Investigator & other Trial Stakeholder Training Course

Essence of GCP & Research Ethics

Learning Objectives

- **Describe principles & scope of Ethics & GCP**
- **Describe definitions & historical background**

Ethics Question #1

- Orphan children were used for the development and production of a vaccine
- The vaccine doses were then brought to and used in another part of the world

Comments

Ethics Question #2

- Prisoners were involved in research that was likely to cause stress and a high risk of bodily damage
- Prisoners were not given a choice to refuse participation

Comments

Ethics Question #3

- An observational study was conducted in a population suffering from a debilatating disease.
- At the study start, no effective treatment was available. Three years after study start, effective treatment was discovered
- This study was continued without making the new treatment available or informing the participants about the new therapy.

Comments

Balmis Expedition

- Francisco Javier Balmis (18th century)
- He infected orphan children with smallpox; took the fluid from the lesions and inoculated it into another child for immunization.
- He brought 22 orphan children along to Puerto Rico, Mexico, Venezuela and Philipine.
- 100,000 and half a million people have been immunized.

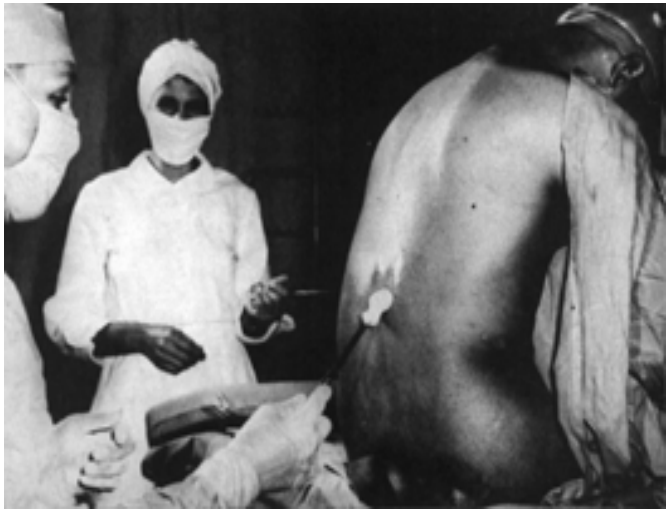
1939-1945: World War II

- "Medical" Experiments on Holocaust Victims & Prisoners of War
- No consent
- Subjects not killed by experiments would be killed and dissected
- 1947: Doctor's trial at Nuremberg

1932-1972: Tuskegee Syphilis Study

- US Public Health Service funded a study to evaluate the natural history of untreated syphilis
- 399 uneducated black men with syphilis were included

No medicine is offered once Penicillin becomes available…

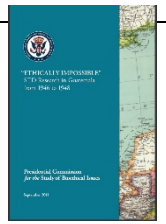


A brief look at history

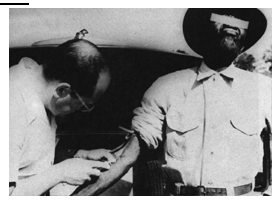
Sulfanilamide
1938

WWII
1939-1945

Thalidomide
1956-1962

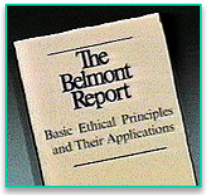


Guatemala
1946-1948



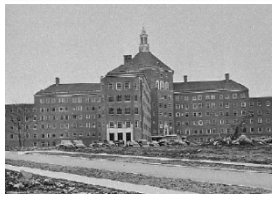
Tuskegee
1932-1972

Nuremberg
Code
1947



Belmont
Report
1979

Willowbrook
1963-1966



Jewish Hospital
1963

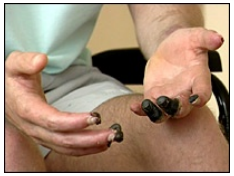
Trovan
1996

Pfizer

Asthma study
2001

JOHNS HOPKINS
MEDICINE

TGN1412
2006



World Health Organization

TDR For research on diseases of poverty
UNICEF • UNDP • World Bank • WHO

WS
QMS

And the Guidelines

- 1947 The Nuremberg (Nürnberg) Code
- 1948 Declaration of Human Rights (UN)
- 1964 Declaration of Helsinki (WMA), amended 64th WMA General Assembly, Fortaleza, Brazil, October 2013
- 1979 The Belmont Report
- 1981 Patient information & informed consent
- 1990 ICH (Safety, Quality & Efficacy)
- 1992 CIOMS (Council of International Organizations of medical Sciences) Guidelines for Biomedical Research
- 1993 WHO International Ethical Guidelines for Biomedical Research Involving Human Subjects.

Declaration of Helsinki

Provides guidance for research on humans, their material and/or data:

- Safeguarding research participants
- Benefits > risks
- Vulnerable groups
- Research protocols
- Ethics committees
- Privacy and confidentiality
- Informed consent
- Use of placebos
- Post-trial access to treatment
- Publishing findings and registering research
- Unproven interventions

Case Study #1

- A patient participated in a drug trial for severe Rheumatoid Arthritis for 2 years.
- The study has ended and the patient has a marked improvement of his condition.
- However, at the end of the trial, he could not afford paying himself for the treatment

What are the challenges of giving the new treatment to this patient?

Belmont Report

Autonomy

- Respect for persons
- The right for an individual to make his or her own choice
  - Protection of persons with impaired or diminished autonomy, i.e. vulnerable groups
    - Informed consent
    - Privacy and confidentiality
    - Right to withdrawal

Beneficence/Non-maleficence

An obligation to secure the well being of the research subjects, maximise benefits and minimise harms

- Do no harm
  - Sound research design
  - Competent investigators
  - Favourable risk benefit ratio

Defining risk and benefits

- Risk refers both to the probability of a harm resulting from an activity and to its magnitude.
- "Risk" stands for the combined probabilities and magnitude of several potential harms.
- Benefit refers to any favourable outcome of the research to the individual or to society
- "Benefit" stands for the combined probabilities and magnitudes of several possible favorable outcomes

Identifying Risks & Benefits

- Physical
  - Bodily harm
  - Simple inconvenience
- Psychological
  - Emotional suffering
  - Breach of confidentiality
- Social /cultural
  - Discrimination
  - Stigmatization
- Economic risks
  - Financial costs
- Legal - Abuse/ Violence

- Physical benefits
  - Improvement of disease
- Psychological benefits
  - Feeling of well being; relief from suffering
- Economic benefits
  - Employment
- Benefit to science/society
  - Effective interventions
  - Change in practice standards decreasing morbidity and mortality

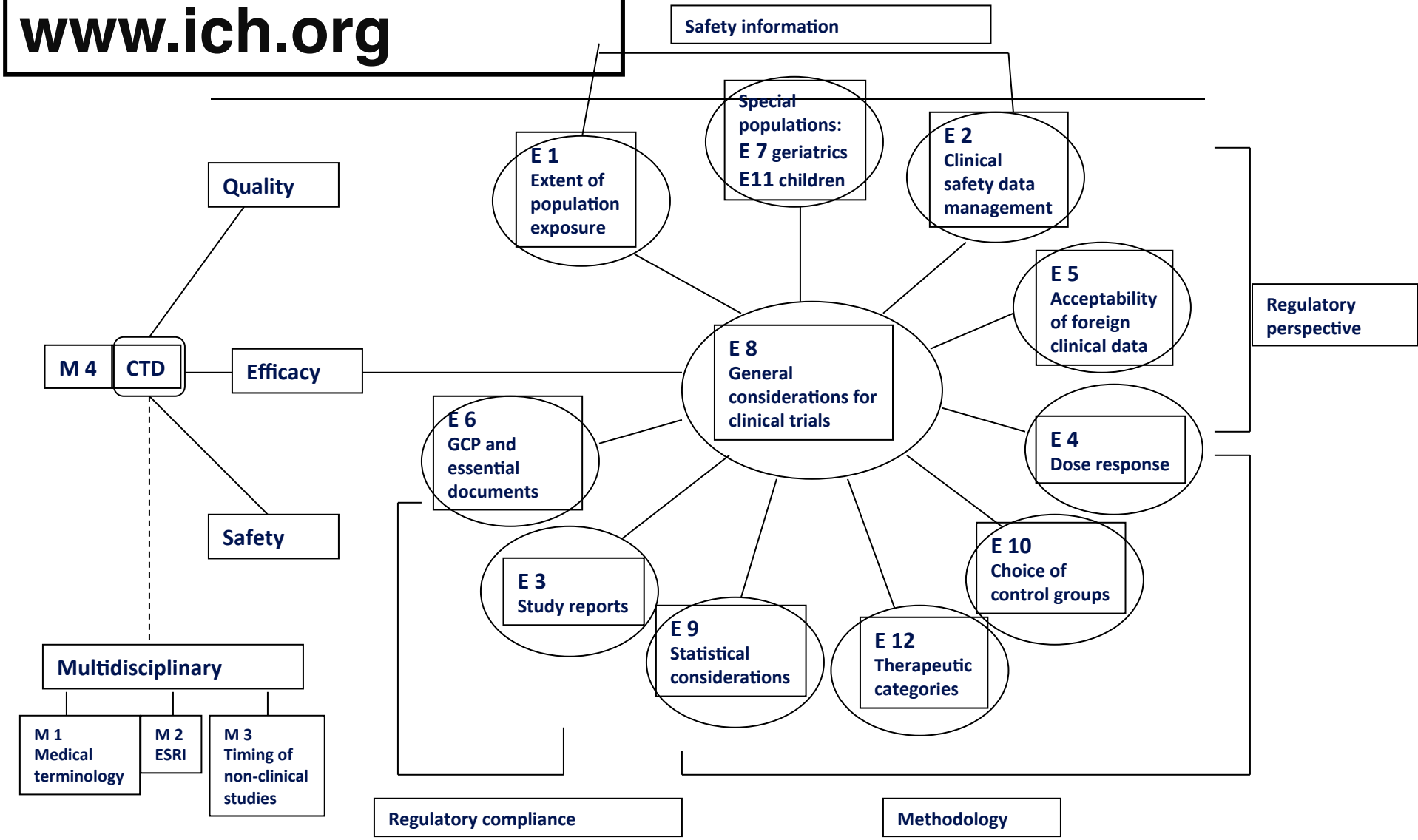
Justice

- To treat each person according to what is morally right and proper
- Equitable distribution of both burdens and benefits of the research
  - Fair subject selection
  - Research be responsive to the health needs of population studied
  - Product developed made reasonably available

Clinical Trial Regulation

- 1931 Food & Drug Administration (US-FDA)
- 1980 Various Clinical Trial & GCP guidelines
- 1989 Japanese GCP law
- 1989 French Loi Huriet
- 1991 European Union - GCP guideline
- 1994 WHO - GCP guideline
- 1997 ICH E6 GCP Guidelines (coming into effect)
- 1998 GCP China Guidelines
- **National Regulation?**

ICH GUIDELINES
www.ich.org



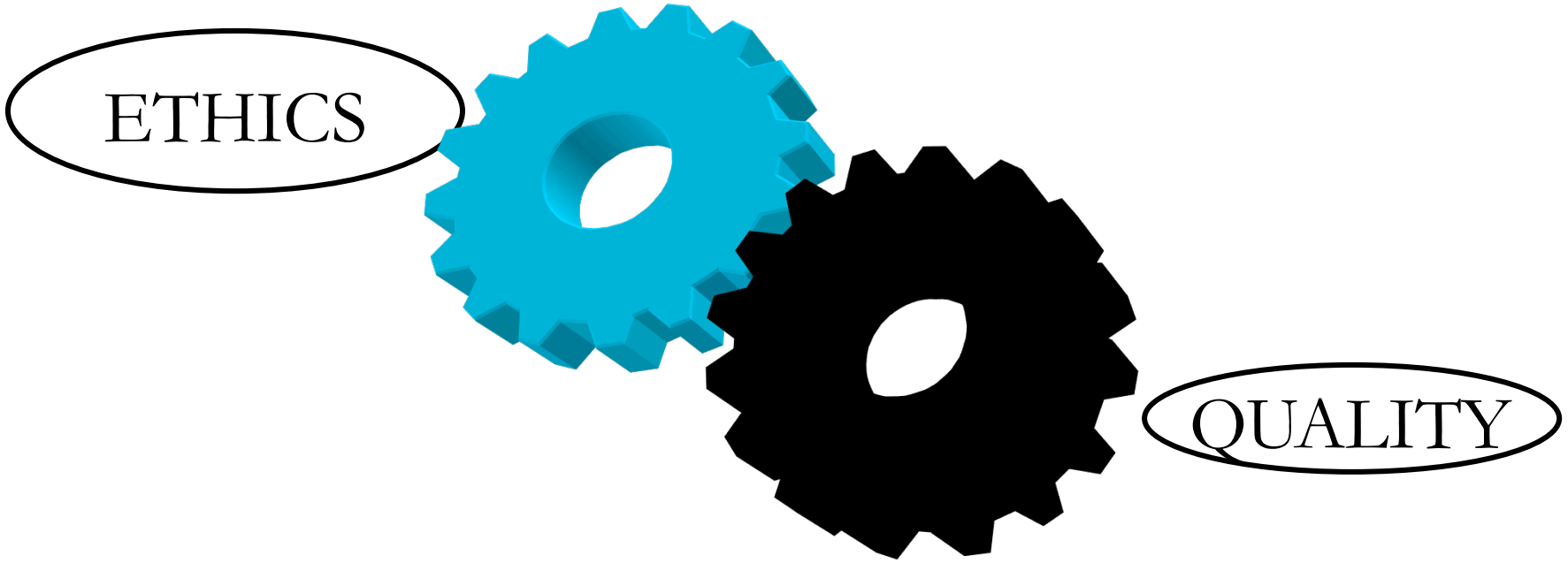
Good Clinical Practice

An international ethical and scientific quality standard for

Designing
Conducting
Recording
Reporting

Trials that involve participation of human subjects

Basic Principles of GCP



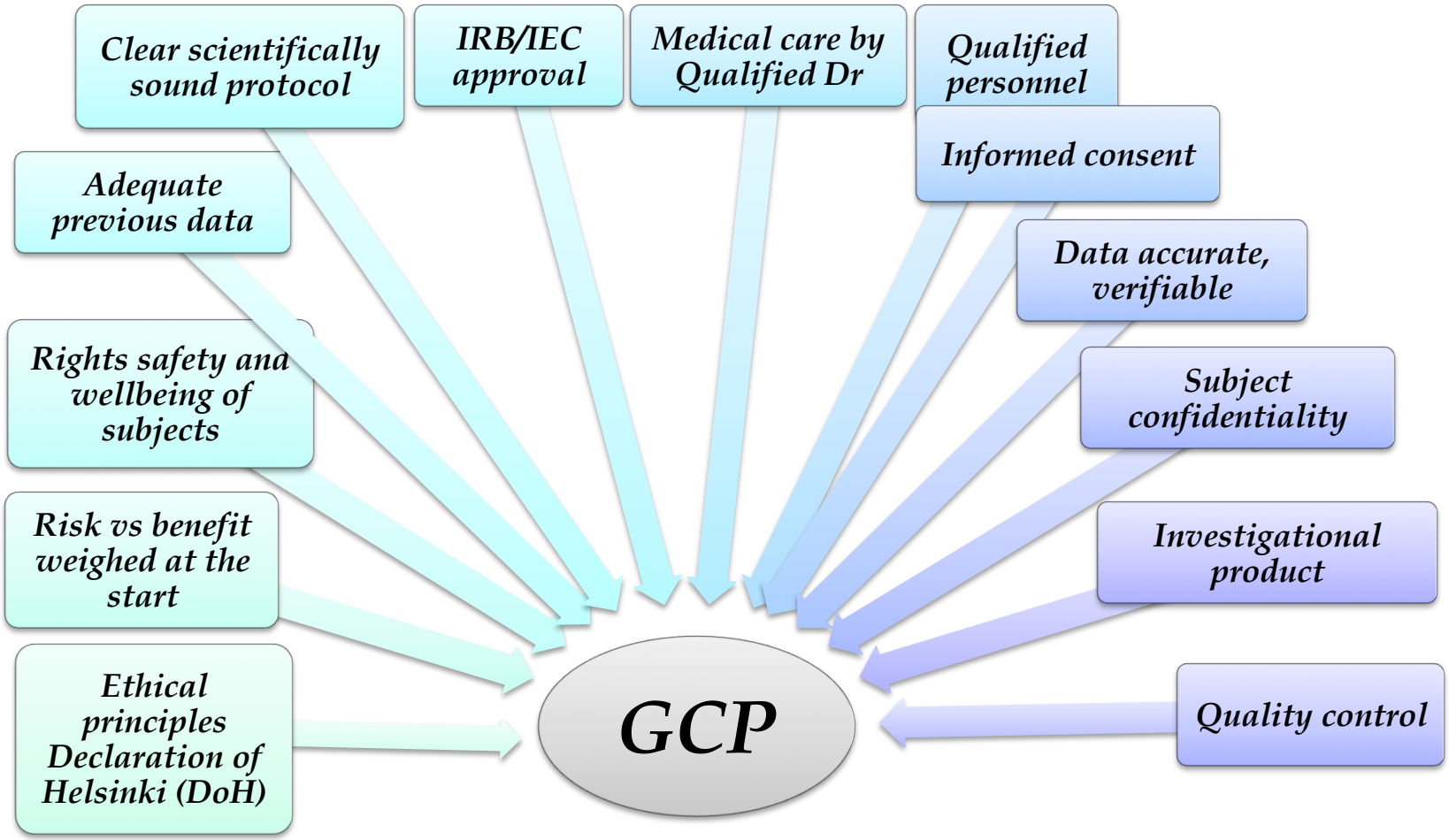
Protection of rights, safety, well-being of trial participants

Credible Clinical Trial Data

When does GCP apply?

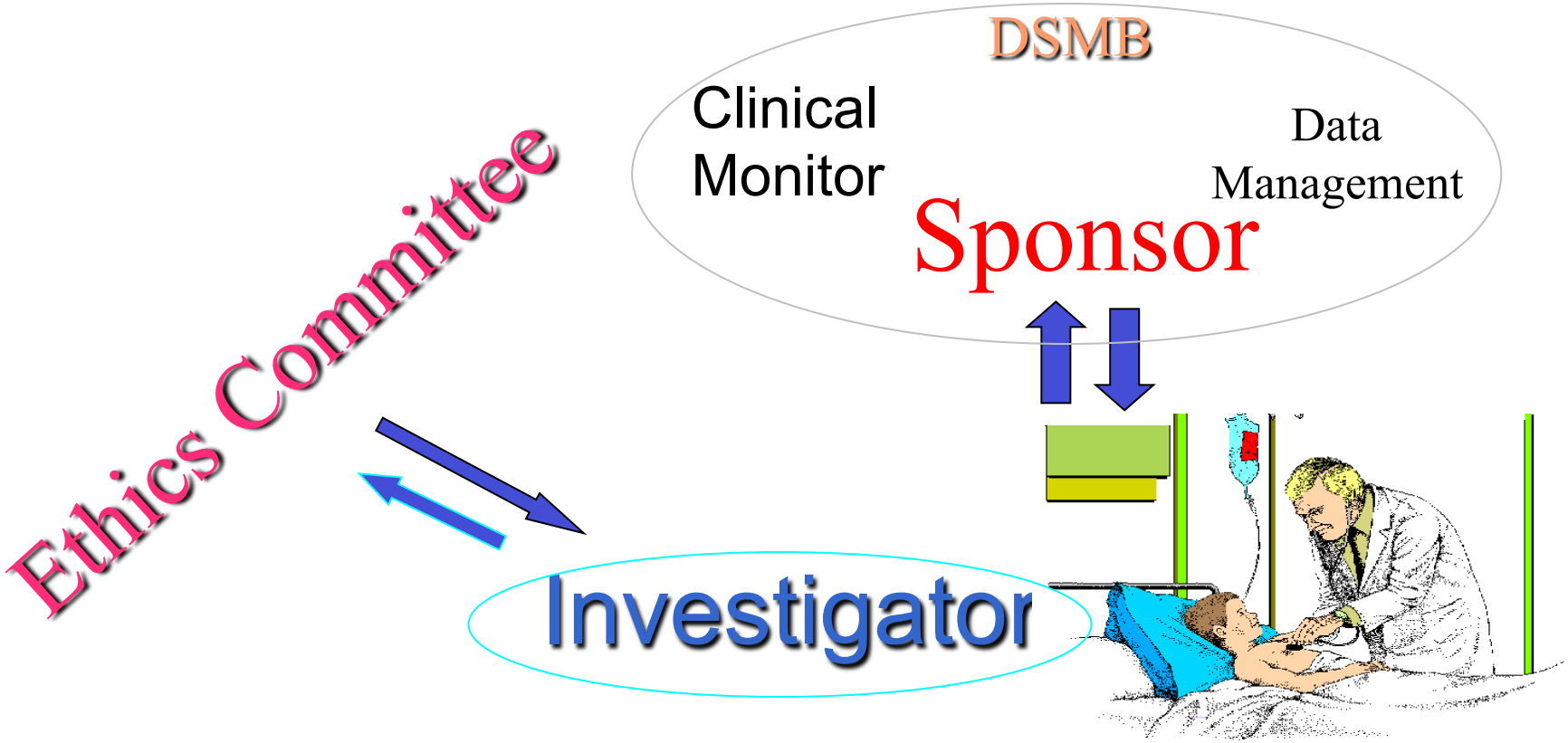
- **ALWAYS!** Basic principles of Ethics and Quality are to be applied to any research that may have an impact on the safety, well-being and rights of human subjects.
- **CRITICAL**, when generating clinical trial data that are intended to be submitted to regulatory authorities or data to be published.

GCP Principles



Who are the Stakeholders in a clinical Trial?

Stakeholders of GCP



DSMB = Data Safety Monitoring Board

Do the Trial Participants have Responsibilities?

- Willingness to participate in the trial
- Follow the instructions of the investigator so protocol provisions are met
- Inform the investigator when they feel unwell or experience other problems: safety-related, trial / study-related procedures or others

Questions or Comments?

THANK YOU