Stem cell transplantation in children

Çok Merkezli Çalışma Düzenlenme

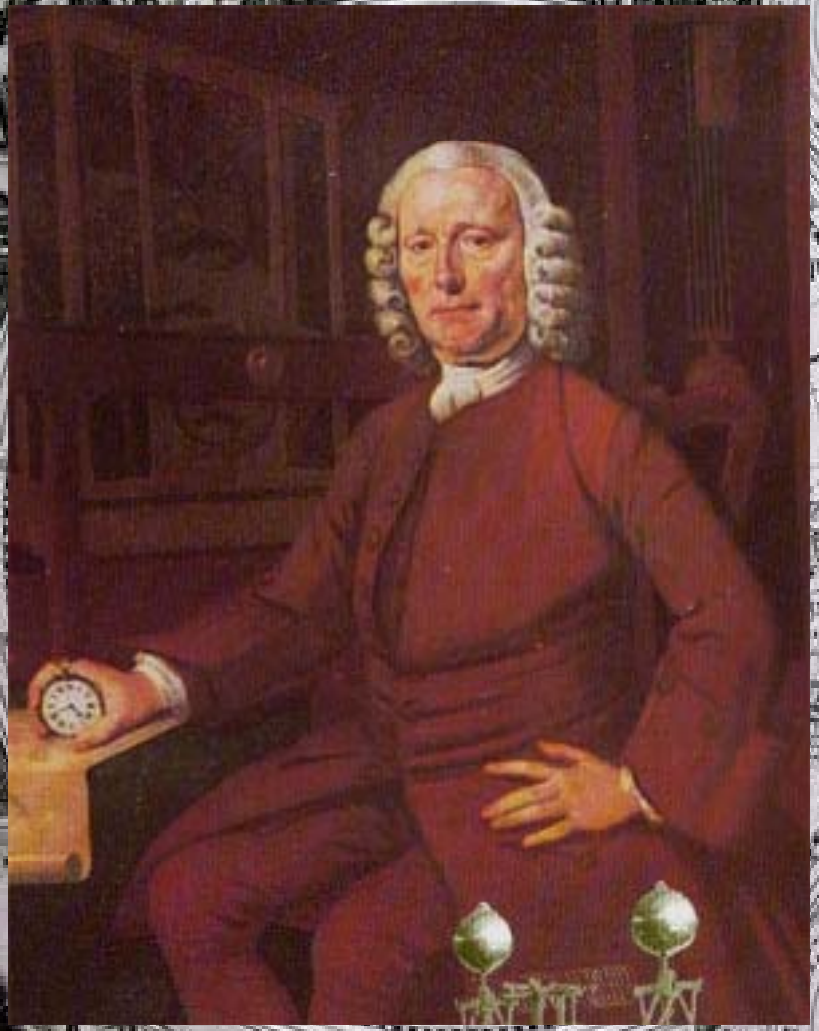
How to design a new study?

TPHD
Kemik Iliği Yetersizliği Sempozyumu
Samsun, 25.04.08

Selim Corbacioglu
Ulm, Germany


ORBIS TERRARUM TYPUS DE INTEGRO IN PLURIMIS EMENDATUS AUCTUS ET ICUNCULIS ILLUSTRATUS
EVROPA
ASIA
AMERICA
MAR DEL
NOVA GUINEA
INDIA
1757

Longitude...

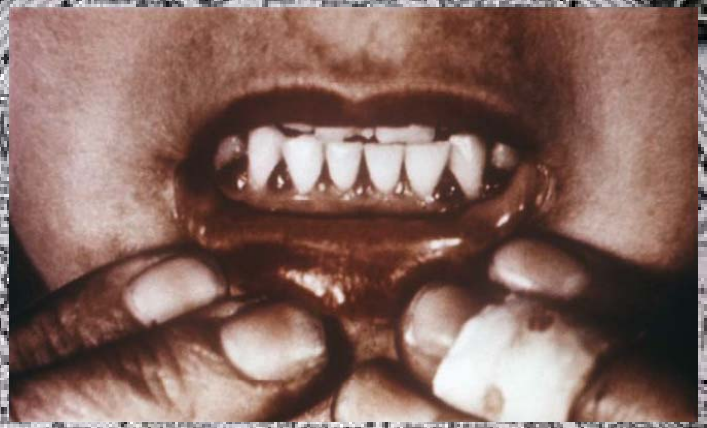


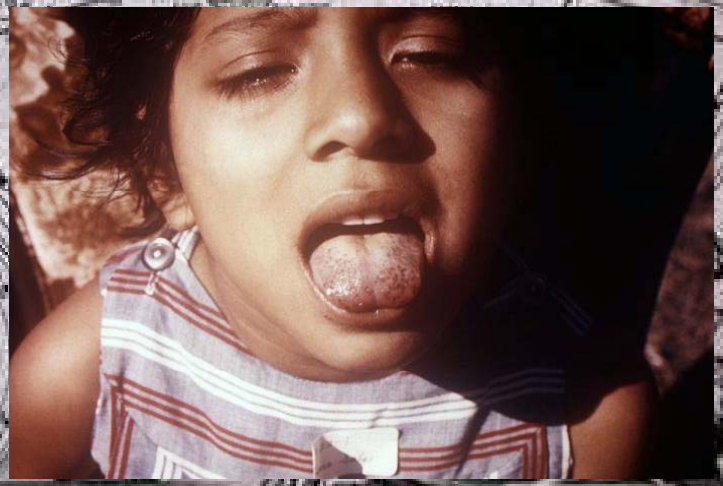
John Harrison 1693 - 1776

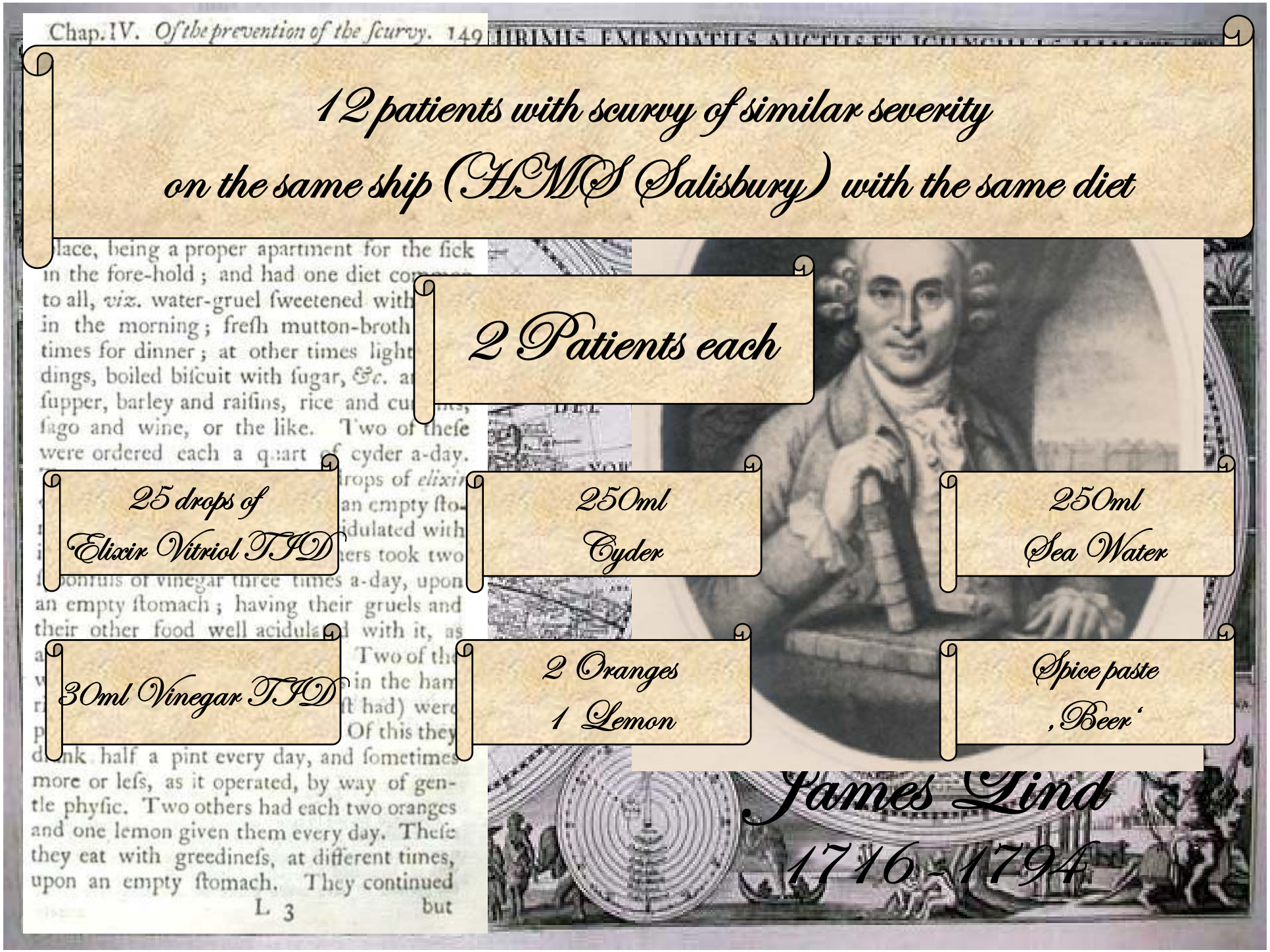
Scurvy…

Vitamine C Deficiency:

- Gingival bleeding
- Infections
- Wound Healing
- Skin Infections & Bleeding
- Muscular Atrophy
- High Fever
- Severe Diarrhea
- Depression






12 patients with scurvy of similar severity
on the same ship (HMS Salisbury) with the same diet
2 Patients each
25 drops of
Elixir Vitriol TID
250ml
Cyder
250ml
Sea Water
30ml Vinegar TID
2 Oranges
1 Lemon
Spice paste
‚Beer‘
James Lind
1716 - 1794

Evidence

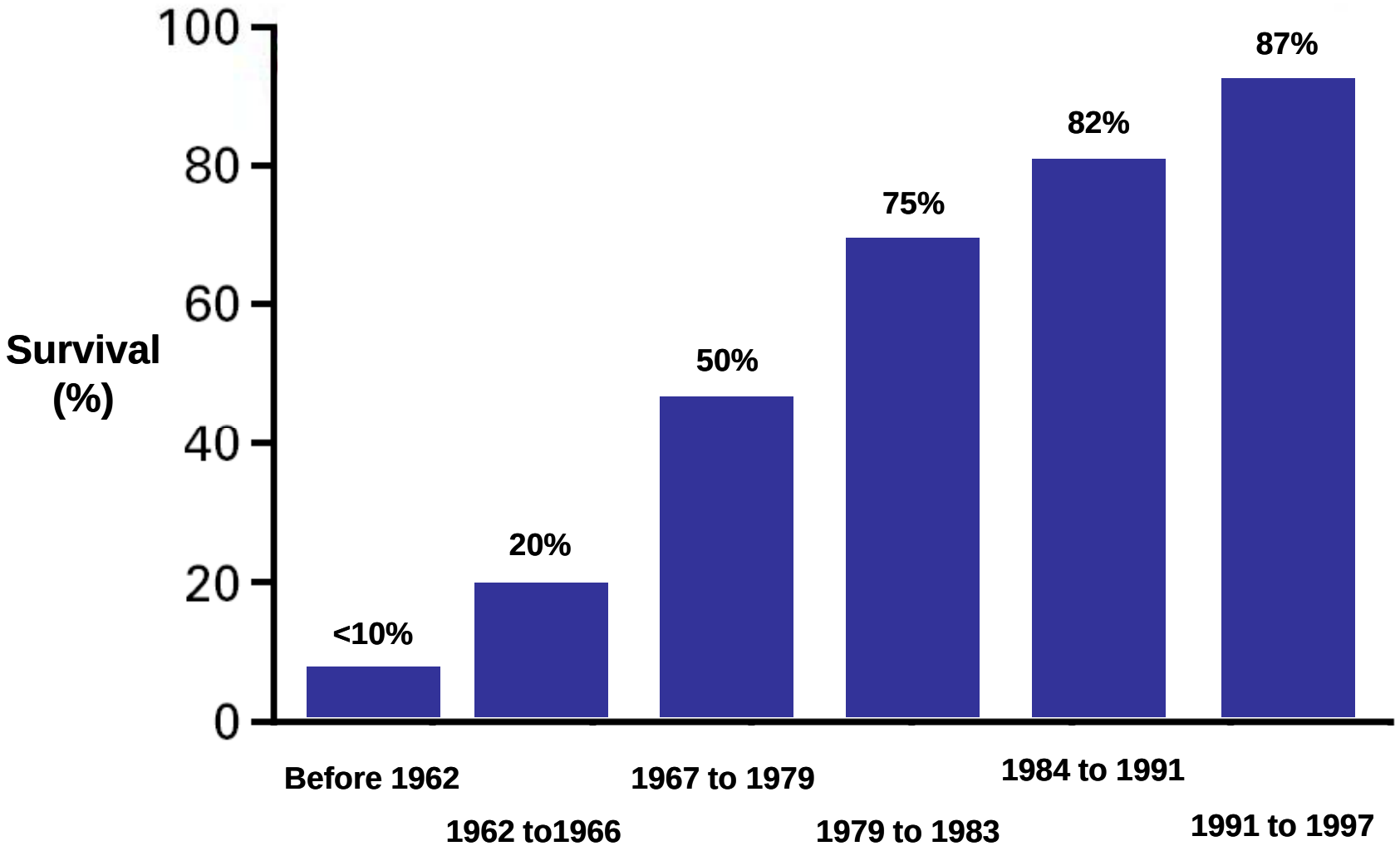
or the rational basis for clinical trials…

Levels of Evidence

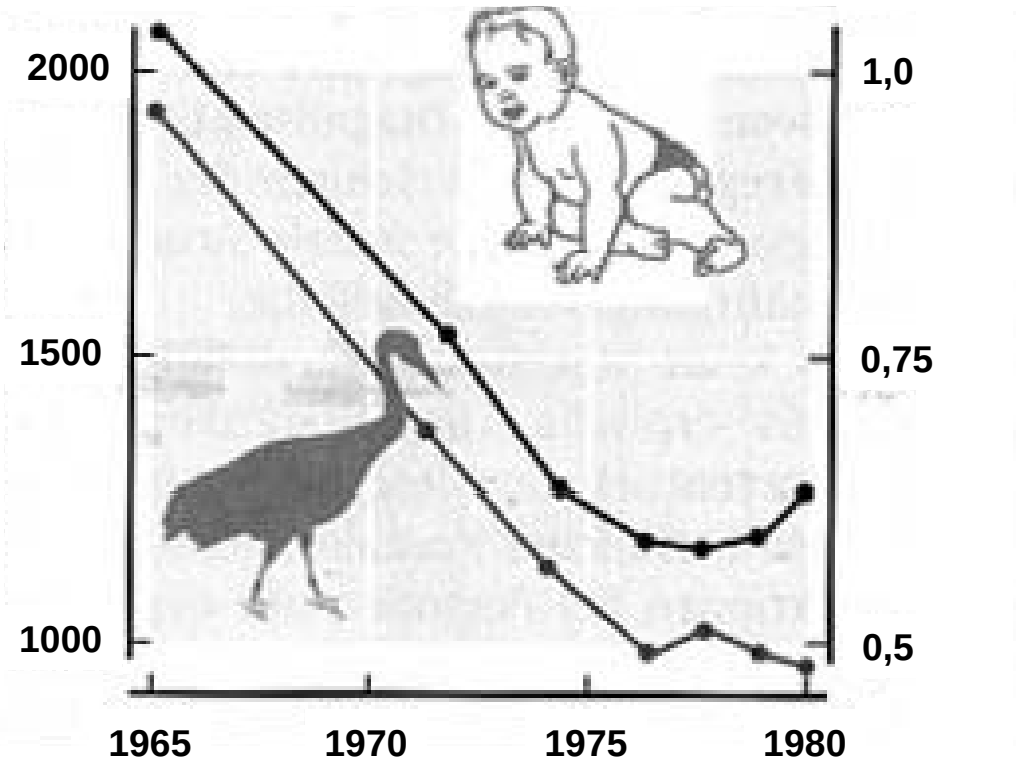
1a	Systematic reviews of randomized controlled trials
1b	Individual randomized controlled trials
1c	All or none randomized controlled trials
2a	Systematic reviews of cohort studies
2b	Individual cohort study or low quality randomized controlled trials
2c	'Outcomes' Research; ecological studies
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Do we need clinical studies in pediatric SCT?

Survival rates of children with acute lymphatic leukemia from 1960 until today



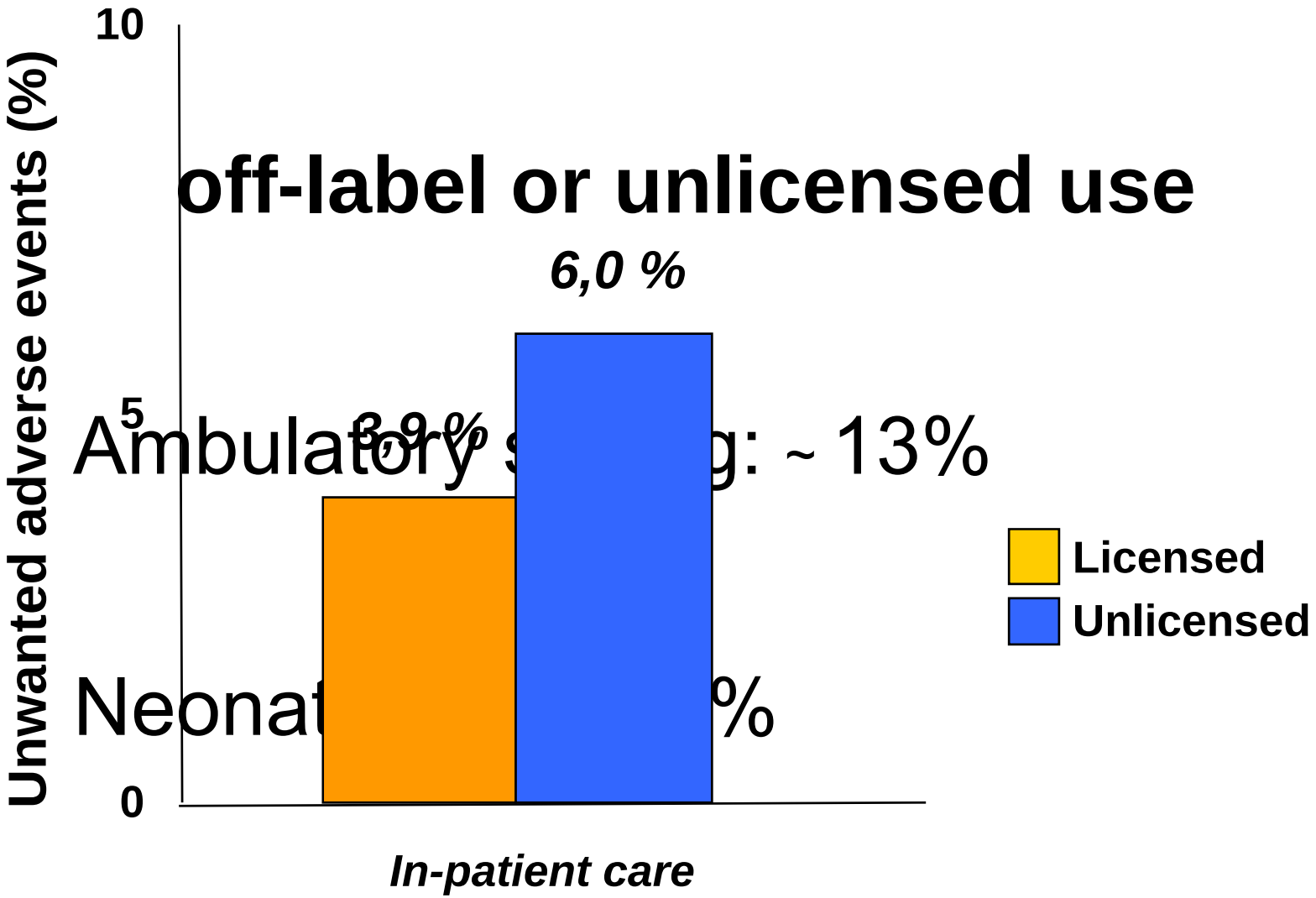
But not every study is a good study...



Korrelation between the decline of breeding storchs and the reduction in birth rate in Germany between 1965 - 1980

The Conroy Study, 1998

- paediatric units of five hospitals in European countries
- 2262 prescriptions for 624 minors
- 46% of the prescriptions were "off label" or "off license"
- 67% of the minor patients were treated without proper evidence of dosage, tolerability and efficacy



Conroy et al, 1998

Why are there so few licensed drugs, pharmaceutical or clinical trials in children?

The ethical dilemma with research in children

The Belmont Principles

Ethical Principles and Guidelines for the Protection of Human in Research

Published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

They provide the philosophical underpinnings for current federal laws that govern research involving human subjects.

1. Beneficence

1. do not harm
2. maximize possible benefits
3. minimize possible harms

2. Justice

- Researchers must be careful not to select already burdened or vulnerable groups who might be more easily coerced to participate.

3. Respect for persons

- Researchers must recognize that individual's judgments and choices about participating in the research must be respected.

- For those not capable of deciding for themselves … are vulnerable subjects (e.g., children,…)

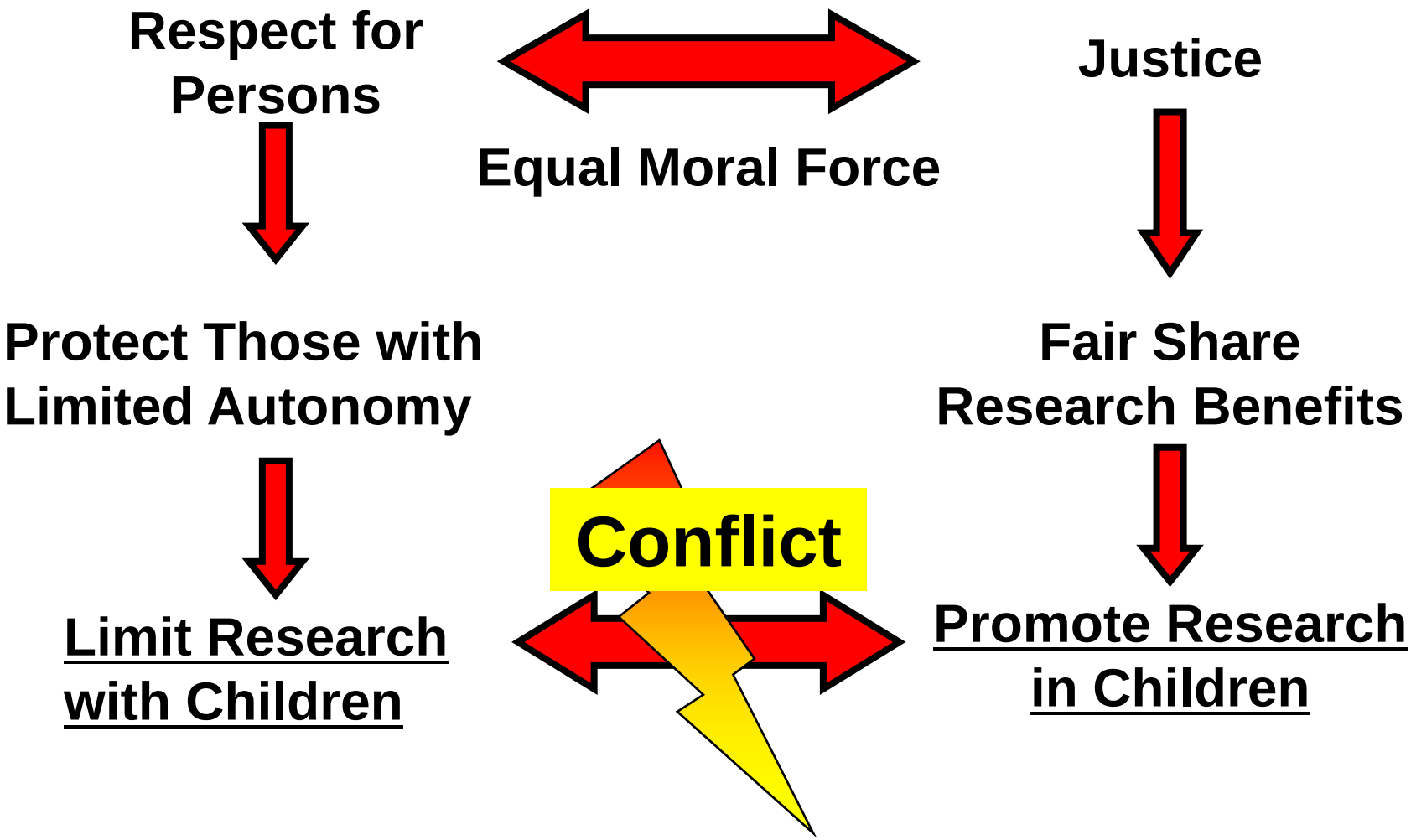
→ Subjects or their legal representative must sign an informed consent form detailing the research to be done, the potential risks and benefits, and anything else that might influence their decision to participate.

Consent in pediatric research

- Parents cannot give true "consent" – legally only an autonomous person can do that for themselves. But parents can and should be respected in their role as responsible for the child's welfare (*Parental permission required*)

- Children cannot give true "consent" – they may not have the legal or cognitive ability to make this decision. But this does not mean they should have no say regarding participation (*Child assent required*)

Conflict in Belmont Principles?



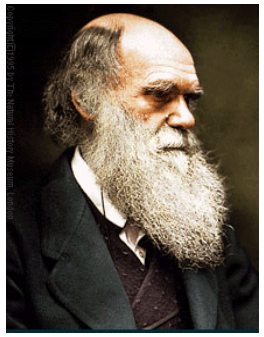
Levels of control to protect the patient

§

National laws, ‚Declaration of Helsinki‘,

GCP (Good Clinical Practice)

Sponsor



Principal Investigator

Ethics, IRB, Authorities

Physician Patient

What is the position of the pharmaceutical industry?

Most Common Causes of Death

- Ages 1-14
  1. *Accidents*
  2. ***Cancer***
  3. *Birth Defects*
  4. *Infections*

Ages 15-34

- *Males*
  1. Accidents
  2. Homicide
  3. Suicide
  4. **Cancer**

- *Females*
  1. Accidents
  2. **Cancer**
  3. Homicide
  4. Suicide

Cancer Occurrence in Children

- **1/300** children will be diagnosed with cancer by 20 yo
- 12,000-13,000 new cases of cancer in children less than age 20 in the U.S. each year
  - vs. 1,368,030 total adults in U.S. 2004
  - vs. 215,990 breast cancer in U.S. in 2004
  - vs. 15,190 breast cancer in NY in 2004

Jemal et. Al. Cancer Statistics, 2004. CA Cancer J Clin 2004; 54;8-29.

Drug Development and Approval Process in the 1990s

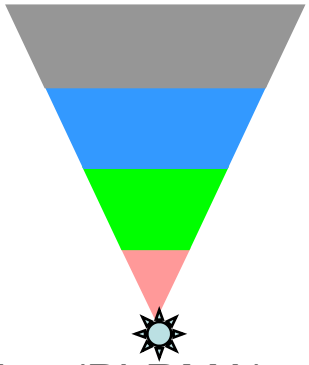
	Preclinical Testing		Clinical Trials			Post Clinical Trials		Total Years for Approval
	Step 1	*Step 2*	*Step 3*	*Step 4*	*Step 5*	*Step 6*	*Step 7*	
	Lab / Preclinical	File IND application	Phase 1	Phase 2	Phase 3	File NDA	FDA Appro.	
PURPOSE	Safety and bio activity in the lab and animal models	FDA approval to begin clinical testing in humans	What dosage is safe, how Rx should be given	Effect and side effects	Is the Rx better than current standard	Inform the FDA of Phase 3 data	Review process	
TIME (average number of years)								
ALL ANTI-CANCER DRUGS	**4.4**		**8.6**			**1.4**		**14.4**
ALL DRUGS*	**3.8**		**10.4**			**1.5**		**15.7**

DiMasi, J.A. (2001). New drug development in the United States 1963-1999. Clinical Pharmacology and Therapeutics May; 69(5); Tufts Center for the Study of Drugs Development, Tufts University; adapted from Pharmaceutical Research and Manufacturers of America.

Rare success

- 5/5000 compounds that enter preclinical testing make it to human testing
- 1/5 of drugs that enter clinical trials are approved

Total 1/5000 new compounds are approved



Pharmaceutical Research and Manufacturers of America (PhRMA), Pharmaceutical Industry Profile 2004, Washington DC, PhRMA, 2004

Average Research & Development Cost to Bring One Drug to Market

$802 Million !

[Six-fold increase between 1975-2000!!!]

DiMasi JA, Hansen RW, Grabowski HG. "The Price of Innovation: New Estimates of Drug Development Costs," *Journal of Health Economics*, 22, 151-185 (2003)

FDA Approval of Cancer Therapies
1948-January 2003

- 120 cancer therapies
- 30 are useful for children
- 15 labeled for pediatric use
  - Often with limited information
- Since 1980, 2 drugs labeled for use in pediatrics (vs. >50 drugs for adults):
  - Teniposide (BMS) – 1980 refractory ALL
  - Clofarabine (Ilex/Genzyme) –2004 refractory ALL

Patient Access to New Therapeutic Agents for Pediatric Cancer: Report to Congress. December 2003. Dept. of Health and Human Services U.S. FDA.

Fifteen Oncology Drugs Approved for Pediatric Use With Pediatric Dosing Information in the Label

L-Asparaginase	Leukemias
Cyclophosphamide	Leukemias, lymphomas, neuroblastoma, retinoblastoma
Cytarabine	Acute nonlymphocytic leukemia in adults and children
Dactinomycin	Wilm's tumor, rhabdomyosarcoma, choriocarcinoma, testicular carcinoma, Ewing's sarcoma, sarcoma botyroides
Daunorubicin	Acute lymphocytic leukemia in adults and children
Doxorubicin	Wilm's tumor, neuroblastoma, soft tissue sarcomas, Hodgkin's disease, other malignant lymphomas, acute lymphocytic leukemia, acute myelogenous leukemia
Lomustine	Brain tumors, Hodgkin's lymphoma
Mercaptopurine	Acute lymphocytic leukemia in adults and children
Methotrexate	Acute lymphocytic leukemia, meningeal leukemia, osteosarcoma, NH lymphomas
Procarbazine	Hodgkin's lymphoma
Thioguanine	Acute Non-lymphocytic leukemia
Teniposide	Refractory childhood acute lymphocytic leukemia
Tretinoin	Acute promyelocytic leukemia
Vinblastine	Histiocytoses, testicular germ cell carcinomas, Hodgkin's lymphoma
Vincristine	Acute leukemias, lymphomas, Wilm's tumor, rhabdomyosarcoma, neuroblastoma

Hirschfeld S., et. al. 2003. *JCO* 21: 1066-1073

Why?

1. Kids don't vote

NCI's total budget for fiscal year 2003
$4.6 billion

Amount spent on ALL pediatric cancer
$160 million

Cancer Research Funding. www.cancer.gov

2. Kids are not profitable

Why put $810 million to develop a drug for 425 children/year with rhabdomyosarcoma, when the same money can go into developing a drug for 215,990 adults/year with breast cancer?

(or millions of men with erectile dysfunction)

The need for evidence in pediatrics was long neglected by politicians and the pharmaceutical industry.

Harry Shirkey, 1968: ‘therapeutic orphans’

in order to highlight the extent to which children are neglected

Orphan drug

An orphan drug is any drug for the treatment of rare diseases (‘orphan diseases’), defined as diseases affecting fewer than **1 in 2000** people in the community.

The reason:

Medical research and development of drugs to treat such diseases is financially disadvantageous

The benefit:

Tax reductions and marketing exclusivity (a "monopoly") on that drug for an extended time

In 2003, the leading orphan drug by worldwide sales revenue was?

Erythropoietin (Epogen®), with sales of $2.4 billion…

It can be quite advantagous to be an orphan

The problem is recognized…

Important steps towards proper clinical studies in pediatrics

1979	Pediatric use	2000	Orphan Drug
1983	Orphan Drug Act	2000	Pediatric Council Resolution
1991	Pediatric Page	2001	Clinical Investigation in the pediatric population
1994	Pediatric Plan	2001	EU-Directive 2001/20/EG
1997	Modernization Act	2004	EU-Decree on medicinal products for pediatric use
2000	Final rule	2006	Draft guidance on ‘specific modalities for non-commercial trials
2003	Pediatric Research Equity Act	2007	Implementation of this decree (01/26/2007)

Consequence: 691 ped. studies in 43.000 children until 2004 in the US

EU-Directive 2001/20/EG

The intention:

– simplify and streamline administration

– raise the quality of clinical trials

The implementation:

All clinical trials must be **GCP** conform

The **same standards** of conduct on non-pharmaceutical or so called **'investigator initiated' trials** (IIT) previously only required for **pharmaceutical**, mostly licensing, trials.

Good clinical practice (GCP)

*"GCP is an international ethical and scientific quality standard for **designing**, **conducting**, **recording** and **reporting** trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the **rights**, **safety** and **well-being** of trial subjects are protected, consistent with the principles that have their origin in the **Declaration of Helsinki**, and that the clinical data are **credible**…."*

The Consequence:

- New legal responsibilities (sponsorship)
- Administration
- Data monitoring
- Safety (AE/SAE reporting)
- Auditing
- etc….

Our Problem:

Children are an economically irrelevant minority burdened with more risks than benefits

EU-Decree on medicinal products for pediatric use (01/26/2007)

This regulation is the most serious attempt to facilitate the development and accessibility of medicinal products for the use in children in Europe. It specifies requirements to protect children participating in clinical trials.

It is comparable to the US regulation “Pediatric Research Equity Act“ adopted in 2003 that eventually had a significant impact on clinical trials in the US over the following years.

Data quality

A high recruitment rate but poor data quality in the end will diminish the power of the study or can even invalidate it.

Stringency

Data gathering

Data Monitoring

Data monitoring

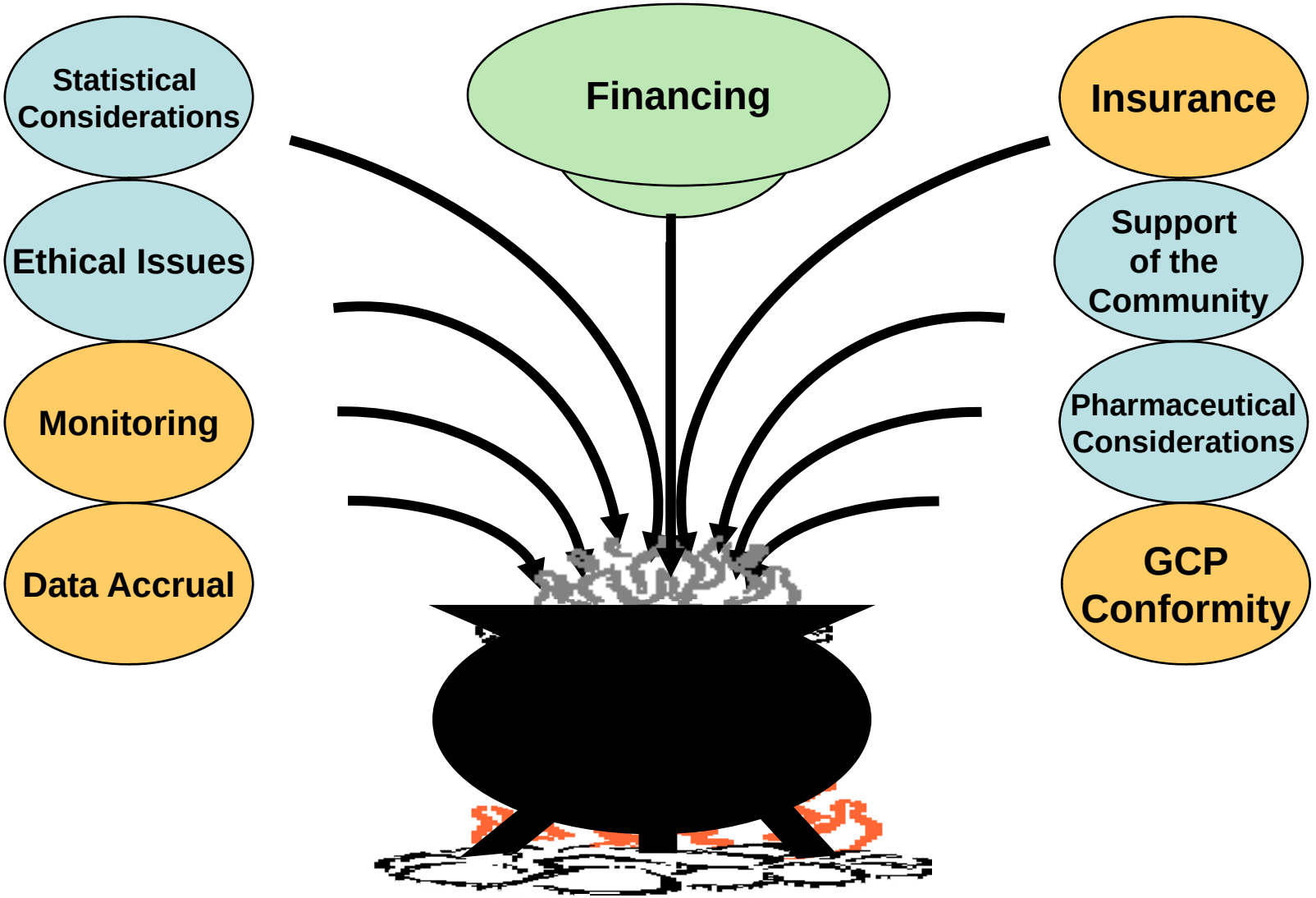
Sponsor responsibilities, Section 5.18

- **Communication** between the sponsor and the investigator
- Verifying qualifications and **resources** of the investigator
- Verifying that the investigator **follows** the approved protocol
- Verifying that written informed **consent** was obtained
- Ensuring that the investigator/investigator's trial staff are adequately **informed** about the trial
- Verifying that the investigator is enrolling only **eligible** subjects
- Verifying that documents and trial records are **accurate, complete**, …
- Checking the **accuracy and completeness** of the CRF entries, …
- Determining whether all **adverse events** (AEs) are appropriately reported
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations

How to design a new study? Basic questions

- Interest, priority?
- What kind of a clinical trial? (Phase I, II, III, IV)
- Statistical considerations? (Incidence & sample size)
- Study design? (Randomized, blinded and placebo controlled, open label, single arm, cohort or observational, etc)
- What is the time frame?
- Regulatory considerations?
- Practicability and accessibility?
- Sponsors and financial resources?

Ingredients of a GCP-conform study



What for and how much money ??

- GCP conform protocol design
- Regulatory Submissions
- Data Management
- Electronic case report forms
- Audit / Monitoring
- Insurance
- Initiation-meetings
- Investigator-meetings
- Advisory board and meetings
- DSMB boards and meetings
- IBR Board meetings
- Statistical analysis
- Drug supply / shipment cost
- Pharmacy fee
- Laboratory fee
- Per patient fee
- Research nurse
- Administrative overheads

€ 300'000 > € 1'000'000+

Issues and difficulties with pediatric studies in stem cell transplantation

- Few pediatric HSCT per centre

  Consequence:

  large multi-centre studies are obligatory

- Financing (lack interest of the pharmaceutical industry, overwhelmed grant givers)
- Lack of ‘study culture’ (according to GCP regulations)
- ‘Ethical difficulties’ with pediatric studies

Our problem

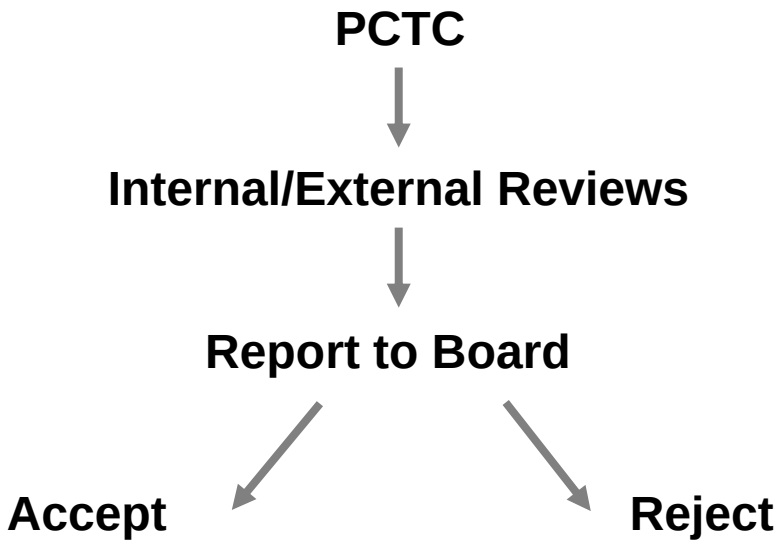
- There were **18620** stem cell transplantations in 2004 registered with the EBMT
- **2515 (13.5%) registered** patients were under 18 years
- There are currently **~20** official EBMT studies, only **one** is in children
- Scientific advancement and clinical rational is often based on mostly retrospective small sample size, observational 'studies'

Conclusion:

Pediatric studies are underrepresented within the EBMT

Prospective Clinical Trials Committee

- **Support protocol development**
- **Oversight of review process**



Roles of the Working Party

Develops protocol in accordance with scientific strategy

Study concept

↓

Presentation to WP

↓

Draft protocol
Rational, Objectives, Eligibility Criteria
Study Design, Statistics, Data Collection

↓

Submission to Prospective Clinical Trials Committee

The aim
Increase the number of pediatric EBMT studies

Possible solution:
‘Pediatric subcommittee’

Basic know-how and ‘step-by-step’ guidance for future PIs

- **Provide basic ‘equipment’**

  in order to

  – **Avoid decoys and frustration**
  – **Shorten the duration between conception and launch**

Possible Proceedings

6 to 8 months

12 to 18 months

Who should be represented in this ‘Subcommittee’ and what are their tasks?

- EBMT/PCTC
- Statistician(s)
- Advisor for ethical issues
- Pharmacist (if needed for particular study questions)
- Board of clinicians of the ‘pediatric’ Working **parties**

Major prerequisites

- Certified GCP-conform database structure quickly available, easy and uniform
- Financing models
  (Grants, industry, EBMT, Institution)
- Monitoring structure?
- Modern statistical designs

Adaptive study designs: “adaptive” if statistical methodology allows the modification of a design element at an interim analysis like:

- sample-size
- randomisation ratio
- number of treatment arms
- et al

“difficult experimental situations” **:**

- small populations
- orphan diseases with constraints to the maximum amount of evidence that can be provided
- ethical constraints to experimentation
- *et al*