Module 1 Summary and Study Examples

Laura Lee Johnson, Ph.D.
Associate Director
Division of Biostatistics III
Center for Drug Evaluation and Research
US Food and Drug Administration
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Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

Overview

- Many different people take the course
  - Some first introduction, some advanced
- Tricks, tips, and concepts
- General objectives
  - Better consumer of medical and scientific literature
  - Enhance conversations inside research team [with study statisticians and epidemiologists]
  - Better science

Introduction to the Principles & Practice of Clinical Research

Module I – Study Design, Measurement, and Statistics

- Choosing a Research Question and Implications for Efficient Clinical Trials
- Overview of Clinical Study Design
- Design of Epidemiologic Studies
- Clinical Research from the Patient's Perspective
- Study Participant Selection
- Issues in Randomization
- Overview of Hypothesis Testing
- Sample Size and Power
- Conceptual Approach to Survival Analysis
- Measures
- Quality of Life
- Designing and Testing Questionnaires
- Using Large Datasets for Population-Based Health Research
- Secondary Data/Meta-Analysis

Asked What You Should Know

- Here are their slides
- A few edits
- Ordered to tell a story

Easy to Write

- The study will use a randomized, double-blind, controlled parallel arm design and an intent to treat analysis.
- Subjects/participants will be consented.

Not Easy

- To implement and maintain the integrity of
  - Randomization
  - Blinding/masking
  - Multiple study arms
  - Data collection
  - Transfer data to regulatory and other groups

How good is the primary research question?

At the end of the day, when the clinical research is completed and the data analyzed, will the *answer* (whatever it is) to the *primary research question* advance scientific knowledge and/or clinical practice?

Wakim 2015

The PICO(T) Question

P: Population/disease
I: Intervention or Variable of Interest
C: Comparison group
O: Outcome
T: Time

In _____(P), how does _____(I) compared to _____(C) influence _____(O) during _____ (T)?

Example:
In patients ages 65 and older (P), how does the use of an influenza vaccine (I) compared to not receiving the vaccine (C) influence their risk of developing pneumonia (O) during the flu season (T)?

Stillwell et al. 2010; Wakim 2015; others

Controls and Interventions

- Specific question being addressed in the study directs the choice of the control group or groups for the study
- Many times it is easier to decide what interventions should be in the intervention arm than the control arm

Effect Modification

- Interaction
- Synergy
  - Could be larger or smaller
- Association between outcome and another variable (e.g. intervention) is modified by different levels of a third variable

Smoking, Asbestos, and Lung Cancer

- Smoking (alone) ↑ risk of lung cancer by A
- Asbestos exposure (alone) ↑ risk of lung cancer by B
- Smoking AND having asbestos exposure ↑ risk of lung cancer by MORE/LESS than A+B

Confounding

- Two or more variables
- Known or *unknown* to the researchers
- Confounded when their effects on a common response variable or outcome are mixed together
- Association between an exposure and outcome is misestimated due to the failure to account for a third factor (the confounder)

Consider

- Association observed between carrying matches in your pocket and lung cancer
  - Carrying matches causes lung cancer

  OR
  - Association between carrying matches and lung cancer is result of confounding by another unmeasured variable associated with both

(Pam Shaw, CTR Course 2013)

A good primary outcome measure is clinically meaningful and simple

Wakim 2015

Two Types of Research Studies

- Observational
  - Goal is to observe and collect data on characteristics of interest without influencing the participant, environment or disease course
- Experimental
  - Researcher deliberately influences course of events and investigates effects of an intervention on a carefully selected population of subjects
  - Experimental studies done on human subjects are referred to as clinical trials or clinical studies

Observational Studies

- Case Reports
- Case Series
- Cross-Sectional or Prevalence Surveys
- Case-Control Study
- Cohort Study (longitudinal)
- Natural History Studies
- Ecological Studies (data on population rather than individual level)

Epidemiology

- Assumes disease has causal and preventative factors that can be identified through systematic investigation

Quasi Experimental, One/Single Arm, or Non-Randomized Experimental Studies

- No control group
  - Early in investigation
- Concurrent control "group"
  - Treatment assignment not by randomization
- Historically controlled
  - Missing data
  - Poor data
  - Non-comparability of groups

Intervention Based Research Spectrum

- Quasi-experimental
- Pre-clinical studies
- Phase 0
- Phase I
- Early/Late Phase II
- Phase III
- Phase IV
- Dissemination and Implementation
- Comparative or Cost Effectiveness

Non-Randomized	Randomized
• Can ONLY show Association • You will never know all possible confounders!	• Can show Association AND Causality • Well done non-adaptive randomization → unknown confounders should not create problems

Ideal Study - Gold Standard

- Treatment / control
- Parallel groups
- Superiority
- Prospective
- Double blind / masked
- Randomized

Types of Randomized Studies

- Parallel Group – classic
- Sequential Trials – physical sciences
- Group Sequential trials – classic
- Cross-over – intervention washout
- Factorial Designs – independence
- Adaptive Designs – gaining popularity
- Enriched Enrollment – regression to the mean
- Cluster Randomized Designs

Drill in a Bit

Intent-to-Treat versus Completers "How Many in the Data Analysis"

- ITT = Intent-To-Treat analysis
  - Include all randomized (if randomized study)
  - Assume all study participants
    - Adhered to study regime assigned
    - Completed the study
- MITT = Modified ITT analysis
  - ITT, but only include people who start intervention they are assigned to
- Completers or Adherers analysis
  - Only the well behaved

Masking/Blinding

- Less common in non-randomized studies, but can mask outcome assessors as to hypothesis
- Specify whom to be masked, why, how, and to what
- Assess effectiveness of masking
- Specify criteria for unmasking, whom to be unmasked
- Mask determination of outcome so that reviewers are unaware of treatment assignment; provide information on "need to know" basis

What is being adapted?
(Types of adaptations)

- Adaptive randomization
- Adaptive dose-finding (dose-ranging)
- Drop-the-loser (or pick-the-winner)
- Adaptive seamless phase II/III
- Biomarker-adaptive
- Group sequential methods
- Sample size re-calculation

Sanchez-Kam et al. 2014, Coffey et al. 2012, Chow & Chang 2008

Wakim 2015

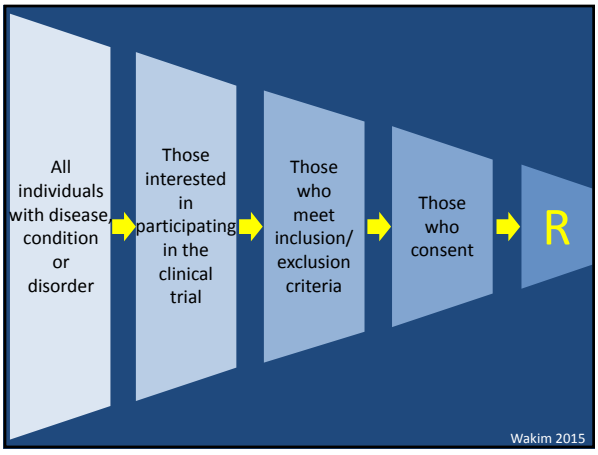
Reproducible Measurements: Regardless of Study Design

- Well defined cohort
- Exclusion and inclusion criteria
- Study conduct
- Outcomes
- Study data, analyses

Biases in Clinical Research

Bias	Remedy
Selection/Assignment	Randomization
Treatment & Assessment	Masking Research Team
Response	Masking Participant
During Data "Cleaning"	Masking Assigned Treatment & Pre-specification
During Analysis	Intention to Treat (ITT) & Pre-specification
Publication	Trial Registration
Reporting	Pre-specification & Disclosure

Wakim 2015



INTRODUCTION TO THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

Issues in Randomization

What was covered:

- What is "random"?
- What is randomization?
- Why randomize?
- Whom/what to randomize?
- How to randomize?

Recommendations
(for common randomization methods)

- Use computer program or online tools
- Use permuted-block randomization with small random block size (<10)
- For multi-site clinical trials, use *site* as a stratification variable and in the statistical model
- Do not use too many stratification variables (≤4)
- Unless necessary, avoid adaptive randomization methods

Recommendations
(for complex randomization methods)

Consult with a biostatistician

Implementation Recommendations

1) Make it possible to reproduce the string of treatment assignments
2) Document randomization method used
3) Put in place features that prevent treatment assignment until conditions for entry into the trial are fully satisfied
4) Mask (blind) assignments to everyone concerned
5) Make it difficult (impossible) to predict future assignments from past assignments
6) Put in place procedures for monitoring departures from established protocols

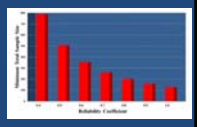
Shaw et al. 2012

Measurement

RELIABILITY: Problems

Lack of reliability introduces error into your measurement

1. Less sensitive statistics
2. Larger sample size
3. Uninterpretable results



RELIABILITY: Improving

1. Provide standardized procedures
2. Train raters
3. Monitor raters
4. Use multiple raters for each rating
5. Take repeated observations

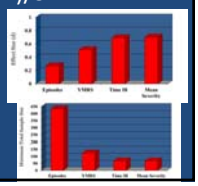
Kraemer, et al., Psychopharm Bull, 1991

SENSITIVITY to CHANGE

Ability to detect improvement or worsening
- Can assess with effect size

Cohen's d = (Mean2 – Mean1)/SD

- Standard Interpretation
  - .8 Large
  - .5 Moderate
  - .2 Small



Clinical Relevance

1. Sensitivity
   If have illness, how often is test positive?
2. Specificity
   If no illness, how often is test negative?
3. Positive Predictive Value
   If test positive, how often have illness?
4. Negative Predictive Value
   If test negative, how often no have illness?

PPV and NPV depend on disease prevalence in the population

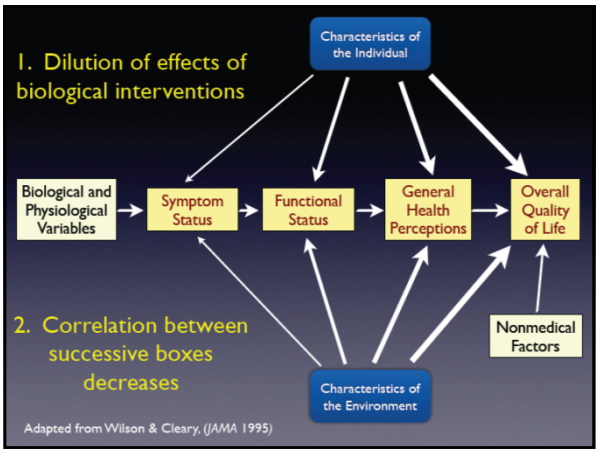
Self-Report Measures

- Used in questionnaires
- Some information not easily observable
- Self-report measures are *estimates* of true scores
- Susceptible to:
  - Respondent's mood, motivation, memory, understanding
  - Context of data collection
  - Social desirability

Rigorous methods will mitigate these pitfalls

Patient-Reported Outcome (PRO)

- "A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else."
- December 2009 FDA Guidance



Put Together Draft Questionnaire

Use existing instruments when possible

– HealthMeasures.net
  - PROMIS, Neuro-QoL, ASCQ-Me, NIH Toolbox

– REDCap

– National field surveys
  - NHIS, NHANES (US)
  - National Health Service Survey (UK)
  - Shared library of data collection instruments

Criteria for Good Survey Questions

- Literacy < 9th grade U.S.
- Specific better than broad
- Culturally sensitive
- Scales consistent
- Terms well-defined
- Instructions clear
- Reference periods clear
- Response options match question
- Multiple concepts separated

Criteria for Good Survey Questions

- Interpreted accurately by people with range of demographic characteristics
- Capturing what researcher intended

Avoid

- Social desirability effects
- Negative wording
- Double barreled
- Jargon
- Ambiguous
- Leading

Development and Evaluation of PRO Measures

1. Determine what PRO concept we want to measure and why
2. Collect qualitative data to understand meaning of the PRO concept
3. Write items you think will measure the concept
4. Test items for understanding (cognitive interviews)
5. Administer items to a large sample of people
6. Use psychometric (statistical) analyses to see how well items are working and develop scoring method
7. Evaluate the reliability and validity of measure

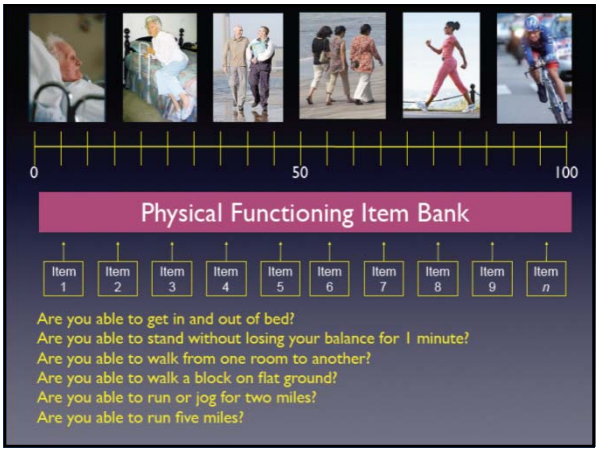
5. Translation

PROMIS Approach

- Harmonization: different words/ languages must mean the same
- Universal approach: One language version for multiple countries
  - People from various countries/dialects involved

Item Bank

- Large collection of items measuring a single domain
- Any and all items can be used to provide a score for that domain
- Dynamic, not fixed



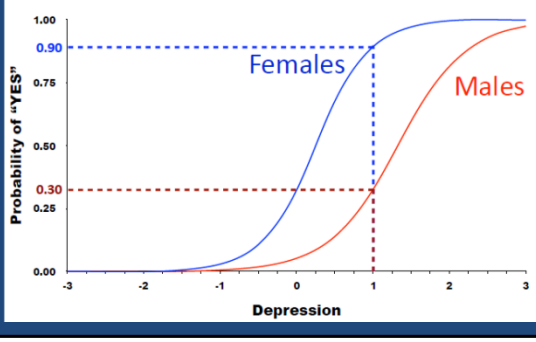
Traditional PRO Measure	PRO Item Bank
All items are required to compute a score	Any and all subsets of items can generate a score
Everyone must take same items	Different people can get different items
Use it "off the shelf"	Use items in bank to create measure for specific use
Scores not easily comparable to scores from another measure of the same domain	Cross-walk between scores from different measures in the same item bank

Differential Item Functioning

Item behaves differently for 2 or more groups.

The "map" between depression and item is different for 2 or more groups.

In the past 7 days, did you cry?

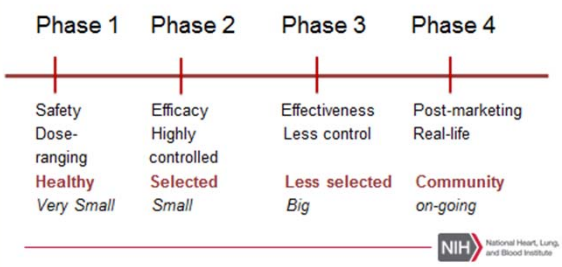


Summary

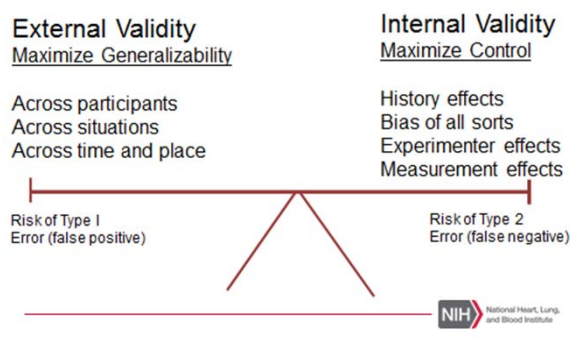
- Questionnaire development requires careful planning
- Use existing validated instruments when possible
- Rigorous methods will reduce response error

Participant Selection

The Research Continuum of a Clinical Trial



The Balance Between Internal and External Validity



Exclusion Criteria

- Safety!
- Reduce potential confounding

Secondary Data: Using Claims and Similar Data

Where Does Data Come From?

- Primary Data – generated for research purposes, including national surveys and disease registries
- Secondary Data – Secondary data is administrative/billing/encounter data
  - Often generated with utilization in mind
  - Enough data to make meaningful population-base conclusions

Why Study Medicare Patients?

- Largest purchaser of health care in the world
  - 54 million enrollees
  - $613 billion in expenditures in 2014
- The percentages
  - **Almost 16% of U.S. budget outlays**
  - 22% of all health care dollars in US
  - 26% of hospital spending
  - 22% of nursing home spending
  - 22% of physician billings
- Single data system

Benefits of Medicare Data

- Pre-existing data
  - less expensive
  - less time
- Large numbers of cases
  - Generalizbility
- Links to other data
  - Zip codes, SSN
- Accurate measure of resource use
- Can measure "effectiveness"

Limitations of Medicare data

- Lots of limitations…
  - Limited data on severity of illness
  - Not generalizable to the US working population
  - Coding and billing errors/bias
  - Limited outcome measures of interest
    - No QOL, Patient Satisfaction, functional assessment, illness severity

Limitations

- Studies limited to non-experimental design (observational studies)
- Difficult to avoid selection bias
- Impossible to control for all possible confounders (eg. severity of illness & functional status)
- HMO patients are excluded
- Cost of obtaining the data
- Administrative overhead

How can I get data access?

- Medicare administrative/billing/encounter data
  - http://www.resdac.org/about-resdac/our-services
  - Available through CCW Data Enclave
- Different countries, different data, different access

INTRODUCTION TO THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

Overview of Hypothesis Testing

Bottom-Line Key Points

- Statistical inference uses results from a sample from the population of interest to draw conclusions about the population
- The null hypothesis is set up with the hope that it will be rejected
- Alpha (α) is the chance of making a Type I error, i.e. of concluding that there is a difference when in fact there isn't
- Beta (β) is the chance of making a Type II error, i.e. of concluding that there isn't a difference when in fact there is
- Power = 1 – β = the chance of concluding that there is a difference when in fact there is

Bottom-Line Key Points (cont'd)

- The investigator controls the chance of making a Type I error (alpha) *and* the chance of making a Type II error (beta) via the sample size
- P-value is the probability of obtaining a result as extreme or more extreme than the one obtained, if there were no difference
- Statistical significance does not mean clinical importance
- Confidence intervals are very useful to better understand results
- Multiplicity adjustment is needed with more than one primary hypothesis
- Bayesian approach is gaining popularity as being more intuitive, and is worth considering

Basic Sample Size

- Changes in the difference of interest have HUGE impacts on sample size
  - 20 point difference → 25 patients/group
  - 10 point difference → 100 patients/group
  - 5 point difference → 400 patients/group
- Changes in difference to be detected, α, β, σ, number of samples, if it is a 1- or 2-sided test can all have a large impact on your sample size calculation

Basic 2-Arm Study's TOTAL Sample Size =

$$2N = \frac{4(Z_{1-\alpha/2} + Z_{1-\beta})^2 \sigma^2}{\delta^2}$$

Lots of Formulas are Not Basic

- Depending on your study design you may need to do simulations

Power is Affected by…..

- Variation in the outcome (σ^2)
  - ↓ σ^2 → power ↑
- Significance level (α)
  - ↑ α → power ↑
- Difference (effect) to be detected (δ)
  - ↑ δ → power ↑
- One-tailed vs. two-tailed tests
  - Power is greater in one-tailed tests than in comparable two-tailed tests

What to Do

- Make a sample size or power table
- Make a graph, or many graphs
- Use a wide variety of possible standard deviations
  - Similarly, think about different possible relationships between the study arms
- Protect with high sample size if possible

Survival Analysis

- Making inference about EVENT RATES
- Rate at t = Rate among those at risk at t
- Look at Median survival (50%) not Mean survival
  - Mean: need everyone to have an event
- Cox Regression is the most robust method
- Kaplan Meier curves do not have sensible interpretations for competing risks
- Independence is key
- Truncation is about *entering* the study
- Censoring is about *leaving* the study

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Powers: Conclusions

- Developing an efficient trial starts with planning and a good research question
- Question comes first, sample size second
- Various methods to increase effect sizes and decrease variability, when applied in the correct setting, can provide valid and reliable answers to important public health questions
- For some diseases, developing the tools (better outcome measures, better data on natural history) is a good start to better trials

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Analysis Follows Design

Questions → Hypotheses →
Experimental Design → Samples →
Data → Analyses →Conclusions

- Take all of your design information to a statistician early and often
  - Guidance
  - Assumptions

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Your Exam Questions

- Will go beyond this, but this is a brief summary

Economist, 12 December 2015 Randomised Controlled Trials

- In praise of human guinea pigs: Doctors use evidence when prescribing treatments. Policymakers should, too
- http://www.economist.com/news/leaders/21679799-doctors-use-evidence-when-prescribing-treatments-policymakers-should-too-praise-human
- Measure for measure: How to test everything from sluggish teenagers to corrupt bureaucrats
- http://www.economist.com/news/international/21679811-how-test-everything-sluggish-teenagers-corrupt-bureaucrats-measure-measure

Norman (Norm) Breslow

- February 21, 1941 - December 9, 2015
- Wilms Tumor Study Group
  - Beginning 20th century 90% of children diagnosed with Wilms tumor died
  - Beginning of 21st century nearly 90% survived and lead relatively normal lives
- Refined treatments
- Long term effects of radiation and chemotherapy
- Multi-modal cooperative group; full members from many disciplines

Obtaining Cure with Minimum Impact on Patient and Family

- High priority on data collection, electronic data collection, careful follow up, registering patients
- Pathologist identified small subgroup with unfavorable histology
  - Differential treatment strategies
- Breslow (biostat) and Day (epi) developed and popularized case-control matched sample designs
  - Findings are not definitive but can inform design of slow and expensive longitudinal large-cohort studies that are (more) definitive

First Child Enrolled 1969

- Over 40 years many studies
  - Some randomized, some not
  - Some interventional, some observational
  - Some small, some large
  - Some with genetic component, some not
- Ethics of lowering dose of life saving therapy?
  - Patients and parents had to assent/consent
  - Late Effects Study
    - Adverse pregnancy outcomes, second tumors at relatively early ages, skeletal and muscle development

Introduction to the Principles & Practice of Clinical Research

Module II – Ethical, Legal, Monitoring, and Regulatory Considerations

- **Legal Issues in Clinical Research**
- **Ethical Principles in Clinical Research**
- **Data and Safety Monitoring Committees**
- **Institutional Review Boards**
- **Mock IRB**
- **Research with Vulnerable Participants**

Questions?

- Thanks!
- Please fill out the course evaluations
- Post specific examples
- Send questions to the appropriate board for each lecture

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