Adaptive Designs and their Impact on Clinical Trials’ Cost Structures  
- An Economic Perspective on Adaptive Designs -  

2015 workshop  
“Adaptive Designs and Multiple Testing Procedures“  
of the German (DR) and Austrian-Swiss (ROeS) Region  
of the International Biometric Society (IBS)
Background

• Adaptive sequential designs have become very popular in clinical trials over the past few years

• Besides methodical challenges and ethical considerations, usually controllability and time saving are mentioned as the main impact and advantage

• Intense discussion about costs is taking place and escalating in…
  … the public health care sector
  … in the pharmaceutical industry
Background

• Since 2001 an average of more than 1200 clinical trials per year have been forwarded to the BfArM as the competent federal higher authority in Germany for approval

• Development costs are rising to more than 1.5 billion US $ for one novel medicinal product

• Intense discussion of outsourcing work packages into countries that are supposed to be low-priced is taking place
Objective

• A set of 3 investigator initiated trials under the German Pharmaceuticals Act have been considered to analyze the impact of interim analyses and adaptive modifications on the total costs of the whole process and trial

Identification of trial specific work load

Consequences of adaptive modifications on each of them

Determine the ideal economic moment for interim analysis
Cost Driver

• Guideline for Good Clinical Practice: …standard for designing, conducting, recording and reporting trials that involve the participation of human subjects
Cost Driver

QUALITY MANAGEMENT

DATA MANAGEMENT

PHARMAKOVIGILANCE

PROJECT MANAGEMENT

STATISTICS

§ 13 GCP V ICH-GCP 5.1, 5.2, 7

Guideline E2A

ICH-GCP 6.6, 6.8, 6.9, E9,
EMA + FDA
Guidelines

§ 40-42, 87 IfS 13

AMG §§ 7.10, 13

GCP V, ICH-GCP

4.4, 5.6

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Economic Background

• In order to show the impact of interim analysis on the budget of a clinical trial we have to differentiate between:
  • Fix costs
  • Variable costs

• Fix costs are part of the overall costs that will stay unchanged
• Variable costs are quantity-dependent and will change with respective reference values
• Relevant reference values:
  • Sample size/ Number of trial participants
  • Number of participating trial sites
Interim Analysis

• Assessment of trial specific parameters at a comparatively early stage

Rationale:

• Risk-benefit analysis of the DMC
• Periodic assessment of trial process by the DMC
• Premature proof of defined endpoints
• Premature termination due to a lack of evidence
• Data controlled modification of the trial
Example

• Trial conditions as planned:
  
  • Intervenional, two-armed, randomized, placebo-controlled, double-blind, multicenter Phase III-trial under the German Pharmaceutical Act
  
  • Recruitment period: 24 months
  
  • Overall trial duration: 42 months
  
  • Sample size: 1520 trial participants
  
  • Number of participating trial sites: 16
  
  • Investigator initiated trial
  
  • Defined primary and secondary endpoints
Example: Cost Center

Data Management
Pharmakovigilance
Project Management
Quality Management
Biostatistics

Insurance
Fees
Travel
Lump sum
Material
Example: Total Overall Costs

**Total Overall Costs (TOC)**

\[
TOC = TC_{DM} + TC_{PV} + TC_{PM} + TC_{QM} + TC_{BST} + TC_{In} + TC_{Fe} + TC_{Tr} + TC_{Ls} + TC_{Ma}
\]

\[
TOC = 293.000\, \text{€} + 60.600\, \text{€} + 217.350\, \text{€} + 131.540\, \text{€} + 57.500\, \text{€} + 63.308\, \text{€} + 20.250\, \text{€} + 23.000\, \text{€} + 101.715\, \text{€} + 258.400\, \text{€}
\]

\[
TOC = 1.226.663\, \text{€}
\]
Fix Costs: Work Packages

- Data Management:
  - Preparation of Data Management/ Validation Plan
  - Design, Set Up and Validation of Database …

- Pharmakovigilance:
  - Configuration of SAE-Database
  - Preparation of AE- and SAE-forms …

- Project Management:
  - Preparation of trial protocol
  - Obtain competent authority approval, ethical vote …

- Quality Management:
  - Preparation of sponsorship
  - Preparation of monitoring strategy and manual

- Biostatistics:
  - Preparation of trial protocol (Biostatistical part)
  - Preparation of statistical analysis plan
Variable Costs: Work Packages

• Data Management:
  – Plausibility checks
  – Data cleaning and query management …

• Pharmakovigilance:
  – Processing of SAE- and SUSAR-reports
  – Preparation and submission of DSUR …

• Project Management:
  – Inhouse review
  – Preparation of trial protocol amendments …

• Quality Management:
  – Onsite auditing
  – Onsite monitoring …

• Biostatistics:
  – Preparation DMC meetings (Biostatistical part)
  – Control for stopping rules
Example: Fix vs. Variable Costs

**Total Fix Costs (TFC)**

\[
TFC = FC_{DM} + FC_{PV} + FC_{PM} + FC_{QM} + FC_{BST} + FC_{In} + FC_{Fe} + FC_{Tr} + FC_{LS} + FC_{Ma}
\]

\[
TFC = 80.500\,€ + 36.000\,€ + 105.900\,€ + 2.900\,€ + 38.334\,€ + 0\,€ + 9.950\,€ + 23.000\,€ + 12.400\,€ + 0\,€
\]

\[
TFC = \boxed{308.984\,€}
\]

→ approx. 25% of Total Overall Costs are **Total Fix Costs**

**Total Variable Costs (TVC)**

\[
TVC = VC_{DM} + VC_{PV} + VC_{PM} + VC_{QM} + VC_{BST} + VC_{In} + VC_{Fe} + VC_{Tr} + VC_{LS} + VC_{Ma}
\]

\[
TVC = 212.500\,€ + 24.600\,€ + 111.450\,€ + 128.640\,€ + 19.166\,€ + 63.308\,€ + 10.300\,€ + 0\,€ + 89.315\,€ + 258.400\,€
\]

\[
TVC = \boxed{917.679\,€}
\]

→ approx. 75% of Total Overall Costs are **Total Variable Costs**
Example: Conclusion

1. conclusion: Assuming that interim analysis can exert maximum influence on variable costs of a clinical trial

and

Showing that approx. 75% of the total costs are variable costs (as shown before)

The influence of interim analysis can be very powerful from the economic point of view.
Example: Reference Values

Total Variable Costs: Sample Size ($TVC_{SS}$)

\[
TVC_{SS} = TVC_{SSDM} + TVC_{SSPV} + TVC_{SSPM} + TVC_{SSQM} + TVC_{SSBST} + TVC_{SSIn} + TVC_{SSFe} + TVC_{SSTr} + TVC_{SSLS} + TVC_{SSMa}
\]

\[
TVC_{SS} = 197.500\,\text{€} + 24.600\,\text{€} + 83.250\,\text{€} + 89.520\,\text{€} + 19.166\,\text{€} + 63.308\,\text{€} + 0\,\text{€} + 0\,\text{€} + 89.315\,\text{€} + 258.400\,\text{€}
\]

\[
TVC_{SS} = 825.059\,\text{€}
\]

→ approx. 90% of Total Variable Costs are Total Variable Costs for Sample Size

Total Variable Costs: Trial Sites ($TVC_{TS}$)

\[
TVC_{TS} = TVC_{TSDM} + TVC_{TSPV} + TVC_{TSPM} + TVC_{TSQM} + TVC_{TSBST} + TVC_{TSIn} + TVC_{TSFe} + TVC_{TSTr} + TVC_{TSLS} + TVC_{TSMa}
\]

\[
TVC_{TS} = 15.000\,\text{€} + 0\,\text{€} + 28.200\,\text{€} + 39.120\,\text{€} + 0\,\text{€} + 0\,\text{€} + 10.300\,\text{€} + 0\,\text{€} + 0\,\text{€} + 0\,\text{€}
\]

\[
TVC_{TS} = 92.620\,\text{€}
\]

→ approx. 10% of Total Overall Costs are Total Variable Costs for Trial Sites
Example: Conclusion

2. conclusion: Assuming that interim analysis can mostly exert influence on the sample size of a clinical trial

and

Showing that 90% of the variable costs are sample size costs (as shown before)

The influence of interim analysis can be very powerful from the economic point of view.
Example: Trial process

- Delayed recruitment
- Stagnating contract management
- Overestimation of recruitment potential
- Competing pharmaceutical trials

- Unplanned masked interim analysis with sample size re-estimation was performed after 477 recruited trial participants
Example: Costs for UIA

Total Unplanned Interim Analysis Costs (TUIAC)

\[ TUIAC = TUIAC_{DM} + TUIAC_{PV} + TUIAC_{PM} + TUIAC_{QM} + TUIAC_{BST} + TUIAC_{In} + TUIAC_{Fe} + TUIAC_{Tr} + TUIAC_{LS} + TUIAC_{Ma} \]

\[ TUIAC = 12.500\,\text{€} + 6.000\,\text{€} + 23.288\,\text{€} + 17.570\,\text{€} + 0\,\text{€} + 4.150\,\text{€} + 7.000\,\text{€} + 0\,\text{€} + 0\,\text{€} \]

\[ TUIAC = \textbf{98.008\,€} \]

- Work packages for UIA:
  - Additional data cleaning and query management
  - Preparation of additional safety report
  - Preparation of additional protocol amendment
  - Additional onsite monitoring
  - Additional data analysis and reporting
  - Additional fees for competent authority and ethics…
Example: Cost Saving Potential

**Total Fix Costs** = 308.984€

**Total Variable Costs** \(_{\text{Trial site}}\) = 92.620€

**Total Variable Costs** \(_{\text{Sample size}}\) = 825.059€ (for 1520 trial participants as planned)

**Total Variable Costs** \(_{\text{Trial participant}}\) = \(\frac{TVCs_s}{1520}\) = \(\frac{825.059€}{1520}\) = 543€ (Costs for 1 trial participant)

\[
TOC_{Ss477} = TFC + TVC_{Ts} + (TVC_{Tp} \times 477)
\]

\[
= 308.984€ + 92.620€ + (543€ \times 477)
\]

\[
= 660.615€
\]

**Cost Saving Potential:** \(TOC_{Ss1520} - TOC_{Ss477} - TUIAC\)

\[
= 1.226.663€ - 660.615€ - 98.008€
\]

\[
= 468.040€
\]

→ approx. 38% of the primary planned costs could have been saved
Example: Break-Even-Point

• Minimal number of patients to be refused to meet the costs for an Unplanned Interim Analysis from the economic point of view

\[
\frac{TUIAC}{TVCRC_Tp} = \text{Sample size (that will expend the costs for TUIAC)}
\]

\[
\frac{98.008 \text{€}}{543 \text{€}} = 180
\]

• Break-Even-Point:

\[1520 - 180 \leq 1340 \text{ trial participants}\]
Next steps

• Comparison of planned vs. unplanned interim analysis

• Development of a programm package for the calculation of economic benefits of adaptive designs

• Address aspects to potential financial sponsors in order to adjust and adapt conditions of sponsoring
Thank you very much for your attention!

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