

Orphan Drugs: Clinical Trials in Reality

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Clinical Development of Orphan Medicines

Patients with rare diseases need medicines that are

- as **safe**
- as **effective**
- of the same **quality**

as any commonly used medicine

Clinical trials



A Clinical Trial

A Prospective study of an intervention

Designed to measure the impact of a treatment

Compared with a control treatment

On a future possible outcome.



King Gustav's Trial

Question: Is tea or coffee the more poisonous ?

Subjects: Two convicts randomly allocated tea or coffee

Assessment: Clinical assessment by Court Physician

Design: Open label (non-blinded) parallel groups

Sponsor: King Gustav



King Gustav's Trial

Outcomes:

- Court physician died
- Sponsor assassinated
- Both subjects survived



The Clinical Trial Process

- Design a workable protocol
- Obtain Ethical and Regulatory approval
- Recruit the right investigators
- Recruit the right subjects

As fast as possible !



The Clinical Trial Process

- Conduct the study to highest quality standards of Good Clinical Practice
- Monitor (quality assure) the study efficiently

At the least financial cost !



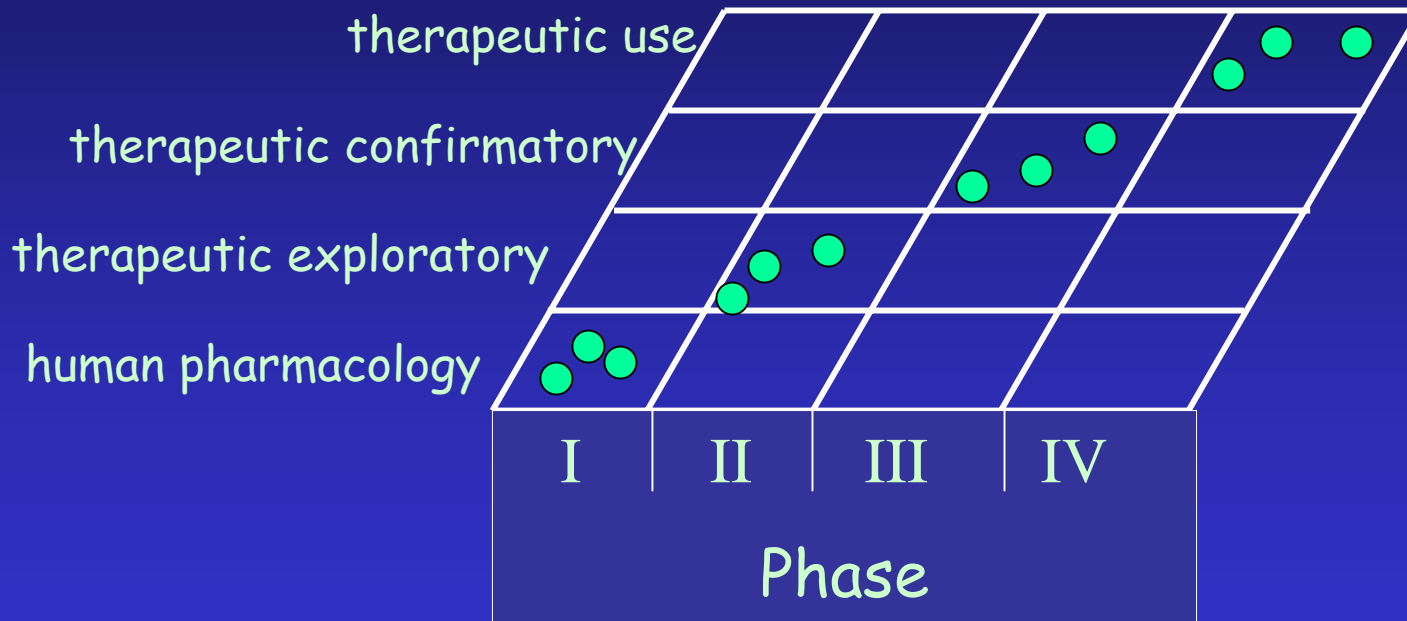
The Clinical Trial Process

- Collect the data
- Process the data
- Interpret the data expertly
- Present the data to the Regulators (EMEA, FDA etc.)
- Communicate the results to the scientific community
- Communicate the results to patients and carers

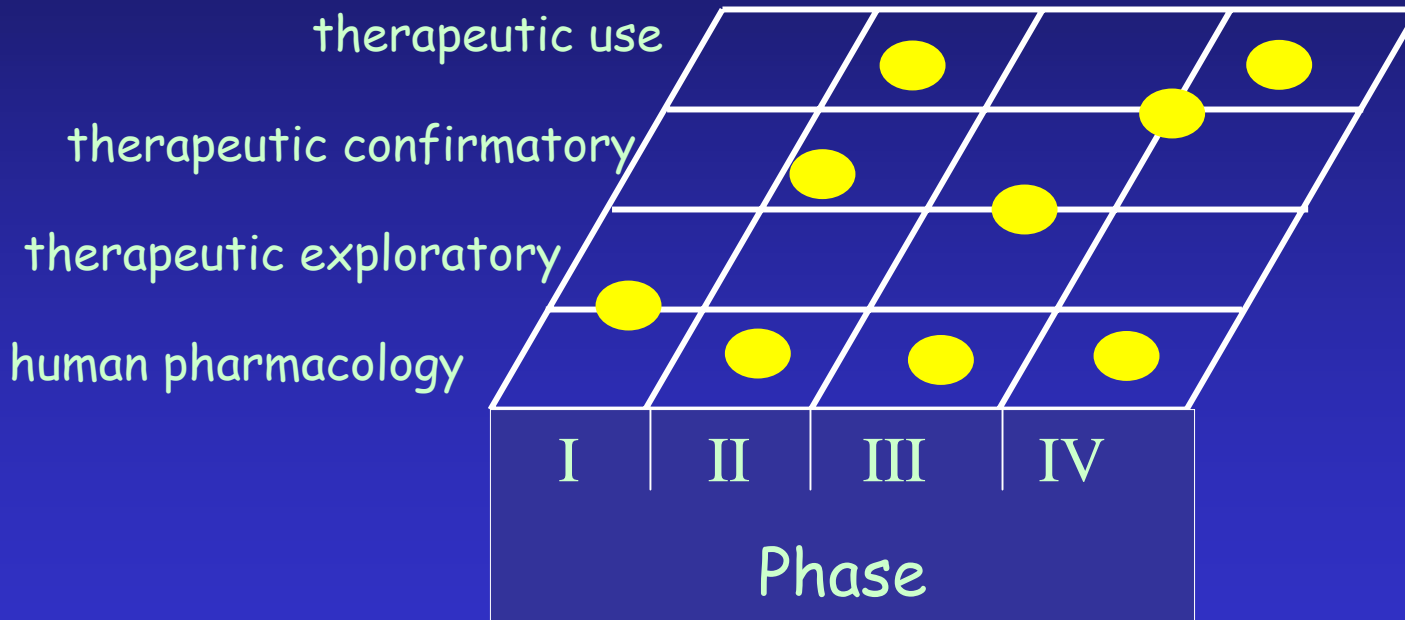
As fast as possible !



Types of study and conventional drug development phase



Orphan drug trials *do not always* fit conventional development phases



Challenges for Developers of Orphan Drugs



A Challenge for Europe

In contrast to the USA

Fragmentation

- Multiple Languages
- Multiple Cultures
- Multiple Medical systems
- Cross-border reimbursement difficulties
- National rather than European Centres of Excellence
- Poor level of direct Funding of research for trials



Challenges of Trials in Rare Diseases

for **Expert Physicians & Academics**

- Few patients per centre
- Lack of funding
- Lack of trials expertise
- New requirements of Directive 2001/20/EC
- Multi-state Europe with diverse medical systems discourage development of major referral centres



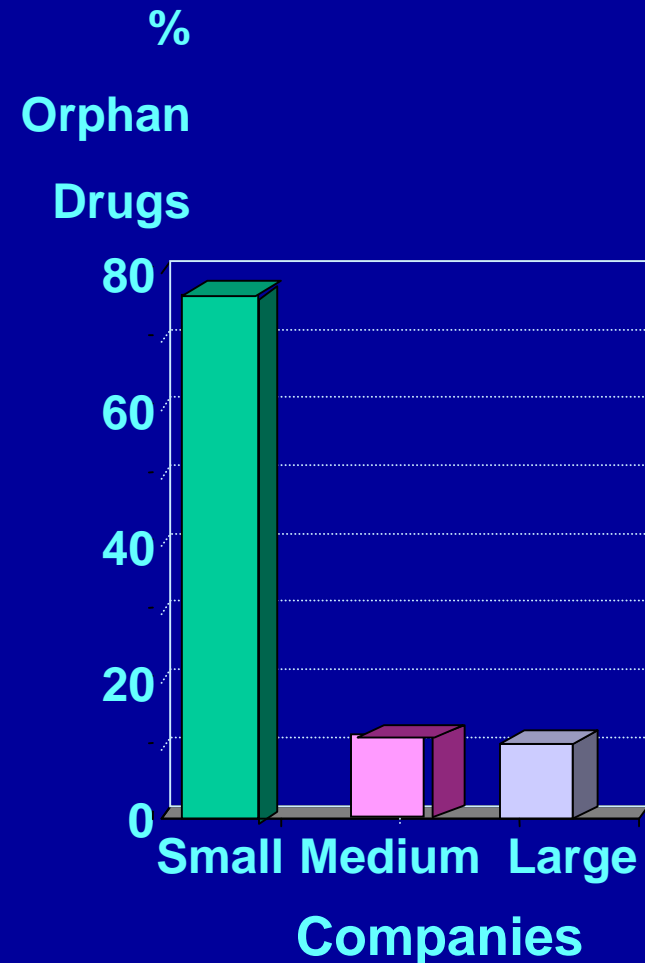
“The Board of Venture-Cap
has agreed to fund your
clinical trial programme as
long as you can prove to us
in advance that your drug is
safe and effective.”



Challenges of Trials in Rare Diseases

for Industry

- Orphan developers are often small
- with limited geographic reach
- with poor access to patients
- lack trials experience
- with limited regulatory experience



Challenges of Trials in Rare Diseases

for Patients

- How to find good trials ?
- Patients' participation wasted in poor trials
- Ineffective channels for research funding (proposed studies too small)
- Disincentive for companies to invest because of difficulties in doing trials



Challenges of Trials in Rare Diseases

for Regulatory Agencies

- Few adequate clinical trials for risk-benefit assessment
- Poor regulatory compliance
- Uncertain adherence to Good Clinical Practice
 - by industry
 - by doctors
- Challenge of biostatistical study design for small cohort studies with non-spectacular benefit



Challenges of Trials in Rare Diseases

for the European Commission

- Protection of trial participants without inhibiting research
- Assuring highest quality of data in trials
- Maximising safety of treatments

L 121/34

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1.5.2001

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
of 4 April 2001

on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

The Directive was fully implemented on 1 May 2004.

Challenge for **the European Commission**

EU Clinical Trials Directive 2001/20/EC

Needs to

- **Audit effects of Directive on research**
- **Acknowledge: 'a work in progress'**
- **Improve uniformity of implementation**
- **Further clarify definitions and responsibilities**
- **Commit to revise and improve.**



Opening the Bottlenecks in Europe

Help Available from EMEA*

- The COMP approval process
- Scientific Advice & Protocol Assistance

* & FDA



Opening the Bottlenecks

Possible Roles for Patient Organisations

Pan-European Centres of Excellence

- Encourage their development
- Lobby for easier trans-national patient access to them
- Support patients who travel from abroad to them



Opening the Bottlenecks

Possible Roles for Patient Organisations

*Act as **True Stakeholders** in the Clinical Trial Process:*

- Help ask the questions to be answered by trials
- Give ethical guidance to Ethics Committees
- Promote recruitment to good trials
- Discourage recruitment to poor trials
- Ensure publication of trial results



Patient Organisations: almost Mini-Drug Companies ?

- Focussed research
- Directed towards a product
- Setting the Europe-wide research agenda
- A leading rôle rather than a mere 'bit-player'



Opening the Bottlenecks

Some Roles for Academia

- Facilitate clinical trials in rare diseases on a not-for profit basis.
- Search for efficiencies in new methods for design of clinical trials.
- Take a European rather than a National View !



Opening the Bottlenecks

Some Roles for Academia

Maximise effectiveness of rare disease trials

- Effective multinational recruitment
- Efficient use of scarce patient resources
- Coordination of multiple study designs to facilitate meta-analyses
- Avoid “compassionate over-use”
- Coordination of biobank use.



The Present Reality

Pharmaceutical Research & Development activity
has decreased in Europe.

European patients risk being at “the back of the line” for
new medicines

The future depends on a long-sighted and creative
partnership between Industry, Academia, Patients and
European Governments





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