Developing Protocols and Manuals of Operating Procedures

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Objectives

Define several parts of a protocol document

Identify resources to assist in development of study designs and documents

Application vs. Protocol vs. MOP

Application

NIH limits 6-12 pages, concise justification and design of clinical study

Protocol

Detailed plan of the clinical study (no page limit)

Manual of Operations and Procedures (MOP)

Finely detailed information describing the conduct and operation of a clinical study

Protocols and Manuals of Procedures

Studies vary

Single detailed protocol

Protocol + Manual of Procedures (MOP)

Multi-site studies

Different institutions may have varying protocol requirements

Using study MOP very useful

Complicated or long procedures: MOP may be more useful

Documents have to all agree!

Study Protocol: Purpose

Road map for performance of study

Next step to operationalize application

Track changes recommended by IRB, clinical monitors, funding agency

Anticipate problems

Safeguard participants' health and safety

Facilitates communication among

Collaborators, employers, funding agency

Assists in manuscript authorship/preparation

Protocol Components

Specific objectives (3-5 aims of study)

Background and rationale

Concise statement of design

Selection and enrollment of participants

Interventions (if applicable), safety

Methods or procedures, statistical considerations, data collection and quality assurance

Participant rights and confidentiality

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."

What is the question of interest?

Interpreting work into new population

Making decision about individual case

Looking at change in a population

Diabetes management

Differences between groups in a study

Biomarker or another outcome?

Level of evidence

Evaluation of evidence

Design and Analysis Problems

Would XYZ be a more appropriate study design to answer the study aims?

Toxicity, tolerability, some efficacy

Pharmacodynamics, pharmacokinetics

Phase I, II, or an observational study

Which adaptive design?

Not everything needs to be on the Phase III design framework

Wide variety of question-appropriate designs

Participant Enrollment

Study enrollment procedures – address

How will you identify and recruit?

Where will you recruit?

How will you document ineligibility and nonparticipation of eligible candidates?

Define consent procedure

Define randomization procedure if applicable

Participant Selection

Define participant / patient population

Specific enough ←→ not too restrictive

Inclusion criteria

Disease or condition under study

Examples: History of chronic pain, sleep disorder

Demographic characteristics

Age range

Sex

Required laboratory results, diagnostic tests

Ability to understand & comply with procedures

Participant Selection

Exclusion Criteria

Each participant must meet specified criteria

Precludes participation: Specify clinical condition or health status that would make study difficult

Participants for whom one treatment or another would be unethical or inappropriate

Laboratory results or diagnostic tests (provide range)

Participants who take certain meds or are engaged in behavioral interventions

Participant Selection

Exclusion Criteria

Safety of participants is primary concern

Pregnancy or pregnancy testing

Drug/alcohol dependence

“Logistic" concerns

Less than 18 years of age

Critically ill

Expected to leave area

Circumstances likely to make determination of outcome difficult or impossible

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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

Interventions

Product

Dose

Quality

Administration and reproducibility of interventions (including training)

Participant Implications

Dose can be Many Things

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

Time and Other Elements

Time is our favorite confounder in uncontrolled studies

Differential time participating is an issue

Differential drop-outs

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

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

Concomitant Interventions

Allowed

Required

Prohibited

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Study Procedures

Schedule of evaluations

Description of evaluations

Screening through final evaluation

Overall study time line

Impacts ability to perform study

Timeline for individual study participant

Impacts people wanting to participate

Outcome Definitions

Appointed panel of experts

Previously widely-recognized study (SHEP, WHI, SOLVD)

Adjudication: submit to panel of masked, unbiased "experts"

Measurement

What difference is scientifically important in units

0.01 inches?

10 mm Hg in systolic BP?

How variable are the measurements (accuracy)? – Pilot!

Plastic ruler, Micrometer, Caliper

Can others measure this and will anyone understand the difference intuitively?

Outcome Measures

Sensitive to the magnitude of change expected

Specific to changes expected in your outcome based on your study hypothesis

May or may not have been used in pervious research

Need to know the reliability and validity of the measure

Preferably in population under study

Is it a good measure?

Do you have reasonable reliability and validity data?

Cost is a study budget question, not a “good” determinant

May not have been published or used in previous research; you may be first!

That is ok, if you have the data to back it up

Other measurements help, too

Statistical Considerations

General design issues

Describe treatment assignment or randomization procedures (if applicable)

Interim analyses and stopping rules

Data analyses

Sample Size

Specific analyses to answer each hypothesis

Appropriate to study design

Why not use a 2-sided test?

Attrition/drop-outs/missing data

Multiple comparisons

Clarity

Multiple outcomes, interventions, time points

Longitudinal/repeated measures

Interim analyses of the outcome data

Analysis Plan

Appropriate analyses for the study design

If it needs to be a two sample t-test, t-test

If it needs to be fancy, fancy

Reconsider repeated measures ANOVA

Consider linear mixed models or generalized estimating equations

Drop outs/missing data in the analyses

Analysis Plan

Detail the interim analysis plan if interim analyses are anticipated (they may not be)

Work with a statistician and/or epidemiologist

Sample size must support analytic plan

Clear can express research findings in a way that is relevant to the field and society AND will have information to plan future research

Intent to Treat versus Completers
"How many in the data analysis"

ITT = Intent To Treat analysis

Includes everyone randomized (if rand. study)

Assume all study participants

Adhered to the study regime assigned

Completed the study

MITT = Modified ITT analysis

ITT, but only include people who start the intervention they are assigned to

Completers or Adherers analysis

Only the well behaved

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Protection of Human Subjects

Monitoring for adverse effects

Informing patient, physician of complications or abnormalities

Interim analyses (pre planned)

Data Safety Monitoring Board (DSMB) or other monitoring committee

Informed Consent

Written informed consent

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

Write the Protocol

Anyone can replicate the study

They may need the manuals of procedures, too

Recommend one-stop document for all study needs

People will not flip to several different places

If information is in several different places it needs to match

Conclusion

Document needs to make sense

Statistical methods and sample size flow with the rest of the proposal

Correctly staffed

Implementable

Practical

Rigorous

Testable hypotheses that address aims and goals of the research

Questions

Resources: General Books

Hulley et al (2001) Designing Clinical Research, 2nd ed. LWW

Rosenthal (2006) Struck by Lightning: The curious world of probabilities

Bland (2000) An Introduction to Medical Statistics, 3rd. ed. Oxford University Press

Armitage, Berry and Matthews (2002) Statistical Methods in Medical Research, 4th ed. Blackwell, Oxford

More Books

Statistical Reasoning in Medicine: The Intuitive P-Value Primer by Lemuel Moye

Designing Clinical Research: An Epidemiologic Approach, edited by Stephen Hulley

Critical Appraisal of Epidemiological Studies and Clinical Trials by Mark Elwood

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

Resources: Articles

Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials. 10:1-10, 1989.

Thall, Simon, Ellenberg. A two-stage design for choosing among several experimental treatments and a control in clinical trials. Biometrics. 45(2):537-547, 1989.

Regulatory Guidances

ICH E9 Statistical principles

ICH E10: Choice of control group and related issues

ICH E4: Dose response

ICH E8: General considerations

US FDA guidance and draft guidance on drug interaction study designs (and analyses), Bayesian methods, etc.

http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234622.htm

REDCap

Research Electronic Data Capture

http://project-redcap.org/

Started by Vanderbilt University

450+ active institutional partners (US+)

Secure web application

Build and manage online surveys and databases quickly and securely

47000+ projects

AssessmentCenter

http://www.assessmentcenter.net/

Online research management tool

Create study-specific websites

Capture participant data securely

PROMIS instruments (short forms, CATs, profiles) are a central feature

Automated accrual reports

Capture endorsement of online consent

Resources: URLs

NIH Office of Science Policy Draft Clinical Trial Protocol Documents(templates)

http://osp.od.nih.gov/office-clinical-research-and-bioethics-policy/clinical-research-policy/clinical-trials

Sample size calculations simplified

http://www.jerrydallal.com/LHSP/SIZE.HTM

Statistics Guide for Research Grant Applicants, St. George's University of London

www-users.york.ac.uk/~mb55/guide/guide.htm

Software: nQuery, EpiTable, SeqTrial, PS
(http://biostat.mc.vanderbilt.edu/twiki/bin/view/Main/PowerSampleSize)

http://tinyurl.com/zoysm