Non-commercial clinical trials  
(Investigator initiated trials (IIT), research-lead trials)

- Definition according to the EU draft guidance on the specific modalities of „non-commercial clinical trials“ (2005):
  
  “Non-commercial clinical trials” are clinical trials conducted by researchers without the participation of the pharmaceutical industry...

- “Non-commercial sponsors commonly study the “effectiveness” of a medicinal product compared to alternatives …”
Characteristics and track record of therapy optimisation studies in paediatric oncology (oncTOS)

- Comparative testing of the effectiveness of standard therapies
- Use of authorised medicinal products (authorisation often does not cover all ages)
- Usually study of treatment concepts (including risk stratification), no single drugs
- Patient recruitment by a large number of study sites in order to ensure nation-wide coverage
- Limited financial resources (non-industrial funding)
- Standard care in paediatric oncology for >30 years
- Surveillance by Data Safety and Monitoring Committees
- Extensive progress in treatment results and non-clinical research through international cooperations
EU Clinical Trials Directive
Official Goals

- Improve protection of patients and reliability of research reporting
- Harmonise and increase the competitiveness of European clinical research

Changes concern non-commercial as well as pharmaceutical industry clinical trials

- If investigational medicinal products (IMPs) with marketing authorisation are used, some simplifications were realized for non-commercial clinical trials regarding
  - access to the IMPs
  - IMP-related data (SmPC instead of IMP Dossier)
  - labelling of the IMPs
  - documentation
EU Clinical Trials Directive
Consequences

• More requirements regarding
  – procedure of approval by authorities and ethical committees
  – trial insurance
  – quality assurance and quality control
  – pharmacovigilance
  – validation of data acquisition systems
  – data archiving

  → resulting in higher administrative efforts and costs
Effect of the EU Directive on trial initiation

- **EORTC:**
  - new trials in 2004: n=19, in 2005: n=7
  - increase of trial costs by 85%
  - increase of insurance costs from 70,000 € to 140,000 €
  - trial initiation ~5 months slower

- **Ethics committee in Helsinki:**
  - protocol amendments in 2003 n=18, in 2005: n=69

- **GPOH:**
    May 2004 - 2007: n=2

*Hemminki et al, BMJ, 2006*
Initiation procedure of INTERFANT 06 in Germany
Preparation of submission to authorities and ethics committees

- Finalisation of the German protocol part
  → size of the complete final protocol version: 317 pages
  (including SmPCs) (INTERFANT 99: 150 pages)
- Patient information: 18 pages (INTERFANT 99: 4 pages)
- Collection of the qualification documents of study clinics (n=47) and investigators (n=150); documents complete about one year later → ~1000 pages
- [Application to the Deutsche Krebshilfe for funding (~9 months)]
- Attempt to conclude the trial insurance using the inexpensive master policy of the German Cancer Association failed because SCT is included in the protocol (although all pts. undergoing SCT (estimated no. per year: 2-3) will in fact enter trial ALL-SZT BFM 2003).
  → Costs for 65 patients: 27.887,- € (instead of 1980,- €)
Initiation procedure of INTERFANT 06 in Germany
Submission to the authorities

• Submission of the protocol to the authorities (15.01.08):
  – authority primarily concerned: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
  – Paul-Ehrlich-Institut (competent authority for clinical trials with sera, blood products...) also involved (hematopoietic stem cells, ATG)

• Submitted documents:
  – Application form Module 1 (315 pages)
  – Trial protocol (317 pages)
  – some other documents
  \[\rightarrow\] Submission of ~2560 pages

• all administered drugs (supportive therapy excluded) were regarded as investigational medicinal products (IMPs)
  \[\rightarrow\] 28 IMPs (considering different pharmaceutical forms)
Initiation procedure of INTERFANT 06 in Germany
Submission to the Ethics Committees

- Submission of the protocol to the ethics committees (EC) (15.01.08):
  - EC in charge (Kiel)
  - 35 involved EC
  \[\text{\rightarrow for 47 trial sites}\]

- Charges by the involved EC: 0,- to 1300,- € \(\rightarrow\) ~ 6000,- €

- Submitted documents:
  - Application form *Module 1* (315 pages)
  - Application form *Module 2* (8 pages)
  - Trial protocol (317 pages)
  - some other documents (18 pages)
  - investigator/trial site qualification docs (3000 pages)
  \[\rightarrow \text{~ 55,000 pages}\]

- + 36 CD-ROMs (1 per EC)
Submission of a TOS to the Ethics Committees

1999

2008
Initiation procedure of INTERFANT 06 in Germany

Remarks by the BfArM (and PEI)

• Initial formal complaints (corrected by 18.02.08):
  – „Complete documents have to be submitted regarding production and application of the stem cells.“
  – „A statement is required, why the study shall recruit underage patients.“ (According to the AMG the conduction of a clinical trial in underage patients is only allowed if sufficient results can not be expected when conducting the trial in adult patients ... )
  – German label for the drug Erwinase was required.

• Still waiting for the final approval...
Major concerns regarding

– Patient information
  • insurance
  • data exchange
  • drug side effects
– Preservation of left-over specimens for future research
– Data protection
Data protection: Specific aspects in oncological TOS

- OncTOS include standard patient care, quality assurance, and research.
- Germany, G-BA (=Gemeinsamer Bundesausschuß, Common Federal Committee of physicians and health insurance companies): „Agreement for Paediatric Oncology“ requires participation in TOS.
- In general, „trial-related“ diagnostics and treatment represent the best available standard for that disease entity.
- Reference laboratories provide results which are relevant for:
  - treatment of the individual patient
  - research
- Study center is concerned with:
  - medical consultation of the clinicians
  - central risk stratification
  - trial execution (e.g. data collection, randomization)
Data exchange in German TOS in paediatric haematology/oncology

Quality assurance
- reference diagnostics/expertise
- central risk stratification

Research
- Collection and analysis of trial-related data
- clinical complications
- use of personal data
- data pseudonymisation

Medical consultations
- use of personal data
- diagnostic problems
Practical reality may be inconsistent with legal regulations

- Clear separation of patient care-associated data (personal data) and research data (pseudonymised) in the study center and diagnostic laboratories is difficult.

- „Trial-related“ treatment is often started before written informed consent has been given.
Impact of EU clinical trials directive on execution of TOS

Conclusions and Questions

• Additional work and expense are substantial
• Decrease of initiation of non-commercial trials is observed → temporary or persistent problem?
• Legal framework in many aspects does not fit to the practical execution of oncTOS
  – data protection
  – necessity of trial insurance
  – definition and reporting regulations of SAR/SUSAR
  – relevance of considering the single drugs instead of the whole treatment concept
• Will the patients benefit from the increased requirements?
##Submitted documents and financial efforts

###INTERFANT 99 vs. INTERFANT 06

<table>
<thead>
<tr>
<th></th>
<th>INTERFANT 99</th>
<th>INTERFANT 06</th>
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<tbody>
<tr>
<td><strong>Study protocol</strong></td>
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<td>(documents to be read by the parents)</td>
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<tr>
<td><strong>Application to the EC</strong></td>
<td>1 copy of the protocol + covering letter</td>
<td>79 copies of the protocol + 25,000 pages additional documents</td>
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Serious Adverse Events (SAE)

**Definition (acc. ICH-GCP guidelines):**

A serious adverse event is any medical occurrence that
- results in death
- is life threatening
- requires inpatient hospitalisation or prolongs existing hospitalisation
- results in persistent or significant disability
- is a congenital anomaly/birth defect
Pharmakovigilance
SAE in oncTOS

- Problem: SAE definition according to ICH/GCP leads to a huge amount of events
- Solution: SAE that do and do not require expedited reporting are clearly defined in the trial protocol
  → Nevertheless ~25% of patients in ALL-BFM 2000 had an SAE.
What is an Adverse Reaction?
• Definition (Directive 2001/20/EC): „All untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered“.
• Suspected causality to IMP is sufficient for classification as Adverse Reaction.

→ ALL-BFM 2000 (- 03/07): 941 collected SAE
  – SAR: 911/941 (96.8%)
  – initial SAE before ALL therapy: 26/941 (2.8%)
  – SAE without suspected causality with study medication: 4/941 (0.4%)
Pharmakovigilance

Suspected Unexpected Serious Adverse Reactions (SUSAR) in oncTOS

What is an Unexpected Adverse Reaction?
• Definition (Directive 2001/20/EC): „an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product)“. 

→ ALL-BFM 2000 (- 03/07): 941 collected SAE
  – SUSAR: 1/941 (0.1%)
Pharmakovigilance

Suspected Unexpected Serious Adverse Reactions (SUSAR) in oncTOS

But:

• „Note for guidance on definitions and standards for expedited reporting” (EMEA, CPMP/ICH/3945/03): „An expected SAR with a fatal outcome should be considered unexpected unless the local/regional product labeling specifically states that the SAR might be associated with a fatal outcome.“

• In German SmPCs of the drugs used in ALL-BFM 2000, fatal outcome of drug reactions are only specifically stated for:
  – Cyclophosphamide, Daunorubicin, Etoposide, Methotrexate

• No „official“ data on the combination chemotherapy

• International experience from previous TOS for ALL shows that 2-3% treatment-related deaths are „expected“

• Fatal events have to be considered in the context of relapse incidence.
• Does the line listing of SAR help the authorities and ethics committees? They have no possibility to assess the impact of frequency and severity of SAR in the context of an oncology treatment with polychemotherapy.

• Useful: historical comparisons, comparisons with other trials → these data are not available