Overview of Clinical Study Design

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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.

Get to Know Each Other Online:
Have you ever….

Taken a class or have a degree in

Biostatistics

Epidemiology

Research design

Used logistic regression?

Designed some type of public health research project outside of a class environment?

Run a study?

Done a data analysis outside of a class environment?

Get to Know Each Other Online: Have you ever….

Written a clinical research protocol?

Read a clinical research protocol?

Read a clinical journal article?

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

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

Tonight's Objectives

Identify study designs used in clinical studies, epidemiology and public health research

Discuss masking/blinding, interventions, comparison groups

Chapters 19, 29, 3rd Edition

Outline

Where to start

Taxonomy and examples

Some general vocabulary

Observational and interventional studies

General good study design

Intervention and dose

Comparisons

Conclusions

Confounding and effect modification

Cervical Cancer

Cultural

Access

Vinegar

Diagnostic biomarker

High negative predictive value

Low cost

Fast

Time table for treatment

Other Examples

Cardiovascular disease

Weight

Hypertension

Infectious diseases

Data collection/mode of administration

Mobile health

Combination of interventions

What is the question of interest?

Interpreting work into new population

Making decision about individual case

Looking at changing a population

Diabetes management

Differences between groups in a study

Biomarker development? What kind of biomarker?

Develop a new outcome?

Level of evidence

Evaluation of evidence

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

How a Statistician Sees a Research Study

Everything impacts the statistical analysis

Outline

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Vocabulary

Arm = Sample = Group

Demonstrate superiority

Detect difference between

Groups

Treatments or study arms

Demonstrate equally effective

Demonstrate non-inferiority

Patient vs. participant vs. subject

Study Design Taxonomy

Intervention vs. Observational

Longitudinal vs. Cross-sectional

Prospective vs. Retrospective

Blinded/Masked or Not Blinded/Masked

Single-blind, Double blind, Unblinded

Randomized vs. Non-Randomized

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)

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

Epidemiology

Quasi-experimental

Pre-clinical studies

Phase 0

Phase I

Early/Late Phase II

Phase III

Phase IV

Dissemination and Implementation

Comparative or Cost Effectiveness

Ideal Study - Gold Standard

Treatment / control

Parallel groups

Superiority

Prospective

Double blind / masked

Randomized

BMJ 14-20 Oct 2013

Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis

Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial

BMJ 14-20 Oct 2013

Risk of moderate to advanced kidney disease in patients with psoriasis: population based cohort study

Prevalent abnormal prion protein in human appendixes after bovine spongiform encephalopathy epizootic: large scale survey

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.

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

Your Question Comes First

May need to rewrite

If you change your question later

May not have the power

May not have the data

Need to know something about the population

This lecture:
focus on intervention studies

26 October 2015:
non-intervention studies Epidemiology

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

Parallel Group

Randomize patients to one of X treatments

Response

Measure at end of study

Change (delta) or % change from baseline

Repeated measures

Function of multiple measures

Variations on Parallel Group Designs

Dose titration (with multiple study arms)

Titrate to the maximum tolerated dose within a subject

Dose Escalation Studies (with a control arm that is simultaneously randomized to)

Not all dose escalation and dose titration studies are randomized

Sequential Trials

Not a fixed sample size/period

Terminates when

One treatment shows a clear superiority or

It is highly unlikely any important difference will be seen

Special statistical design methods

Group Sequential Trials

Popular

Analyze data after certain proportions of results available

Early stopping

If one treatment clearly superior

Futility

Adverse events

Careful planning and statistical design

P = 0.00006

Preventing Mother-Infant HIV Transmission (D.O. Dixon, NIAID)

Zidovudine able to slow progression of HIV in adults with advanced disease

AIDS Clinical Trials Group Protocol 076 designed to assess both safety and efficacy of Zidovudine in preventing transmission of HIV from infected (not advanced) women to their babies

Preventing Mother-Infant HIV Transmission

Powered (80%) to detect a 33% reduction of transmission rate (through 78 weeks of baby's life) relative to projected rate of 30%

Target N was 748; began April 1991

Projected accrual to take at least 5 years and 15% dropouts

Crossover Trial

Cross over example

2 treatments

2 period crossover

Use each patient as own control

Must eliminate carryover effects

Need sufficient washout period

Not always known what length of time is needed

Not everything can wash out

Women's Alcohol Study
JNCI 2001

Three 8-week dietary periods

30 g alcohol/day

15 g alcohol/day

0 g alcohol/day [alcohol free beverage]

Order of assignment to 3 alcohol levels was random

Washout periods

Double blind

Factorial Design

Each level of a factor (treatment or condition) occurs with every level of every other factor

Selenomethionine (Se) and Celecoxib (C) Gastroenterology 2002; 122:A71

Factorial Design

Factor 1: Selenium

Yes, No

Factor 2: Celecoxib

Yes, No

Factorial Design

Factorial Design

Factorial Design

Power for the interaction or not?

Is this a 4 arm study?

2-2 arm studies?

MsFLASH Factorial Design

Incomplete/Partial/Fractional Factorial Trial

Nutritional Intervention Trial (NIT)

4x4 incomplete factorial

A,B,C,D

Did not look at all possible interactions

Not of interest (at the time)

Sample size prohibitive

Adaptive Designs

Gaining popularity

2-8+ arms

Dose ranging (perhaps)

Smaller overall sample size (potentially)

Run-in then analyze data continuously or at fixed points

Need to be clear

What is adapted

When is it adapted

Based on what evidence does the adaptation take place, and who decides and implements

What are adaptive designs?

By adaptive design we refer to a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.

Gallo et al. (PhRMA Working Group) 2006

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

Their rules for adaptation are pre-specified in protocol

Changes are made by design, not on an ad hoc basis

They are not ad-hoc fixes for poorly-designed trials

They require understanding by investigators, reviewers, DSMB members, and journal editors

Adaptive Designs

Adaptive Designs

Some act like group sequential designs

Close an arm early

Re-estimate sample size based on a nuisance parameter (variance)

Big negative: any time a decision to continue is made, information is provided to the study investigators, public, investors….

Enriched Enrollment Designs

Sometimes variant of crossover or n-of-1 study design

Identify potential ‘responders’

Enter ‘responders’ on to 2nd prospective comparison study

Results not generalizable to entire patient population

Regression to the mean

Average 10 hot flashes a day for 14 days, and 3 on study in the placebo arm

Group or Cluster Randomized Studies

Unit of randomization is not the individual

School

Community

Clinic

Change eating patterns to impact obesity and other health outcomes

Altering supermarket environments

School based nutrition programs

Charges for bed nets and impact on infant malaria cases

Outline

Where to start

Taxonomy and examples

Observational and interventional studies

General good study design

What is the question

Comparisons

Conclusions

Confounding and effect modification

How to Start Designing a Study

Study aims, background, rationale

Endpoints or outcome variables, other assessments

Specific variables, how measured, specific & sensitive to changes expected, reliability & validity of measure

Inclusion/Exclusion criteria

How to Start Designing

Accrual plan and preparatory tasks

Timeline for overall study

Timeline for individual study participant

Treatments? Participant implications?

Product, dose, quality, administration, and reproducibility of interventions (including training)

Intervention Definition

What is it; can someone replicate it?

Dose; choices based on what?

Does it interfere with patient management

Generalizability often lost in quest for specificity

Specify criteria for withdrawal from study or deviation from protocol or definitions

List concurrent medications, procedures, etc. that are prohibited, permitted, must be recorded in certain way

What is a Dose?

Number of sessions/pills/treatments/social media attempts

Frequency

Length of sessions (each, total treatment time)

Amount of practice

Leader

Contact time

Who that person is

Many different combinations

Practitioner Impact

False negatives and positives

Details of protocol

Examples

Massage for low back pain

Surgery

Prevention course

Study Analysis Population

Mechanistic, proof of concept

Throw best at it

Per protocol

General use

Like intent-to-treat analysis

What is the question?

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

Superiority vs. Equivalence

Non-Inferiority

Comparison Groups

Experimental intervention vs control

Case vs control

Exposed vs unexposed

Various levels of exposure

Men vs women

Old vs young

BMI>25 vs ≤ 25

Usual or standard care or practice

History; pre-post

Placebo, Standard of Care, and Attention Controls

Experimental treatment

Supportive care

Current treatment

Yoga

Exercise or stretching

Cooking classes

Book club

Nothing

Control Usually Costs Money = Larger Sample Sizes

Control everything except smallest element of intervention that you want to test

Be careful it is not too small a difference

Consequences if study has

More control imposed

Less sensitive or precise outcome measures

Plan accordingly

Differences

Time at the intervention or study-participant contact

1 to 3 hours / week

Time spent at home

15 to 60 minutes / day

Have a ‘match’ in the control group or enough variance to put in the analysis

What is the control group?

Placebo

Most widely accepted treatment

Standard treatment

Most accepted prevention intervention

Condoms and HIV?

Usual care

Accepted means of detection or diagnostic test

Non-diseased population

Control Groups

Ethical

Control intervention itself

Assigning ANYONE meeting study criteria to ANY study group

If “standard of care” (SOC) evidence: is really standard practiced usual care in that format?

Good controls can always be masked?

No, sometimes IV versus pill of same medication

Try to mask interventions

No Placebo/Control = Problems

People tend to do ‘better’ receiving some treatment, even placebo or standard of care

Care matters

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

Comparing population incidence rate to beginning of program does not take into account many factors (may look worse before better)

No Control Group:
Additional Problems

No blinding

Researchers and participants tend to interpret findings in favor of new treatment

Investigator/participant bias

No randomization

Impossible to distinguish effect of time from treatment effects

Confounding

What is the right control group for a randomized study?

Waitlist control

Placebo control

Remove ‘active’ component; may still have an impact on outcomes

Active controls

Standard of care

Alternative intervention

Fewer parts of multi-part intervention

Attention control

No universally-appropriate control group

Controls Also Present in Many
Non-Randomized Studies such as
Case-Control Studies

Siblings

Community controls

Hospital controls

Worked in same area but not present for workplace exposure

Match on many different variables or not

Multiple control groups

Consider

If it has effects

Positive

Negative

Do the effects plateau?

Time

Long term differences

Attenuation

Delayed response

Time and Other Elements

Time is our favorite confounder in uncontrolled studies

Differential time participating is an issue

Differential drop-outs

Time in an environment, age, season

Social support

Meeting in a group may have an impact

Talking to someone, empathy, may impact

Exercise

Exercise helps cardiovascular risk factors

Exercise helps stress

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

Reproducible Measurements:
Regardless of Study Design

Well defined cohort

Exclusion and inclusion criteria

Study conduct

Outcomes

Study data, analyses

Biases in Clinical Research

Studies ≠ Gold

True for randomized and non-randomized studies

Volunteer bias

Inclusion/exclusion criteria

Measures

Artificial interventions/treatment definitions

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And who cares

Your Question Comes First

May need to rewrite

If you change your question later

May not have the power

May not have the data

Need to know something about the population

Consider

Questions you want to ask

Hypotheses you want to test

Key factors you wish to control

Ethical issues and constraints

What can be said with each control group?

More than one control group?

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Effect Modification and Confounding

Different Variables May Be

Effect Modifier(s)

Potential Confounder(s)

Other things

If measured these are usually “covariates” in the statistical model

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

Effect Modification

A Short Introduction to Epidemiology

Neil Pearce chapter (2005)

The phrase effect modification, defined for different professions

Biostatisticians, public health workers, physicians, lawyers, biologists, epidemiologists,….

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)

Coffee and Pancreatic Cancer

Coffee and Smoking

Confounding Example

Relationship between coffee and pancreatic cancer, BUT

Smoking is a known risk factor for pancreatic cancer

Smoking is associated with coffee drinking

Coffee drinking is associated with smoking

Smoking is not a result of coffee drinking

Coffee and Pancreatic Cancer

What is Confounding

If an association is observed between coffee drinking and pancreatic cancer

Coffee actually causes pancreatic cancer, or

Coffee Causes Pancreatic Cancer

What is Confounding

If an association is observed between coffee drinking and pancreatic cancer

Coffee actually causes pancreatic cancer, or

The coffee drinking and pancreatic cancer association is the result of confounding by cigarette smoking

Smoking is a Confounder: Coffee does NOT cause Pancreatic CA

How to Handle Confounding

Identify potential confounders

MEASURE THEM!

In the data analysis use

Stratification, or

Adjustment (add the variable to the model)

Fear the unknown!

More to Confounding? Yes!

Residual confounding

Poor measure of the confounder

Physical activity

Even when we put the confounder as measured in the model, not really explaining the effect of real physical activity in the model

Example

Ever Smoked yes/no; pack years

Randomization =
No Confounders! Wrong!

Side note

Randomization helps protect against confounding

Does not prevent confounding

Non-random drop-out or attrition

Patients testing substance

And then dropping out, or taking more of item

Confounding and Effect Modification

Thanks!

Please submit questions and comments electronically so all several thousands of us can share in the dialog