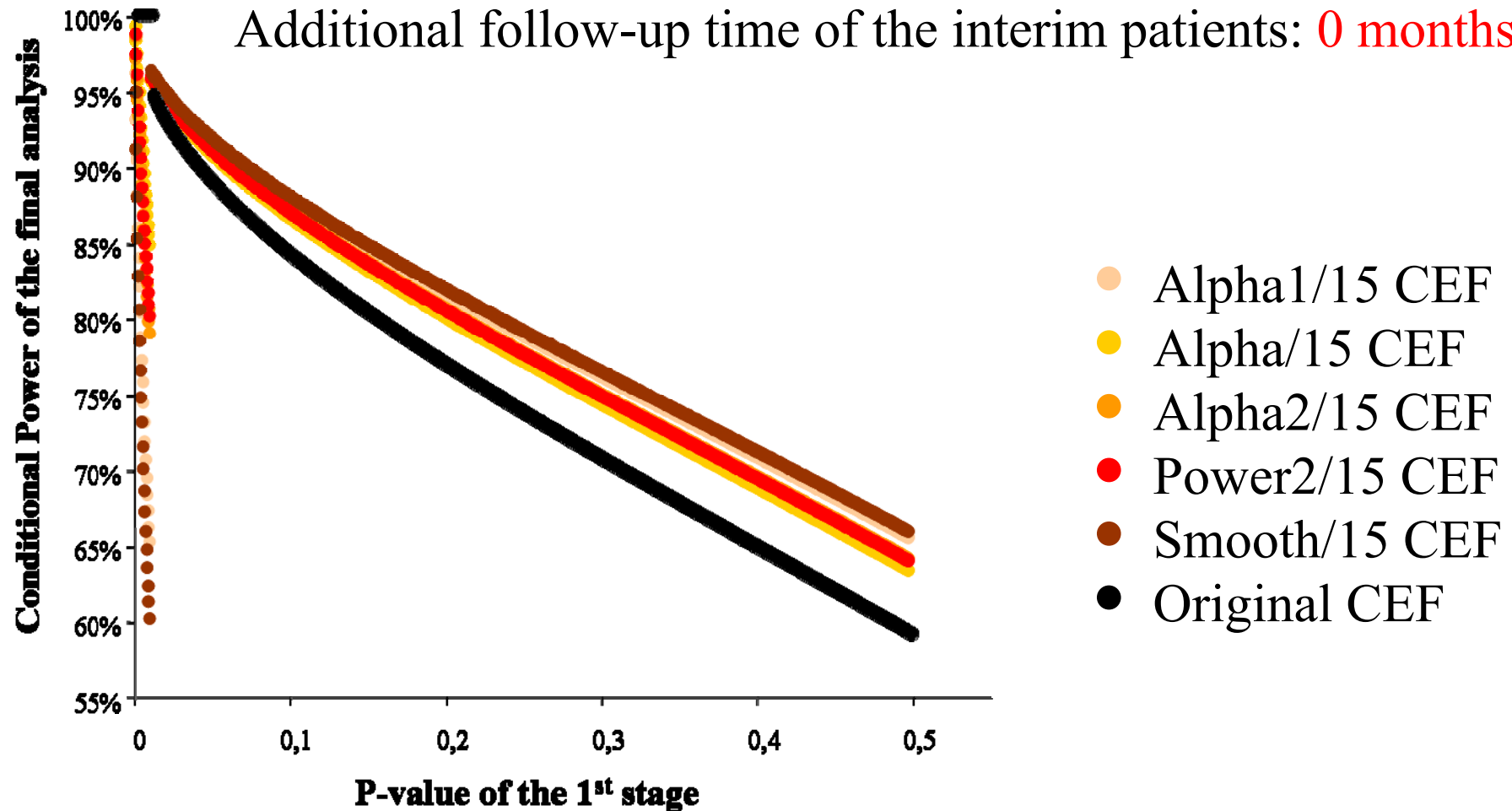


Conditional Power of the Final Analysis



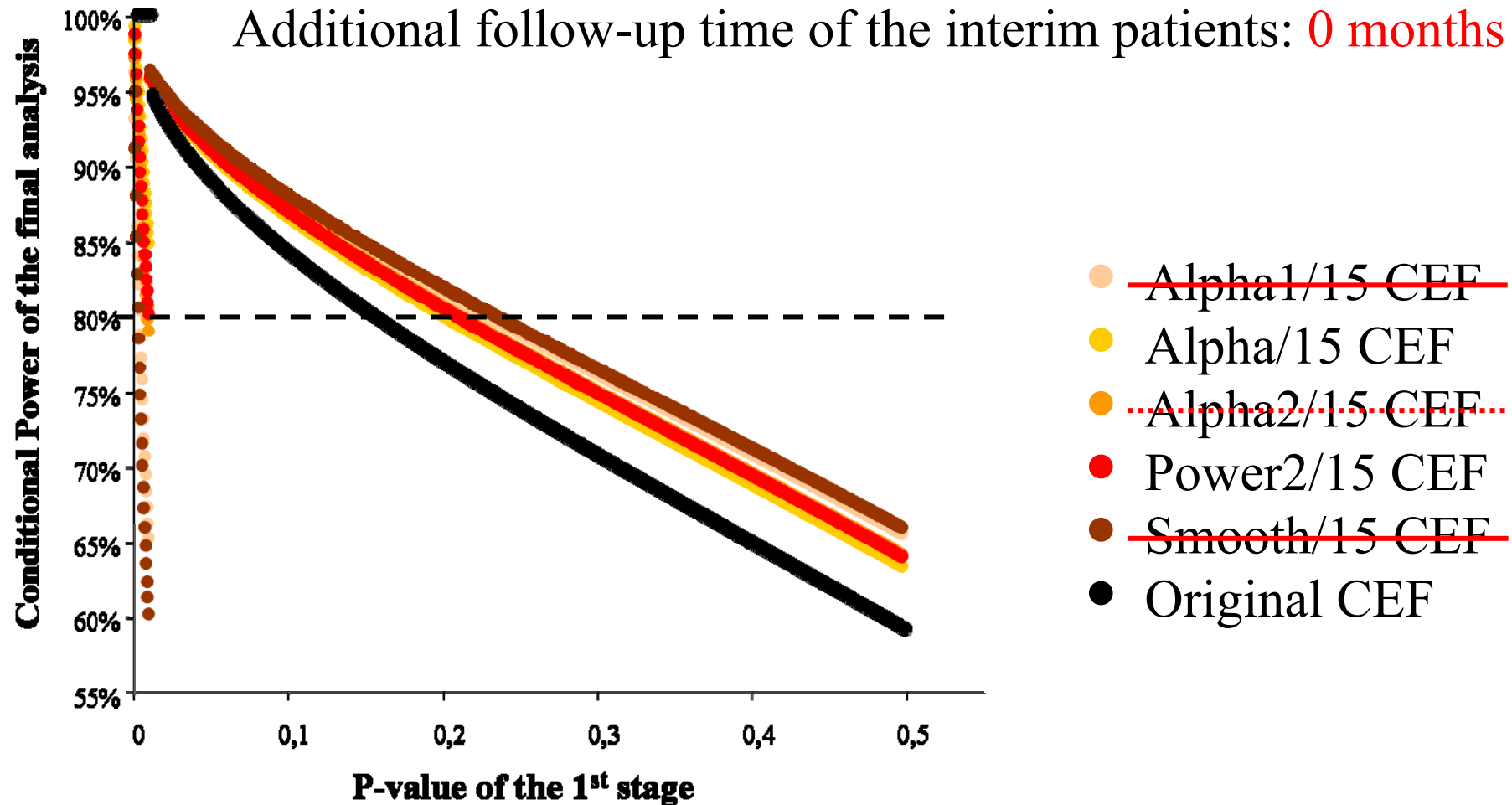
Conditional Power of the Final Analysis

Additional follow-up time of the interim patients: 0 months

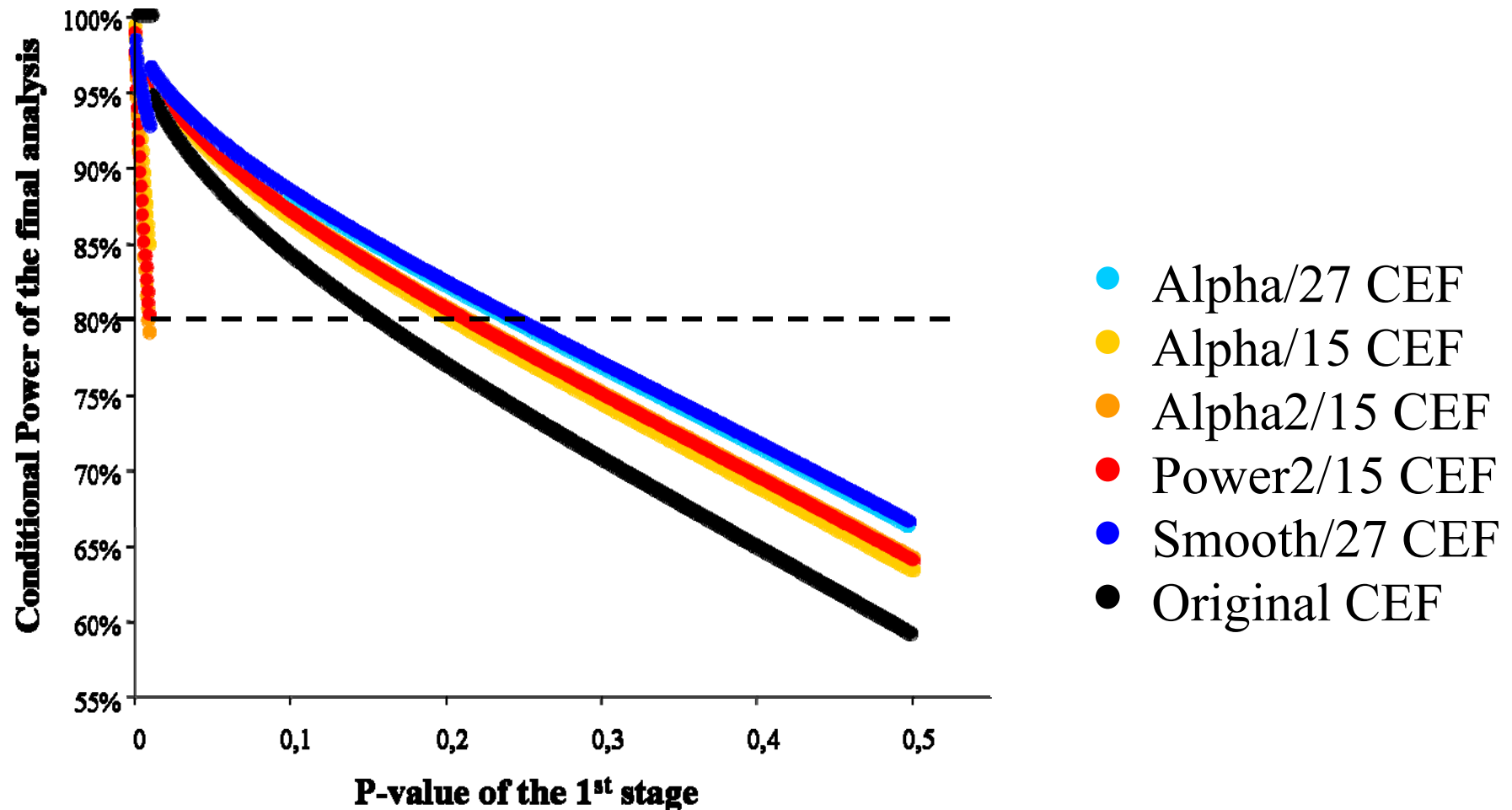


Conditional Power of the Final Analysis

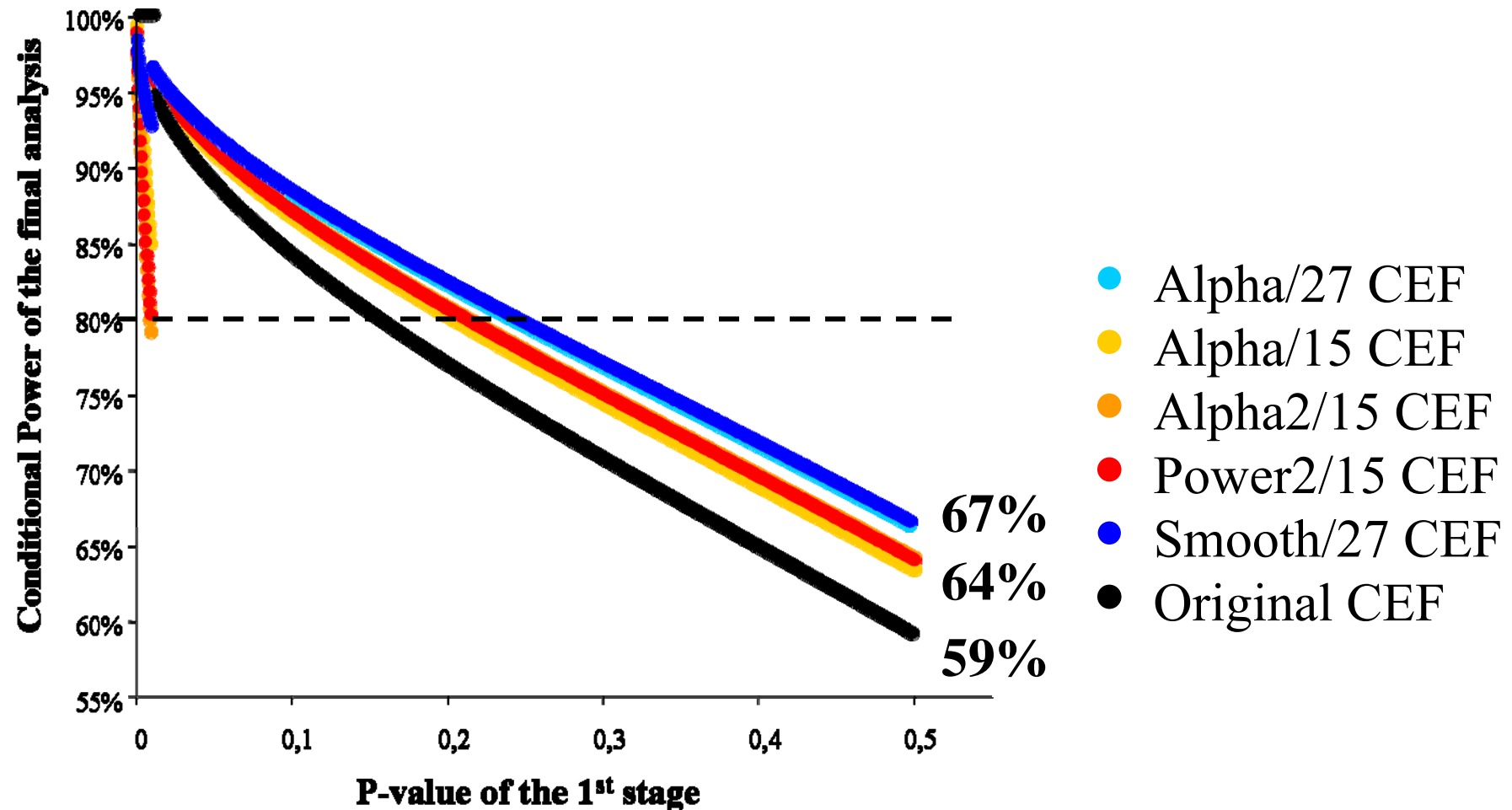
Additional follow-up time of the interim patients: 0 months



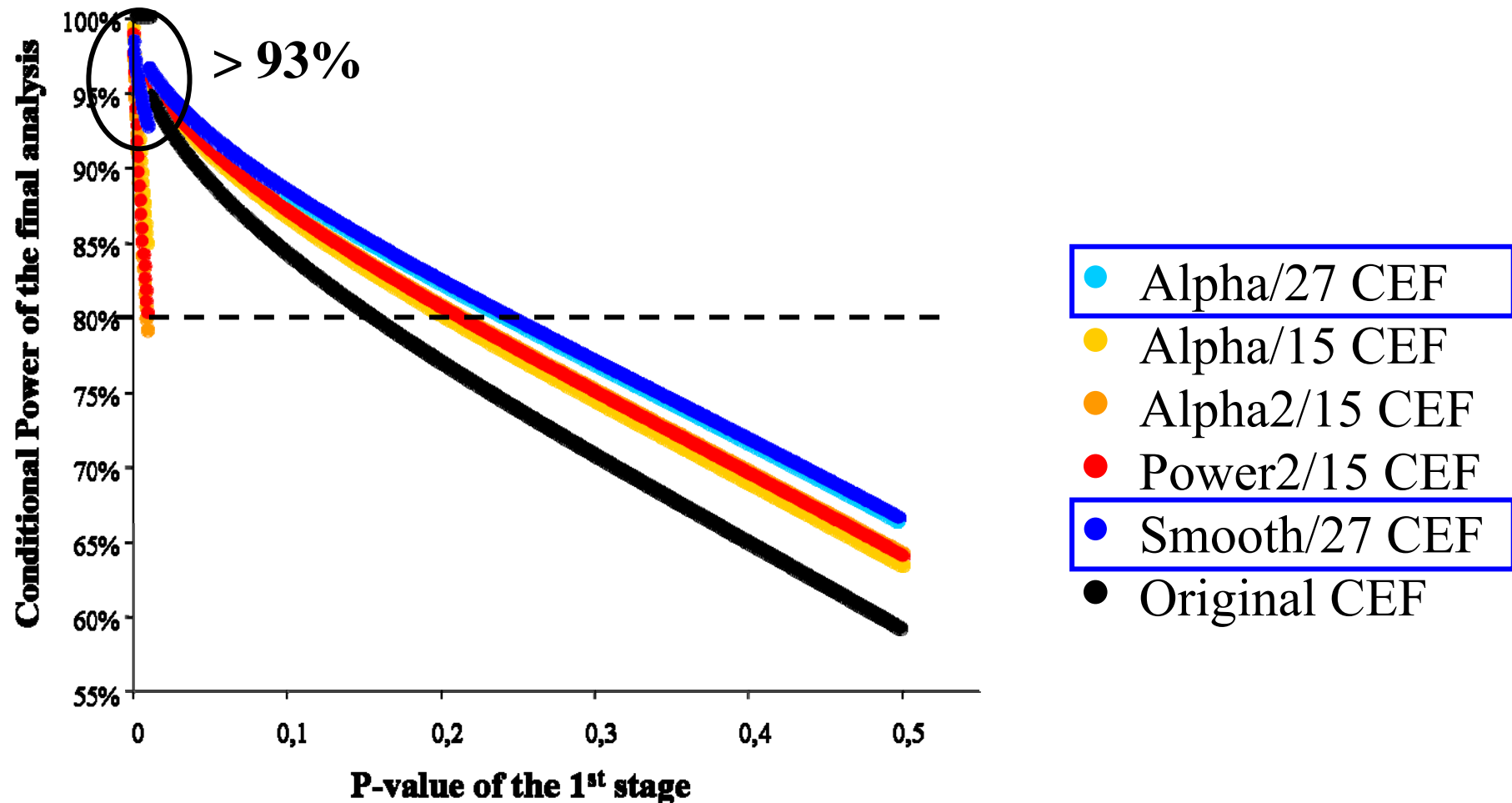
Conditional Power of the Final Analysis



Conditional Power of the Final Analysis



Conditional Power of the Final Analysis



Conclusion

- Usually, adequate consideration of interim patients is a
 - ethical requirement
 - request from regulatory authorities
- Appropriate adjustment of the CEF in $]\alpha_1, \alpha_0]$ results in
 - increase in power (here: +8%)
 - reduction of the number of required events (here: -9%)
- Adjusted CEF have to be checked for monotonicity and power
- Here, it is worth waiting until the interim analysis is repeated
 - with full level α test or
 - a smooth adjusted CEF

Sponsors and Collaborating Partners

- Deutsche Forschungsgemeinschaft ([DFG](#))
- Bundesministerium für Bildung und Forschung ([BMBF](#))
- PD Dr. D. [Mauer](#), Region Mitte der Deutschen Stiftung für Organtransplantation
- Dr. K. [Kronfeld](#), Koordinierungszentrum für Klinische Studien, Universität Mainz
- D. [Wachtlin](#), Koordinierungszentrum für Klinische Studien, Universität Mainz



UNIVERSITÄTS**medizin.**
MAINZ

Andreas Faldum

Privatdozent Dr. rer. nat. et med. habil.
Diplom-Mathematiker und Arzt

faldum@imbei.uni-mainz.de
06131-173938

IMBEI Institut für Medizinische Biometrie,
Epidemiologie und Informatik
