The German approach: GCP-conform monitoring in IITs

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Outline of the presentation

- Non-commercial investigator initiated trials (IITs) in Germany
  - past and current situation
- Quality Management in IITs
  - current activities in Germany
- GCP-conform monitoring in IITs:
  - Preparatory project of the TMF
  - Proposal for an adaptive monitoring strategy for IITs
  - Validation of the adaptive monitoring strategy:
    Planned randomised trial

Non-commercial clinical trials in Germany

Public funding of non-commercial trials

1982 - 94	**BMBF*-program „Therapeutical studies“** Ca. 50 Mio € in 12 years ⇨ **Study groups in cancer, rheumatism, psychiatric** and **cardiovascular diseases**
Since 1987	**Deutsche Krebshilfe** (charity): grants for **trials in oncology** In 2005 10 Mio € for clinical trials
Until 2004	**Clinical trials not in the focus of the DFG** (Deutsche Forschungsgemeinschaft – German Research Foundation), the central research funding organisation
Since 2004	**Joint program of DFG and BMBF for “Clinical Study research”** First call (2004): 10 Mio €, about 350 applications ⇨ 16 trials granted Second call (2005): 20 Mio €, about 200 applications, review ongoing
	Further programs for clinical trials e.g. for innovative therapies, health care research etc. **ongoing**

* BMBF = Federal Ministry of Education and Research

Non-commercial clinical trials in Germany

Infrastructure for clinical research

1998-2008 **BMBF-program „Competence networks in medicine“**

- establishment of supraregional medical networks concerning specific diseases
- 17 networks for diseases like Lymphoma, Leukaemia, Paediatric oncology, Dementia, Hepatitis, Heart Failure etc.
- Central offices and facilities
- Project funding (basic research, epidemiology, clinical trials)

1999-2008 **BMBF-program “KKS” (Coordinating centres for clinical trials)**

- comprehensive advice and support for planning, conducting and evaluating clinical research projects.
- 12 KKS organised within KKS-network

Since 1999 **TMF** “Telematikplattform für Medizinische Forschungsnetze”

- meta-organisation which works to solve logistic, technical, and administrative problems for clinical research networks.
- Members: competence networks, KKS, further networks

Quality management in non-commercial trials

Competence Networks

- Several activities (e.g. Templates for trial documents, central document review, Standard Operating Procedures)

KKS-Network

- Working group on quality management

⇨ **Harmonisation** of **Standard Operating Procedures** covering all essential aspects of clinical trials

TMF

Working Group „Management of Clinical Trials“ (since 2004)

- Focus in 2004 / 2005: **handling of the new regulatory requirements** resulting from the EU-Directive
  - ⇨ **Checklists and guidebooks** for regulatory aspects of clinical trials
  - ⇨ **Training courses and materials** for study groups and investigators

GCP-conform monitoring in IITs in Germany

- **Survey of non-commercial trials** in Germany:

⇨ **Extent** of on site **monitoring** depends on

- **Budget** available (and deemed necessary during planning!)
- Usual **practice / preference** of the study group or coordinating centre
- **Not** (or only to a minor degree) on **study characteristics**

- **Dogmatic discussion** with opinions ranging from:
  - On site monitoring **not necessary** for IITs
  - Extensive on site monitoring (industrial standard) is **crucial** for GCP-conform trials

- Experience from **grant applications**:
  - Requested **budget** for quality assurance: **none – exorbitant sums**

GCP-conform monitoring in IITs in Germany

Project funded by the TMF

Hypothesis:

It is possible to define monitoring strategies specifically adapted to the characteristics and “critical points” of a trial which

- Meet the requirements of Good Clinical Practice
- Are cost effective

Objectives:

- Research and compile available published information on quality assurance and quality control in clinical trials with focus on monitoring and audits
- Develop trial-adapted monitoring strategies for non-commercial trials in Germany
- Develop a study protocol for validation of the adapted monitoring strategy within a randomised setting

Quality management in clinical trials

What is quality management in clinical trials for?

- The rights, integrity and confidentiality of trial subjects are to be protected
- The data and reported results are to be credible and accurate

Good Clinical Practice

+

- The results are to be meaningful and interpretable

"Good Scientific Practice"

Quality management in clinical trials

- **On site Monitoring** is an **important component** for **quality assurance** in clinical trials

but

- on site monitoring has to be **integrated** into an **overall concept for quality management**.

- A strategy for reduced **on-site monitoring alone**, without additional provisions for
  - **Central monitoring / Data management**
  - **Training and information**
  - **Specific support** for trial sites and investigators
- **will not suffice.**

Adaptive Monitoring

Proposal for adaptive monitoring is based on 3 components:

Basis Monitoring

Risk classification of the trial determines **frequency** of **visits** and **percent** of **patients and items for SDV**

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Trial specific monitoring components

Provisions to **avoid** or **minimise specific risks** derived from a thorough analysis of the trial

+

For cause monitoring

On site visits scheduled in case of **irregularities** detected by close central monitoring

Basis Monitoring: Classification

Class	Risk potential	Clinical trial
K1	**Very low**	• **Phase IV** – **therapy optimization**: - established study group - ≥ 2. trial of the study group in the particular indication - therapy plan similar to usual medical care - trial sites involved in previous trials of the study group
K2	**Low**	• **Phase III - related indication and non vulnerable population** • **Phase IV** (if not K1) • Clinical trial for **routinely used medical device, surgery, radiotherapy** etc. (if not K1)
K3	**Inter-mediate**	• **Phase III - new indication or vulnerable population** • **Phase IIb - new indication** of a registered drug • **Early efficacy clinical trial** for **medical device, surgery, radiotherapy** etc. not routinely used
K4	**High – very high**	• **Phase I, Phase I/II, Phase II** • **First clinical trial** of a new medical device, surgery, radiotherapy etc.

Basis Monitoring: Extent

	K1	K2	K3	K4
Pre-study visit	-	May be replaced by **phone / mail contact**	May be replaced by **phone / mail contact**	**obligatory**
Initiation	**May be replaced** by investigator meetings	May be performed **after recruitment of 1. patient**	May be performed **after recruitment of 1. patient**	**obligatory**
Regular visits: frequency	**One visit** for a **sample of 10-20% of trial sites**	**Once per year**	Every **3 – 6 months**, at least after every 10 patients	Every **4 – 8 weeks**
Regular visits: source data verification	Only for visited sites: **100% key data** for at least **20% of patients** **100% of further data** for at least **1 patient**	**100% key data** for **50% of patients** **100% of further data** for at least **1 patient**	**100% key data** for **100% of patients** **100% of further data** for **10-20% of patients**	**100% key data** for **100% of patients** **100% of further data** at least **50% of patients**
Contact by phone / email	If necessary	If necessary	At least every **8 weeks**	At least every **2 weeks**
Close out	-	For a sample of **25% of trial sites**	**obligatory**	**obligatory**

Trial specific monitoring components

Provide a **detailed guideline** listing possible **“critical points”** of a clinical trial **with respect to**

- **Safety** of trial subjects
- **Rights and confidentiality** of trial subjects
- **Error-prone procedures** which may lead to **protocol deviations**, e.g.
  - complex design, unusual requirements, time-critical procedures, long duration
- **Critical interfaces** between involved institutions, e.g.
  - different diagnostic and therapeutic departments involved at the trial sites, reference institutions, study office
- Sources of **variance**
- Sources of **bias**

and

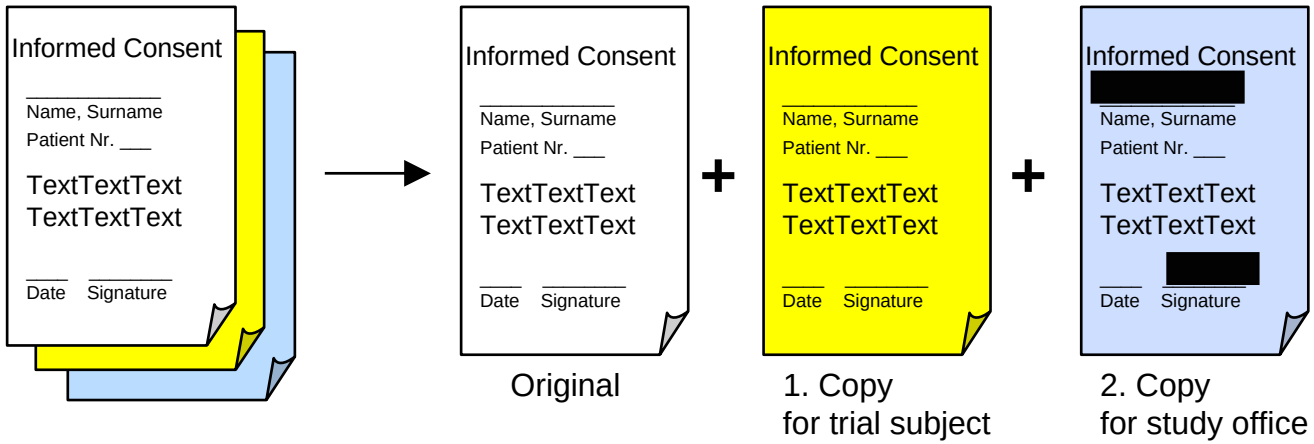
provide corresponding **lists of suitable provisions** to prevent the specific problems identified

Trial specific monitoring components

Provide a toolbox of **optional procedures for central monitoring**, which may reduce the necessary extent of control during on-site visits, e.g.

Trial site ➔ study office

- Send copy informed consent (name / signature illegible on copy) form (as proposed within the OPTIMON protocol)



- Send documentation of **eligibility criteria** to study office prior to inclusion

Study office ➔ trial site

- Provide **individual visit plan (with optimal dates)** for each patient included
- **Remind** the trial sites of **upcoming follow-up visit**

For cause monitoring

- **Pre-requisite**
- **Close central monitoring** and **data management**:
  - Query management
  - Statistical data monitoring
  - Reminder system for expected CRFs

- **For cause monitoring** visit in case of
  - **Significant protocol deviations** in several patients
  - Significantly **lower or higher incidence** of **serious adverse events**
  - **Suspected fraud**

- In **K1 (very low risk)** additionally in case of
  - **Missing CRFs** or **unanswered queries** despite reminders

Adaptive monitoring strategy: retrospective analysis

Retrospective analysis in IITs already finished:

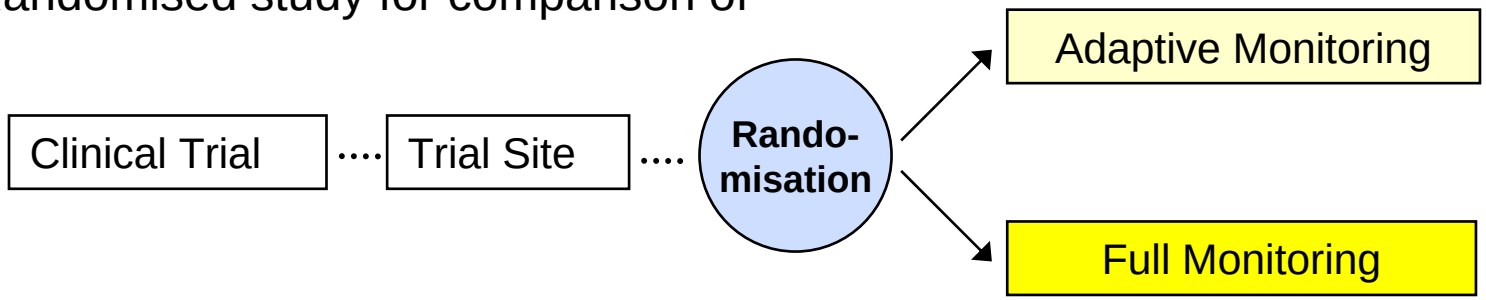
- Is the **classification feasible** and distinct (unambiguous)?

- Is the proposed **risk analysis feasible** and does it result in **different and specific procedures**?

- Simulation of the **number of site visits** required
  - Given the known distribution of trial sites, patients per trial site and recruitment dynamics in the trial sites
  - How does this compare to the number of visits with a full, industrial standard monitoring?

Adaptive monitoring strategy: validation

Randomised study for comparison of



- Are the **two strategies equivalent** with respect to the incidence of **major audit findings**?

Need for a validation study in Germany:

- **Preconditions for non-commercial clinical trials differ** across EU-countries
  - GCP knowledge and awareness of investigators very heterogeneous
  - Involvement of experienced institutions for trial management is not mandatory
  - No established procedures for quality control from funding organisations
  - Extent of GCP inspections still low
- Unique chance for **active implementation** of the concepts
  - Without active implementation impact considerably lower

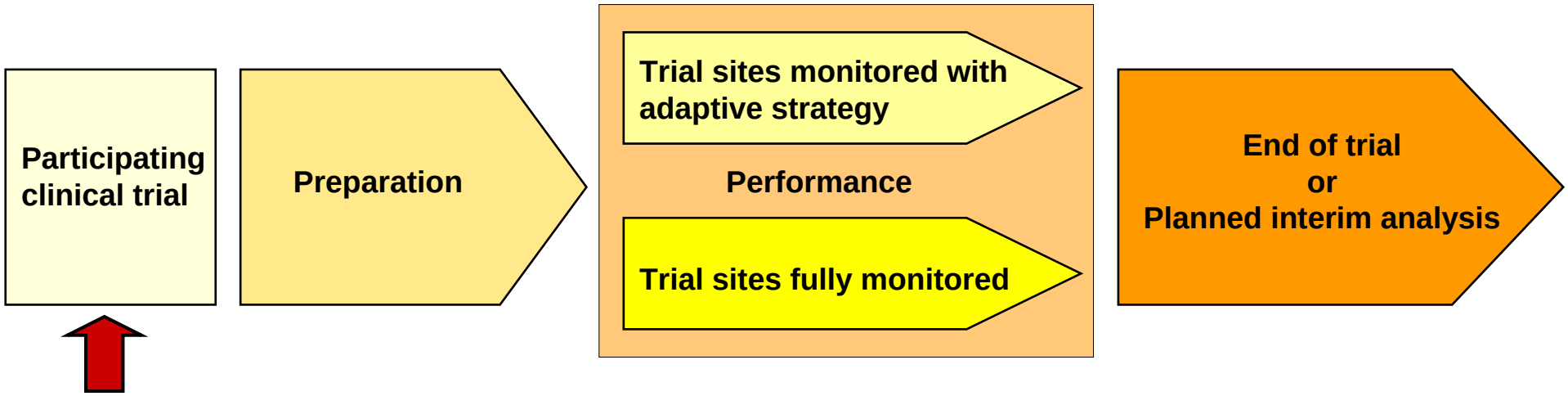
Selection of trials for the randomised comparison

Comparison within **clinical trials willing to participate**,
which fulfil the following inclusion criteria:

- Clinical trials classified as **K1, K2** or **K3**
- **Multicentre** trials (≥ 8 trial sites)
- **Non-commercial sponsor**
- **Public funding**
- Standardised processes for data management
  - E.g. Consistency checks, query management, reminders

Randomised comparison: Implementation

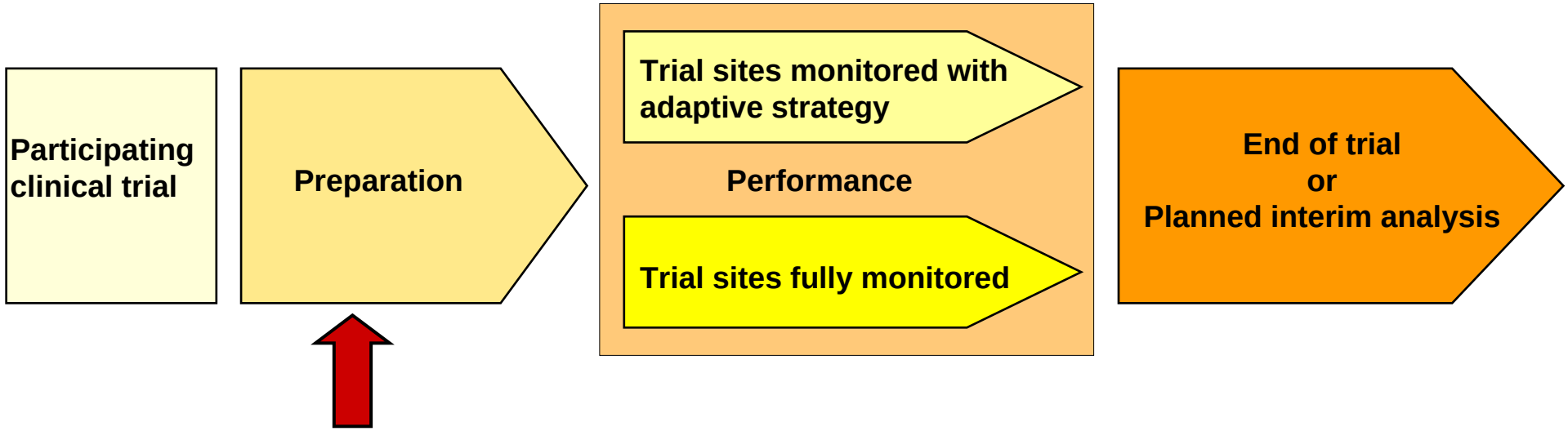
- Selection of trials funded by DFG / BMBF starting in 2007
  (+ possibly trials funded by Deutsche Krebshilfe starting in 2007)



The clinical trials included should be representative for non-commercial trials in Germany.
If possible each class should be represented by:

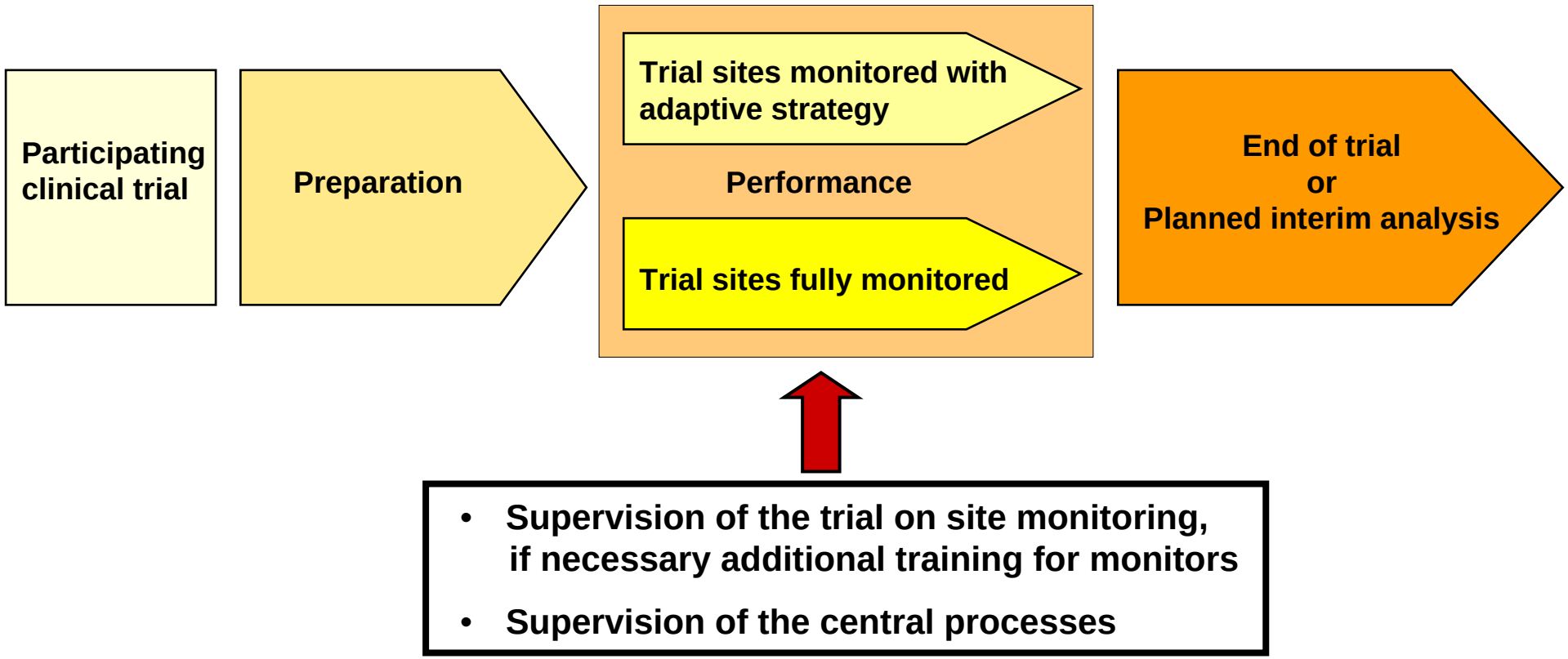
- **Trials with different complexity of design**
- **Trials with different methods of data capture (paper-based, eCRF)**

Randomised comparison: Implementation



- Trial specific definition of major audit findings; audit manual
- Trial classification and trial specific risk analysis
- Preparation of the 2 monitoring manuals for the trial (including risk analysis)
- Training of the trial monitors (at least 2 persons!)
- Check of requirements for central monitoring and data management
- Randomisation of the trial sites

Randomised comparison: Implementation



Randomised comparison: Implementation