



Clinical Trials: Highlights from Design to Conduct

Masha Kocherginsky, PhD
Biostatistics Collaboration Center
Department of Preventive Medicine

Statistically Speaking ...

What's next?

- Friday, October 21 **Clinical Trials: Highlights from Design to Conduct** Masha Kocherginsky, PhD, Associate Professor, Division of Biostatistics, Department of Preventive Medicine
- Tuesday, October 25 **Finding Signals in Big Data** Kwang-Youn A. Kim, PhD, Assistant Professor, Division of Biostatistics, Department of Preventive Medicine
- Friday, October 28 **Enhancing Rigor and Transparency in Research: Adopting Tools that Support Reproducible Research** Leah J. Welty, PhD, BCC Director, Associate Professor, Division of Biostatistics, Department of Preventive Medicine

All lectures will be held from noon to 1 pm in Hughes Auditorium, Robert H. Lurie Medical Research Center, 303 E. Superior St.

BCC: Biostatistics Collaboration Center

Who We Are



Leah J. Welty, PhD
Assoc. Professor
BCC Director



Joan S. Chmiel, PhD
Professor



Jody D. Ciolino, PhD
Asst. Professor



Kwang-Youn A. Kim, PhD
Asst. Professor



Masha Kocherginsky, PhD
Assoc. Professor



Mary J. Kwasny, ScD
Assoc. Professor



Julia Lee, PhD, MPH
Assoc. Professor



Alfred W. Rademaker, PhD
Professor



Hannah L. Palac, MS
Senior Stat. Analyst



Gerald W. Rouleau, MS
Stat. Analyst



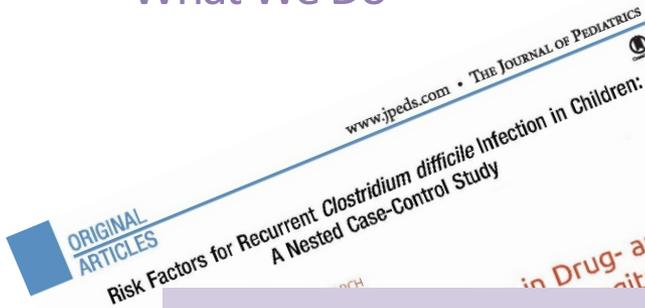
Amy Yang, MS
Senior Stat. Analyst

- Not Pictured:
1. David A. Aaby, MS
Senior Stat. Analyst
 2. Tameka L. Brannon
Financial | Research
Administrator

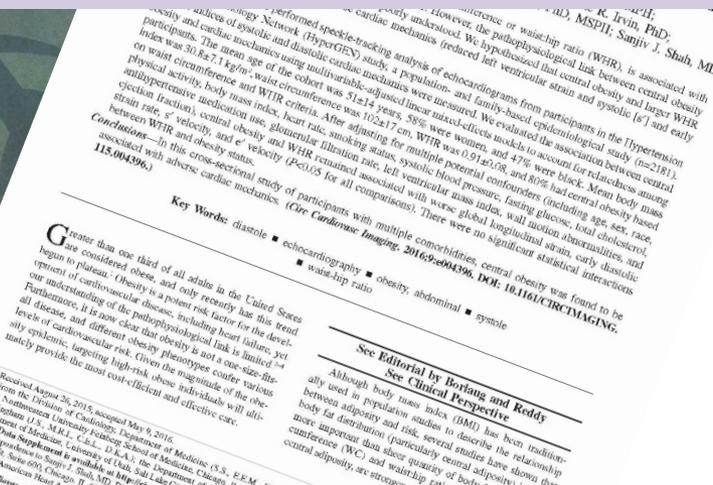
Biostatistics Collaboration Center | 680 N. Lake Shore Drive, Suite 1400 | Chicago, IL 60611

BCC: Biostatistics Collaboration Center

What We Do

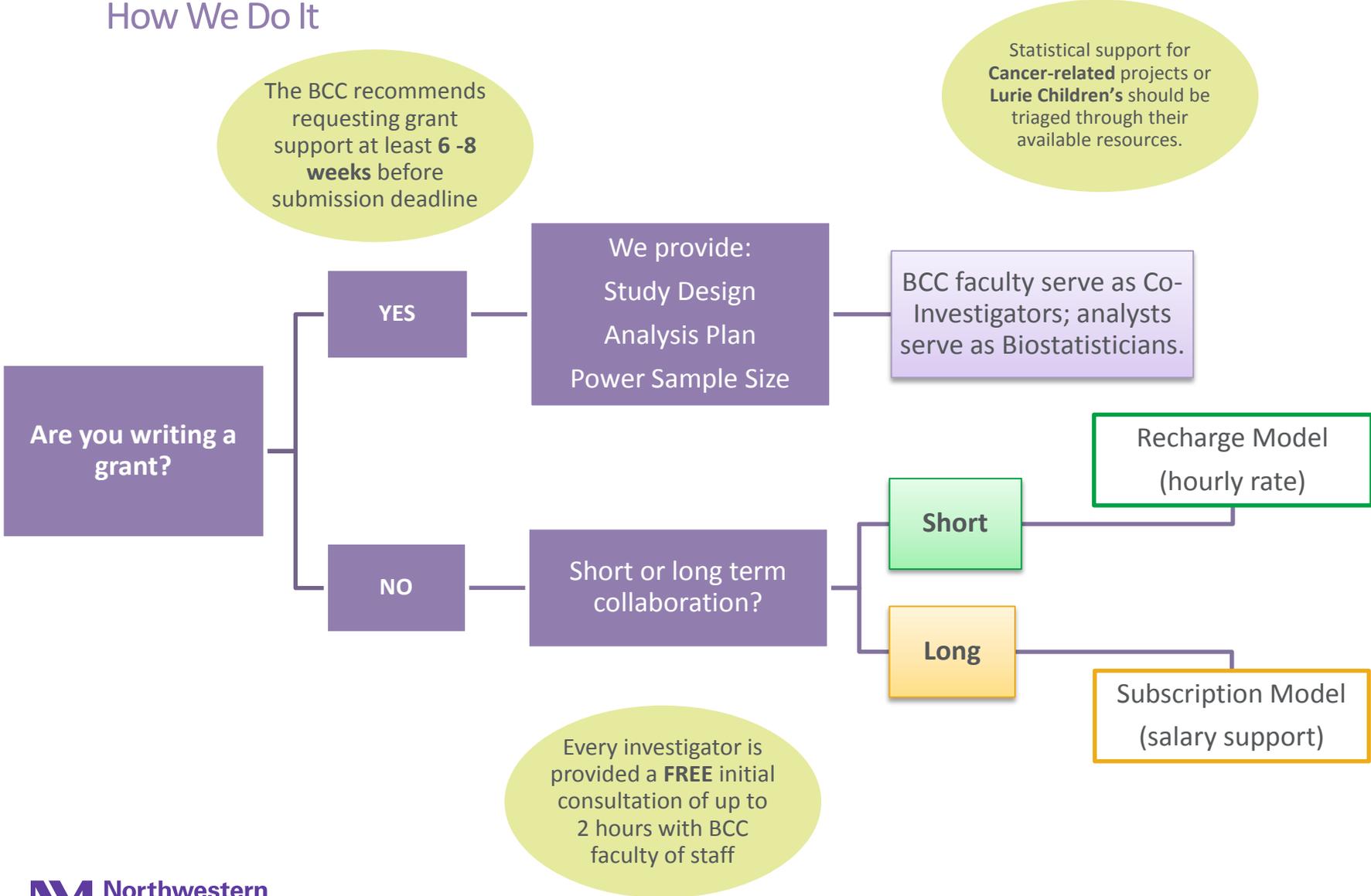


Our mission is to support FSM investigators in the conduct of high-quality, innovative health-related research by providing expertise in biostatistics, statistical programming, and data management.



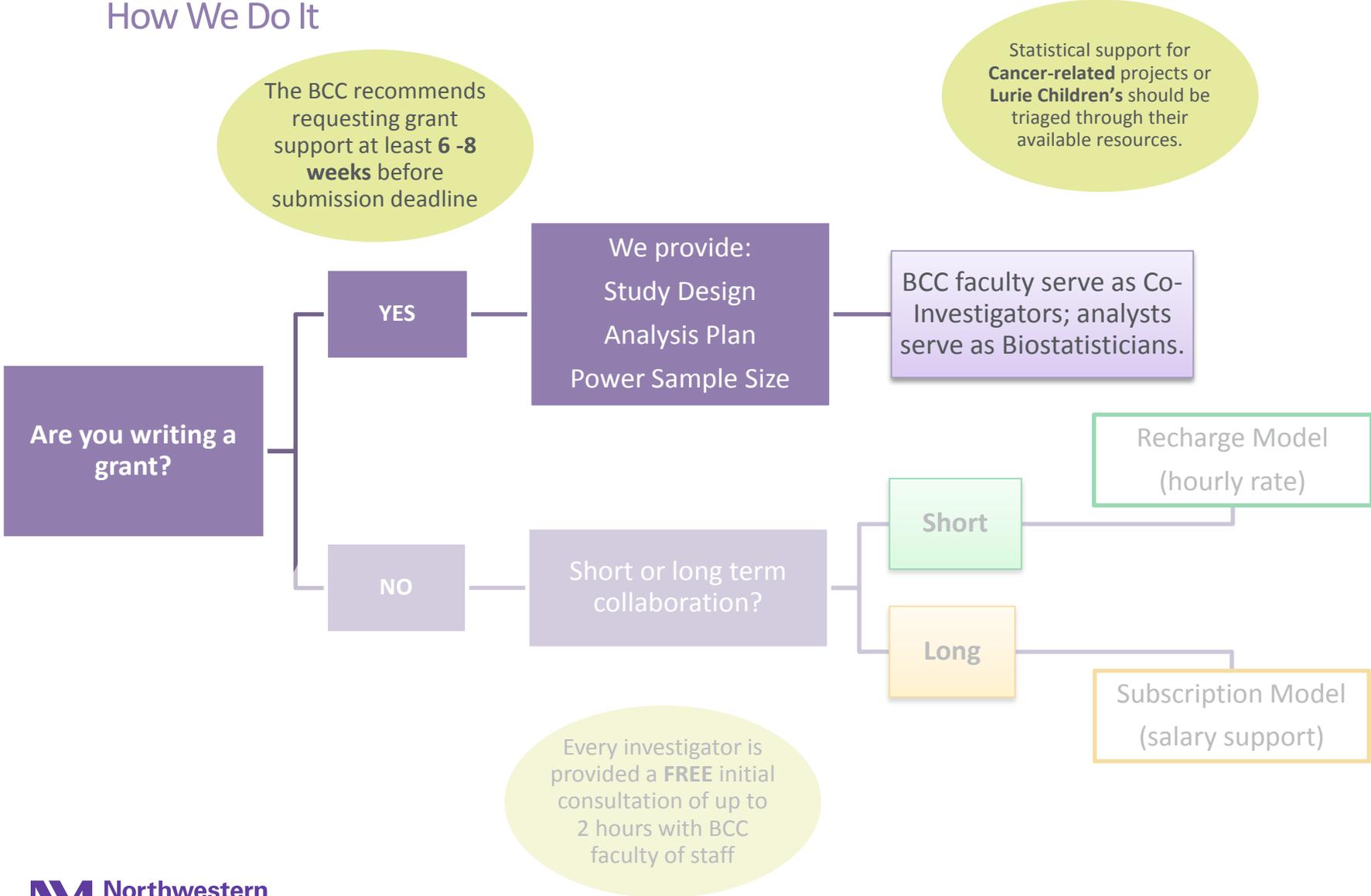
BCC: Biostatistics Collaboration Center

How We Do It



BCC: Biostatistics Collaboration Center

How We Do It



BCC: Biostatistics Collaboration Center

How can you contact us?

- Request an Appointment
 - <http://www.feinberg.northwestern.edu/sites/bcc/contact-us/request-form.html>
- General Inquiries
 - bcc@northwestern.edu
 - 312.503.2288
- Visit Our Website
 - <http://www.feinberg.northwestern.edu/sites/bcc/index.html>

Biostatistics Collaboration Center | 680 N. Lake Shore Drive, Suite 1400 | Chicago, IL 60611

What we'll be talking about today

Outline

- What is a clinical trial?
- Why a clinical trial?
- What do we think of when we hear “clinical trial”?
- Highlights of clinical trial design and conduct:
 - What’s the big question?
 - Choosing endpoints
 - Clinical trial phases and designs
 - Logistics
- Conclusions

What is a clinical trial?

What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A [research study](#)¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

- *Research* means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

45 CFR 46.102(d)

What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

- *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
 - (1) data through intervention or interaction with the individual, or
 - (2) identifiable private information

45 CFR 46.102(d)

What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

- *Prospectively assigned* refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.
- *Note: all subjects in a trial could be assigned to the same intervention (single arm trials)*

What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

- *Intervention* - a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include:
 - drugs
 - biologics
 - devices
 - procedures (e.g., surgical techniques)
 - delivery systems (e.g., telemedicine, face-to-face interviews)
 - strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise)
 - prevention strategies
 - diagnostic strategies

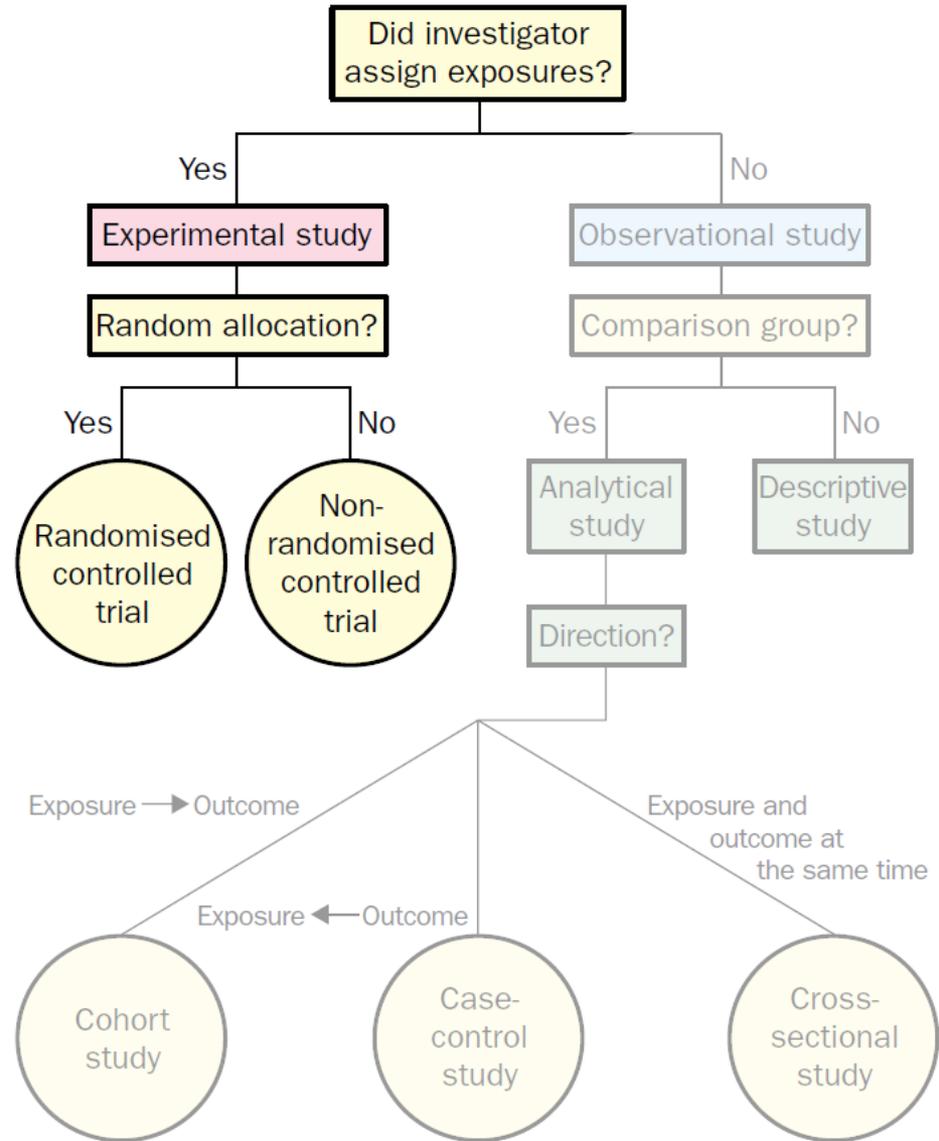
What Is a Clinical Trial?

NIH Definition (October 23, 2014, NOT-OD-15-015)

A research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.⁵

- *Health-related biomedical or behavioral outcome* - pre-specified goal(s) or condition(s) that reflect the effect of the intervention on human subjects' biomedical or behavioral status or quality of life.
- Examples include changes in:
 - physiological or biological parameters (e.g., improvement of lung capacity, gene expression)
 - psychological outcomes (e.g. mood management intervention in smokers)
 - neurodevelopmental outcomes (e.g. school performance in children)
 - disease processes
 - health-related behaviors
 - quality of life

Classification of clinical research



Grimes, D. A, & Schulz, K. F. (2002). Epidemiology 1: An overview of clinical research: the lay of the land. *Lancet*, 359(9300), 57–61

Figure 1: **Algorithm for classification of types of clinical research**

Why a clinical trial?

Clinical Trials vs. Other Study Designs

- Other types of studies include:
 - Case reports and anecdotal evidence
 - Case series and observational studies
 - Database analyses
 - Case-control studies
 - Prospective cohort studies
- A variety of limitations:
 - selection bias
 - lack of appropriate controls
 - recall bias (retrospective assessment)
 - confounding
- Clinical trials:
 - prospective and planned
 - assign treatment by design
 - eliminate many biases via randomization, blinding, and appropriate controls



Example: Women's Health Initiative (WHI) trials

- Leading causes of mortality and morbidity among postmenopausal women:
 - osteoporosis
 - cardiovascular disease (CHD)
 - cancer
- Age-related estrogen deficiency believed to play a role
- Based on [observational studies](#), hormone replacement therapy (HRT) was widely used for disease prevention via treatment of *postmenopausal estrogen deficiency*
- 1991: NIH policy to require [inclusion of women in clinical research](#)

Example: Women's Health Initiative (WHI) trials

- Women's Health Initiative (WHI) was initiated by NIH, and conducted three large randomized controlled prevention clinical trials
 - Postmenopausal women, age 50-79, 40 clinical centers
 - 15 years, \$625M funding, >112,000 women enrolled
 - Findings:
 - HRT increased risk of CHD, stroke and dementia, breast cancer
 - No effect on overall mortality
 - Many of the original hypotheses were not supported by the clinical trials
 - Overall risks far outweigh the benefits
 - Dramatic reduction in HRT use, followed by reduction in breast cancer rates
 - \$37.1B return on investment (reduction in health expenditure and better quality adjusted life-years)

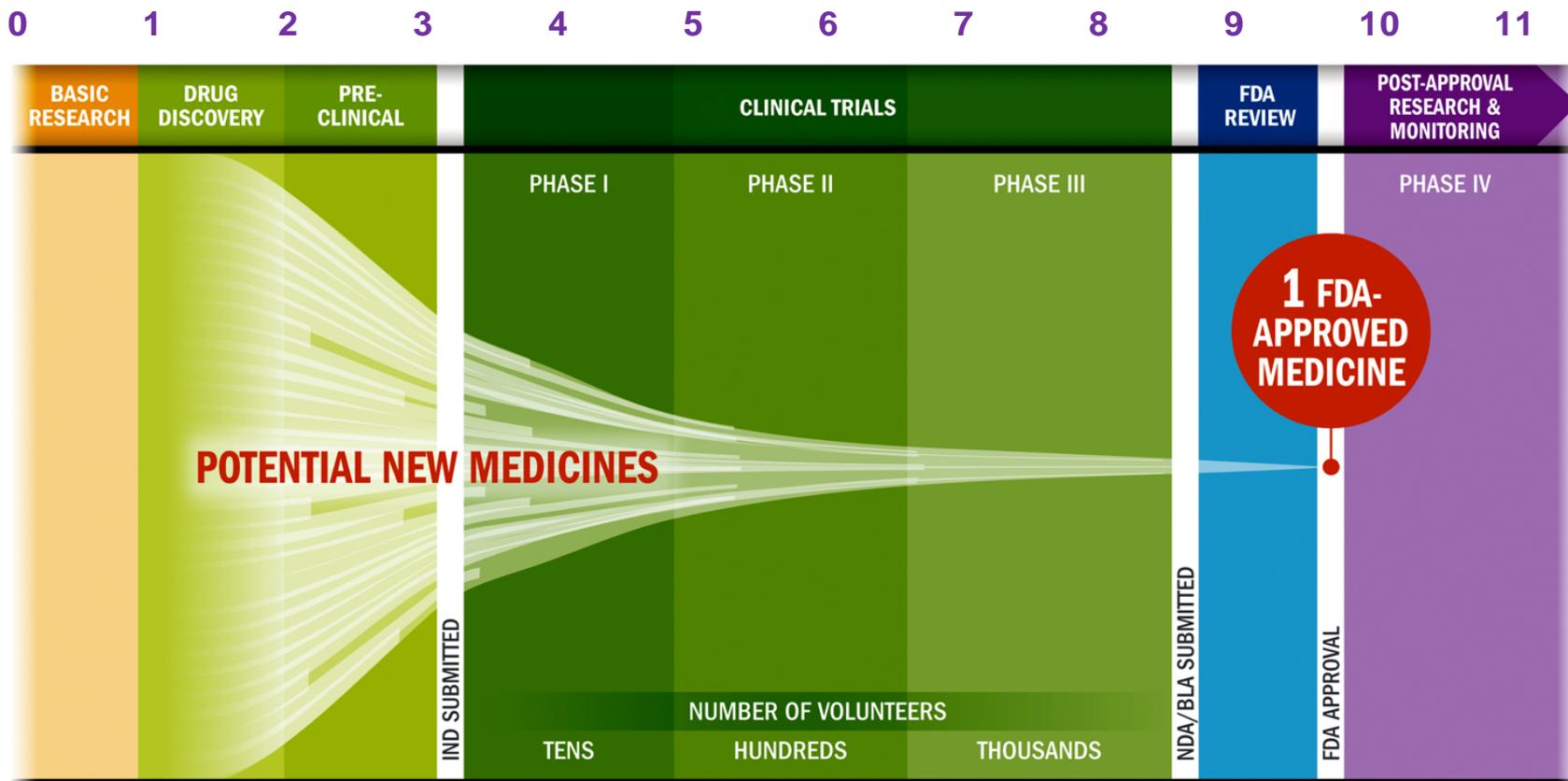
What do we think of when we hear “clinical trial”?

What do we think of when we hear “clinical trial”?

- Clinical trials frequently get reported in the news
 - Large trials
 - Expensive trials
 - *Or when things go wrong*

Drug Development Cycle

Time in years



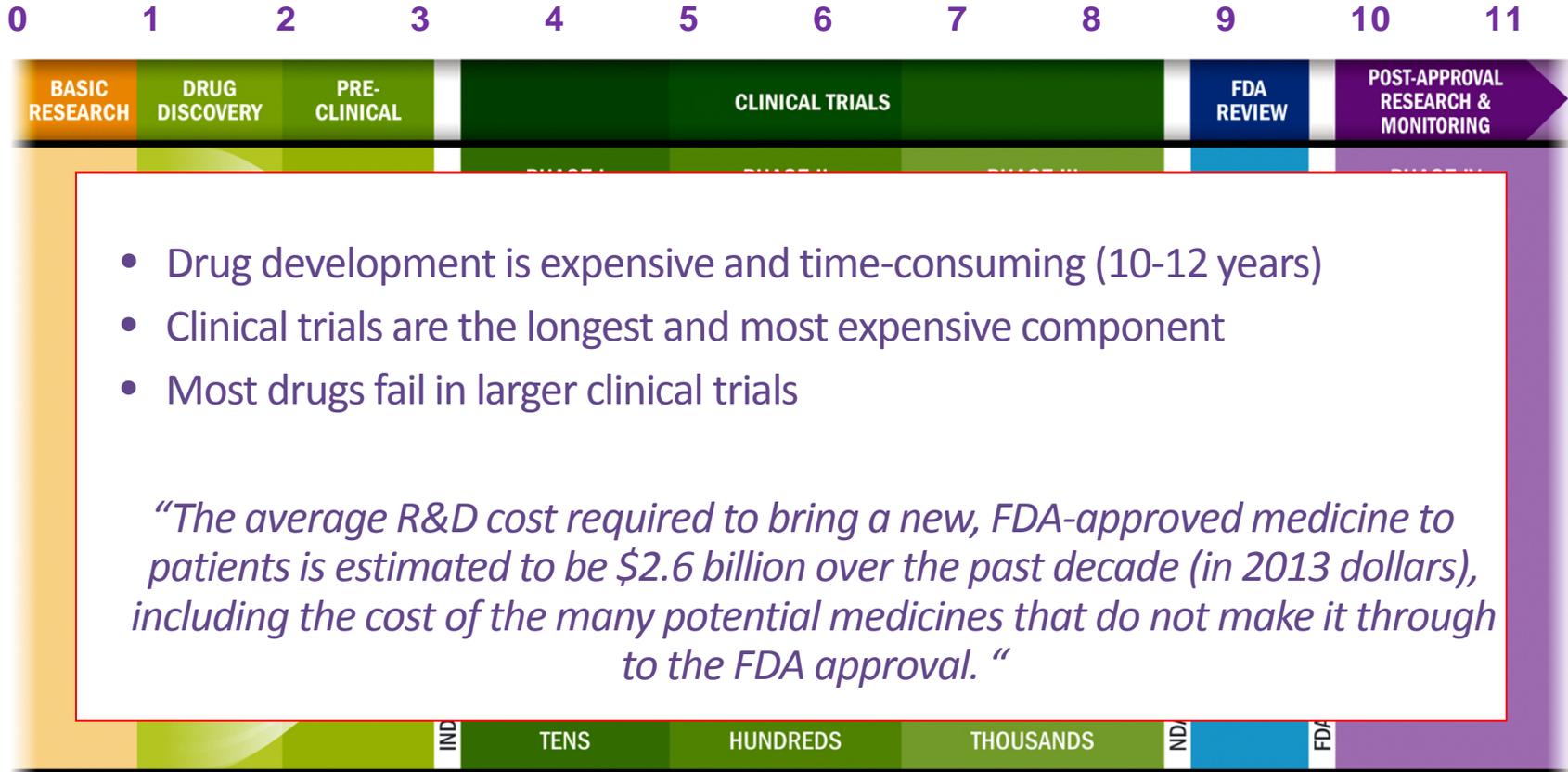
Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: "Cost of Developing a New Drug," Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, "Drug Approval Process," <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).

Drug Development Cycle

Time in years



Key: IND: Investigational New Drug Application, NDA: New Drug Application, BLA: Biologics License Application

* The average R&D cost required to bring a new, FDA-approved medicine to patients is estimated to be \$2.6 billion over the past decade (in 2013 dollars), including the cost of the many potential medicines that do not make it through to FDA approval.

Source: PhRMA adaptation based on Tufts Center for the Study of Drug Development (CSDD) Briefing: “Cost of Developing a New Drug,” Nov. 2014. Tufts CSDD & School of Medicine., and US FDA Infographic, “Drug Approval Process,” <http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf> (accessed Jan. 20, 2015).

ClinicalTrials.gov: 183,164 registered trials globally

Types of Registered Studies

The table below shows the number and types of studies that are registered and have results available on ClinicalTrials.gov.

Study and Intervention Type (as of October 18, 2016)	Number of Registered Studies and Percentage of Total	Number of Studies With Posted Results and Percentage of Total***
Total	228,174	22,874
<u>Interventional</u>	183,164	21,363 (93%)
<u>Type of Intervention*</u>	Drug or biologic	112,204 (61%)
	Behavioral, other	53,287 (29%)
	Surgical procedure	19,845 (11%)
	Device**	21,051 (11%)
<u>Observational</u>	43,972	1,511 (6%)
<u>Expanded Access</u>	367	N/A

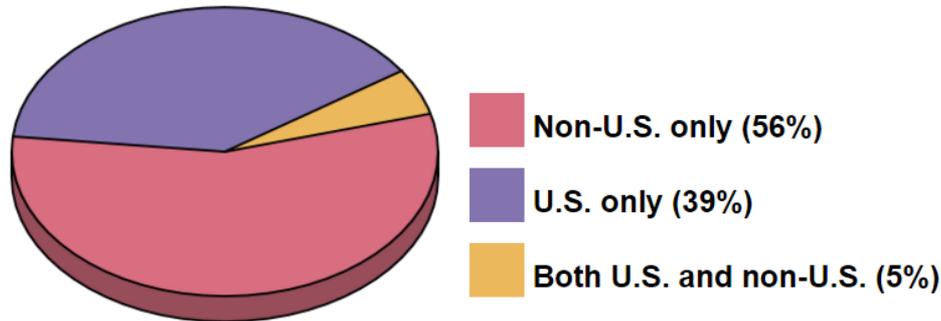
Registered trials that are currently recruiting patients (N=40,072)

Locations of Recruiting Studies

The chart below shows the distribution of locations for recruiting studies registered on ClinicalTrials.gov.

Percentage of Recruiting Studies by Location (as of October 18, 2016)

Total N = 40,072 studies



Location	Number of Recruiting Studies and Percentage of Total (as of October 18, 2016)
Non-U.S. only	22,331 (56%)
U.S. only	15,581 (39%)
Both U.S. and non-U.S.	2,160 (5%)
Total	40,072

How do we design and conduct clinical trials?

Investigator-initiated trials (IIT)

- We are an academic medical center, not a pharma or medical device company
- Industry clinical trials
 - Typically designed and developed by pharma
 - Hospitals (such as NM) are asked to join as one of the sites
 - Can accept or decline participation, but usually little say in study design
- Investigator-initiated trials (IIT)
 - If you are designing a trial, it will likely be an IIT
 - Can still be supported by industry (financial support or drug supply)
 - Why?
 - New ways of using or combining existing treatments or regimens
 - Evaluate new technologies developed at a research institution
 - Comparison of competitor treatments

Example of an Investigator-initiated trial:

- Drug interaction clinical trial
 - Grapefruit juice is known to interact with many drugs
 - Usually it's a problem, but we thought "Why not decrease the drug dose?"
 - ~150 patients enrolled in a series of Phase I trials; looked at PK
 - Were able to reduce the dose of sirolimus (cancer drug) from 90mg/week (effective dose) to about 25-35mg
 - Fewer side effects and cheaper



By **Steven Reinberg**
HealthDay Reporter

TUESDAY, Aug. 7 (HealthDay News) – In a small study of patients with incurable cancer, drinking 8 ounces of grapefruit juice day boosted the effect of a drug they were given during the study.

Although some participants had a response, tumors did not disappear after using the drug, which is mostly used to treat conditions unrelated to cancer. The study's main finding was that grapefruit juice might allow treatment using smaller drug dosages, therefore reducing side effects and perhaps costs.

Sirolimus (Rapamune) is an immunosuppressant and not approved as a cancer drug. Its primary use is to prevent rejection after kidney transplants. It is also used as a treatment for psoriasis, the researchers noted.

Some early studies suggest that sirolimus may have tumor-fighting effects. Derivatives of the drug are used in kidney cancer and breast cancer.

The drug, however, has what is called poor bioavailability, which means the body can't use it efficiently. Only about 14 percent of it gets absorbed, said lead researcher Dr. Ezra Cohen, assistant professor of medicine at the University of Chicago Medical Center.

"We thought if we could manipulate it we could increase the availability, make it easier to take and make it more effective," Cohen said.

Key steps in designing and conducting a clinical trial?

- Ethics and patient protection (IRB)
- What's the Big Question?
- Clinical trial designs
- Study Logistics
 - Recruitment and retainment
 - Treatment administration
 - Safety monitoring
 - Follow-up
- Data: collection, storage and safety
- ClinicalTrials.gov registry
- Data analysis and interpretation of the results

Ethics in clinical trials

- Conflicting goals of **gaining scientific knowledge** and **helping the patient**
 - *and sometimes from financial or other conflicts of interest*
- **Clinical trials are an ethically appropriate way to acquire new knowledge**
- Aspects of ethical conduct of clinical trials:
 - **Randomization**
 - when there is genuine uncertainty about the best treatment (equipoise)
 - **Informed consent (IC)**
 - informs of the potential risks and benefits of study participation, and of alternatives and the voluntary nature of participation
 - **Confidentiality**
 - privacy of personal health information (PHI and HIPAA)
 - **Interim monitoring**
 - ability to stop trial early for safety, futility or efficacy (especially larger trials)

Institutional Review Board (IRB)

- “The IRB Office is primarily responsible for developing and directing the University’s Human Subject Protection Program (HSPP) [...]. The HSPP mission is to be a model program of excellence in protecting the rights and welfare of human subjects involved in research.”
- Northwestern IRB Web site contains [useful resources](#), including:
 - Good Clinical Practice (GCP) document
 - Information on submitting protocols for review
 - Templates of *clinical trial protocols, consent forms and letters to subjects*
 - Guidelines on recruitment materials
- Register in eIRB+ which is Northwestern University’s electronic submission and review system for human subjects research projects
- <http://www.irb.northwestern.edu>

What's the Big Question?

How to form an answerable clinical question?

- **PICO(T)** – approach for summarizing research questions
 - **(P)** – patient population (among.....)
 - Among **postmenopausal women**
 - **(I)** – intervention (does....)
 - Among postmenopausal women, does **hormone replacement therapy (HRT)**
 - **(C)** – comparison (versus)
 - Among postmenopausal women, does hormone replacement therapy **(HRT) vs the standard of care (placebo)**
 - **(O)** – outcome (affect...)
 - Among postmenopausal women, does hormone replacement therapy (HRT) vs the standard of care (placebo) **reduce the risk of coronary heard disease?**
 - **(T)** – time (duration of study and data collection)

Primary and secondary objectives and endpoints

- Clinical trials must have a **primary objective** and a **primary endpoint**
 - **Objectives** are study goals
 - To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States.
 - **Endpoints** are quantitative outcome measures
 - The primary endpoint was coronary heart disease (CHD) (nonfatal myocardial infarction and CHD death), with invasive breast cancer as the primary adverse outcome.
 - Objectives and endpoints should be **clearly defined** in the study protocol

Hierarchy of Clinical Trial Objectives

- **Primary objective/endpoint:**
 - Usually just one
 - Power and sample size are based on this outcome
- **Secondary objective(s)/endpoint(s):**
 - Usually several planned and pre-specified secondary objectives
 - Less weight
 - Don't pick too many!
- **Exploratory objective(s)/endpoint(s):**
 - Exploratory and hypothesis-generating
 - Often evaluating non-validated biomarkers, sub-studies, etc.
- **SAFETY outcomes:**
 - Always collected/reported (especially adverse event (AE))

Choosing the Primary Endpoint: Cancer Trials Example

- In cancer, the ultimate outcome of interest is **overall survival (OS)**
 - **Poor-prognosis cancers:** events (deaths) can be observed during the trial → OS may be a feasible primary outcome
 - **Better-prognosis cancers:** longer-term survival → OS is not a feasible primary outcome
- Treatment may still have other benefits, for example:
 - Shrink or stabilize tumors
 - Delay tumor growth
 - Improve a biomarker (e.g. CA-125 in ovarian cancer)

Choosing the Primary Endpoint: Cancer Trials Example

- Such endpoints are called **surrogate endpoints**:
 - A measure of the effect of a treatment that correlates with a real clinical endpoint
 - May be used instead of real endpoints (e.g. OS)
 - Trial results can be obtained sooner (may allow earlier approval – *can be good or bad*)
 - **But:** surrogate endpoints are not always true indicators of how well a treatment works; they must be validated

Choosing the Primary Endpoint: Cancer Trials Example

- **What is the most clinically relevant endpoint, and can we use it?**
- **If not, is there a well-validated surrogate endpoint?**
 - E.g. tumor response and progression-free survival (PFS) are validated surrogate endpoints in cancer
- **How is the endpoint measured?**
 - Tumor size is measured by radiographic imaging using RECIST criteria
 - Inter-rater variability in tumor diameter measurements?
 - Continuous tumor size vs. standard response categories (*complete (CR) or partial (PR) response, stable (SD) or progressive (PD) disease*)?
 - PFS – also based on RECIST

Choosing the Primary Endpoint: Cancer Trials Example

- **Is the endpoint relevant for the mechanism of action of the treatment?**
 - Historically, most drugs in cancer were cytotoxic (cause tumor shrinkage)
 - Newer drugs stabilize tumor growth (cytostatics) → clinical benefit
 - Immunotherapy (e.g. delayed response in some PD-1/PD-L1 checkpoint inhibitors)?
- **Is the detectable effect size clinically important?**
 - Want a realistic effect size that can be detected, and is it “worth it”

Core outcome sets (COS) for clinical trials

- Heterogeneity in **outcomes** in other disease areas
- Proposed solution: develop **core outcome sets** - an agreed, standardized collection of outcomes measured and reported in all trials for a specific disease
- Some COS's already exist:
 - Rheumatology (OMERACT, since 1992)
 - More than 50 groups have been working on COS including pain, maternity care, and some pediatric specialties
 - COMET Initiative – defined an approach to development of COS's
 - Check your specific disease area

Williamson, P. R., Altman, D. G., Blazeby, J. M., Clarke, M., Devane, D., Gargon, E., & Tugwell, P. (2012). Developing core outcome sets for clinical trials: issues to consider. *Trials*, 13(1), 132.

Get a statistician involved

- Why?
 - Not all questions can be answered with data
 - Not all endpoints are created equal (e.g. some more variable than others)
 - Clinical trial design depends on the objectives and endpoints
 - Sample size and feasibility depend on the design
 - Fancy statistical analyses cannot fix poor study design
 - Because we are fun people (especially Dr. Kwasny)

Get a statistician involved at this early stage!

Clinical trial design

Clinical Trials Phases

- *Pre-clinical – animal and other lab studies*
- Pilot and Feasibility Trials
 - Obtain preliminary data for larger studies
 - Work out logistical details
- Phase I
 - Dose finding – recommended Phase II dose (RP2D)
 - Safety
- Phase II
 - Further evaluation of safety at RP2D
 - Preliminary evidence of efficacy

Clinical Trials Phases

- Phase III
 - Gold standard
 - Safety and Efficacy
 - Usually randomized, parallel control
- Phase IV (post-market)

Design considerations

- Primary endpoint and objective determine design and sample size
- Endpoint data types:
 - Continuous (e.g. blood pressure)
 - Binary (e.g. disappearance of an infection after antibiotic treatment)
 - Time-to-event (e.g. time from randomization to death or to CHD)
 - Other types (count data, ordinal scales, competing risks)
- Continuous endpoints allow more power
 - E.g. comparing time to death (OS) vs. comparing 2-year survival rates

Be prepared

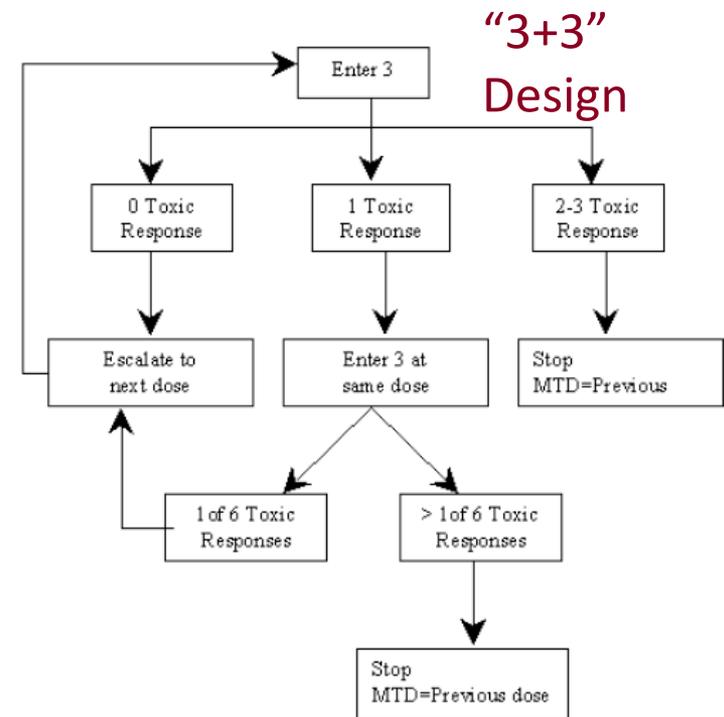
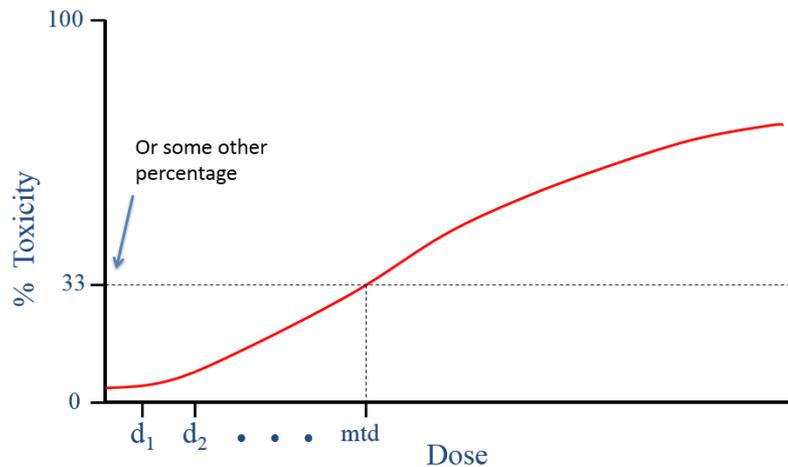
- Preliminary data for the primary endpoint
 - Response rates
 - Median survival
 - Mean and variance
- From where?
 - Your own preliminary data
 - Published literature
- Choose
 - Type I error rate α (pursuing a false positive)
 - Power (missing a promising treatment)

Pilot and feasibility clinical trials

- Why conduct a pilot study?
 - Scientific - obtain preliminary data for larger study design
 - Process – recruitment rates, logistics, time and budget, data collection
- Must have a clear decision rule for a “go-no-go” decision, e.g.:
 - Can we enroll at least 10 pts/month?
 - Is enrollment rate $\geq 75\%$?
- Pilot trials need to have well-defined endpoints and objectives, e.g.:
 - Obtaining preliminary data – base the sample size on the desired precision of the estimate (the [confidence interval](#) approach)

Phase I

- Typically 10-20 subjects
- Goals: dose finding, typically for safety
- Basic idea: assess toxicity at a variety of doses
- Many ways to do this, depending on the disease setting
- In cancer, “3+3” design is the most common



Phase II

- Typically 30-100 subjects
- Assess efficacy
- Continue safety assessment
- Make the “go-no-go” decision for the subsequent Phase III trial

- Design considerations:
 - Historic controls vs. parallel control arm
 - Single arm vs randomized
 - Play-the-winner design if multiple treatments
 - Multi-stage designs

Phase III

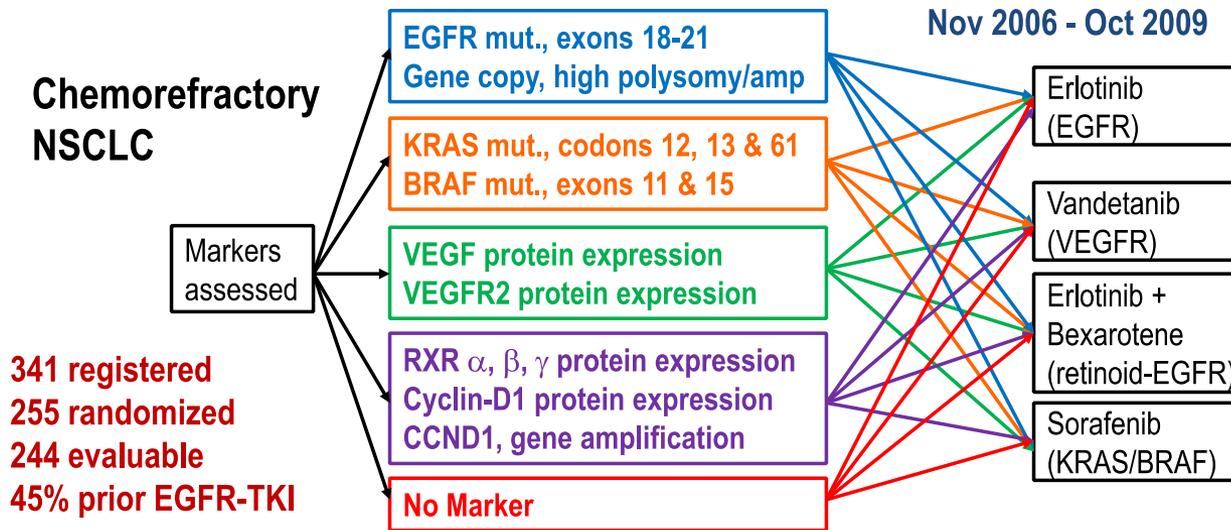
- Usually large randomized controlled trials (100's or 1000's of subjects)
- Usually straightforward question, comparing treatments A vs. B
 - Null hypothesis, H_0 : no differences between A and B
 - Alternative hypothesis, H_A : A is better than B by $\geq \delta$ (effect size)
 - Typically $\alpha = 0.05$ (false positives) and 90% power
- Usually must have interim analyses and stopping rules:
 - early stopping rules (futility or efficacy)
 - pre-specified in the design and statistical analysis plan
 - independent Data and Safety Monitoring Board (DSMB)

Randomized Trials: Intent-to-Treat Analysis

- Intent-to-treat analysis - one of most fundamental principles underlying analysis considerations for randomized clinical trials
- Two major elements:
 - Once randomized, always analyzed (regardless of adherence/dropout)
 - Analyzed according to group to which randomized (regardless of adherence)
- ITT allows for unbiased hypothesis testing

Example of an adaptive design

BATTLE-1 Trial: Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination



- Primary endpoint: 8-wk disease control (DCR = rate of PR, CR or stable at 8 wks)
- Equal randomization until 40% accrual, then switch to outcome adaptive randomization based on DCR estimates dependent on treatment & markers
- Success: Bayesian estimated Prob[8-week DCR > 30%] > 80% for treatment in a marker subgroup

22

Additional considerations and Clinical Trial Logistics

Clinical Trial Protocol

- A comprehensive document that describes how a clinical trial will be conducted
- Pre-specifies all objectives, endpoints, design and statistical analysis plan
- Includes:
 - Background and preliminary data
 - Objective, purpose and study rationale
 - Study design
 - Patient population (inclusion/exclusion criteria)
 - Treatment administration details
 - Study assessments (efficacy, safety, adverse events)
 - Statistics (design, sample size, interim monitoring and statistical analysis plan)
 - Other details including ethics, quality control, data management, publication policy, and any relevant supplementary material

Protocol Template from FDA and NIH (Draft, 61 pages)



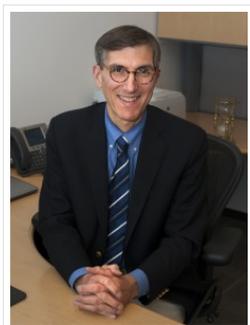
← Previous Next →

FDA and NIH Release a Draft Clinical Trial Protocol Template for Public Comment

Posted on March 18, 2016 by FDA Voice

By: Peter Marks, M.D., Ph.D.

Enhancing important efforts around clinical trials continues to be a key scientific priority. Another way we can encourage clinical trials is to look for ways to help clinical investigators make clinical trials more efficient, potentially saving development time and money. Today we're announcing a draft clinical trial protocol template developed by the Food and Drug Administration (FDA) and National Institutes of Health (NIH) that should help with that.



The clinical trial protocol is a critical component of any medical product development program. It's defined in the *International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice: Consolidated Guidance*, as describing "the objective(s), design, methodology, statistical considerations, and organization of a trial...[and] usually also gives the background and rationale for the trial". Similarly, for medical devices, some direction has been provided in the *International Organization for Standardization (ISO) Clinical Investigation of Medical Devices for Human Subjects — Good Clinical Practice (ISO 14155:2011)*. Although guidance provides

information on the important content that should be included in a protocol to help ensure human subject protection and data quality, it does not describe a standardized format for

- ☐ PREFACE
 - ☐ How To Use This Template
 - ☐ References
- ☐ <Title>
 - ☐ Table of Contents
 - ☐ LIST OF ABBREVIATIONS
 - ☐ STATEMENT OF COMPLIANCE
 - ☐ PROTOCOL SUMMARY
 - ☐ SCHEMATIC OF STUDY DESIGN
 - ☐ 1 KEY ROLES
 - ☐ 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE
 - ☐ 3 OBJECTIVES AND PURPOSE
 - ☐ 4 STUDY DESIGN AND ENDPOINTS
 - ☐ 5 STUDY ENROLLMENT AND WITHDRAWAL
 - ☐ 6 STUDY AGENT
 - ☐ 7 STUDY PROCEDURES AND SCHEDULE
 - ☐ 8 ASSESSMENT OF SAFETY
 - ☐ 9 CLINICAL MONITORING
 - ☐ 10 STATISTICAL CONSIDERATIONS
 - ☐ 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS
 - ☐ 12 QUALITY ASSURANCE AND QUALITY CONTROL
 - ☐ 13 ETHICS/PROTECTION OF HUMAN SUBJECTS
 - ☐ 14 DATA HANDLING AND RECORD KEEPING
 - ☐ 15 STUDY ADMINISTRATION
 - ☐ 16 CONFLICT OF INTEREST POLICY
 - ☐ 17 LITERATURE REFERENCES
 - ☐ APPENDIX

Study Logistics

- Usually need a study coordinator and a data manager
- Pilot clinical trial to work out logistics details
 - Recruitment
 - Subject retention (establishing a personal relationship or financial incentives)
 - Development of data collection tools
 - Safety monitoring and reporting (regulatory issues and cumulative safety assessment procedures)
 - Follow-up (minimize the loss to follow-up)

Data Management



- We recommend using REDCap: [Research Electronic Data Capture](#)
- Web-based application for building and managing research databases
- REDCap Consortium has over **295,000** projects

- Why REDCap?
 - Easy to create data collection forms
 - Web-based data entry and access from multicenter studies
 - Audit trails for tracking history of database and entry
 - Compliant with HIPAA standards for security
 - Free (to the investigator) to use at NU

- Must attend mandatory [New Project Owner Intro Session](#)

Please use your most recent available 12-month period for the following questions.

1) **Site number** 
** must provide value*

2) **Time Period** 
** must provide value*

≤ 3 mo.

3) **# QNS Patients (≤ 3 mo.)**
** must provide value*

4) **Total # Patients Tested (≤ 3 mo.)**
** must provide value*

5) **% QNS (≤ 3 mo.)**

> 3 mo.

6) **# QNS Patients (> 3 mo.)**
** must provide value*

7) **Total # Patients Tested (> 3 mo.)**
** must provide value*

8) **% QNS (> 3 mo.)**

9) **Comments**

Expand

REDCap Form
example

ClinicalTrials.gov - registry and results database

- [ClinicalTrials.gov](https://www.clinicaltrials.gov) is a database of clinical studies of human participants conducted around the world
 - Initial law passed by Congress (1997)
 - NIH Releases ClinicaTrials.gov website (2000)
 - “The Final Rule” (*effective January, 2017*)
- Applicable clinical trials must be registered on www.clinicaltrials.gov
 - Non-NIH funded trials
 - Drug, biological, and device products and pediatric post-market surveillance (essentially FDA-regulated)
 - Does not apply to phase 1 trials or small feasibility device studies
 - NIH-funded trials
 - **All clinical trials funded NIH** (wholly or partially)
 - Includes Phase 1 clinical trials and trials that do not involve any FDA regulated product such as trials involving only behavioral interventions
- Results must be reported (within 12 months of study end) :
 - participant flow information
 - demographics and baseline characteristics of the enrolled participants
 - primary and secondary outcomes, including results of any appropriate statistical tests
 - adverse events

Statistical data analysis

- Clinical trial was well-designed, and statistical analysis plan developed
- Statistical analysis plan is **pre-specified**

- Statistical analysis should be easy – but it never is!
 - Data quality (late data, missing data, outliers, etc)
 - Protocol deviations
 - Unanticipated problems (e.g. slow accrual)
 - Loss-to-follow-up

- Primary analysis + many more (secondary and exploratory analyses)
- Sensitivity analyses

Conclusions

- **Clinical trials:**
 - The most definitive method of determining whether an intervention has the postulated effect!
 - Usually a time-consuming and expensive endeavor!
 - Many scientific and logistical details to consider
 - Are a statistics-heavy endeavor, because they are essentially designed experiments, and data will be collected and analyzed
- **Team science between clinicians and statisticians to:**
 - Refine study objectives and hypotheses
 - Select appropriate endpoints
 - Develop clinical trial design, sample size and statistical analysis plan

Talk to a statistician as early as possible – we can help!

Thank You

Questions?

Statistically Speaking ...

What's next?

Friday, October 21

Clinical Trials: Highlights from Design to Conduct Masha Kocherginsky, PhD,
Associate Professor, Division of Biostatistics, Department of Preventive Medicine

Tuesday, October 25

Finding Signals in Big Data Kwang-Youn A. Kim, PhD, Assistant Professor, Division
of Biostatistics, Department of Preventive Medicine

Friday, October 28

**Enhancing Rigor and Transparency in Research: Adopting Tools that Support
Reproducible Research** Leah J. Welty, PhD, BCC Director, Associate Professor,
Division of Biostatistics, Department of Preventive Medicine

All lectures will be held from noon to 1 pm in Hughes Auditorium, Robert H. Lurie Medical Research Center,
303 E. Superior St.