15.482 Healthcare Finance
Spring 2017

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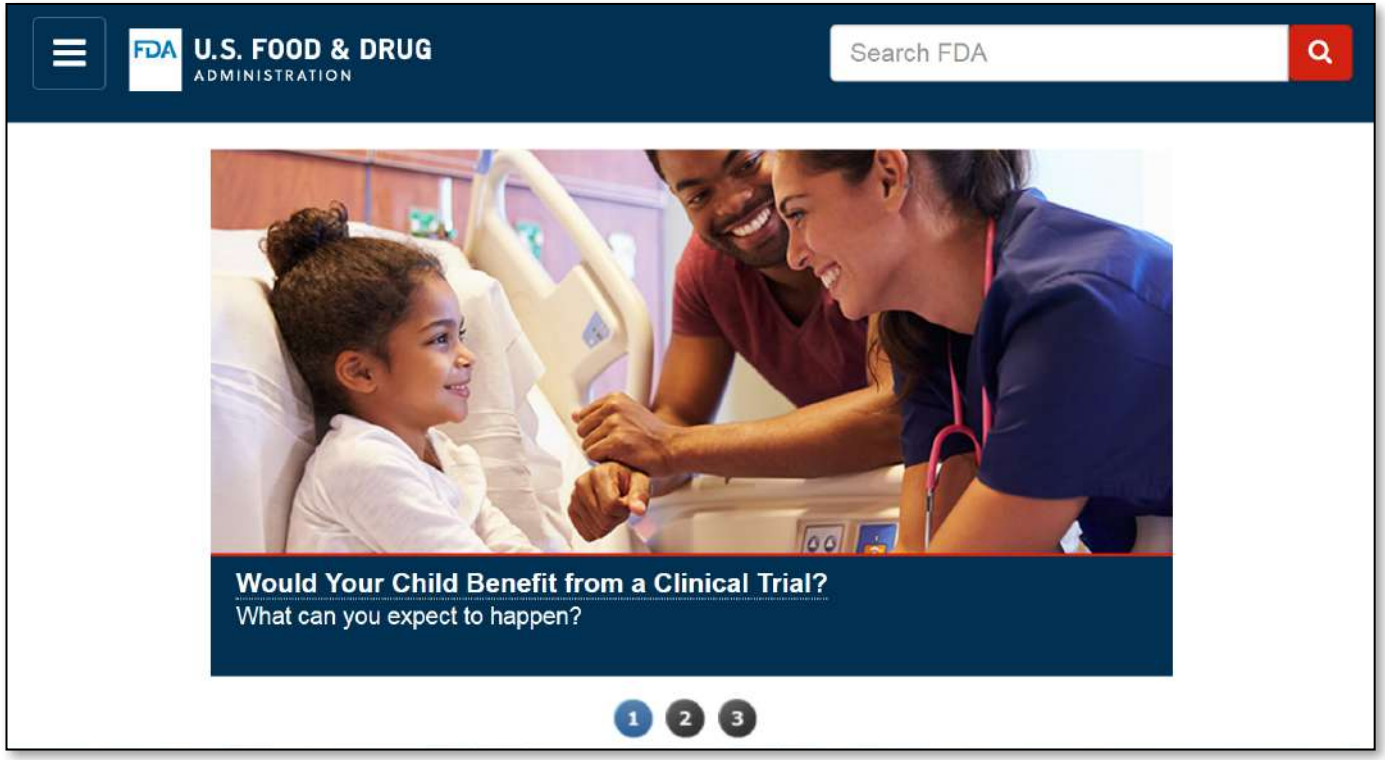
Unit 6, Part 1: Drug Development and Clinical Trials

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



Source: fda.gov

The Drug Development Process

"Maximum Tolerated Dose"

"Biological Activity"

"Clinical Effectiveness"

Source: FDA.gov

The Drug Development Process

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.

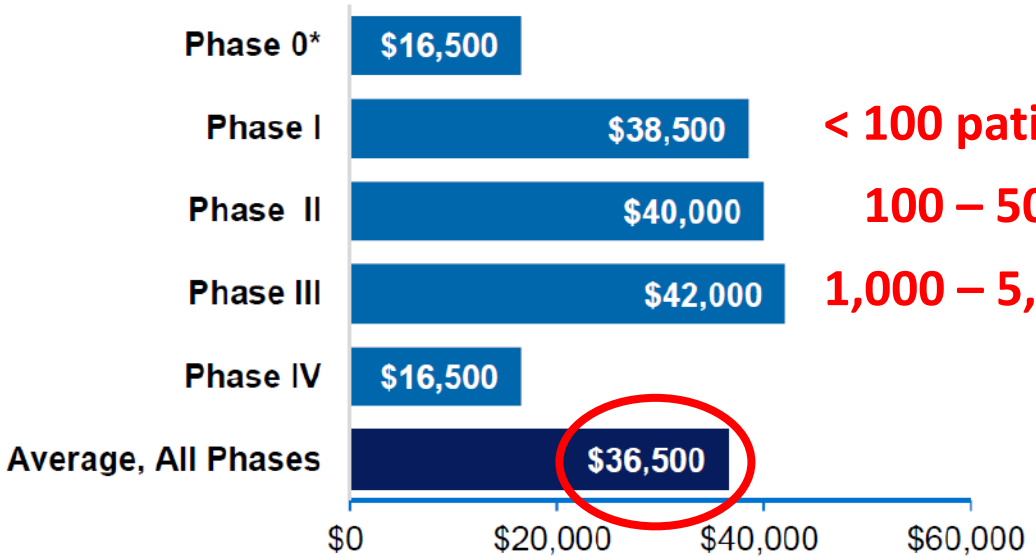
Clinical Trials By The Numbers

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

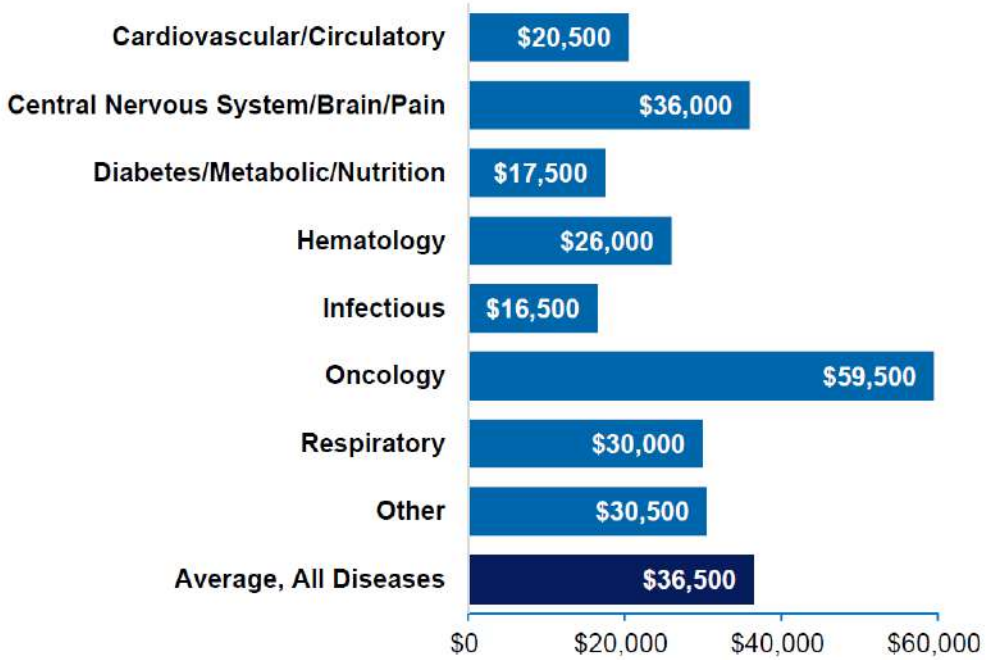
Figure 1. Estimated Average Per-Patient Clinical Trial Costs, by Phase, 2013



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

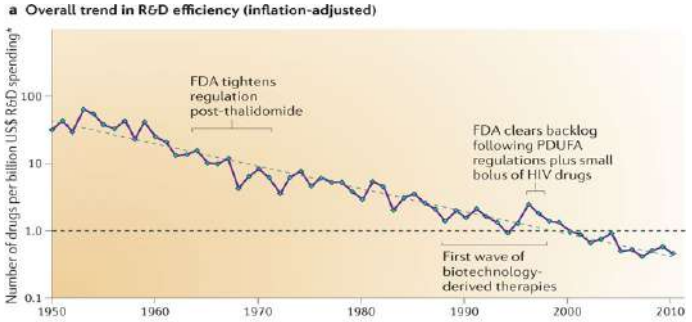
FDA User Fee Schedule

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

UROLOGIC ONCOLOGY

Seminar article

A primer on clinical trial design

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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 2*n* 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.

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].