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Interim Patients
in
Adaptive Survival Trials

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One-sided Adaptive Standard Design with Two Stages
Interim Patients in Adaptive Survival Trials

One-sided Adaptive Standard Design with Two Stages

Conditional Error Function (CEF): $\alpha(p_1)$
Interim Patients in Adaptive Survival Trials

One-sided Adaptive Standard Design with Two Stages

Conditional Error Function (CEF): $\alpha(p_1)$
Interim Patients in Adaptive Survival Trials

One-sided Adaptive Standard Design with Two Stages

- Rejection of $H_0$
- Acceptance of $H_0$

$p_2$

$p_1$
Interim Patients in Adaptive Survival Trials

One-sided Adaptive Standard Design with Two Stages

Stop after the 1st stage for efficacy

\[ p_2 \]

\[ \alpha_1 \]

\[ p_1 \]
One-sided Adaptive Standard Design with Two Stages

Stop after the 1\textsuperscript{st} stage for \textit{futility}
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.)

Repeated analysis with interim patients

Conditional Error Function (CEF)
Interim Patients in Adaptive Survival Trials

Proposal for Improvement (F.)

Repeated analysis with interim patients

Adjustment of the Conditional Error Function (CEF)
Proposal for Improvement

STRATEGIES FOR INCLUDING PATIENTS RECRUITED DURING INTERIM ANALYSIS OF CLINICAL TRIALS

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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
Interim Patients in Adaptive Survival Trials

Adaptive Group Sequential Survival Trials

STATISTICS IN MEDICINE

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

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Adaptive Group Sequential Survival Trials

Planning and Analyzing Adaptive Group Sequential Survival Trials

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Adaptive Group Sequential Survival Trials

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

Planning and Analyzing Adaptive Group Sequential Survival Trials

Gernot Wassmer*†

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: $\alpha_{IP}$
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 \( \alpha \).
   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.
Interim Patients in Adaptive Survival Trials

Adjustment of the Conditional Error Function

P-value of the 1st stage

- Original CEF
Interim Patients in Adaptive Survival Trials

Adjustment of the Conditional Error Function

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

- Alpha1/15 CEF
- Alpha/15 CEF
- Alpha2/15 CEF
- Power2/15 CEF
- Smooth/15 CEF
- Original CEF
Adjustment of the Conditional Error Function

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

- Alpha1/15 CEF
- Alpha/15 CEF
- Alpha2/15 CEF
- Power2/15 CEF
- Smooth/15 CEF
- Original CEF
Interim Patients in Adaptive Survival Trials

Adjustment of the Conditional Error Function

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

![Graph showing the adjustment of the Conditional Error Function with different lines representing Alpha1/27 CEF, Alpha/27 CEF, Alpha2/27 CEF, Power2/27 CEF, Smooth/27 CEF, and Original CEF.]

P-value of the 1st stage vs. Conditional Error Function
Interim Patients in Adaptive Survival Trials

Adjustment of the Conditional Error Function

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

- Alpha1/27 CEF
- Alpha/27 CEF
- Alpha2/27 CEF
- Power2/27 CEF
- Smooth/27 CEF
- Original CEF

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Adjustment of the Conditional Error Function

Additional follow-up time of the interim patients: 12 months
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Conditional Power of the Final Analysis

![Graph showing the conditional power of the final analysis vs. P-value of the 1st stage]
Conditional Power of the Final Analysis

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

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Conditional Power of the Final Analysis

Additional follow-up time of the interim patients: 0 months
Interim Patients in Adaptive Survival Trials

Conditional Power of the Final Analysis

P-value of the 1st stage

- Alpha/27 CEF
- Alpha/15 CEF
- Alpha2/15 CEF
- Power2/15 CEF
- Smooth/27 CEF
- Original CEF

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Conditional Power of the Final Analysis

> 93%

P-value of the 1st stage

- Alpha/27 CEF
- Alpha/15 CEF
- Alpha2/15 CEF
- Power2/15 CEF
- Smooth/27 CEF
- Original CEF
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 $\alpha$ test or
  – a smooth adjusted CEF
Sponsors and Collaborating Partners

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