

# **Clinical Drug Development: What are the questions and how do we answer them?**

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# Outline

- Background on drug development
- Defining data needed
- Ethics and regulation
- Study design
- Implementation
- Data collection, analysis and reporting

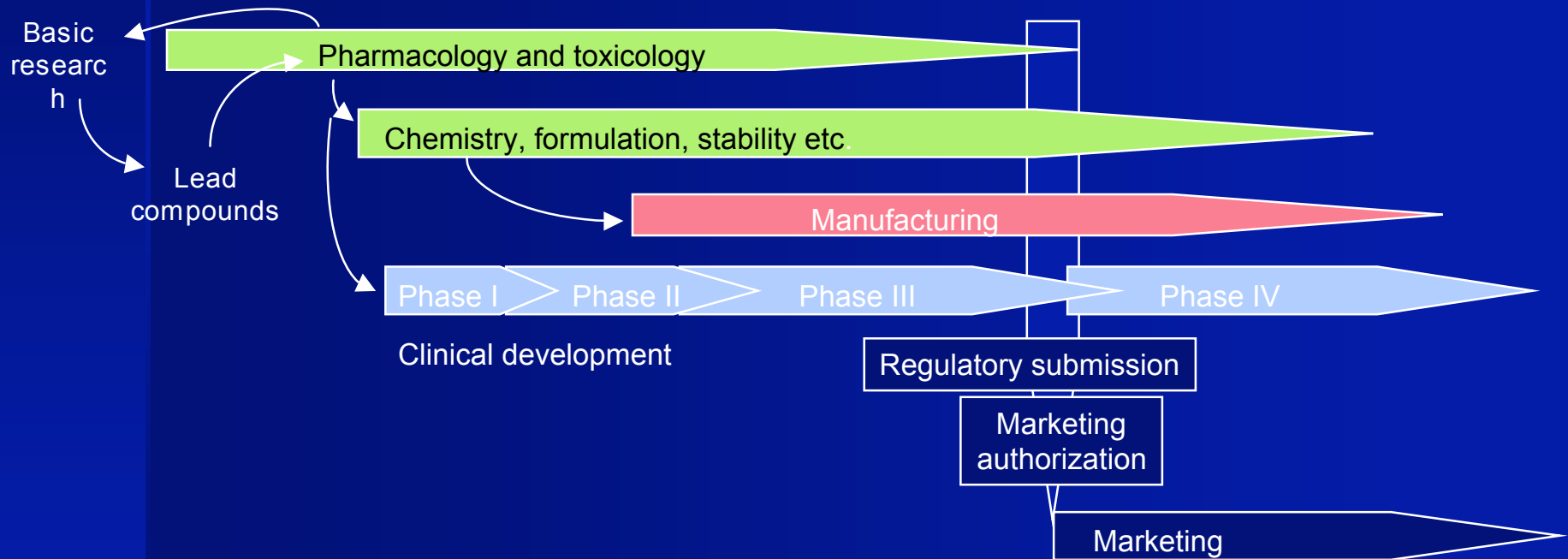
# What Is A Drug?

FDA definition:

A drug is a article (other than food) intended for the use in the diagnosis, cure, treatment or prevention of disease in man or other animals



# Drug Development



# Phases of Clinical Research

PHASES OF DRUG DEVELOPMENT					
Average Time/Study	2 weeks to 2 years	1 week to 1 month	Several months to 2 years	Several months to 4 years	Several months to several years
Average Number of Subjects		20 to 100	Several hundred	Several hundred to several thousand	50 to several thousand
Type of Subjects	Animals	Healthy Volunteers	Subjects	Subjects	Subjects
Main Purpose	Predict toxic effects in man	Determine safe dose in man	Determine effectiveness at safe dose	Determine safety & effectiveness in varied large population over a long time period	As a condition for approval. Approval for a new indication. Other
		I	II	III	IV
	Preclinical	Clinical			
		Pre-marketing			Post-marketing

# Why is Clinical Research Important?

- Enhances our understanding of human physiology and pathophysiology.
- Translates basic research into medical care.
- Informs and drives basic research.
- Improves diagnostic tools and preventive care.
- Improves human health!

# What Can Clinical Research Accomplish?

- Research in human physiology and pathophysiology translates basic research into knowledge of disease mechanisms and medical therapeutics.
- Clinical trials establish safety and efficacy of new interventions.
- Epidemiological and behavioral research identify high risk populations with potential to benefit from prevention, early detection, or therapeutic intervention.
- Outcomes and health services research assess the health impact and cost-effectiveness of interventions.

# What Data do we need?

- Depends....
  - On the intent of the trial
  - On the compound under investigation
  - On the disease under study
  - On regulatory considerations
  - On commercial considerations

# Trial Design

- Protocol – A step by step recipe for the execution of the study and the collection of data for a specific need
- Requires input from multiple disciplines
  - Scientists (clinicians, statisticians, others)
  - Those performing the study (clinicians)
  - Regulatory (guidances, discussions)

# Ethical Considerations

- Nuremberg Code 1949
- Declaration of Helsinki

# How is Clinical Research Regulated?

- Local Institutional Review Boards
  - Conducts initial review of research proposal.
  - Ensures participants are not exposed to unreasonable risks and that they give informed consent.
  - Conducts continuing review of approved research to ensure that human-subject protections remain in force.
- Food and Drug Administration
  - Regulates approval process for medical therapies

# Ethics Committees

- Purpose is to Protect Human Subjects enrolled in Clinical Trials
- Institutional Affiliations or Private for Profit
- Region or Country Specific
- In the US – 21 CFR p 56 (ethics committee) and 21 CFR p 45 (Informed Consent)

# Ethics Committees









- Composition (United States)
  - At least 5 members including 1 physician
  - At least 1 member unaffiliated with the institution
  - Must not be composed of entirely men or women of one profession
  - At least 1 member must be a non-scientist

# Ethics Committees

- Protocol
- Informed Consent/Assent
- Any subject information (includes advertisement for participants)
- Known information about the compound under consideration
- Grant approval to perform study
- Receive ongoing updates on compound information and safety events throughout the trial

# Informed Consent

## Eight Required Elements

-  Statement of research
-  Description of Risks
-  Description of Benefits
-  Availability of Alternative Procedures
-  Statement of Confidentiality
-  Explanation of Compensation for Injury
-  Who to Contact
-  Voluntary (i.e. refusal to participate = no penalty)

# Subject Recruitment

- The study population is strictly defined by the study protocol
  - Healthy Volunteers
  - Patients
  - Special Patient groups (i.e. pediatrics, comorbid disease)

# Subject Recruitment

- Private practice physicians
- Specialty Research groups
  - Mostly Healthy Volunteers
  - More Patient specific
- HMOs
- Financial Incentives
- Advertisement

# **Data Collection, Analysis and Reporting**

Study results are only as good as  
the data collected

# Clinical Data

- Demography
- Physical Exam
- Medical History
- Concomitant Medication
- Adverse Events
- Vital Sign Measures
- Outcome data (Rating Scales, Clinical Evaluation, Interviews)

# Lab/Bioanalytical Data

- Clinical Chemistry
- Hematology
- Urinalysis
- Specific Analyte (PK, PD)

# Specialized Data

- ECG
- EEG
- X-Ray
- MRI
- Mammogram
- Diary Information

**Subject**

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graph LR; Subject[Subject] --> Clinical[Clinical]; Subject --> Lab[Lab/Bioanalytical]; Subject --> Specialized[Specialized Data];
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**Clinical**

**Lab/Bioanalytical**

**Specialized Data**

# Case Report Form (CRF)

- Demography
- Physical Exam
- Medical History
- Concomitant Medication
- Adverse Events
- Vital Sign Measures
- Outcome data (Rating Scales, Clinical Evaluation, Interviews)

# Direct Data Transfer

- Lab/Bioanalytical Data
- ECG
- EEG
- Vital Signs
- Diary Information

# Electronic Data Capture

- Bubble Sheets
- Fax
- Laboratory/Bioanalytical
- Specialized data

# “Real-time” Data Collection

- Direct Computer entry
- Via local software
- Remote Data Capture
- Web-based
- “Internet Shopping”

# Monitoring

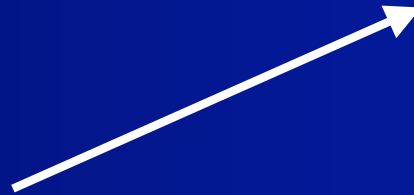
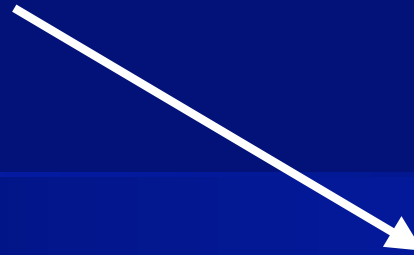
- Liaison between study sponsor and the clinic
- Source vs. Data collected
- Logical
- Consistent
- Entered Correctly
- Legible

**Clinical**

**Lab/Bioanalytical**

**Specialized Data**

**Database**



# Building the Database

- Design
- Timing
- Everything has a place

# Cleaning the Data

- Electronic Cleaning
- Range and Logic checks (Edit Specifications)

# Queries

- Generated from edit specifications
- Sent back to data source for resolution
- Changes to source data
- Heavy documentation (bias, manipulation)

# Programming

- Data Analysis Plan (Statistical Analysis Plan)
- Detailed Statistical plan based on protocol
- Created prior to data lock/unblinding
- Empty tables
- Test programming prior to use of real data

# Data Review

- Review of data prior to analysis
- Blinded
- Unblinded
- Systematic errors
- Audit of data base

# Data Analysis/Interpretation

- According to planned procedures
- Additional analysis may be required
  - Subpopulation analysis
  - Characterize discrepancies in data
  - Data driven analysis

# Clinical Study Report

- Formal Technical document
- Multidisciplinary approach
- Reports all findings of a trial
- All data is provided
- Document is reviewed by multiple disciplines
  - Technical/Scientific
  - Clinicians
  - Quality Assurance
  - Regulatory

# Pharmaceutical Careers

- Biology
- Chemistry
- Statistics & Data Analysis
- Medical & Pharmacy
- Marketing & Sales
- Legal & Government/Regulatory
- Human Resources
- Finance & Accounting
- Manufacturing
- Information Technology
- Quality Assurance

# Drug Development

## Formulation Development

Characterization  
 Drug Delivery  
 Clinical Material  
 Packaging  
 Analytical Testing/Stability  
 Process Development

Formulation Scientists  
 Analytical Chemists  
 Microbiologists  
 Chemical Engineers

## Clinical Studies

Drug Efficacy and Safety in Humans  
 Drug Label Development

Biologists  
 Physicians  
 Pharmacists  
 Statisticians

## Safety & Toxicology

Drug Metabolism  
 Toxicology  
 Drug Label Development

### Staffing

Biologists  
 Toxicologists  
 Physicians

## Regulatory Affairs

Compilation of Data for New Drug Application and Submission  
 Meetings with the FDA  
 Communication with FDA and R&D Groups  
 Drug Label Development

Regulatory Scientist  
 Pharmacists  
 Biologists  
 Physicians

# Drug Product Commercialization

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graph TD; Root[Drug Product Commercialization] --> Manufacturing[Manufacturing Operations]; Root --> QualityControl[Quality Control]; Root --> QualityAssurance[Quality Assurance]; Root --> Marketing[Marketing/Sales];
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## Manufacturing Operations

Chemists

Biologists

Engineers

Pharmacists

B.S., M.S.,

High School/Junior College

## Quality Control

Chemists

Biologists

B.S., M.S.,

Junior College/College

## Quality Assurance

Chemists

Biologists

B.S., M.S.,

Junior College/College

## Marketing/Sales

Business Training

B.B.S

M.B.A.

Pharmacists

Chemists

# Chemical & Pharmaceutical Development (CPD)

- Development of new formulations for improved therapeutic benefit
- Development of new formulations for new drug molecules
- Manufacturing process development
- Process improvements
- Technology and analytical methods transfers to manufacturing locations

# Chemical & Pharmaceutical Development (CPD)

## Pharmaceutical Development

Formulations  
Process Development  
New Drug Delivery

Chemists  
Engineers  
Pharmacists

## Analytical Development

Analytical methods  
(Drug compounds & Products)  
Stability Studies

Chemists  
Microbiologists

## Laboratory Systems Support

Standard Operation Procedures (SOPs)  
GMP Compliance  
Training  
Equipment Calibrations

Chemists  
Biologists  
Engineers