COMPREHENSIVE CANCER CENTER VIENNA

EINE EINRICHTUNG VON MEDUNI WIEN UND AKH WIEN

CECOG

Central European Cooperative Oncology Group

Principles of Clinical Trials: From phase 1 – phase 3

Thomas Brodowicz

SARCOMA

PLATFORM AUSTRIA

S.P.A.

What is a Clinical Trial?

- A Clinical trial tests potential interventions in human volunteers to determine if the intervention represents an advance and should be adopted for general use.

FDA Consumer Magazine September-October, 2003

Clinical Trials Test Research Hypotheses

- The best clinical trials test specific research hypothesis
- A clinical research hypothesis is a carefully formulated assumption, often based on labaratory investigations, developed in order to test its logical consequences
- An example:
- - Inhibiting angiogenesis will result in a better outcome for patients with advanced cancer.

Attributes of a successful trial:

1. Addresses an important question
2. Well designed/conducted
3. Feasible
4. Adequately supported
5. Informs clinical practice
6. Ethical Issues
7. Legal Issues

Is the Trial well designed ?

- Specific aspects of trial design depend on trial phase

- For randomized trials usually divided into:
  - Internal validity
  - External validity

Internal Validity

- Degree to which we can accurately state that the treatment/intervention produced the observed effect

- Need to consider:
  - Selection of endpoints
  - Sample size
  - Stopping rules
  - Statistical analysis
  - Ethical issues

Common threats to internal validity

- Inappropriate endpoint selection and/or reporting, for example
  - Use of RR as primary endpoint in phase III trials
  - Selective reporting of positive endpoints
- Inadequate power
- Improper analyses

External Validity

- The degree to which the results of a trial are likely to hold true in real practice
- Usually most important for phase III trials
- Key determinants include:
  - Eligibility criteria
  - Appropriate control arm

Common threats to external validity

- Too strict eligibility criteria that are not reflective of real patient population
  - Excellent performance status for patients with advanced cancer
- Study compares two experimental treatments

Implications of poor design

- Unethical
- Bad for career

Benefits of good design

- Expedite approval process
- Increase likelihood of funding
- Increase likelihood that your study will have impact on knowledge or clinical care

Is the trial feasible ?

- Before embarking on a trial need to consider whether there are enough patients and resources to complete the trial in a timely fashion:
  - Role of patients
  - Role of referring physicians
  - Clinical trials infrastructure

Are there enough patients to complete the trial ?

- Consider the patient population at your institution:
  - Number of patients seen
  - Prior recruitment record

- If the question is good, but recruitment at your institution may not be feasible, consider involvement of other sites but be aware that there is increased complexity in multi-center studies

What referring physicians think of the trial ?

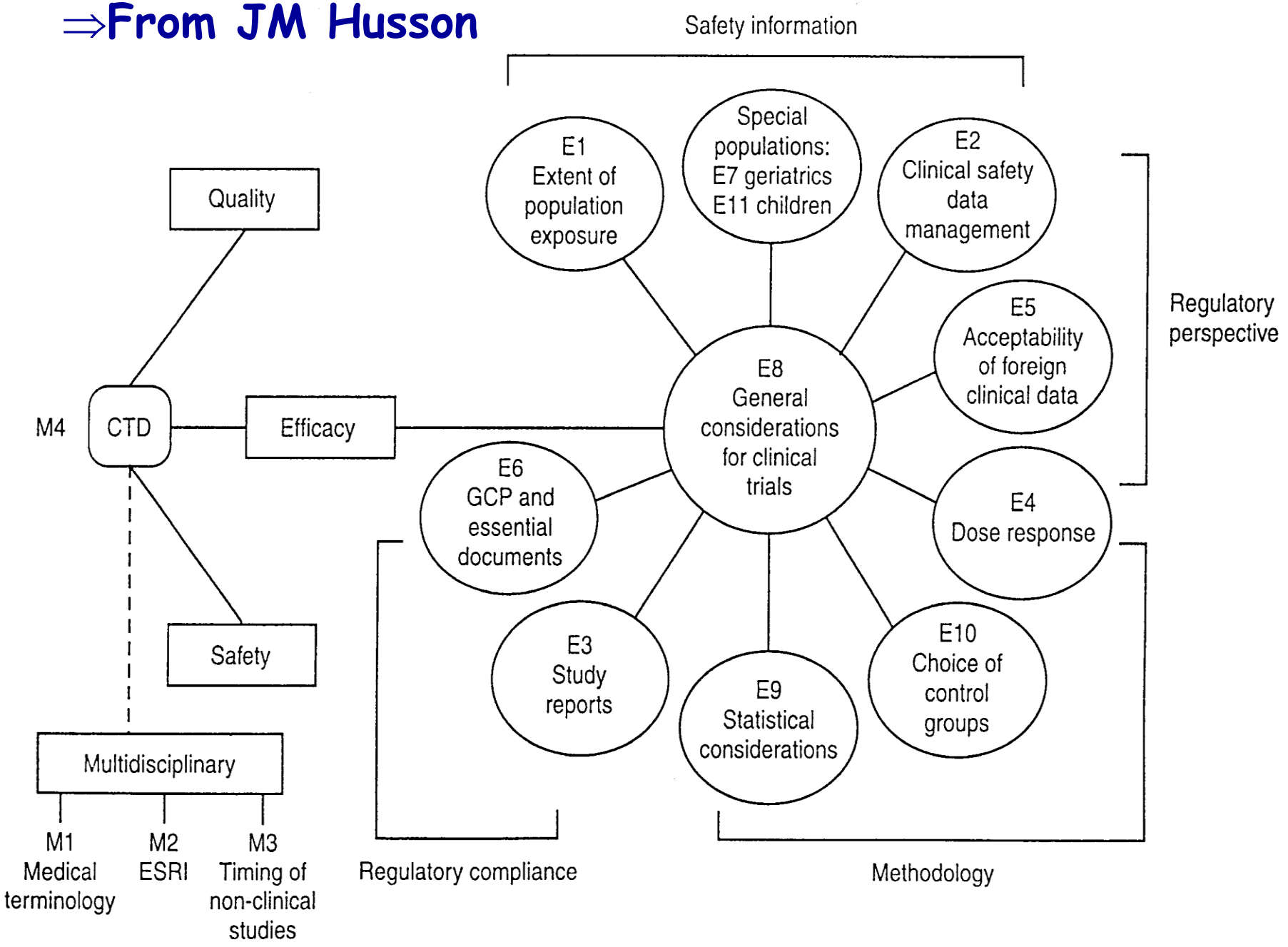
- Deeply entrenched practice patterns even if not substantiated by evidence can be a big barrier to trial accrual

- Therefore, it is essential to understand what are the prevailing preferences of referring physicians for treatment under study

Is there adequate infrastructure to conduct the trial ? cont.

- Funding
  - Essential for hiring clinical trials personnel and to purchase equipment and/or drugs necessary for conducting the trial
- Clinical trials infrastructure
  - Clinical trials nurses/co-coordinators/PI/Sponsor
  - Labs & imaging
  - Data management & analysis
  - Contracts
  - Insurance
  - CRO/CRA
  - SAE/SUSAR-Reporting
  - MOH/EC-Submissions
  - ……..

⇒From JM Husson



Potential funding sources

- Government
- Foundations
- Industry

Potential funding sources cont.

- When deciding where to apply for funding for your trial consider:
  - Trial characteristics (phase, sample size, disease site)
  - Projects previously funded by a given agency
  - Advice from mentors/collaborators

Can the trial inform clinical practice ?

- Yes, but only if its results are communicated !

- Logistic aspects of knowledge translation:
  - Presentation of results
    - » Presentation at conferences
    - » Publication
  - Trial registration

- MAIN ETHICAL & LEGAL ISSUES

Case

- Patients with imatinib-refractory GIST
- Offered participation in RTC of SU11248 versus placebo
  - includes open-label access to drug at time of progression
- "two prestigious medical centers, MD Anderson … & U Michigan …refused to join

Mishra R. Placebos break taboo in cancer drug tests
(Boston Globe, A1, July 4, 2004)

Case (Cont`d)

- “When patients have an advanced cancer & the cancer
- is growing, there isn't any way the placebo can be helpful (to the patient)
- To argue that a placebo trial is in society's interests has nothing to do with helping these patients”

-Assoc. Director, U of Michigan Cancer Center (quoted in R. Mishra,
- Boston Globe, July 4, 2004)

Definition of Clinical Research

- **practice**: "interventions designed solely to enhance the well being of an individual patient or client"

by contrast …

- **research**: "class of activities designed to develop or contribute to generalizable knowledge"

Belmont Report,1979

Clinician – Investigator

- Dual allegiance
  - to study /community
  - to patient /subject

- Creates (legitimate) conflict of interest
- Important to be aware of this tension

Miller et al. JAMA 280:1449

Criteria for Ethical Research

- Social value
- Scientific validity
- Fair subject selection
- Reasonable balance of risks & benefit
- Independent review
- Informed consent
- Respect for enrolled subjects

Emanuel et al. JAMA 283:2701

The Responsibility of Ethical Review

- To researchers
- To patients
- To sponsors
- To regulatory agencies
- To the public

Projection of the trial subject

- Written informed Consent (also for translational research, retrospective studies on data)
- Right to Withdrawal
- Data Protection

Performance of the trial

- Amendment to Protocol
- Management/Reporting of SAE/SUSAR to respective authorities within specific timelines

Investigational Medicinal Products

- Good Manufacturing Practices
- Import Licenses
- Labeling
- Provision

Inspections/Audits

- What ?

  Competent authority/company verifying whether Good Clinical Practice and Good Manufacturing Practice, and national regulations been respected.

Practical advice

- Spend a lot of time thinking about design and feasibility prior to starting
- Identify mentors and collaborators for your research
- Apply for funding
- Look for good clinical trials personnel

Summary

- Successful clinical trials can be extremely rewarding but are time and resource intensive
- It is essential to ensure that a trial addresses an important question, is well-designed and is feasible before recruiting the first patient

Summary cont.

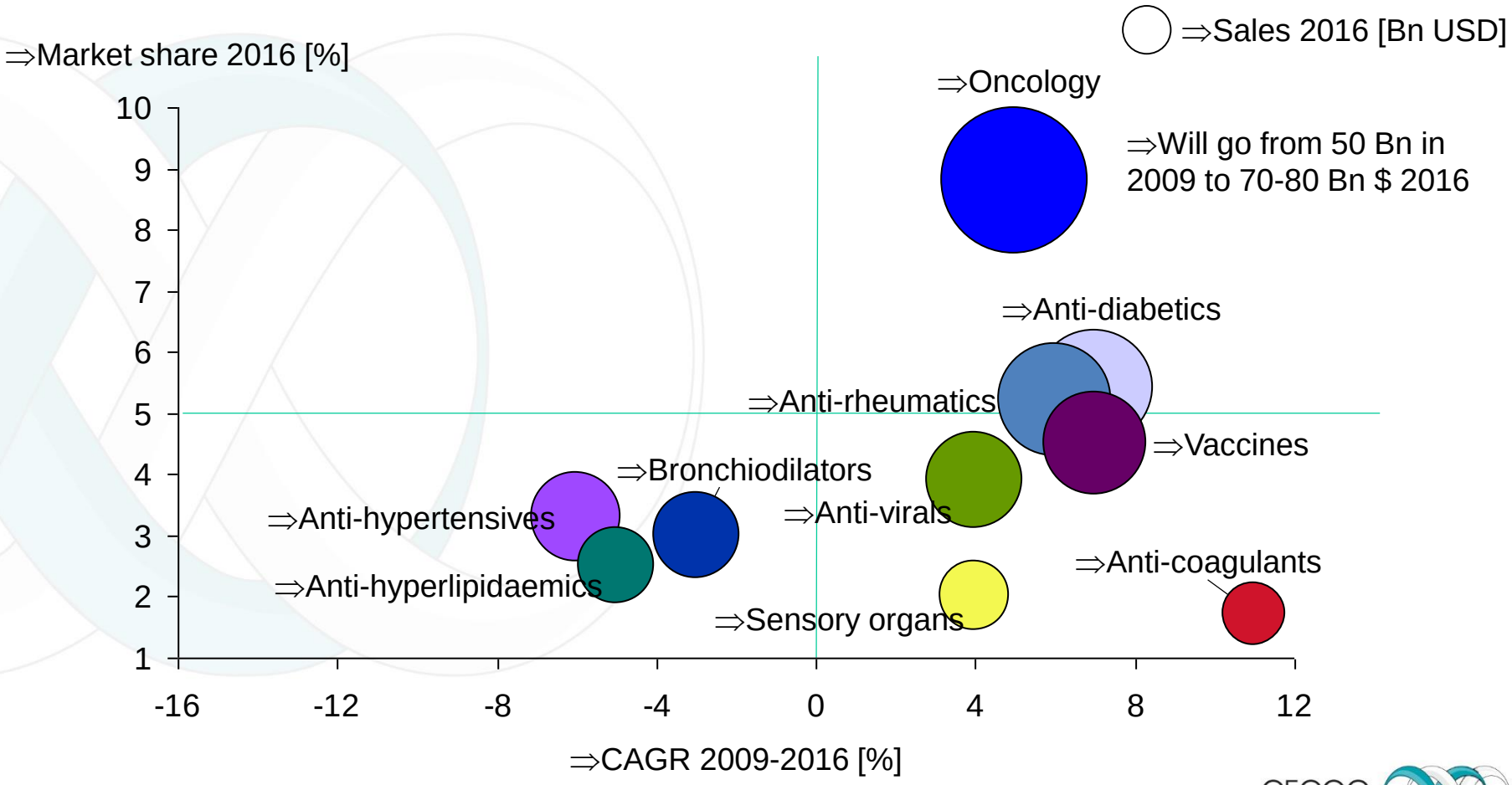
- Funding and the right people are mandatory for a trial to succeed
- Unless its results are published, a clinical trial is likely to have served its purpose
- Clarify and fix infrastructure and logistics in advance

The New York Times
ON THE WEB

THURSDAY, AUGUST 5, 2004

In Drug Research, the Guinea Pigs of Choice Are, Well, Human

Oncology is the largest market in 2016



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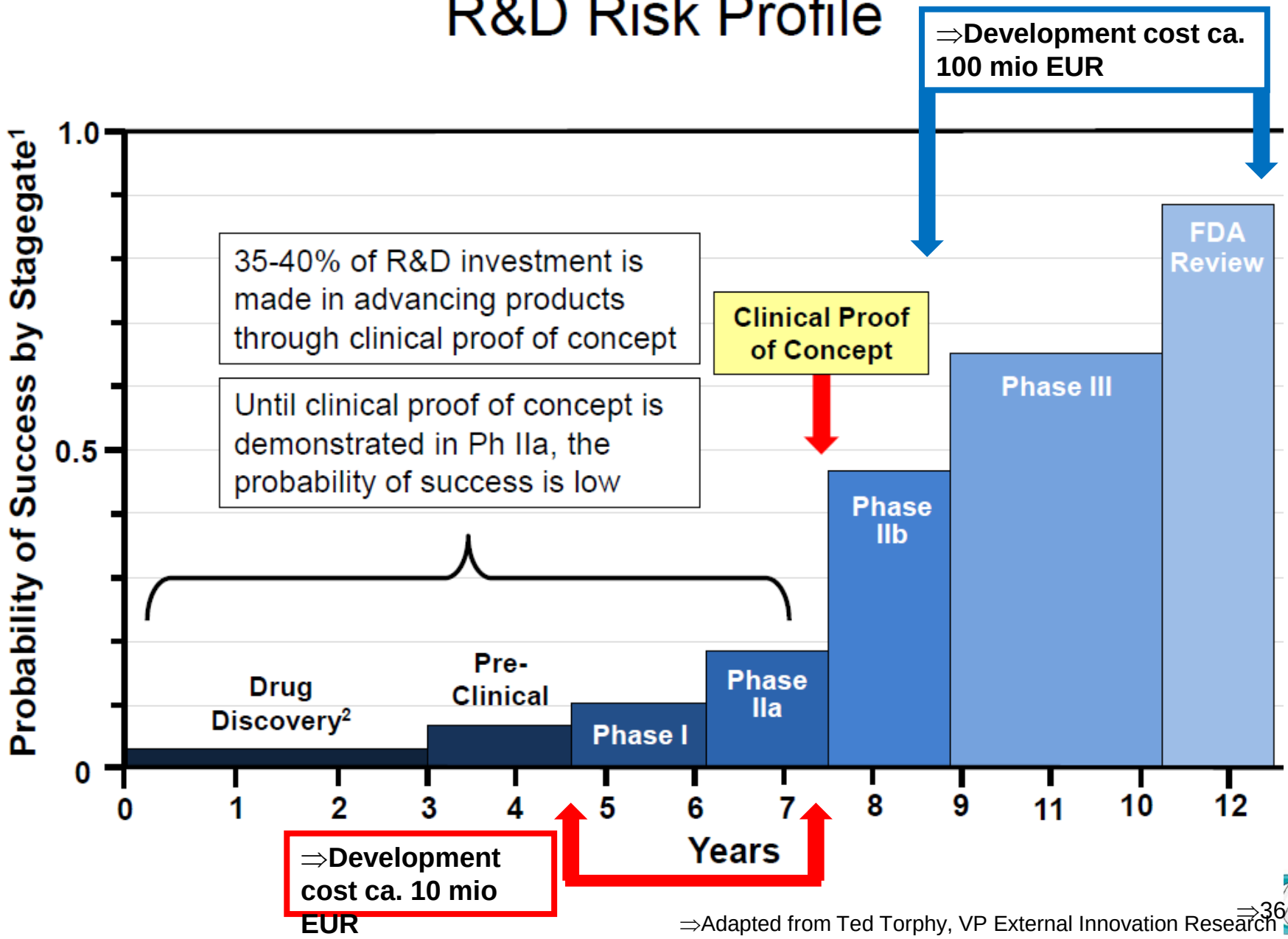
R&D Risk Profile



[1] CMR benchmarks used to calculate risk-adjusted values at various stages

⇒Adapted from Ted Torphy, VP External Innovation Research Capabilities; Johnson & Johnson Pharmaceutical R&D

What are the objectives of clinical trial ?

STEP

- **S**afety : likelihood of long term or serious side effects.
- **T**olerability : measured by comparing the withdrawal rates between the drug and the reference treatment.
- **E**fficacy : how the drug compares with the reference treatment ? What is the best end-point ?
- **P**rice : Cost / Effectivness, Quality of life.

The drug discovery process

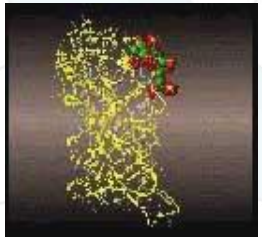
Choice of biological targets

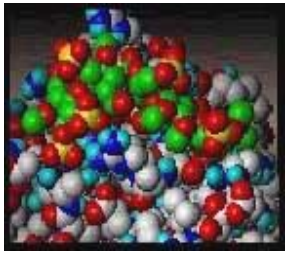
Develop-ment of screening assays

Screening of chemical libraries

Identification of "hits" Optimisation into "leads"

Optimisation of "leads" into development candidates





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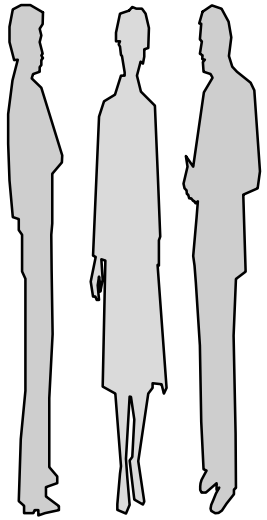
Phases of drug development



Non clinical data

Clinical data

DISCOVERY RESEARCH

PRECLINICAL DEVELOPMENT

CLINICAL DEVELOPMENT

Phas e I

Phas e II

Phas e III

REGISTRATION

MARKETING

Phase IV

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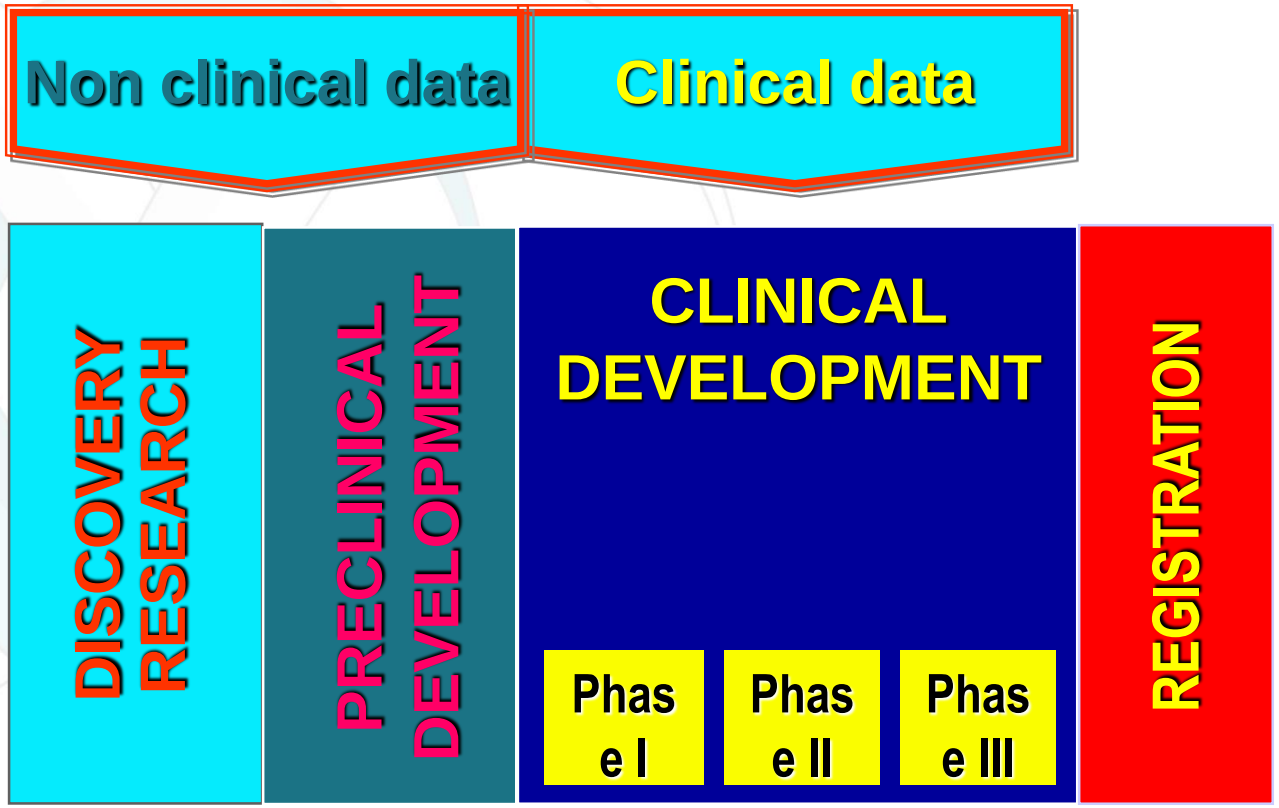
Success rate

Cost to develop a new drug :
from $ 300 million to $1 000 million.



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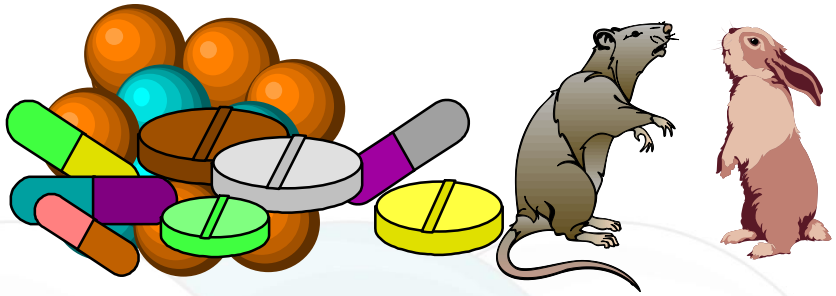
Preclinical Development

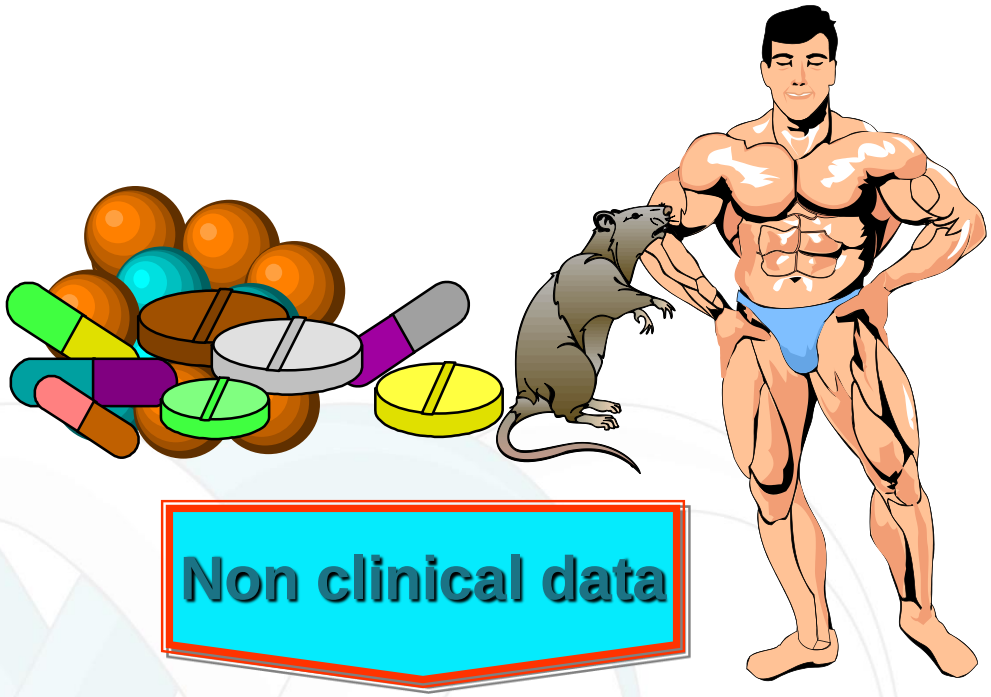


Non clinical data

DISCOVERY RESEARCH

PRECLINICAL DEVELOPMENT

- **Pharmacology : animal models**
- **Toxicity : acute**
  - **sub-acute**
  - **chronic**
  - **carcinogenicity**
  - **mutagenicity**
  - **reproduction**
- **Pharmacokinetics : Absorption**
  - **Distribution**
  - **Metabolism**
  - **Elimination**



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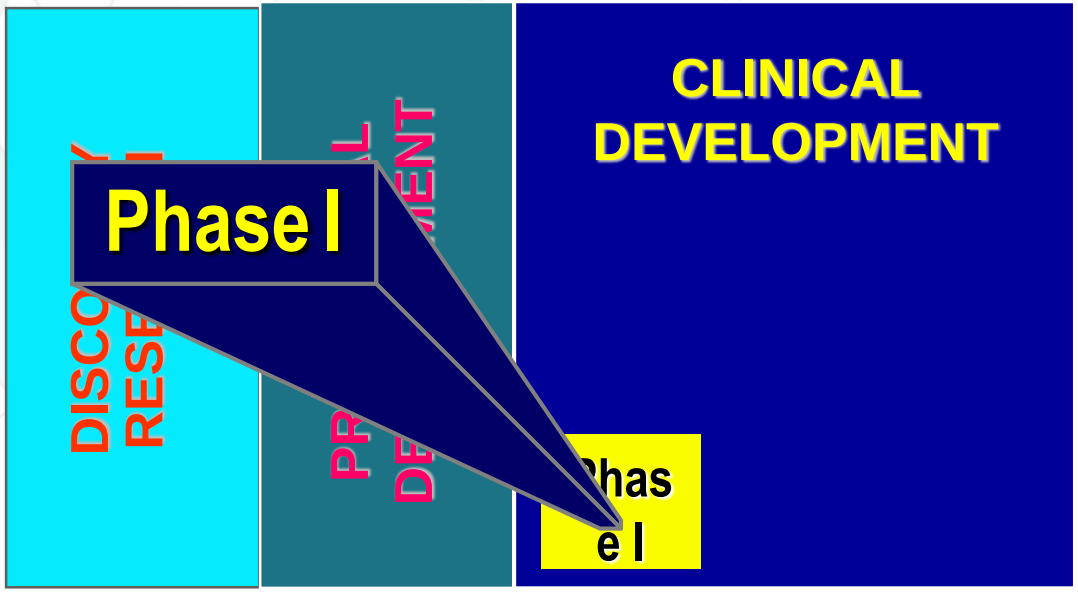

- **First** time in humans
- Healthy volunteers (usually)
- < 100 volunteers (or patients)
- Short Duration
- Endpoints:
  - Safety/Tolerability
  - Pharmacokinetics
  - Bioavailability
  - Dose-response
  - Interactions
  - Exploratory

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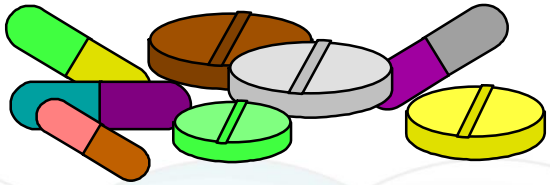
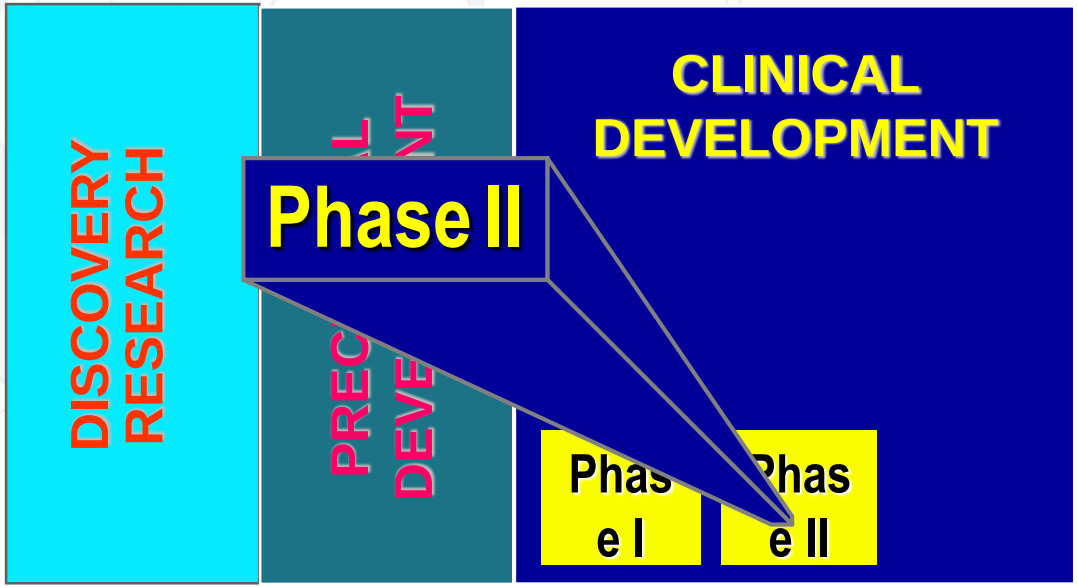
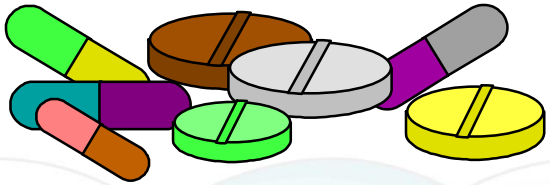
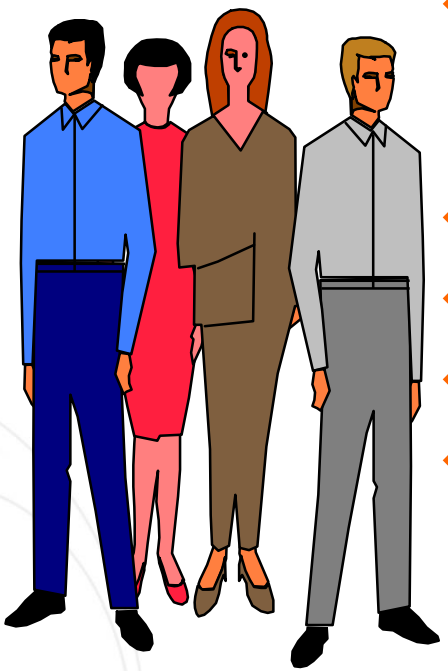


- Targeted disease population
- Small group of patients (usually ≤100)
- Variable duration (weeks to months)
- Endpoints include:
  - **Efficacy/proof of concept**
  - **Safety of different doses**
  - **Mechanism of action**
  - **Dose response (lowest effective)**







- Specific indications for labeling
- Multi-centered
- 1000’s of patients
- Variable duration
- Endpoints include:
  - **Efficacy**
  - **Safety**
  - **Quality of life**
  - **Health economics**

Non clinical data

DISCOVERY RESEARCH

PRECLINICAL DEVELOPMENT

CLINICAL DEVELOPMENT

Phas e I

Phas e II

Pha e III

Phase III

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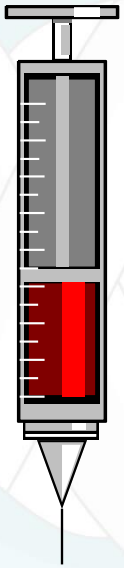
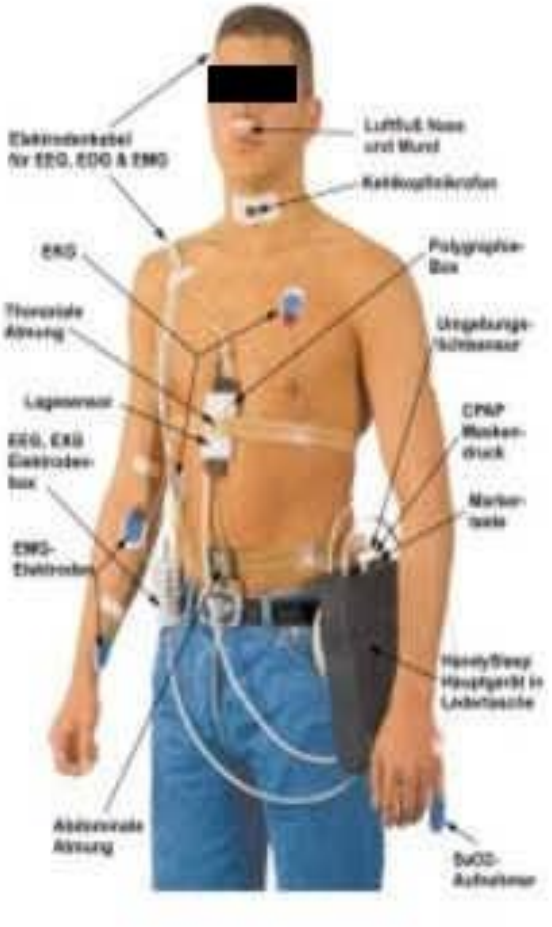
Phase I studies



1st.



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Phase I - First Application to Humans

GOALS:

- to estimate the **maximum tolerated dose**
- to determine which organ systems are affected by drug toxicity
- to determine the extent, duration and reversibility of the toxicity
- pharmacokinetics
- to observe possible drug activity

Setting

- special units;
- independent from patient care
- but close to ICU
- specially equipped
- staff trained for purpose

Types of phase I studies

- **Ia Single dose**
- **Ib several doses/day**

increasing doses

Participants

Healthy volunteers

- frequently men only 18 - 50 years of age
- All race, gender and age (in future)

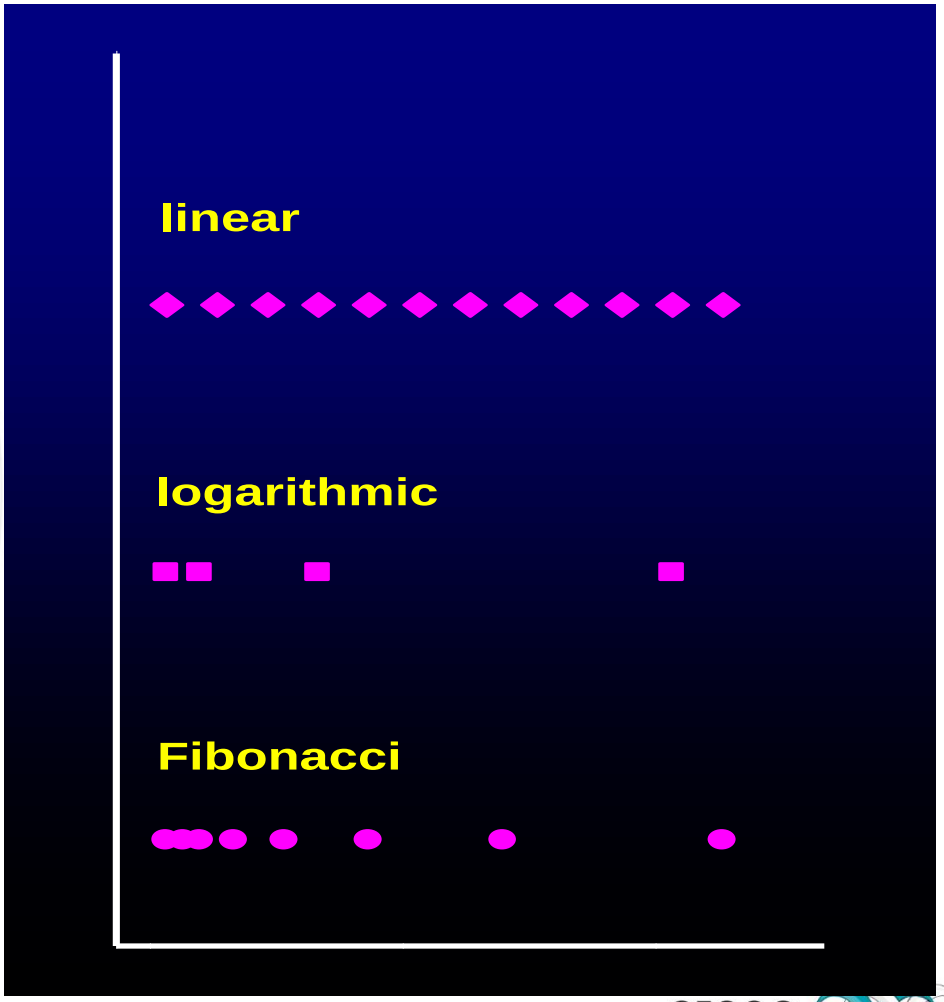
Special situations

when healthy voluntees are not considered for phase I (Oncology, HIV, gynecology / obstetric, pediatric, Alzheimers vaccine)

Initial dose

- **Initial dosage**
  - 1/100 to 1/10 of the "no effect" dose from most susceptible animal in toxicology studies (consider 1/600 of LD_{50} of most sensitive animal or 1/5 of minimal effective dose)
  - *Oncology studies: 1/5 to 1/3 of the LD_{10} to MTD*
- **Dose escalation**
  - logarithmic scale
  - doubling the dosage
  - (modified) Fibonacci scheme

Leonardo Pisano Fibonacci (1170-1250)



Traditional design

No toxicity

escalate dose

toxicity

current dosage

No toxicity

toxicity

(stop the trial)

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Escalation / De-Escalation

No toxicity

escalate dose

(stop the trial when pre-set sample size is attained)

1 toxicity

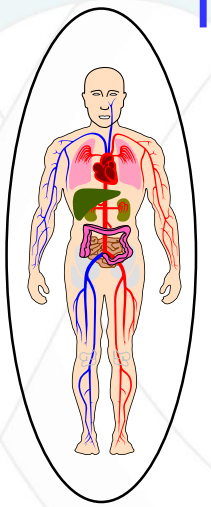
>1 toxicity

De-escalate dose

current dose

Phase I studies

Phase I



Safety

Tolerance

Pharmacokinetic

Pharmacodynamic

Dosis / activity

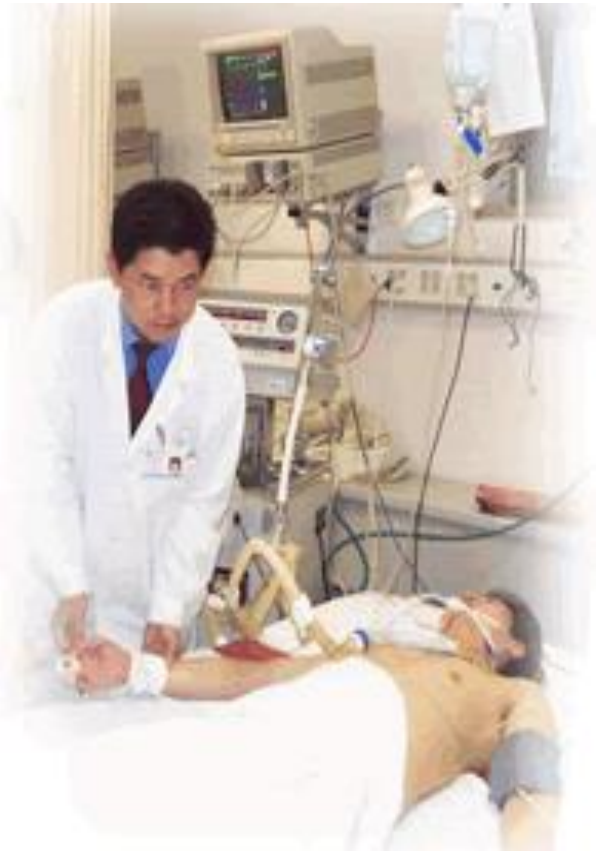
Concentration / activity

Duration of activity

Phase II,III

Phase II studies

Phase II



Therapeutic pilot studies

Selected patients

Controlled studies

Dose ranging

Safety

Efficacy

Phase II (=therapeutic pilot study)

GOALS:

- to demonstrate **activity**
- frequently bio-/ surrogate markers
- to assess short term safety and tolerability of different dosing schedules

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Phase III define the therapeutic role

GOALS:

- To test **efficacy** of the drug and to compare this data with standard treatment or an untreated control group
- To analyse the pattern and profile of adverse drug reactions

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Phase III studies

Phase III

Large and variable patient groups

Controlled studies

Safety

- Short & long term
- Patterns and profiles

Efficacy

Therapeutic value

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The controlled clinical trial

split group

experimental group

control group

known or unknown confounders

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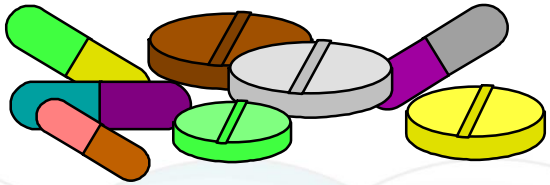

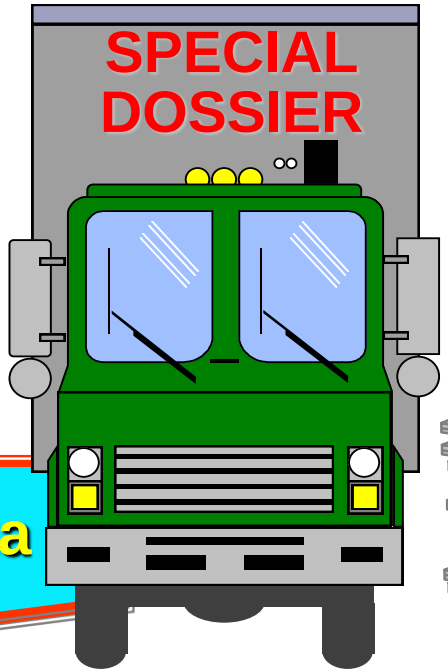

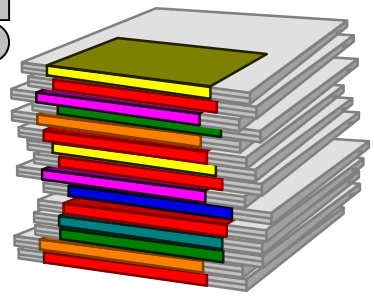

Non clinical data

Clinical data

DISCOVERY RESEARCH

PRECLINICAL DEVELOPMENT

CLINICAL DEVELOPMENT

Phas e I

Phas e II

Phas e III

REGISTRATION

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Phase IV

GOALS:

- To further define drug profile characteristics and therapeutic **value of the product**.
  - Experimental studies
  - observational or non-experimental studies (eg. post-marketing surveillance studies)

powerful brand names ...

According to Merck about 105 million U.S. prescriptions were written for Vioxx from May 1999 through August 2004. Based on these figures, Merck has said about

20 million people

in the U.S. have taken Vioxx.

www.onlinelawyersource.com

Phase IV - side effects

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Mibefradil, Troglitazone,

Trovafloxacin, Cisaprid,

Terfenadin, Cerivastatin,

Rofecoxib

Phase IV studies

Phase IV

After registration of the drug

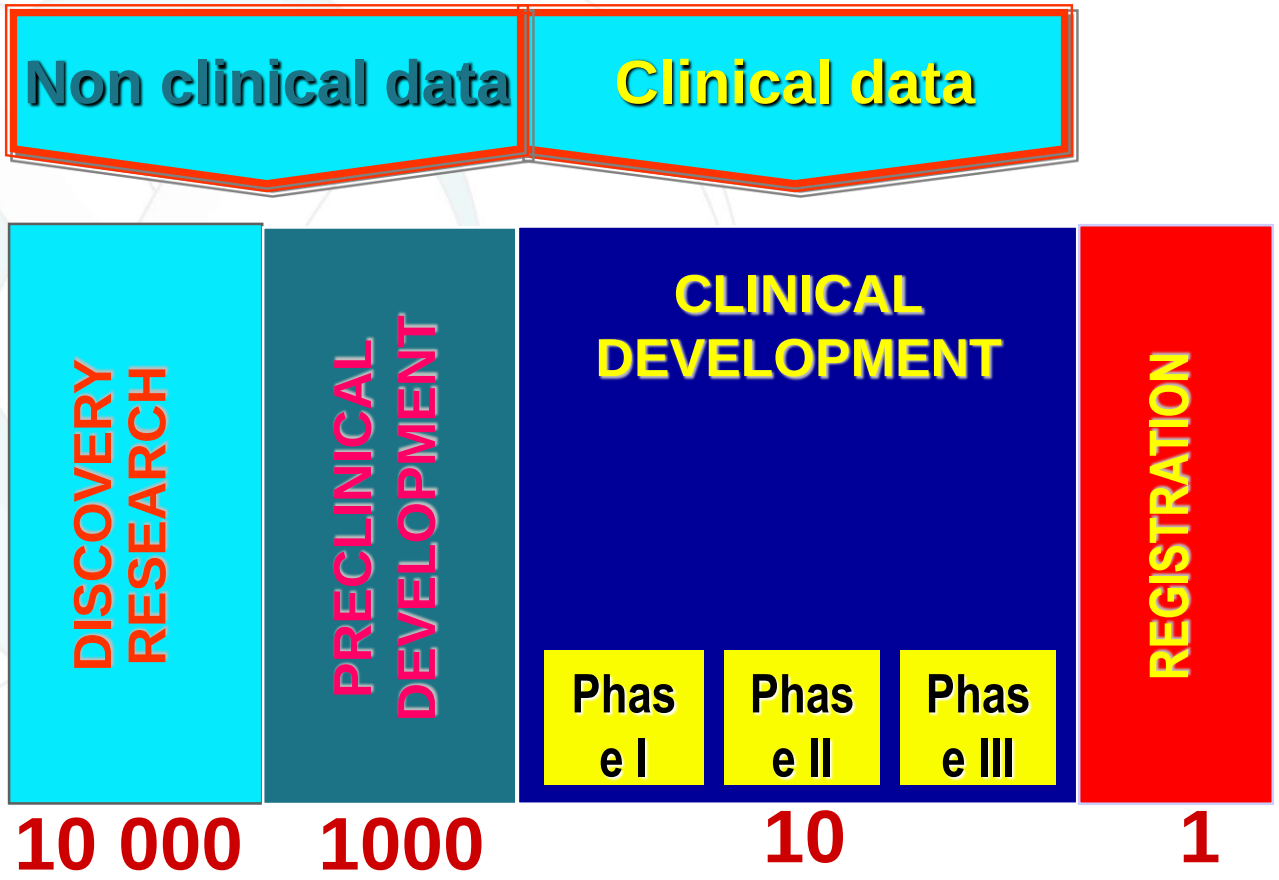
Post-marketing-surveillanc

Evaluation of the therapeutic value

Marketing tool

In addition to long development times, new drug development is associated with a high degree of risk.

Cost to develop a new drug : from $ 300 million to $1 000 million.



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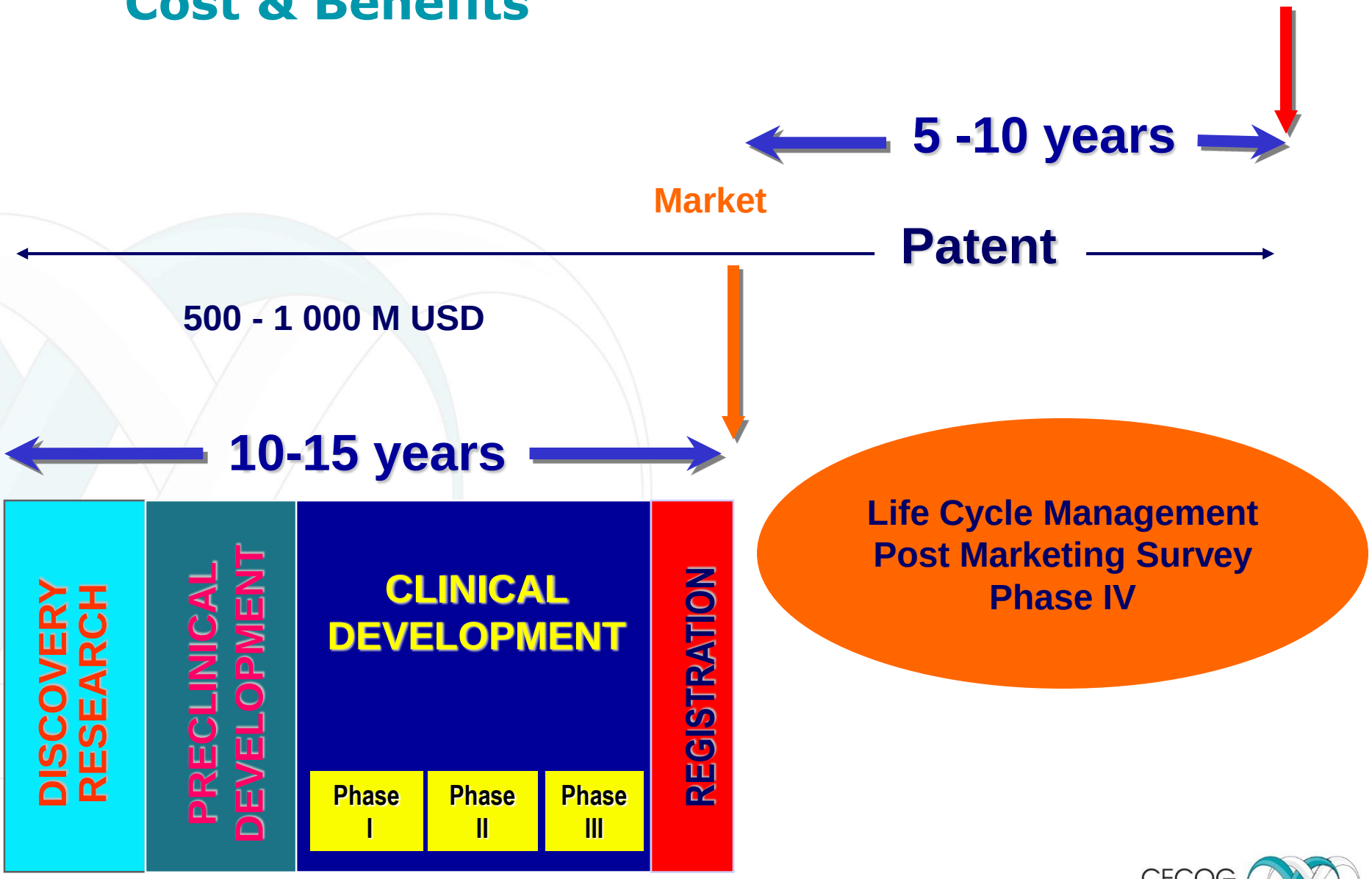
Cost & Benefits



Marketing Authorisation and Evaluation

B. Haynes, A. Cochrane
CECOG
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Pharmacological Evaluation – Determining the Degree of Innovation

1. Same active ingredient, same strength and practically the same pharmaceutical form as one or more previously listed products
2. Same active ingredient and practically same pharmaceutical form, but new strength
3. New combination of active ingredients already listed
4. New pharmaceutical form of already listed ingredient(s)
5. New active ingredient belongig to an already listed therapeutic group with a uniformly defined active principle
6. New active ingredient with a new active principle for treating an illness für which treatments are already listed
7. New active ingredient providing first treatment with a drug for an illness previously treated otherwise
8. First treatment of a disease