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SYNDROMES

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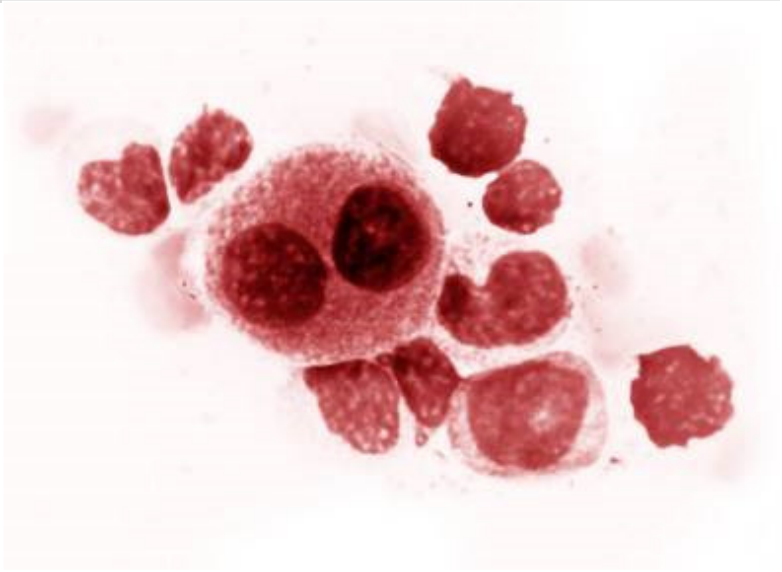

The European MDS studies coordination office

How to *properly* cost your Multi-national MDS Clinical Trial

BAXTER BOEHRINGER NOVARTIS CELGENE

What are the major cost categories?

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1. Pre-Study Activities
2. Pass-through Costs (Ethics Committees, Agencies, Insurance)
3. Honorary Fee for tasks required (includes laboratory costs)
4. Pharmacy
5. Monitoring
6. Pharmacovigilence
7. Data Management
8. Statistical Analysis
9. Other costs (printing, meeting costs, DSMB, amendments, audits)
10. Labor (central lab, cytogenetics, morphology, biobanking, flow cytometry, other exotic tests), Shipping for diverse lab tests
11. Project management costs
12. Head of the clinic trial / other overhead

What are the major cost categories?

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Cost Category	Comments	Proportion of Budget
Pre-study Costs	Development, Review	< 8%
Pass-through Costs (Ethics Committees, Agencies, Insurance)	Bfarm / PEI, Ethics	< 15%
Pharmacy/Study drug	preparation by pharmacy, Drug Account	< 8%
Honorar	Site fees / PI & study nurse effort	10 - 40%
Monitoring (Queries)	Visits, Travel	10 - 40%
Pharmacovigilence	SAE, SUSAR Management, reporting: DSUR	< 10%
Data Management	CRF development, Data entry, Licence fees	< 10%
Statistics	Statistic	< 10%
Other costs	Feasibility, site visits, archiving, printing, meetings DSMB, amendments, audits	< 10%
Lab / Central Lab / diagnostics	Materials, Shipping	10 - 25%
Project Management	Project responsibility over the entire trial	12 – 30%
LKP/ Trial Head/ Overhead	General management	10 – 33%

What is the difference between an industry trial and an academic clinical trial?

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Academic research suffers from a lack of financial and human resources

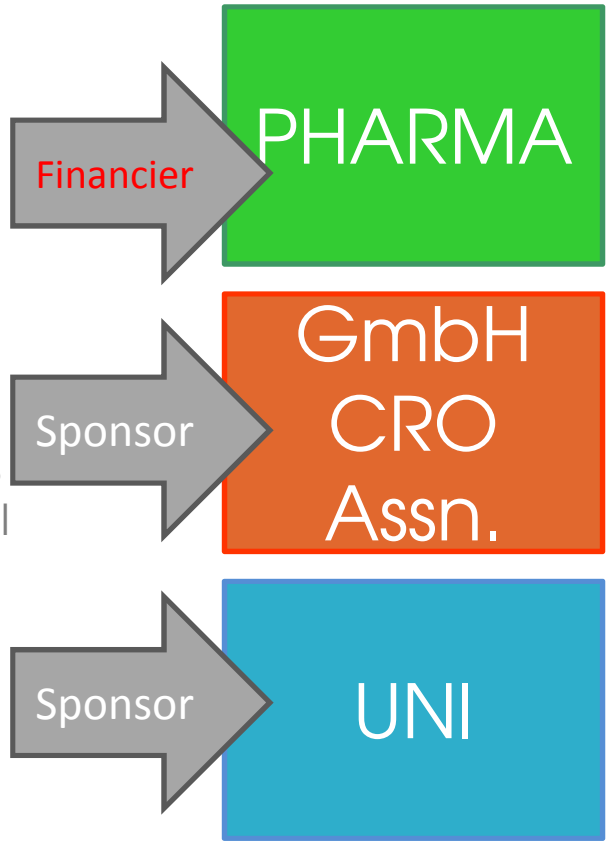
The financial resources allocated to academic clinical trials are considerably lower compared to industry trials:

- No 100% SDV / Monitoring – as low as 20% monitoring
- Reduced investigator fees – sometimes no fees at all
- Reduced dedicated personnel (CRAs, clinical research nurses)

The assumption is that the value of the data generated is lower than data generated by industry sponsored clinical trials

However, academic (IIT) clinical trials must adhere to the same regulatory requirements and must have the necessary resources.

There is a financial limit below which IITs are not feasible



Who should be the Sponsor?

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Groupe Francophone des Myélodenysplasies (GFM)

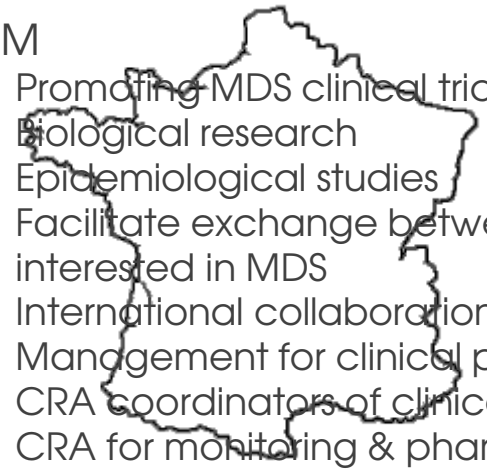
Groupe Francophone des Myélodysplasies

GmbH
CRO Assn.

Group (Gesellschaft) for Medical Innovation in Hematology and Oncology (GMIHO)

GMIHO
INNOVATION IN HEMATOLOGY AND MEDICAL ONCOLOGY

GFM



1. Promoting MDS clinical trials
2. Biological research
3. Epidemiological studies
4. Facilitate exchange between specialists interested in MDS
5. International collaboration in MDS
6. Management for clinical projects
7. CRA coordinators of clinical trials
8. CRA for monitoring & pharmacovigilence

GMIHO

1. Sponsoring for clinical trials in Hematology and Oncology
2. Service Platform
3. Clinical Research and Translation
4. Professional Management of Trials
5. Services including CRA
6. Monitoring, Coordination
7. Biostatistics, pharmacovigilence
8. Support of Translational Research

GCP 5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

The Sponsor is responsible for the financing of the trial.

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UNIVERSITY	Association/GmbH/CRO	Pharma

If the Sponsor calculates that the trial is not sufficiently financed, the Sponsor has a legal and ethical responsibility to stop enrolment.

- "regarding the financing of clinical trials, it must be ensured, that the allocated funding amounts for the trial are sufficient until its conclusion"*
- "A **termination** for reasons that are specific to the Sponsor (e.g Sponsor insolvency) can be considered **unethical**. This applies not only in terms of the patients who have given their consent, but also in terms of the doctors involved in the trial. (...)"*

*22nd Annual Meeting of the AK Medical Ethics Committees (November 2004) during a discussion of GCP and from a related excerpt from the German Physcians Journal ", 2004)..

Agency Fees – why do I have to pay for the Ethics Committee?

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Germany –	
• lead EC	2500 – 4000 EUR
• participating	avg 750 per district
• Ministry of Health (BfarM/PEI)	4500 and 5500 EUR
• Amendments	per district
France –	
• Ethics committee (CPP)	0 EUR
• Ministry of Health (ANSM)	0 EUR
Italy –	
• Ethics committee –(non-profit)	0 EUR
• Ministry of Health (non-profit)	0 EUR

different **EU countries** have different systems and costs

How much should the participating sites be offered?

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The amount differs from country to country, routine lab tests are often included in the fees

- **France - Participating sites in GFM trials are offered a budget for:**
  - Clinical trial personnel (CRA)
  - ancillary costs (cytogenetics, pharmacy, and administration)
- **Germany - Gebührenordnung für Ärzte (GOÄ)**
  - governs accounting of all medical services outside the statutory health insurance.
  - basis for accounting for both private patients, and all services provided by a licensed physician in Germany
  - For clinical trials GOÄ (overhead is included) can be charged at a maximum of **3.5x** the listed amount.

The company said it would provide the study drug.

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- Does that mean that there are no pharmacy costs?
- Does the drug come with a label? Is the label conform with Annex 13 and local (French/German/Italian) regulations?
- Is the study drug a tablet (RT storage) or an injectable (4 degrees)?
- How will the study drug be distributed at the site? Who will administer the study drug on site?

GCP 5.13.1 The sponsor should ensure that the investigational product(s) (including … placebo, if applicable) …is manufactured in accordance with .. GMP, and is coded and labeled in a manner that protects the blinding... In addition, the labeling should comply with applicable regulatory requirement(s).

Why are the data management costs so high?

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- Costs of Data Management are primarily fixed costs related to hosting and server access
- The variable components are
  - number of patients and sites
  - complexity and length of the CRF/eCRF
  - duration of the trial
- An eCRF saves costs by reducing the effort in data entry and in queries; these savings are realized later in the trial

Do I really save costs with an eCRF?

Depending on the number of patients, the answer is almost always YES

Did we underestimate the cost of diagnostics and shipping?

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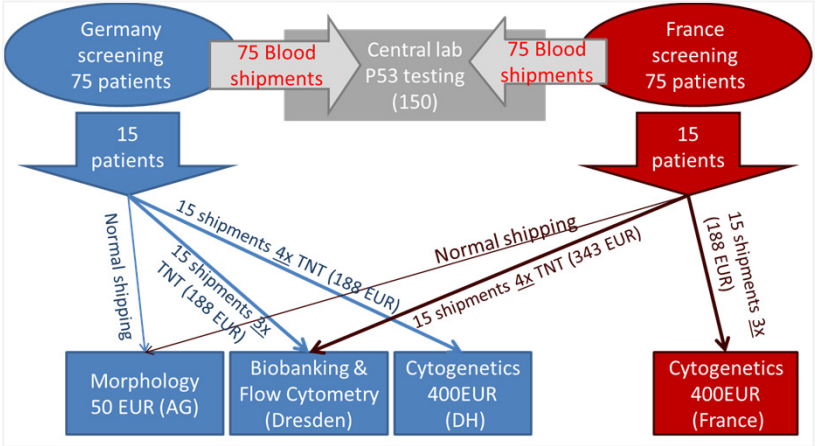
- Diagnostics Are increasingly important for screening
- An array of tests are necessary at different timepoints
- Clinical shipping is insured, temperature controlled, and overnight

Diagnostics
- Morphology
- Cytogenetics
- Flow Cytometry
- Immunocytochemistry
- Molecular Genetics (i.e. FISH, p53)



Why Sites should be carefully chosen

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- De-registering non-performing sites and re-registering new sites causes delays in recruiting and also adds additional costs that are not calculated from the start of the trial
- **Country Specific Site Mapping** can prevent this in advance. ICD-10 from "Qualitäts-Berichte" that German hospitals must make available every 2 years are listed on www.kliniken.de
- Feasibility and Medical controlling reports can confirm good sites

Monitoring – a critical tool to ensure data integrity

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- Usually the single most expensive cost category and the first category to be cut when looking to save on expenses
- Distance from the CRO makes a difference when calculating travel costs
- A critical tool in managing recruitment. The more visits the better the enrollment
- Initiation visit teaches the site personnel how to efficiently and accurately record the data and reduces drastically the number of queries
- Depends critically on the number of CRF pages! Think carefully about the number of data points which are required to achieve the endpoints



The Authorities say they want to audit some sites – does this cost anything?

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- Although GCP does not explicitly require audits, it assumes that the Sponsor will audit sites, vendors and suppliers for the trial to ensure quality management.
- Auditing is a responsibility of the Sponsor
- The regulatory agencies also audit trials, sponsors and sites on a regular basis.
- In Germany the Sponsor is charged for the cost of the audit (between 10,000 and 15,000 EUR) (In France there is no charge)
- The high costs of an audit by the ministry of health can cause problems in budgeting for a clinical trial

Was there ever a trial that finished on time and within budget?

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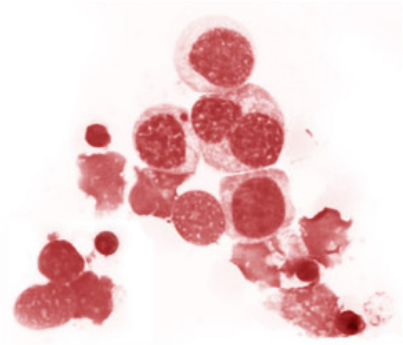
- What is a “Risk Premium”?
- There are normally unexpected costs in a clinical trial
- Cost of inflation is normally not calculated in a trial although a trial may last from 3-7 years



Thank you for your attention!

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