



15.482 Healthcare Finance

Spring 2017

Andrew W. Lo, MIT

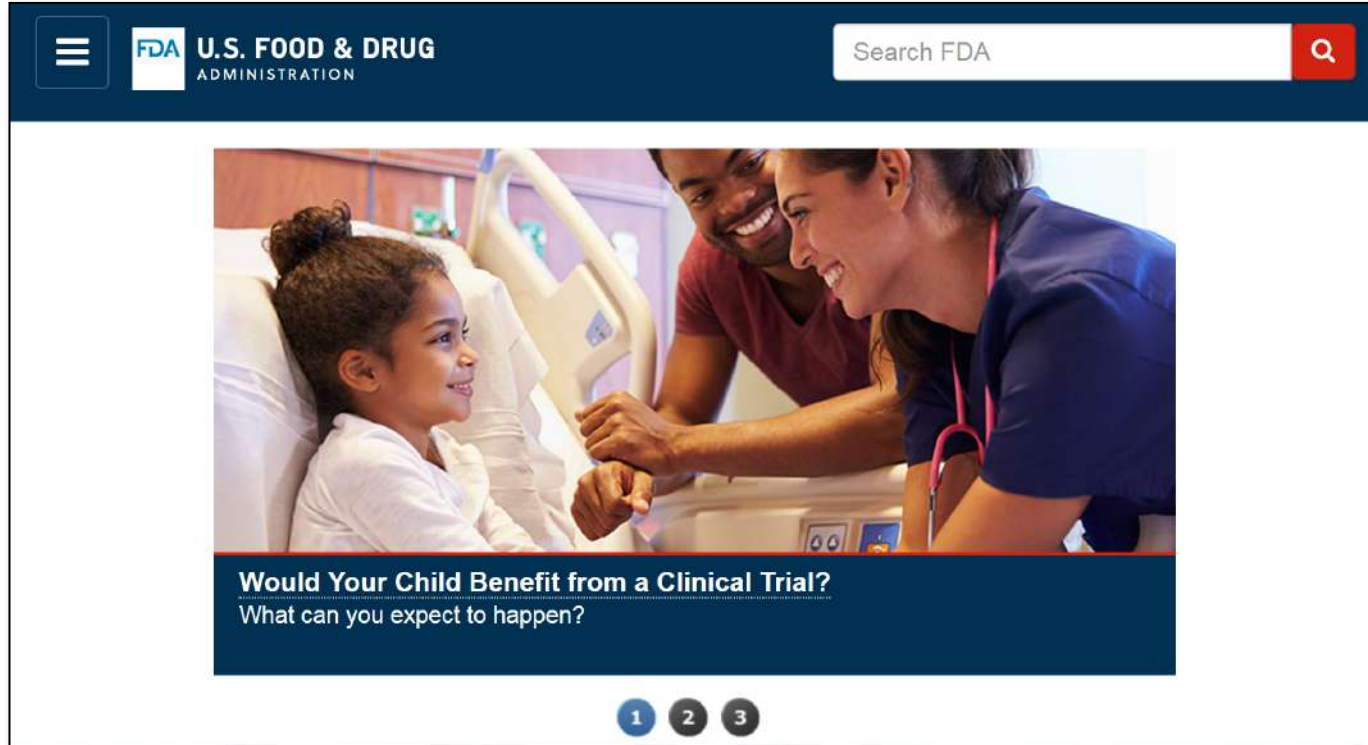
Unit 6, Part 1: Drug Development and
Clinical Trials

Unit Outline

- Overview of the Drug Development Process
- Randomized Clinical Trial Design
- Size, Power, and Cost
- Formal Statistical Analysis

Overview of the Drug Development Process

The Patient Perspective



The screenshot shows the top navigation bar of the FDA website. On the left is a hamburger menu icon. Next to it is the FDA logo and the text "U.S. FOOD & DRUG ADMINISTRATION". On the right is a search bar with the text "Search FDA" and a magnifying glass icon. Below the navigation bar is a large banner image showing a young girl in a hospital bed, smiling, with a male doctor and a female nurse leaning over her, holding her hands. Below the image is a dark blue text box with white text that reads: "Would Your Child Benefit from a Clinical Trial? What can you expect to happen?". At the bottom of the banner are three circular navigation buttons labeled "1", "2", and "3", with the first button being highlighted in blue.

Source: fda.gov

The Drug Development Process

U.S. Food and Drug Administration
FDA Drug Approval Process

What is a drug as defined by the FDA?
A drug is any product that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and that is intended to affect the structure or any function of the body.

PRE-CLINICAL
Drug Sponsor's Discovery and Screening Phase

1 **Drug Developed**
Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

2 **IND Application**
The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from initial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.

3 **IND REVIEW**
FDA reviews the IND to ensure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protections.

4 **Animals Tested**
Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

CLINICAL
Drug Sponsor's Clinical Studies/Trials

PHASE 1
20-80
The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

PHASE 2
100's
The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment—usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

PHASE 3
1000's
The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

Page 1

→ **“Maximum Tolerated Dose”**

→ **“Biological Activity”**

→ **“Clinical Effectiveness”**

The Drug Development Process

Who reviews new drug submissions?
A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists review the drug sponsor's data and proposed labeling of drugs.

What other drug products are regulated by FDA?
Drugs include more than just medicines. For example, fluoride toothpaste, antiperspirants (not deodorant), dandruff shampoos, and sunscreens are all considered drugs.

NDA REVIEW

FDA's New Drug Application (NDA) Review

10 Drug Labeling

FDA reviews the drug's professional labeling and assures appropriate information is communicated to health care professionals and consumers.

11 Facility Inspection

FDA inspects the facilities where the drug will be manufactured.

8-9 Application Reviewed

After an NDA is received, FDA has 60 days to decide whether to file it so it can be reviewed. If FDA files the NDA, the FDA Review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.

12 FDA Drug Approval

FDA reviewers will approve the application or issue a response letter.

7 NDA Application

The drug sponsor formally asks FDA to approve a drug for marketing in the United States by submitting an NDA. An NDA includes all animal and human data and analyses of the data, as well as information about how the drug behaves in the body and how it is manufactured.

6 Review Meeting

FDA meets with a drug sponsor prior to submission of a New Drug Application.

POST-MARKETING

FDA's Post-Approval Risk Assessment Systems

FASTER APPROVALS

The Accelerated Approval program allows earlier approval of drugs that treat serious diseases and that fill an unmet medical need. The approval is faster because FDA can base the drug's effectiveness on a "surrogate endpoint" such as a blood test or X-ray result, rather than waiting for results from a clinical trial.

The Fast Track program helps reduce the time for FDA's review of products that treat serious or life-threatening diseases and those that have the potential to address an unmet medical need. Drug sponsors can submit portions of an application as the information becomes available ("rolling submission") instead of having to wait until all information is available.

PHASE 4

Because it's not possible to predict all of a drug's effects during clinical trials, monitoring safety issues after drugs get on the market is critical. The role of FDA's post-marketing safety system is to detect serious unexpected adverse events and take definitive action when needed.

Once FDA approves a drug, the post-marketing monitoring stage begins. The sponsor (typically the manufacturer) is required to submit periodic safety updates to FDA.

FDA's MedWatch voluntary system makes it easier for physicians and consumers to report adverse events. Usually, when important new risks are uncovered, the risks are added to the drug's labeling and the public is informed of the new information through letters, public health advisories, and other education. In some cases, the use of the drug must be substantially limited. And in rare cases, the drug needs to be withdrawn from the market.

PDUFA Prescription Drug User Fee Act

Since the PDUFA was passed in 1992, more than 1,000 drugs and biologics have come to the market, including new medicines to treat cancer, AIDS, cardiovascular disease, and life-threatening infections.

PDUFA has enabled the Food and Drug Administration to bring access to new drugs as fast or faster than anywhere in the world, all while maintaining the same thorough review process. Under PDUFA, drug companies agree to pay fees that boost FDA resources, and FDA agrees to time frames for its review of new drug applications.

Page 2

Clinical Trials By The Numbers

Table 1. Estimated Number of Industry-Sponsored Clinical Trials and Trial Participants by Phase, 2013



March 2015

Phase	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Phase 0	35	3,222
Phase I	1,392	119,536
Phase II	2,562	215,740
Phase III	1,680	644,684
Phase IV	530	165,158
Total	6,199	1,148,340

Source: Battelle estimates based on information from ClinicalTrials.gov. Represents industry-sponsored trials testing a potential medicine and active for at least one day during the one-year period ending September 30, 2013.

Clinical Trials By The Numbers

Table 2. Estimated Number of Industry-Sponsored Clinical Trials and Trial Participants by Selected Disease Area, 2013

Disease Area	Number of Active Clinical Trials	Estimated Total U.S. Enrollment
Cardiovascular/Circulatory	361	191,336
Central Nervous System/Brain/Pain	525	107,321
Hematology	180	15,454
Infectious	513	210,466
Metabolic/Diabetes/Nutrition	352	78,485
Oncology	2,560	215,176
Respiratory	208	87,498
Other	1,500	242,604
Total	6,199	1,148,340

Source: Battelle estimates based on information from ClinicalTrials.gov. Represents industry-sponsored trials testing a potential medicine and active for at least one day during the one-year period ending September 30, 2013.

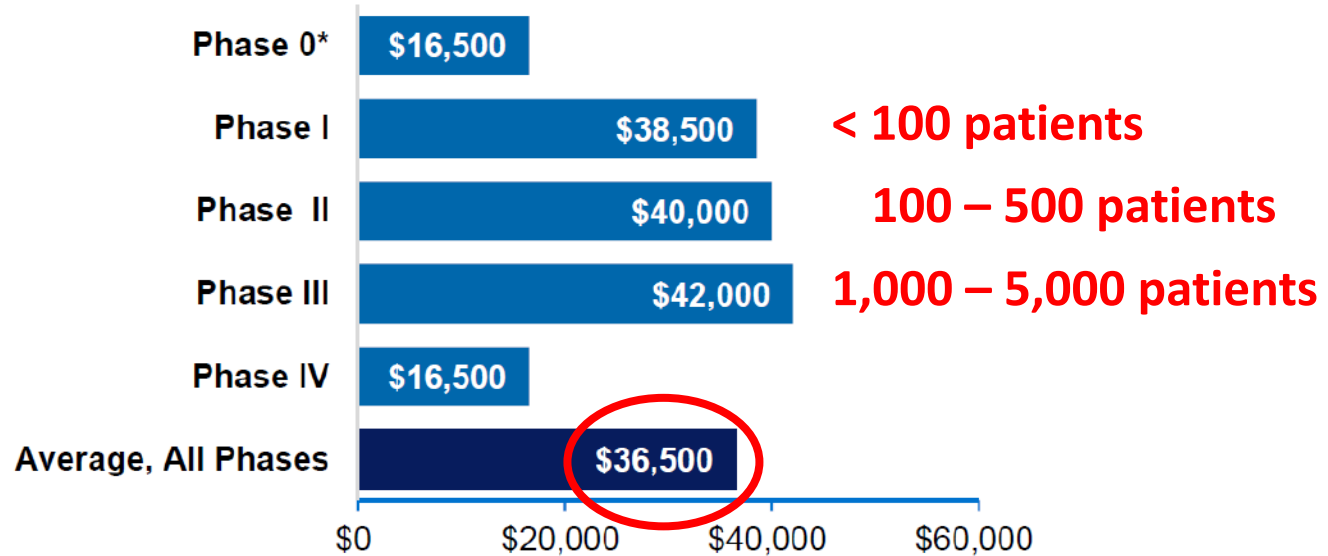
Clinical Trials By The Numbers

Typical Costs in a Clinical Study:

- Investigator and site: Institutional overhead, investigator honoraria and fees, ethics review, Institutional Review Board , investigator meetings (travel)
- Patient enrollment: Recruitment costs (advertising, travel stipend, etc.), screening, office visits (equipment, diagnostics, etc.)
- General trial procedures: Initial exam, physical exam, vital signs, detailed medical history
- Materials: Drug supply, comparator drug, other equipment, shipping, etc.
- Efficacy assessments: MRIs, CT scans, other diagnostic tests
- Laboratory: Local lab fees, storage, shipping of samples, etc.
- Site-based IT/data management: Trial master file, electronic data capture, Interactive Voice/Web Response System
- Site-specific CRO expenses: Monitoring, randomization, biostatistics, travel, meetings, etc.

Clinical Trials By The Numbers

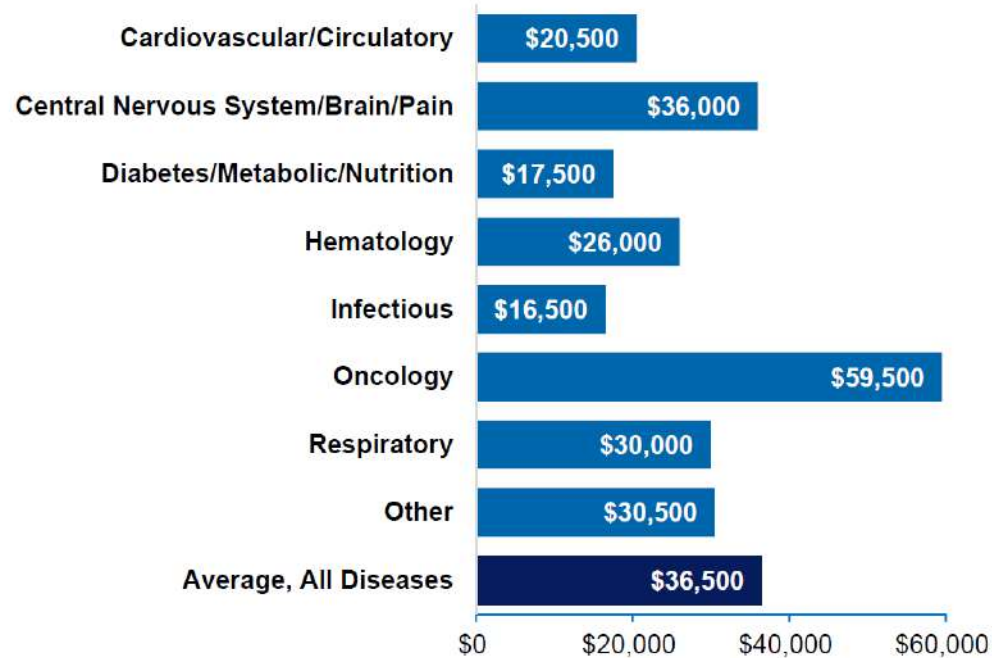
Figure 1. Estimated Average Per-Patient Clinical Trial Costs, by Phase, 2013



Source: Battelle, based on survey data from Cutting Edge Information. Because Cutting Edge Information did not develop estimates for Phase 0 studies, Phase 4 estimates, which were the lowest, were used for the very small number of Phase 0 biopharmaceutical trials included in the ClinicalTrials.gov database.

Clinical Trials By The Numbers

Figure 2. Estimated Average Per-Patient Clinical Trial Costs, by Selected Condition, 2013



Source: Battelle, based on survey data from Cutting Edge Information.

Clinical Trials By The Numbers

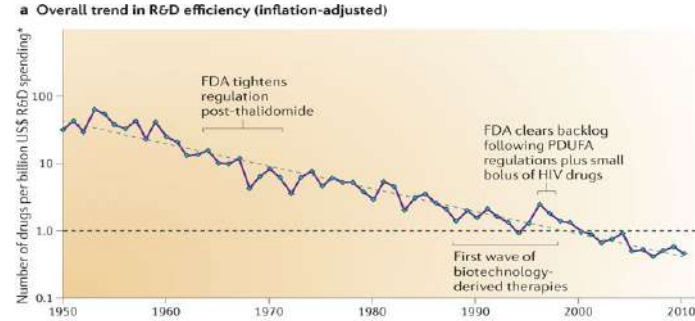
FDA User Fee Schedule

Prescription Drug User Fee Act (PDUFA)	2017	2016	2015
New Drug Application (With Clinical Data)	\$2,038,100	\$2,374,200	\$2,335,200
New Drug Application (Without Clinical Data)	\$1,019,050	\$1,187,100	\$1,167,600
New Drug Application Supplement With Clinical Data	\$1,019,050	\$1,187,100	\$1,167,600
NDA Establishment	\$512,200	\$585,200	\$569,200
Annual Product Registration	\$97,750	\$114,450	\$110,370
Medical Device User Fee Act (MDUFA) [Small Business]	2017	2016	2015
Premarket Application	\$234,495 [\$58,624]	\$261,388 [\$65,374]	\$250,895
Product Development Protocol	\$234,495 [\$58,624]	\$261,388 [\$65,374]	\$250,895
Biologics Licensing Application	\$234,495 [\$58,624]	\$261,388 [\$65,374]	\$250,895
Premarket Report	\$234,495 [\$58,624]	\$261,388 [\$65,374]	\$250,895
BLA Efficacy Supplement	\$234,495 [\$58,624]	\$261,388 [\$65,374]	\$250,895
Panel-Track Supplement	\$175,871 [\$43,968]	\$196,041 [\$49,010]	\$188,171

Source: raps.org

Clinical Trials By The Numbers

Recall Eroom's Law:



Source: Scannell et al. (NRDD 2012)

Complexity Indicator	2000-03	2008-11	Change
Median Clinical Trial Treatment Period	140 days	175 days	25%
Median Clinical Trial Site "Work Burden"	28.9 units	47.5 units	64%
Number of Eligibility Criteria (increases recruiting costs)	31 criteria	46 criteria	58%
Number of Case Report Form Pages per Protocol	55 pages	171 pages	227%
Number of Procedures per Trial Protocol	105.9	166.6	57%

Source: Phrma Battelle (2015)

Randomized Clinical Trial Design

Randomized Clinical Trials



ELSEVIER



CrossMark

UROLOGIC
ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 33 (2015) 116–121

Seminar article

A primer on clinical trial design

Chad Ellimoottil, M.D., M.S.^{a,*}, Sandeep Vijan, M.D., M.S.^b, Robert C. Flanigan, M.D.^a

^a *Loyola University Medical Center, Department of Urology, Maywood, IL*

^b *Department of Internal Medicine, University of Michigan, Ann Arbor, MI*

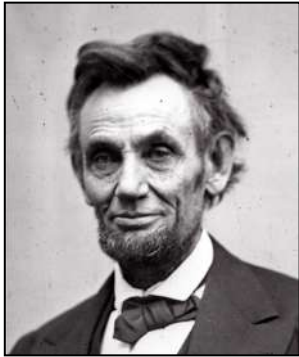
Received 4 September 2014; received in revised form 15 December 2014; accepted 17 December 2014

Randomized Clinical Trials

- **Prospective** study for determining whether a therapy is **safe and effective** (“gold standard”)
- For example, balanced two-arm RCT
 - In a sample of $2n$ patients, treat n random patients and give placebo/standard of care to the remaining n patients
- Compare the outcomes after a certain period of time
- If treated group is **significantly improved**, therapy is approved; if not, therapy is rejected

Overfitting, Data-Snooping, Pre-Test Bias, etc.

- Important objective of RCTs and regulations is to reduce chances of “**false positives**”
- Human tendency to detect patterns, even when they don't exist



Overfitting, Data-Snooping, Pre-Test Bias, etc.

10/17/2015

Over half of psychology studies fail reproducibility test : Nature News & Comment

NATURE | NEWS

Over half of psychology studies fail reproducibility test

Largest replication study to date casts doubt on many published positive results.

Monya Baker

27 August 2015

Don't trust everything you read in the psychology literature. In fact, two thirds of it should probably be distrusted.

In the biggest project of its kind, Brian Nosek, a social psychologist and head of the Center for Open Science in Charlottesville, Virginia, and 269 co-authors repeated work reported in 98 original papers from three psychology journals, to see if they independently came up with the same results.

The studies they took on ranged from whether expressing insecurities perpetuates them to differences in how children and adults respond to fear stimuli, to effective ways to teach arithmetic.



Brian Nosek's team set out to replicate scores of studies.

Endpoints

- Primary endpoint: main effect of the therapy that is to be tested, e.g., mortality, tumor size, BP, viral load, etc.
- Secondary endpoint: other features, e.g., rate of tumor growth,
- Subgroup analyses are common, e.g., men/women, young/old, risk-factor stratifications
- Endpoints are specified in advance (why??)
 - Ethical and scientific reasons (avoid “fishing expeditions”)

Patient Selection and Accrual

Table 1
Methods of sampling

Sampling design	Description	Advantages	Disadvantages
Convenience	A sample is generated by asking participants who are easily accessible (e.g., all patients who arrive in clinic today will be asked to enroll)	Inexpensive and quick	Prone to bias
Simple random	A sample is randomly generated from the entire population of interest (e.g., patients are selected from a list of all patients who underwent prostatectomy in the United States)	Unbiased and highly representative	Expensive
Stratified random	Subgroups of interest (e.g., race, ethnicity, and age) are determined a priori and random samples are drawn from within these groups	Study can be powered to evaluate subgroups of interest	Hard to implement
Cluster	All patients within a cluster are selected (e.g., teaching hospitals, all patients in Friday clinics are enrolled)	Convenient	Prone to cluster-based bias
Systematic	Begin at a random starting point and systematically select participants (e.g., select every fifth patient who arrives in clinic)	Simple to implement	If there is a pattern in the population, some subgroups may be overrepresented

Patient Selection and Accrual

- Sample should be representative of target population
- Biomarkers now play a bigger role (patient stratification, e.g., Herceptin and HER2 gene)
- Clinical trials often conducted by third-party contract research organizations (CROs), e.g., QuintilesIMS
- Cost varies depending on the trial (oncology is highest)
- Quality control is important

Trial Design

Motivation: Compare patient outcomes with and without intervention (therapy)

- Parallel design: Two-arm trial with treatment vs. control group (either placebo or standard-of-care)
- Cross-over: all patients will receive treatment but at different times (patients “**cross over**” at some point)
- Historical control: treatment group is compared to historical outcomes (not very compelling)

Trial Design

Randomization

- Balanced trial: 50/50 chance of being assigned to treatment group
- Ethical issues in this process (who wants to be in the placebo group??)
- “Clinical equipoise”: genuine doubt about which arm is better for the patient
- Be careful that your sample is “representative”

Trial Design

Blinding

- Single-blinded trial: patients do not know which group they're in, but investigators do
- Double-blinded trial: neither patients nor investigators know
- Purpose is to reduce bias, which can be quite subtle but large (Lincoln vs. Kennedy)

Trial Design

Reporting:

Table 3

Selected examples of CONSORT guidelines for reporting clinical trials

Section	Checklist item
Introduction	(1b) Structured summary of trial design, methods, results, and conclusions
	(2a) Scientific background and explanation of rationale
Methods	(3a) Description of trial design (such as parallel, factorial) including allocation ratio
	(6a) Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed
	(7b) When applicable, explanation of any interim analyses and stopping guidelines
	(8a) Method used to generate the random allocation sequence
Results	(13a) For each group, the numbers of participants who were randomly assigned, received intended and were analyzed for the primary outcome
	(19) All important harms or unintended effects in each group

Adapted from Moher et al. [1].