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)

Gefördert vom

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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

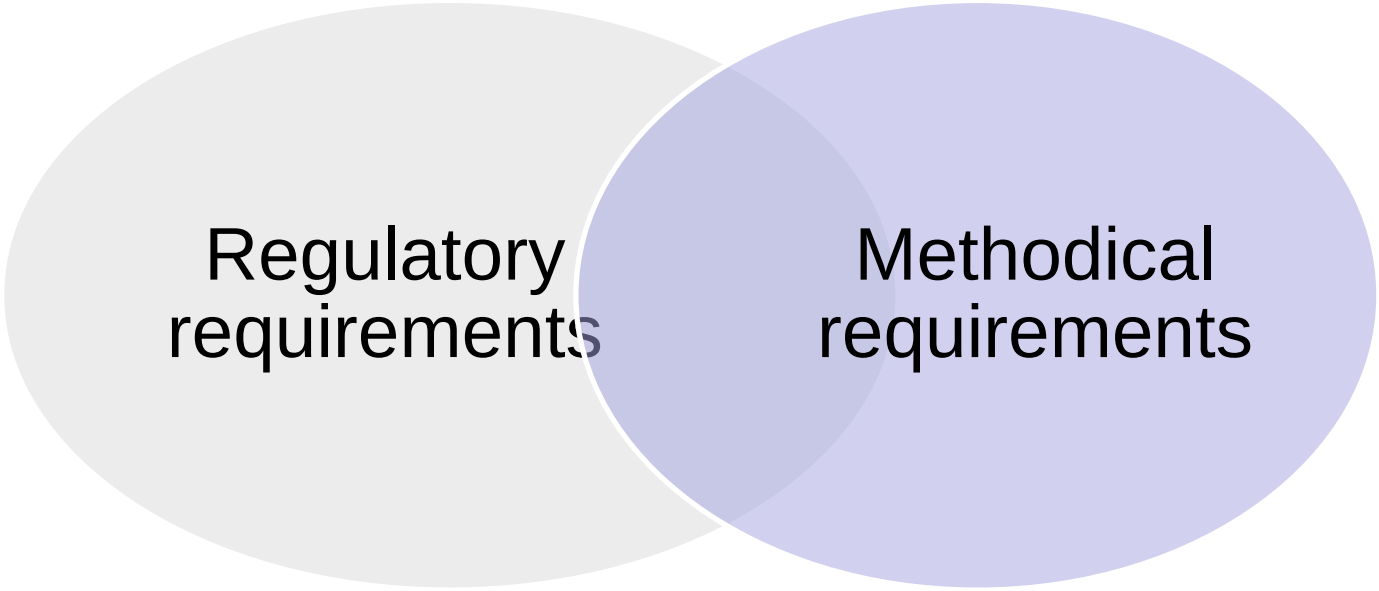
- Intense discussion of outsourcing work packages into countries that are supposed to be low-priced is taking place

Objective

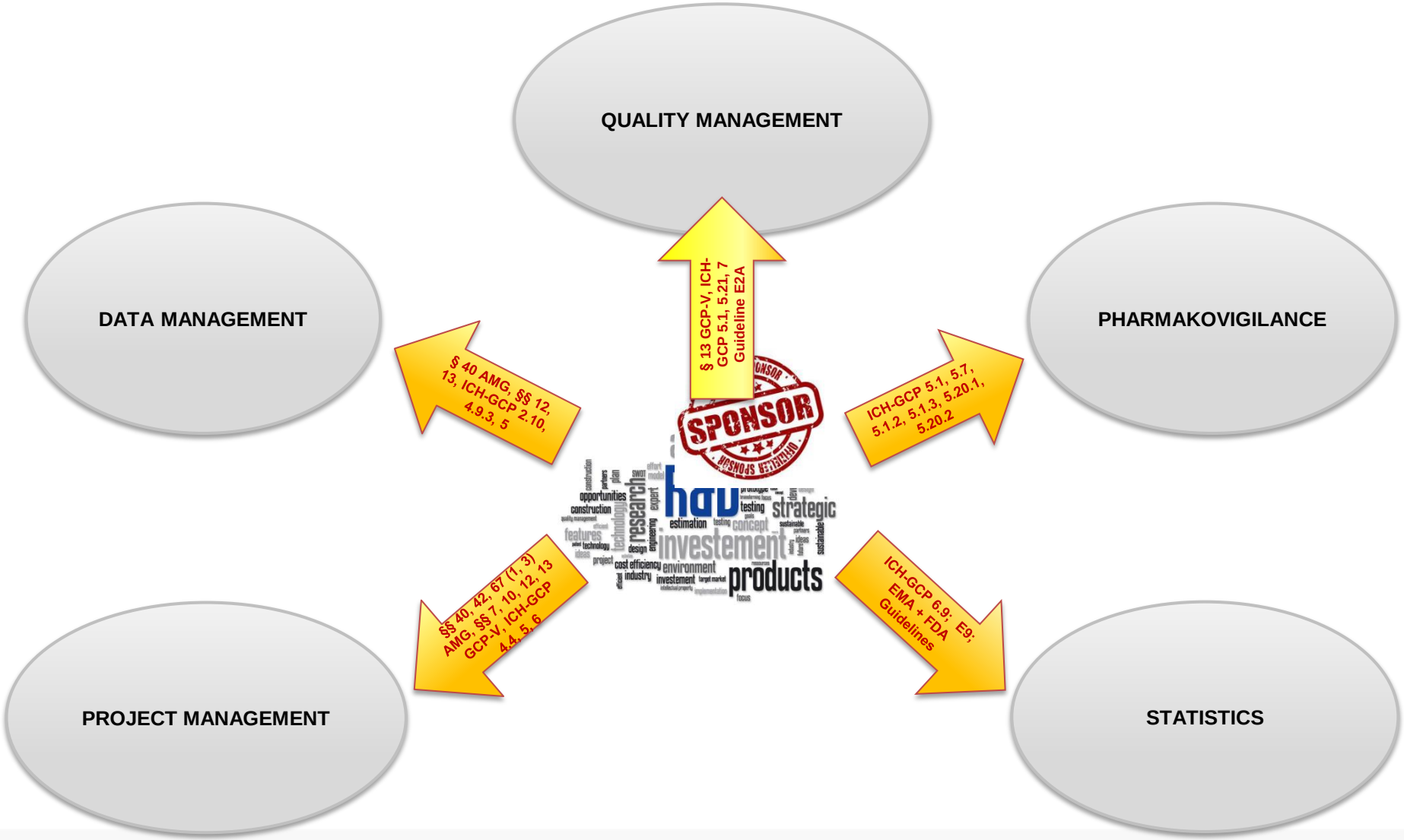
- A set of 3 investigator initiated trials under the German Pharmaceuticals Act have been considered to analyze the impact of interim analyses and adaptive modifications on the total costs of the whole process and trial

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
§ 13 GCP-V, ICH-GCP 5.1, 5.21, 7 Guideline E2A
DATA MANAGEMENT
§ 40 AMG, §§ 12, 13, ICH-GCP 2.10, 4.9.3, 5
PHARMAKOVIGILANCE
ICH-GCP 5.1, 5.7, 5.1.2, 5.1.3, 5.20.1, 5.20.2
SPONSOR
PROJECT MANAGEMENT
§§ 40, 42, 67 (1-3) AMG, §§ 7, 10, 12, 13 GCP-V, ICH-GCP 4.4, 5, 6
STATISTICS
ICH-GCP 6.9; E9; EMA + FDA Guidelines

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:

- Interventional, 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)

$$TOC = TC_{DM} + TC_{PV} + TC_{PM} + TC_{QM} + TC_{BSt} + TC_{In} + TC_{Fe} + TC_{Tr} + TC_{Ls} + TC_{Ma}$$

$$TOC = 293.000€ + 60.600€ + 217.350€ + 131.540€ + 57.500€ + 63.308€ + 20.250€ + 23.000€ + 101.715€ + 258.400€$$

$$TOC = \mathbf{1.226.663€}$$

DM:	Data Management
PV:	Pharmakovigilance
PM:	Project Management
QM:	Quality Management
BSt:	Biostatistics
In:	Insurance
Fe:	Fees
Tr:	Travel
Ls:	Lump sum
Ma:	Material

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)

$$TFC = FC_{DM} + FC_{PV} + FC_{PM} + FC_{QM} + FC_{BSt} + FC_{In} + FC_{Fe} + FC_{Tr} + FC_{Ls} + FC_{Ma}$$

$$TFC = 80.500€ + 36.000€ + 105.900€ + 2.900€ + 38.334€ + 0€ + 9.950€ + 23.000€ + 12.400€ + 0€$$

$$TFC = 308.984€$$

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

Total Variable Costs (TVC)

$$TVC = VC_{DM} + VC_{PV} + VC_{PM} + VC_{QM} + VC_{BSt} + VC_{In} + VC_{Fe} + VC_{Tr} + VC_{Ls} + VC_{Ma}$$

$$TVC = 212.500€ + 24.600€ + 111.450€ + 128.640€ + 19.166€ + 63.308€ + 10.300€ + 0€ + 89.315€ + 258.400€$$

$$TVC = 917.679€$$

→ 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})

$$TVC_{Ss} = TVC_{SsDM} + TVC_{SsPV} + TVC_{SsPM} + TVC_{SsQM} + TVC_{SsBSt} + TVC_{SsIn} + TVC_{SsFe} + TVC_{SsTr} + TVC_{SsLs} + TVC_{SsMa}$$

$$TVC_{Ss} = 197.500€ + 24.600€ + 83.250€ + 89.520€ + 19.166€ + 63.308€ + 0€ + 0€ + 89.315€ + 258.400€$$

$$TVC_{Ss} = 825.059€$$

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

Total Variable Costs: Trial Sites (TVC_{Ts})

$$TVC_{Ts} = TVC_{TsDM} + TVC_{TsPV} + TVC_{TsPM} + TVC_{TsQM} + TVC_{TsBSt} + TVC_{TsIn} + TVC_{TsFe} + TVC_{TsTr} + TVC_{TsLs} + TVC_{TsMa}$$

$$TVC_{Ts} = 15.000€ + 0€ + 28.200€ + 39.120€ + 0€ + 0€ + 10.300€ + 0€ + 0€ + 0€$$

$$TVC_{Ts} = 92.620€$$

→ 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)

$$TUIAC = TUIAC_{DM} + TUIAC_{PV} + TUIAC_{PM} + TUIAC_{QM} + TUIAC_{BSt} + TUIAC_{In} + TUIAC_{Fe} + TUIAC_{Tr} + TUIAC_{Ls} + TUIAC_{Ma}$$

$$TUIAC = 12.500€ + 6.000€ + 23.288€ + 17.570€ + 27.500€ + 0€ + 4.150€ + 7.000€ + 0€ + 0€$$

$$TUIAC = \mathbf{98.008€}$$

- 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€

$Total\ Variable\ Costs_{Trial\ site} =$ 92.620€

$Total\ Variable\ Costs_{\ Sample\ size} =$ 825.059€ (for 1520 trial participants as planned)

$Total\ Variable\ Costs_{\ Trial\ participant} = \frac{TVC_{Ss}}{1520} = \frac{825.059€}{1520}$ = 543€ (Costs for 1 trial participant)

$$\boldsymbol{TOC_{Ss477}} = TFC + TVC_{Ts} + (TVC_{Tp} \times 477)$$
$$= 308.984€ + 92.620€ + (543€ \times 477)$$
$$= \mathbf{660.615€}$$

Cost Saving Potential: $\boldsymbol{TOC_{Ss1520}}$ - $\boldsymbol{TOC_{Ss477}}$ - $\boldsymbol{TUIAC}$

$= 1.226.663€ - 660.615€ - 98.008€$

$= \boldsymbol{468.040€}$

→ 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

$$\frac{TUIAC}{TVC_{Tp}} = \text{Sample size (that will expend the costs for TUIAC)}$$

$$\frac{98.008€}{543€} = 180$$

- Break-Even-Point:

$$1520 - 180 \leq \textbf{1340 trial participants}$$

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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