Study Development

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Introduction to the Principles and Practice of Clinical Research

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Your Question Comes First

* May need to rewrite
* If you change your question later
  - May not have the power
  - May not have the data

* COME TO THE STATISTICAN EARLY AND COME OFTEN

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

Outline

* *Phase I-IV studies*
- Build-A-Study
- Analyses (small)
- Control groups (or lack thereof)
- Books and Articles (1)
- Outline Study Protocol
- Outline Manual of Procedures (MOP)
- Questions
- Components of Good Clinical Trials Report

Phase I to Phase IV Trials

* National Cancer Institute: Dictionary of Cancer Terms

* Phase I - The first step in testing a new treatment in humans
* Test the best way to give a new treatment (for example, by mouth, intravenous infusion, or injection) and the best dose

Phase I

* Dose increased little at a time
* Find the highest dose that does not cause harmful side effects
* Little known about possible risks and benefits of the treatments being tested
* Trials usually include only a small number of patients who have not been helped by other treatments

Phase II

* A study to test whether a new treatment has an anticancer effect (for example, whether it shrinks a tumor or improves blood test results) and whether it works against a certain type of cancer
* *Surrogate endpoints*

Phase II Designs

* Screening of new therapies
* Not to prove ‘final’ efficacy, usually
  - Efficacy based on surrogate outcome
* Sufficient activity to be tested in a randomized study
* Issues of safety still important
* Small number of patients

Phase III

* A study to compare the results of people taking a new treatment with the results of people taking the standard treatment (for example, which group has better survival rates or fewer side effects)

Phase IV

* After a treatment has been approved and is being marketed, it is studied in a phase IV trial to evaluate side effects that were not apparent in the phase III trial.

* Thousands of people are involved in a phase IV trial

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Study Design Taxonomy (new/old)

* Randomized vs. Non-Randomized
* Blinded/Masked or Not
  - Single-blind, Double blind, Unblinded
* Treatment vs. Observational
* Prospective vs. Retrospective
* Longitudinal vs. Cross-sectional

Aspirin and Mortality

* What is the best way to design a study to test if aspirin use reduces all cause mortality?

Aspirin and Mortality

* Several ways to design the study

* Two of them are ‘best’

Aspirin and Mortality

* ID a large group of people from a population at Time 0
* Give them aspirin
* Wait 5 years and observe all-cause mortality

Aspirin and Mortality

Aspirin and Mortality

* Turn back time
* Start over with the same large group of people at Time 0
* Give them ‘no aspirin’
* Wait 5 years observing all-cause mortality
* Compare outcomes aspirin vs. no aspirin
* Estimate average aspirin effect

Aspirin and Mortality – Try 2

* ID a large group of people from a population at Time 0
* Clone them perfectly
* Give one in clone pair aspirin, other no aspirin
* Wait 5 years and observe all-cause mortality in each pair
* Compare outcomes aspirin vs. no aspirin
* Estimate average aspirin effect

Aspirin and Mortality – Try 2

* Clones are a great idea!
* Identical in all ways we can, and cannot, measure

* But since we are not in Hollywood features what to we do?

Aspirin and Mortality – RCT

* ID a large group of people from a population at Time 0
* Divide into 2 groups, at random
* Give one group aspirin, one no aspirin
* Wait 5 years and observe outcomes in each group
* Compare outcomes aspirin vs. no aspirin
* Estimate average aspirin effect

Aspirin and Mortality – RCT

* Aspirin and no Aspirin groups should be comparable since randomizing yields groups with similar baseline characteristics
  - Except when randomization does not
  - Next lecture

Aspirin and Mortality – Observational Study *Prospective*

* ID a large group of people from a population at Time 0
* Some take aspirin, some do not
* Wait 5 years and observe outcomes in each group
* Compare outcomes aspirin vs. no aspirin
* Estimate average aspirin effect

Aspirin and Mortality – Observational Study

* Aspirin and no aspirin groups may not be comparable since they may not have similar baseline characteristics

Aspirin and Mortality (new) – Obs. Study *Retrospective*

* ID a large group of people from a population at Time *Today (but if all-cause mortality = outcome?)*
* In the past 5 years (prior to death) some took aspirin, some did not
* Today observe outcomes over the past 5 years in each group
* Compare outcomes aspirin vs. no aspirin
* Estimate average aspirin effect

Aspirin and Mortality – Case Control Study (new)

* Aspirin is an ‘exposure’, BUT
* Take people after ?first heart attack? and a group of controls
  - Match some risk factors?
* Assess prior aspirin use
  - Dose
  - Frequency
* Plus assess a million other risk factors

Aspirin and Mortality – Case Series and Survey (new)

* May have started with case series
* Now might be late
  - Unless you have seen something interesting
* May have done a survey next (late now)
  - If interested in preliminary duration of use information could be useful
  - Likely to incorrectly evaluate temporal
    * Dead do not answer surveys
    * Surrogate responders may not help

Analyses

* Fancy methods
* Bread and butter
  - Chi-square, T-tests, Wilcoxon tests
  - Linear or logistic regression
  - Basic survival (K-M, Cox PH)
* Extensive Exploratory Data Analysis
* Plots to match analysis

Banish ANOVA

* ANOVA has its place
  - Rarely in the study of humans
* Great when computers less memory than a cell phone
  - More robust methods will run on modern computers
  - Exciting methods run on PS3 game console
* *Repeated measures ANOVA is worse*

What Do We Test?

Effect or ***Difference***

* Difference in Means or Proportions
* Odds Ratio (OR)
* Relative Risk (RR)
* Hazard Ratio (HR)
* Correlation Coefficient

* And many other things……

Risk: Difference vs. Ratio (new)

* Difference in the absolute risks
  - Attributable risk
  - Excess risk attributable to exposure
* Relative Risk (RR)
  - Ratio of two absolute risks
* Hazard Ratio (HR)
* Is ratio the best to talk to people?

Difference vs. Ratio (new)

* Invasive breast cancer WHI (JAMA 288[3]:321-33)
* Increase observed estrogen+progestin group
  - Difference in risk
    * 38 vs 30 per 10 000 person years
  - Hazard Ratio (HR)
    * 26%
* Is your personal risk 26%? No
* 8 more invasive breast cancers per 10 000 person years? Yes

What Do We Test?

* Clinically important difference
  - Smallest difference considered biologically or clinically relevant

* Medicine: usually 2 group comparison of population means

Do Not Confuse

* Association
* Causality
* Confounding

* *Correlation*
* *Prediction*

High OR
Does Not a Good Test Make

* Everyone loves prediction. BUT
* Diagnostic tests need separation
  - Not logistic regression with high OR
* Strong association between 2 variables does not mean good prediction of separation
* *Measure of evidence should match the Question*

Ideal Study - Gold Standard

* Randomized
* Double blind / masked
* Treatment
* Prospective
* Parallel groups

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

Observational Studies

* Case Reports/Case Series
* Cross-sectional Survey
  - NHIS (National Health Interview Survey)
* Case-Control Study
  - Groups with or without outcome
  - Determine who was exposed to risk factor
* Cohort Study
  - Follow a group for a while
  - Cardiovascular Health Study

Experimental?

* Are ‘experimental’ and ‘randomized’ interchangeable?
  - Depends. In text, yes.
* Quasi experimental
  - Experimenting
  - No control
  - Not randomized

Quasi Experimental or Non-Randomized Experimental Studies

* No control group
  - Early in investigation
* Concurrent control “group”
  - Treatment assignment not by randomization
* Historically controlled
  - Missing/poor data
  - Non-comparability of groups

No placebo/control = problems

* Patients tend to do better by receiving some treatment, even placebo or standard of care (soc)

* Comparing a patient on treatment to baseline does not take this into account

Additional Problems

* Researchers tend to interpret findings in favor of the new treatment
  - Investigator/participant bias
* Impossible to distinguish the effect of time from treatment effects
  - Confounding

Human Assumptions and Concurrent Control Groups

* Newer = better
* Systematic allocation is unreliable and many times NOT systematic
  - Bias
  - Manipulation
* No randomization -- impossible to establish if comparable groups

Historical Control Study

* Small patient pool
  - Pediatrics
  - Cancer research
* Responses compared to controls from previous studies
* Only half the patients
* No “placebo exposure”

Historical Control Problems

* Serious bias for assessing treatment efficacy
* Controls not a good comparison group

Historical Controls and Time

* Treatments, technology, patient care changed over time
* Patient population characteristics have changed over time

Non-randomized Phase II design problems

* Placebo effect
* Investigator bias
* Unblinded treatment/assessment
* Regression to the mean
  - Natural reduction in disease activity over time

Observational Studies

* Why can observational studies only find a weaker degree of connection?
  - Subject to confounding
  - Can correct for what you know, but nothing to be done about the unknown

* Sometimes it is unethical to do a randomized trial (e.g. smoking)

Causation vs. Association

* Causation
  - Established by randomized experimental studies and clinical trials
* Association
  - Observational studies can merely find association between a risk factor and an response

Example

Example

* JAMA 2004 recommendations for adult HIV
  - Optimal time to initiate HAART to maximize survival/AIDS-free survival
* CD4 cells/mu L: greater than 200 but = to or not less than 350
* Dynamic treatment regime
  - Waiting on a person’s CD4 count, which changes over time

Study Needs

* Cohort recently diagnosed/infected with HIV
* Antiretroviral naive

Nonrandomized Observational

* System to ID treatment status over time
  - Time *t* changed treatment status
* Record data on confounders until the end of study, AIDS, or death
  - All time-varying risk factors used to decide to change treatment status at time *t*
* Survival analysis
  - Comparing what groups?
* HIV OutPatient study (HOPS)

Distinguish

“Observational studies are often analyzed as if they had resulted from a controlled study, and yet the tacit assumption of randomness can be crucial for the validity of inference.”

Copas, J.B. and Li, H.G. (1997). Inference for non-random samples (with discussion).
***Journal of the Royal Statistical Society*, 59: 55–95.**

Another Design?

Randomized Study

* Always treat/never treat
  - Regardless of CD4
* Use intent to treat (ITT) analysis
* Follow until end of study/death/AIDS
* Survival analysis

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Books

* *Statistical Rules of Thumb* by Gerald van Belle (vanbelle.org for updates & monthly rule)
* Hosmer and Lemeshow books
* *Epidemiology* by Leon Gordis

More Books

* *Statistical Reasoning in Medicine: The Intuitive P-Value Primer* by Lemuel Moye
* *Designing Clinical Research: An Epidemiologic Approach*, edited by Stephen Hulley

And More Books

* *Data Monitoring Committees in Clinical Trials: A Practical Perspective* by Ellenberg, Fleming, DeMets.
* *Fundamentals of Clinical Trials* by Friedman, Furberg, DeMets
* *The Statistical Evaluation of Medical Tests for Classification and Prediction* by Margaret Sullivan Pepe

Articles

* British Medical Journal: Statistics Notes
  - Link broke; search in BJM or via your favorite search engine
* Statistics in Medicine
* NEJM: Equivalence trials
  - October 16, 1997

FDA Guidance

* ICH E9 Statistical principles
* ICH E10: Choice of control group and related issues
* ICH E4: Dose response
* ICH E8: General considerations
* FDA draft guidance on drug interaction study designs (and analyses), Bayesian methods, etc.

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Conducting a Clinical Study: Study Protocol

* Road map for performance of study
* Anticipate problems
* Facilitates communication with potential collaborators, employers, funding agencies
* Assists in manuscript preparation

Protocol Components

* Background and rationale
* Specific objectives (3-5 aims of study)
* Clinical trial should include specific hypothesis regarding primary outcome
* Concise statement of design
* Methods and analysis
* Responsibility and authorship

Statement of Design

* "An observational study of decline in pulmonary function in persons living in heavily industrialized areas compared to persons in non-industrial areas."
* "A prospective, non-concurrent study of postoperative pneumonia in patients receiving regional *vs*. general anesthesia for peripheral vascular grafting."

Methods: Inclusion Criteria

* Definition of patient population
  - Specific as possible (but not too restrictive)
* Inclusion criteria
  - Disease or condition under study
    * Prior myocardial infarction, smokers
  - Other information
    * Age
    * Sex
    * Area of residence or hospitalization

Methods: Exclusion Criteria

* Participants must not have *any* specified criterion
* Generally include conditions making study difficult or impossible
* Patients in whom one treatment or other is inappropriate or unethical
  - Coronary Artery Surgery Study excluded patients with left main coronary artery disease

Methods: Exclusion Criteria

* "Logistic" concerns
  - Aged under 18
  - Critically ill
* Circumstances making determination of outcome difficult or impossible
  - Expected to leave area
  - Unable to communicate in language study team uses
  - Pregnancy

Common Mistakes

* Unnecessary exclusion/inclusion criteria
* Plans for the trial made without any reliable data on participant availability
  - Pilot recruitment
* Unrealistic timetable for recruitment or no recruitment goals
* Revision of sample size calculations to make them consistent with recruitment realities

Outcome Definitions

* Be specific and as clear as possible
* Primary *vs*. secondary outcomes
* Standard clinical definitions
  - Textbook: usually not specific enough
  - Consensus conference
    * Definition of hypertension
  - Recognized expert body (WHO, AHA)

Outcome Definitions

* Appointed panel of experts
* Previously widely-recognized study (SHEP, WHI, SOLVD)
* Adjudication: submit to panel of masked, unbiased "experts"

Treatment Definition Treatment Definition

* Specify as much as possible without interfering with patient management
* Realize that generalizability often lost in quest for specificity
* Specify criteria for withdrawal from study or deviation from protocol
* List concurrent medications, procedures, etc. that are prohibited or permitted

Masking/Blinding

* 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

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MOP: Manual of Procedures or Manual of Operations

* Can another investigator step into the study (or reproduce it) at any time?
  - Hope so!
* Which data to be collected, how
* Timetable for follow-up

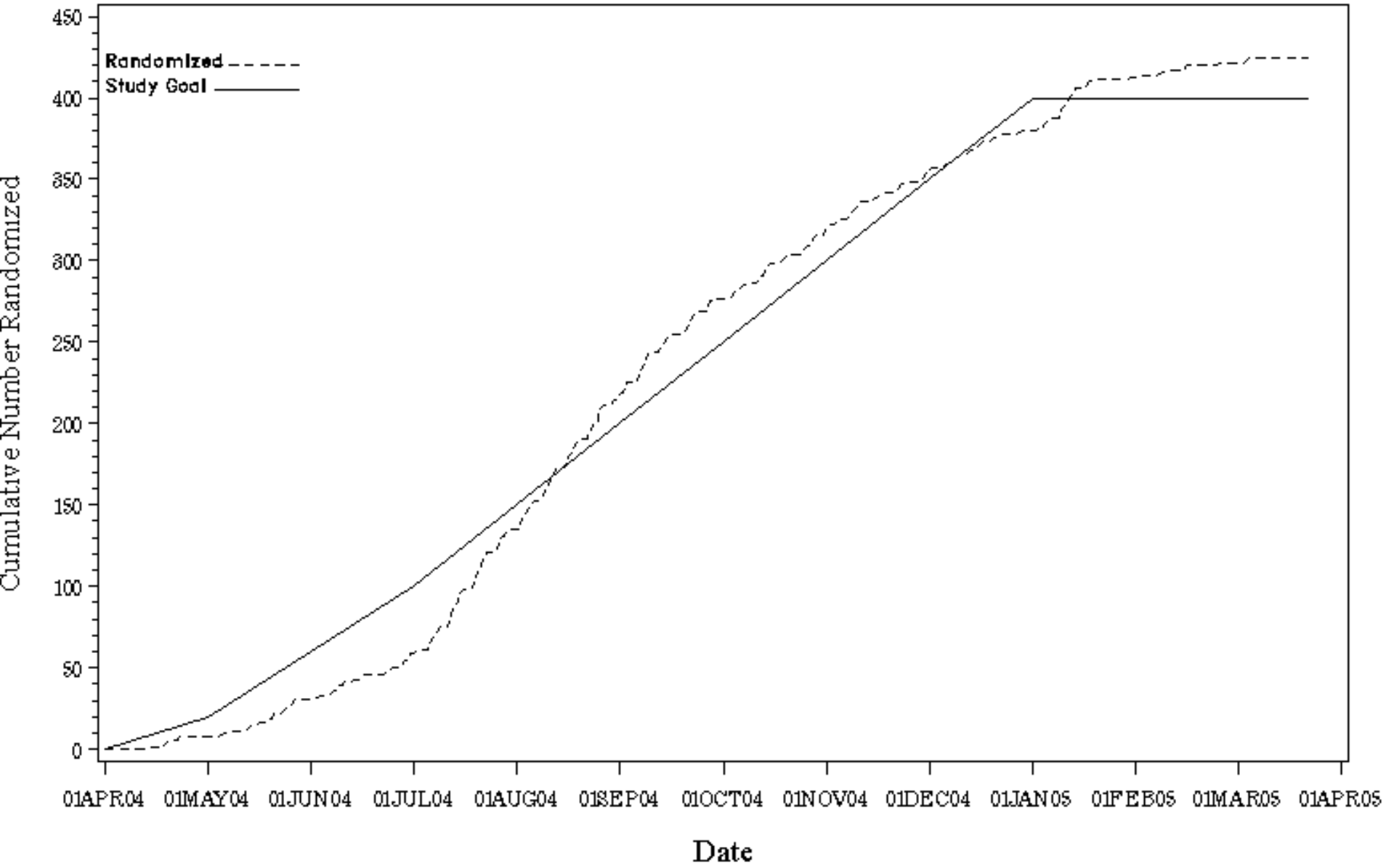
Examples of Chapters in MOP

* Overview
* Recruitment
* Eligibility
* General procedures
* Informed consent
* Screening
* Randomization
* Follow-up visits
* Retention
* Intervention
* ECG
* Blood collection
* Physical assessment
* Fitness testing
* DXA scanning
* Health events
* Participant safety
* Adverse events
* Data management
* Quality control
* Interviewing
* Study organization
* Study website

Subject Recruitment aka The Facts of Life

* Early estimates unrealistically high
* Takes a major effort
* People presumed eligible for study during planning will disappear mysteriously as soon as the study starts
* Recruitment will be more difficult, cost more, and take longer than planned

LIFE
Cumulative Number Randomized vs. Study Goals
For All Clinics
424 Randomized (106.0% of the Original Study Goal of 400)



Prepare!

* Collect reliable data to estimate participant availability
* If matching, allow for screening twice as many controls per discrete variable matched upon
* Decide on general recruitment approach
* Outline steps in recruitment process
* Establish necessary recruitment contacts

Recruitment Mistakes/Problems

* Competing with private physicians for patients
* Providing basic care rather than referring patient back to primary care physician
* Failure to maintain adequate contact with referring physician

Recruitment Mistakes/Problems

* Attempting recruitment without the support of colleagues
* Taking access to medical records for granted
* Failing to secure enthusiasm and commitment of staff
* Inadequate publicity

Protection of Human Subjects

* Monitoring for adverse effects
* Informing patient, physician of complications or abnormalities
* Interim analyses (*pre planned)*
* Data Safety Monitoring Board (DSMB)

Informed Consent

* Written informed consent
* Institutional review board (IRB): independent review and monitoring by panel including members outside institution

Informed Consent: Approach

* Find proper setting: quiet, private
* Provide adequate time
* Encourage *potential participant* to discuss with others (family members, physician), ask questions
* Ensure participant's competence to give consent
* Provide copy of signed consent
* In unblinded studies, must be willing to participate regardless of random assignment

Mistakes in Consent Process

* Inadequate time
* Failure to specify required procedures
* Inadequate documentation
* Vague or inaccurate statements
* Making commitments that cannot be met
* Use of untruths to protect study design
* Consent after the fact
* Speaking for the patient ("I understand that...")

Specifics of Laboratory Methods

* Enzyme determinations: laboratory methods?
* Chest x-rays
  - PA and/or lateral
  - Supine or erect
* Clinical measurements
  - Blood Pressure (BP)
    * Supine or standing
    * How many times? Average?
    * Rest periods between measurements?
    * Feet on floor? Arm is where? Cuff size?
  - Heart sounds in left lateral decubitus

Data Management and the Subject Record

* Each participant should have his or her own study record stored in locked area when not in use
* Each participant should have a study number for use as identifier - name should not be in data base, coding forms, etc.

Data Management

* If multiple data sources are needed, use separate forms and system to keep track of progress in data collection (e.g., colored-dots, transmittal forms, etc.)

Subgroup Analysis

* Often performed when no overall effect found
* Used to look for high-risk or peculiar groups with marked treatment effect
* Beware of "data-dredging"- looking at many, many subgroups until one "significant" effect found

Subgroup Analyses

* Limit number of subgrouping variables
* Look at all members of the subgroup
* *a priori* and *a posteriori*
* Choose cut points independent of treatment differences
  - Blood pressure treated to goal of 140/90
  - Cut blood pressure at 140 *vs*. greater than 140 will introduce bias of successful *vs*. unsuccessful treatment

Subgroup Analyses

* Stringent significance testing, especially if number of hypotheses tested is large
* When possible, validate findings before reporting on an *a posteriori* (data-driven) subgrouping variable
* Report methods and procedures
* Be cautious regarding conclusions

Other Problems

* Changes in procedures necessary
* Changes in inclusion or exclusion
* Changes in data collection procedures
* Revisions as needed, dated, with replacement pages in MOP
* Drift in measurements
* Change in health and treatment patterns or practices within the community

Write the MOP

* So anyone you might hire for any position can follow then entire document and run the study

* Undergrad, post doc, statistician, anyone

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Questions?

Components of Good Clinical Trials Report: Design Specifies

(after Dr. Curtis L. Meinert, Professor of Epidemiology, Johns Hopkins School of Hygiene and Public Health)

* Purpose of study
* Primary outcome measure
* Test and control treatments
* Level of treatment masking: unmasked, single- or double-masked
* Planned recruitment goal
* Eligibility and exclusion criteria
* Method of patient recruitment

Continued

* Number of patients enrolled
* Number of patients in analyses
  - Equal to number allocated to treatment, or explanation should be given
* Method of treatment allocation
* Stratification variables
* Methods measuring treatment adherence
* Planned and actual length of patient follow-up

Patient Safeguards

* Informed consent, Institutional Review Board (IRB) approval
* Measures taken to protect patient confidentiality
* Procedures to monitor study results for evidence of treatment effects

Data Collection Schedule

* Frequency of baseline visits
* Frequency of follow-up visits
* Definition of dropouts

Results

* Number of patients enrolled by treatment group
* Number of deaths observed
* Comparison of treatment groups for the primary outcome measure

Results: Completeness of Follow-up

* Number of missed examinations
* Number of dropouts and withdrawals
* Number of participants lost to follow-up

More Results

* Selected baseline characteristics
* Multiple regression analyses using baseline characteristics to provide adjusted treatment comparisons
* Treatment comparisons by level of adherence

Conclusions

* Test of primary hypothesis/outcome
* Test of secondary hypotheses as applicable
* Limits on generalization of the results indicated
* Discussion of statistical power if no treatment difference is detected
  - Although I am not a big fan of this depending…

Thank you!