Reading, Interpreting, and Appreciating the protocol

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Protocol Purpose – Clinical Research

- Why
- What
- Who
- How

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Research Team Members

- Principal investigator and other investigators
- Clinical study coordinator(s), project managers, research assistants
- Clinical staff interacting with study participants
- Specialty team members (depends on study), e.g., psychologist, nutritionist, radiologist

Why – Meeting the "who cares" Test

- Epidemiology of disease
  - Who affected, how many, where
- Course of disease
  - Progressive? Stable? Resolves on its own?
  - Outcomes of disease, impact
- What don't we understand about the disease
  - Time course
  - Variability of presentation (genetics, environment)
  - Variability of response to treatment

Why – Clinical trials

- Current treatments, what they accomplish (or not), side effects, invasiveness
- Information on adults/children
- Pre-clinical information on proposed treatment(s)
- Adult studies information on proposed treatment(s)
- Pediatric studies information on proposed treatment(s)

Why - Research Hypothesis and Study Objectives – Observational Study

Overarching hypothesis

- Example: Duchenne muscular dystrophy patients have altered calcium homeostasis due to abnormalities in calcium absorption from the gut, calcium uptake into bone and calcium resorption from bone that is likely influenced by vitamin D nutritional status.

Stated objectives

- Aim 1: To determine 1) total fractional calcium absorption from the intestine (TFCA) and bone calcium deposition rate (V_0) 2) serum levels of vitamin D and parathyroid hormone (PTH) and 3) bone mineral density.
- Aim 2: To estimate calcium homeostasis by correlating TFCA and V_0^+ with vitamin D and PTH levels.
- Aim 3: To correlate the parameters of estimated calcium homeostasis determined in Aim 2 with bone mineral density.

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Why conduct a clinical trial

- No current effective treatment

  or

- Current effective treatment cannot be given to everybody due to side effects or new treatment will reduce side effects

  or

- Unknown which treatment works better

  or

- Looking at a combination of treatments

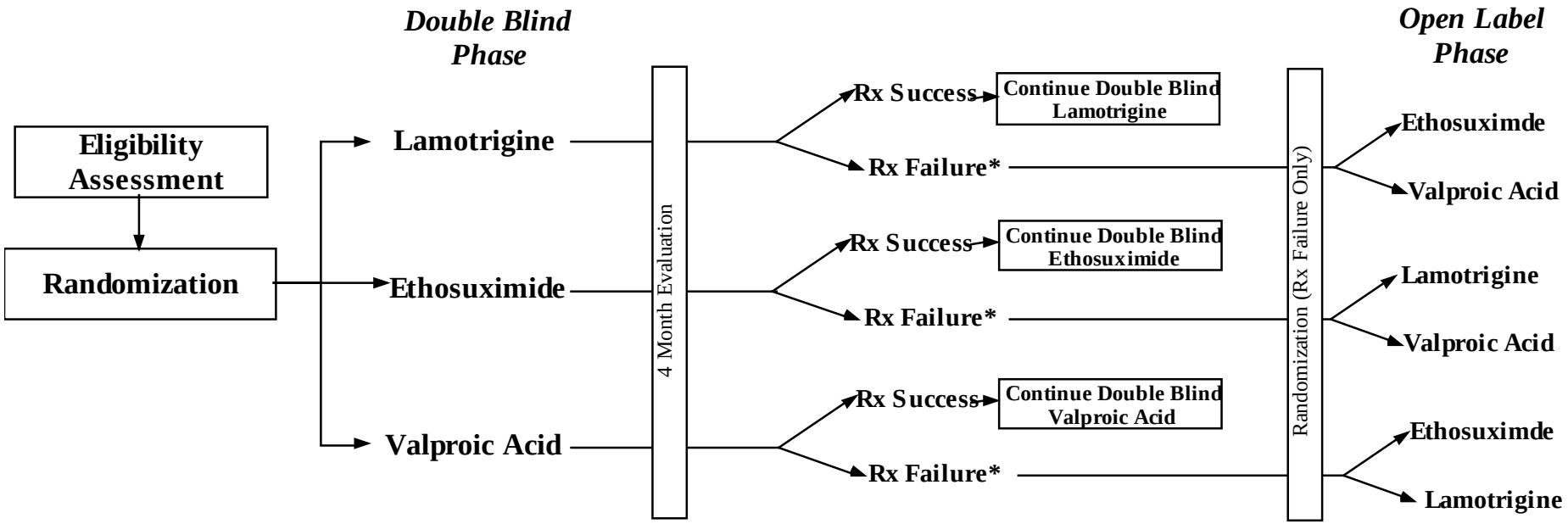
Typical Hypotheses

- Drug or Device A works better than Drug or Device B or placebo
- Drug or Device A is equally effective but safer than Drug or Device B
- Drug or Device A is equivalent to Drug B on disease primary outcome but better on secondary outcome
- Drug or Device A is no worse than B (but maybe cheaper, easier to administer, etc.)

What – the Design of the study

- Example – Clinical trial in Childhood Absence Epilepsy
- Rationale – have common treatments, never compared to each other, variability in results
- Compare head-to-head 3 most common treatments
- Effects on seizures, cognitive abilities, and side effects on weight, behavior, GI, rash

Example of a Clinical Trial Design



1. Pts. exiting due to a generalized tonic clinic seizures will not be randomized to ethosuximide
2. Pts. exiting due to a rash will not be randomized to lamotrigine
3. Pts. exiting due to hepatitis/pancreatitis will not be randomized to valproic acid

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Who – Inclusion and Exclusion

- Define target population(s) by disease, age, size
- Additional detailed disease inclusion criteria (e.g., genetic criteria, certain tests results)
- Ability to participate – consent/assent, compliance assessment
- Exclusion criteria
  - May bias results
  - Study may be harmful to
- Balancing act between homogeneity (better chance to find answers) and generalizability
- Feasibility considerations

How – Time and Events Schedule Example

Visit	Elig.	DB0	P1	DB1	DB2	DB3	DB4	DB4e	P2	DB5-DB12
Week	-7 to 0	0	2	4	8	12	16	20	20	26
Month										9,12,15,18,21,24,30
Informed consent	X									
Complete medical history	X									
Interval medical history			X	X	X	X	X	X	X	X
Physical examination (Ht, Wt, VS)	X[1]			X	X	X	X	X		X
Neurologic examination	X			X	X	X	X	X		X
1 hour video EEG		X		X[3]	X[3]	X[3]	X	X		X[5]
Pharmacogenetic sample				X						
PK sampling				X	X	X	X[4]	X[4]		X[6]
Urine sample for metabolites							X			
Clinical Laboratory	X			X	X	X	X	X		X[2,6]
Full neuropsych. battery		X								X[5]
Continuous Performance Test							X	X		
Behavior/QOL assessment		X					X	X		X[5]
Adverse events recorded			X	X	X	X	X	X	X	X
24 hour diet recall (DDEC)		X					X	X		X[5]
Dispense study drug		X		X	X	X	X	X		X
Drug accountability				X	X	X	X	X		X

How– Description of Evaluations

- What is done (e.g., questionnaires, lab draws, ECG, EEG, MRI)
- Where it is done (outpatient clinic, CRC, inpatient unit, phone, home) or combination of those
- By whom (investigator, coordinator, [research] nurse, specialist e.g. psychologist)
- How long will take
- If have specimens – where and how to collect, ship
- Describe how to collect and store the data

How – Some Considerations in Descriptions of Evaluations

Within protocol, purpose of description is to let all research team and otherwise affiliated with conducting the study (IRB, clinical staff not of research team) have a sense of all that will happen

Not overly detailed – further detail provided in Manual of Operations or Procedures

Important to identify what is standard of care and what is additional from study

How – Clinical Trial Treatment

- Which medications – dosing, formulation, blinding
- Where are the medications and how dispensed, administered
- Expected side effects

Information is general – may have a Manual of Procedures for/from Research Pharmacy, in addition to further details in Manual of Operations.

Also wish to assess whether treatment could have been given outside the protocol as standard of clinical care.

How – Safety in the Protocol

- What adverse events to expect
  - Adverse events can occur both in observational studies and clinical trials
- How to treat from the protocol perspective
- If clinical trial, what to do about study treatment
- Does the participant need to be withdrawn from the study?
- Regulatory reporting requirements
- Stopping rules for the study
- Oversight by a Medical Monitor or committee

How - Regulatory

- Responsibilities of investigator and other team members
- Human subjects research considerations
- Data collection and storage
- If applicable – what to do with drug
- Other

Statistics – Putting Why and What Together

- Describes how data will by analyzed, using the study design, to answer the research hypothesis, meet the study objectives

- Describes based on Background how the sample size and number and type of evaluations will be successful in answering the research questions of the study

General Structure of Research Protocols

- Background/Introduction
- Study hypothesis/objectives/ rationale
- Study design
- Eligibility – Inclusion/Exclusion
- Schedule of visits and evaluations/outcomes
- Treatments and modifications, if applicable
- Discontinuations/ withdrawals
- Safety
- Shipping of specimens
- Statistical analyses plan
- Data management
- Regulatory and Human Subjects

Questions

- If asked – would you know to say what the study is about, why it matters, and in general, who is included in the study, what occurs in the study, how it happens?
- Would you have interest in the published paper(s) describing the results of the study?