RESEARCH 101
Session 2:

Clinical Trials: The Drug Development Process

Janie Gardner, MS, CCRP, CIM

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The Drug Development Process

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Janie Gardner, MS, CCRP, CIM
Clinical Research Development

Key Takeaways

Two major categories of clinical trials

Stages of the Drug Development Process

Phases of a clinical trial (FDA and ICH)

Clinical Trials

A Clinical Trial is a special type of Clinical Research that evaluates the effects of an intervention (or no intervention) on biomedical or health -related outcomes.

Two broad types of Clinical Trials

- **Observational**
- **Interventional**

There are many study designs to choose from within these two broad categories of observational and interventional studies.

Observational studies,

-also called epidemiological studies, are those where the investigator does not act upon study participants, but instead observes natural relationships between factors and outcomes.

These studies are often retrospective and are used to assess potential causation in exposure-outcome relationships and therefore influence preventive methods.

Common study designs include:

Case-control, case-crossover, retrospective and prospective cohorts.

Interventional studies

-also called experimental studies are those where the researcher intervenes or interacts with the participants/ subjects at some point during the study.

These studies are often prospective and are specifically tailored to evaluate direct impacts of treatment (therapeutic) or preventive measures on disease.

Two Major Types of Interventional Studies

- Controlled clinical trials in which individual subjects are assigned to one or another of the competing interventions, or
- Community interventions, in which an intervention is assigned to an entire group.

Two Major Study Designs of Interventional Studies

Experimental or Randomized Controlled Trial (RCT) *
considered the most robust of the evaluation methodologies. By randomly allocating the intervention among eligible beneficiaries, the assignment process itself creates comparable treatment and control groups that are statistically equivalent to one another, given appropriate sample sizes.

Non- Randomized or Quasi-experimental research
is an empirical study, almost like an experimental design but without random assignment.
Quasi-experimental designs typically allow the researcher to control the assignment to the treatment condition but using some criterion other than random assignment (e.g., an eligibility cutoff mark).

- **The randomized controlled trial is considered the gold standard for today's clinical investigations.**

Drug Development Process

Drug Development
IND Trial

A drug development plan describes all aspects of the development of a product from the target product profile through post-approval activities.

The plan is usually prepared prospectively and updated as the development progresses and new information becomes available.

Drug development plan is ideally a logical, step-wise process in which information from small early studies is used to support and plan later larger, more definitive studies.

Pre-clinical Stage of Drug Development

Discovery
Product Activity

Safety Studies
Toxicity

Manufacturing
Quality

Stability

Discovery

Discovery typically begins with basic research where researchers seek to understand the processes behind a disease, often at a cellular or molecular level.

These new insights into disease processes and pathways can lead to identification of targets for new treatments

For example,
a gene or protein essential to the disease process that a new treatment could interfere with, for example, by blocking an essential receptor.

Once targets are identified , researchers may identify

- molecular compounds to find possible beneficial effects against target/ disease
- existing treatments that have unanticipated effects.
- new technologies that provide new ways to target medical products to specific sites within the body or to manipulate genetic material.

2 – 10 years

Preclinical Testing

Novel drug products undergo laboratory and animal testing to answer basic questions about safety. Manufacturer completes synthesis and purification of the drug and conducts stability studies.

Safety and drug activity tests are conducted

Using computerized models,

Cells

and Animals

3 – 6 years

FDA
Investigational New Drug Application

- Request submitted to the FDA to allow human exposure to the experimental drug
- Request for exemption from the FDA to ship an unapproved product through interstate commerce
- Creates an ongoing file at the FDA containing data on the investigational product as it passes through the development process ("living application")

Preparing for an IND Submission

Key Elements for and IND(a)

- **Proof-of-concept scientific data**
  Should include considerations of product activity, ability to replicate results and a reasonable explanation how the product will prevent, diagnose, treat or cure disease.
- **A target clinical Indication**
- **Clinical plan/ protocol**
- **Animal toxicology data**
  Usually obtained in two species that supports the dose, dosing schedule, administration, and study duration proposed in the clinical protocol.
- **Manufacturing process**
  Provides evidence that product is manufactured according to GMP, including analytical tests results confirming the quality of the product several batches of the product.
- **Stability Information**
  Data demonstrating the stability of the drug, under defined storage conditions, or the period of use for the clinical trial

Good Manufacturing Practices

FDA
21 CFR Part 210. Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs.
21 CFR Part 211. Current Good Manufacturing Practice for Finished Pharmaceuticals.

ICH
Quality guidelines (ICH Q1 A – Q14)

Good Laboratory Practices (Non- clinical laboratories)

FDA
21 CFR Part 58. Good Laboratory Practice for Nonclinical Laboratory Studies

ICH
Safety guidelines (ICH S1A – S12)

Clinical Trials

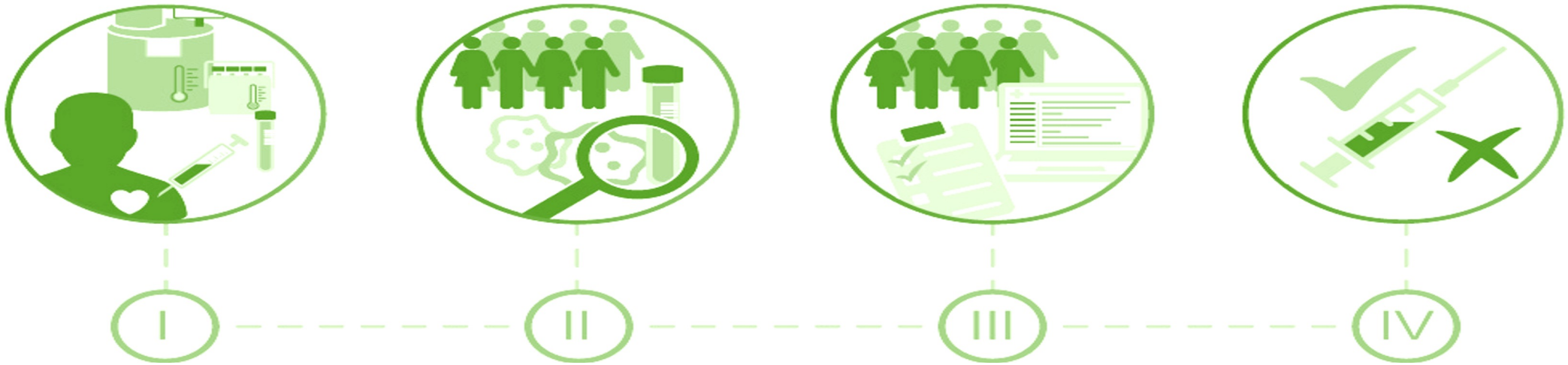
6 - 8 years

Clinical Research

FDA Requirements
(Oversight)

SPONSOR	SITE/ PI
Site Selection	
Confidentiality Agreement	
Feasibility Assessment	Feasibility Assessment
Legal / Financial Activities	
	Regulatory submissions
Collect Regulatory Documents	
Site Initiation and Training	
Monitoring	Study Execution
	Study Close- out
Data Analysis	
NDA Submission	

Phases of a Clinical Drug Trial
Phase 0 - Phase IV



Phase 0 Clinical Trial (Micro-dosing)

Question: *Does it affect target?*

Defining Characteristics

Duration :
Usual <7 days

Population:
< 10 subjects

Study Design:
Sub -therapeutic dose to obtain preliminary pharmaco-kinetic and pharmaco-dynamic data in humans

Focus:

- Gives no safety or efficacy information
- Allows product to be evaluated on human data instead of animal
- Supports decision to go forward with development - or not
- No therapeutic intent

Phase I Clinical Trial (PK, Safety, Toxicity)

Question: *Is this drug candidate safe?*

Defining Characteristics

Duration :

Short term – rarely over 30 days

Population:

20 – 50 Normal healthy volunteers

Occasionally, where the drug is to be used in patients with a particular disease (e.g., cancer) these patients may participate as subjects.

Study Design:

Dose escalation studies to establish Maximum Tolerated Dose (MTD)

Focus:

Safety and Tolerability in Humans

Studies of pharmacokinetics, bioavailability, bioequivalence, metabolism and toxicity

Phase II Clinical Trials (Dose Response)

Question: *Does this drug candidate work?*

Defining Characteristics

Duration:
Short to medium - < a year

Population:
Few hundred (200 - 500) volunteers with the target disease

Design:
Randomized blinded trials, strict eligibility criteria
Usually not compared to standard of care therapy

Focus:
Dose estimate for subsequent studies, establish effectiveness for a specific population and disease, collect additional safety information

Minimum Effective Dose

Phase III Trials (Pivotal Trial)

Question: ***Is this drug candidate more effective than existing treatment options?***

Defining Characteristics

Duration:

Parallels anticipated treatment – often can be years

Population:

Hundreds to thousand in populations the investigational product is intended to treat

Design:

Expanded randomized double -blind controlled trials,
broader subject eligibility criteria - are often multi- center

Focus:

Additional safety information and efficacy data with a selected dose
Risks/benefit analysis, dosing intervals, labeling information, safety profiles

Phase IV Clinical Trials (Post Market Approval)

Question: *How does this new drug perform in general use over time?*

Defining Characteristics

Duration : Years

Population:
Hundred to thousands
May involve additional age or ethnic groups

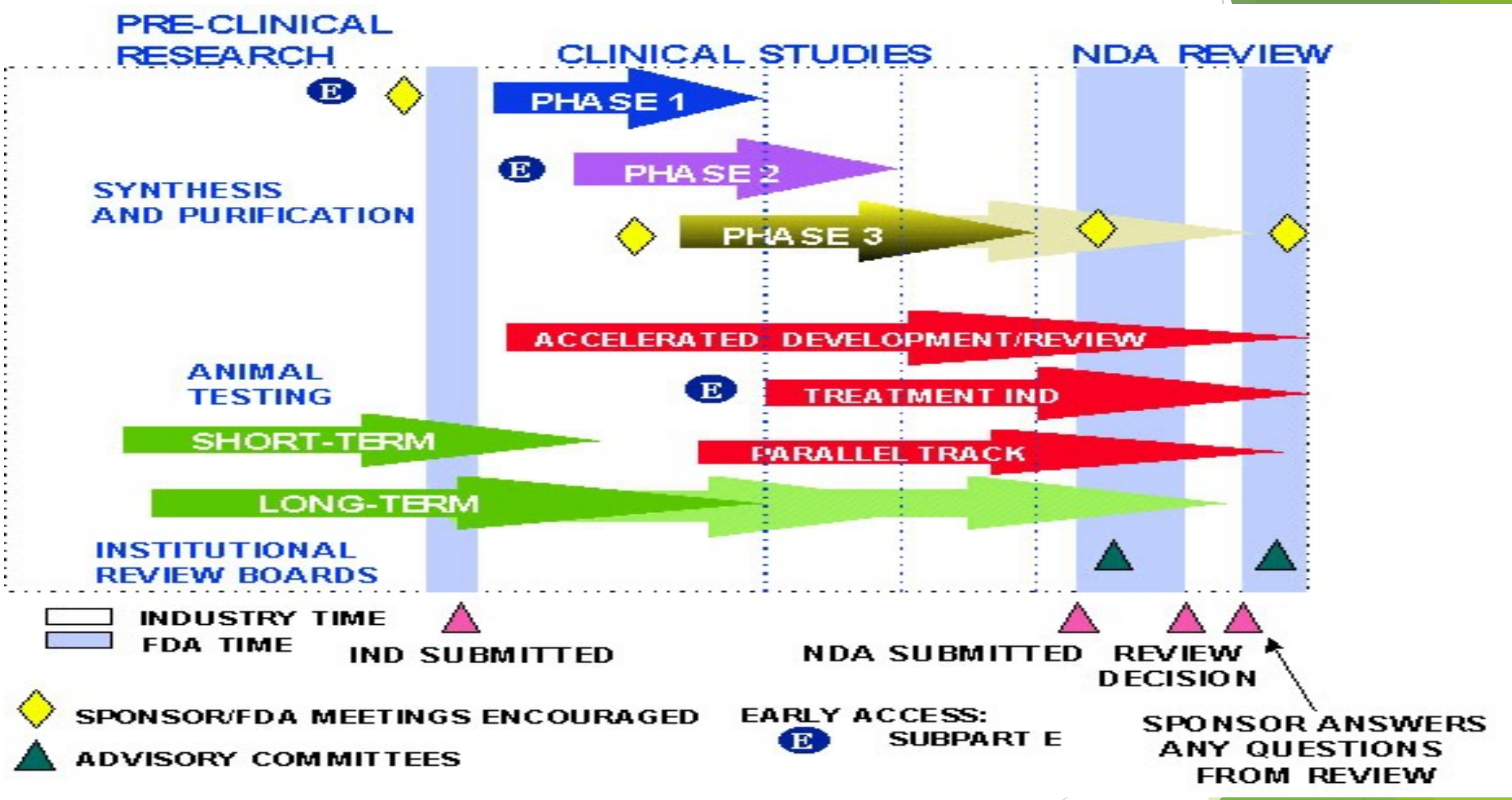
Focus:

Additional safety /efficacy data
Identify rare side effects
Familiarize physicians with the compound
Patient satisfaction

FDA Phases of Drug Development
(ICH Types of Clinical Drug Trials)

FDA Phases	ICH Types*	Objectives
Phase I	**Human Pharmacology**	•Assess tolerance •Drug metabolism and drug interaction •Estimate drug activity
Phase II	**Therapeutic Exploratory**	•Assess use for target indication •Estimate dosage for subsequent studies
Phase III	**Therapeutic Confirmatory**	•Confirm efficacy •Collect information for assessing risk /benefit relationship to support licensing •Monitor side effects
Phase IV	**Therapeutic Use**	Identify less common adverse effects Refine dosing recommendations Refine risk benefit relationship in general or special populations

ICH E8


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
E
PHASE 1
E
PHASE 2
SYNTHESIS AND PURIFICATION
PHASE 3
ACCELERATED DEVELOPMENT/REVIEW
ANIMAL TESTING
E
TREATMENT IND
SHORT-TERM
PARALLEL TRACK
LONG-TERM
INSTITUTIONAL REVIEW BOARDS
INDUSTRY TIME
FDA TIME
IND SUBMITTED
NDA SUBMITTED
REVIEW DECISION
SPONSOR/FDA MEETINGS ENCOURAGED
EARLY ACCESS:
E
SUBPART E
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW
ADVISORY COMMITTEES

FDA Review

Stages of FDA Review

Pre- IND Review

FDA reviews results of preclinical testing in laboratory animals and the plan to carry testing into human populations. At this stage, the FDA decides whether it is reasonably safe for the company to move forward with testing the drug in humans.

IND Review

The FDA review team has 30 days to review the original IND submission. The process protects volunteers who participate in clinical trials from unreasonable and significant risk in clinical trials.

Clinical Trials Review

Two commonly scheduled meetings with the FDA during clinical trials in the drug development process.

End of Phase II – safety and efficacy data from phases I and II are reviewed and the FDA and sponsors come to an agreement how large scale studies in Phase III should proceed.

Pre- NDA Submission - is held to ensure the submission is well-organized, complete and properly formatted. Also an opportunity to obtain the FDA thoughts on your product application's readiness for filing and likelihood of approval.

FDA Oversight

FDA BIMO Compliance Program

FDA BIMO Program is
A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research

BIMO Compliance Programs include:

- Sponsors, Monitors and Contract research organizations
- Institutional Review Boards (IRBs
- **Clinical investigators**
- Nonclinical (animal) laboratories, and bioequivalence analytical laboratories

BIMO inspections can be conducted by FDA at any time during a clinical study, either “for cause,” near the time of study closure, or during agency review of a marketing application.

FDA Post-market Safety Surveillance Program
MedWatch

MedWatch is FDA's medical product safety reporting program for health professionals, patients and consumers.

Serves two main purposes.
It offers AERS tools that allow medical professionals and the public to report medication errors and medical product injuries.

MedWatch also provides clinical information about prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products, such as medical foods, dietary supplements, and infant formulas.

MedWatch Forms

Voluntary Report forms for observed or suspected adverse events or product problem

- Form 3500 for Health professionals,
- Form 3500B for Consumers and Patients

Mandatory reporting for use by IND reporters, manufacturers, distributors, importers, user facilities personnel.

- Form 3500A – Effective June 15, 2015, All adverse event reports for approved drugs are required to be submitted by a manufacturer to FAERS electronically, specifically using theelectronic **format that replicates form FDA 3500A.**

For approved drugs, manufacturers are required by law to submit to FDA an individual case safety report (ICSR) for any adverse event that is reported to them, regardless of causality.

In its evaluation of the event, the manufacturer must decide whether the event was serious and unexpected, serious and expected, or non-serious.

thankyou!

Useful Resources

Categories of clinical studies –

https://clinicaltrials.gov/ct2/about-studies/learn

Drug development process –

https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

Phases of Clinical Trials

https://www.centerwatch.com/clinical-trials/overview

Phase 0 clinical trials -

https://journals.lww.com/oncology-times/Fulltext/2006/08100/FDA_Introduces_New_Phase_0_for_Clinical_Trials_.6.aspx

FDA Review

https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-continued

BIMO

https://www.fda.gov/science-research/clinicaltrials-and-human-subject-protection/bioresearch-monitoring-program-bimo

MedWatch

https://www.accessdata.fda.gov/scripts/medwatch/index.cfm