-Basics of Clinical Trial Design-
Design, Population, Intervention, Outcomes

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Clinical Investigator Training Course

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Prelude

- This talk is designed for clinical investigators.
- Many features of the topics in this presentation are usually a sponsor's responsibility
- As a clinical investigator, YOU are responsible for:
  - Enrolling subjects who have the disease of interest
  - Not committing protocol violations
  - Successfully migrating data to the sponsor or contract research organization
  - Assuring subject safety
  - Assuring that each subject enrolled has been fully informed of the risks via a documented informed consent
  - Questioning aspects of the protocol felt to be harmful to the subject or felt to not be properly designed to evaluate a clinically meaningful primary efficacy endpoint (i.e., **YOU ARE ENCOURAGED TO QUESTION THE SPONSOR, EITHER INDIVIDUALLY OR AT THE INVESTIGATOR MEETING**)

Learning Objectives

After participating in this session, you will be able to:

- DESIGN:
  - Appreciate what all trial designs have in common
- POPULATION:
  - Identify the appropriate patient population for the hypothesis under investigation
- INTERVENTION:
  - Understand various protocol designs
  - Appreciate factors to consider in the design of clinical trials
- OUTCOME:
  - Describe primary and secondary endpoints

DESIGN

What All Trials Have in Common

- Pursuant to the code of federal regulations (21 CFR 314.126):
  - Adequate: the trial design can discern the purported treatment effect based on a pre-specified criteria for success
  - Well-controlled: usually a randomized trial that attenuates baseline imbalances of patient characteristics that could confound the results and jeopardize data interpretation

KEY MESSAGE (Common Trial Features)

- Data from the trial must be interpretable with a discernable treatment effect for drug approval
- Trial design should include pre-specified criteria for success: acceptability of type 1 (false positive) and type 2 (false negative) errors
- Speak up if you feel the trial does not address a clinically meaningful issue or the trial is not properly designed to meet the statutory requirements

POPULATION

Description of Patient Populations

- Intention-to-Treat Population (ITT)
  - All randomized patients, regardless of treatment
- Modified ITT Population (mITT)
  - All randomized patients who took at least one dose of study drug
- Per-Protocol Population (PPP)
  - All randomized patients who followed the protocol exactly as written

Description of Patient Populations

- ITT population is preferred
  - ITT analysis preserves the prognostic balance afforded by randomization, thereby reducing any risk of bias that may be introduced by comparing groups that differ in prognostic variables.
- mITT population is tolerable
  - The risk here is excluding subjects that could introduce bias and lead to misleading results
- PP population seldom endorsed
  - By excluding subjects who deviated from the protocol, it introduces attrition bias, in which groups of subjects being compared no longer have similar characteristics

Strategy for inclusion criteria

Inclusion Criteria

- Include subjects likely to benefit from the intervention:
  - not too sick (i.e., too late to treat)*
  - not too well (i.e., enrichment with higher risk factors to increase the chance of a patient experiencing an endpoint)*

* Careful about regression to the mean

A word about Regression to the Mean

- One may select a subject experiencing a bad or good day at baseline (tail ends of intrasubject variability)
- Such a subject may revert to their average level of illness during the trial
  - Drug could be erroneously seen as effective if the subject had a bad day at baseline (type 1 error)
  - A subject having a good day at baseline may empirically decrease the treatment effect of the drug (type 2 error)

A word about Regression to the Mean

Remediation strategies

- Measure baseline values multiple times
- Consider remote therapy monitoring (RTM) as it would apply to any eligibility criterion with intrasubject variability
- RTM may also capture extreme values beyond the tail ends that may not have been captured because of an exclusion criterion; thus, avoiding potentially mistaking these findings as a treatment effect or an adverse effect beyond intrasubject variability for the index disease presentation
- Best defense: control group in a randomized trial

A word about Subgroups

- The population of patients within the ITT that have similar characteristics. Examples:
  - Age
  - Gender
  - Race/Ethnicity
  - Region in the world
  - Smokers
  - History of diabetes
  - History of past MI

Subgroup Analysis

Key questions:

- Are the results the same for each subgroup?
- Are the results of the trial driven by only one subgroup?
- Is there a subgroup for which the drug is harmful?

As an investigator, be cognizant of subgroup categories

Subgroup Analyses

Two Subgroup Categories

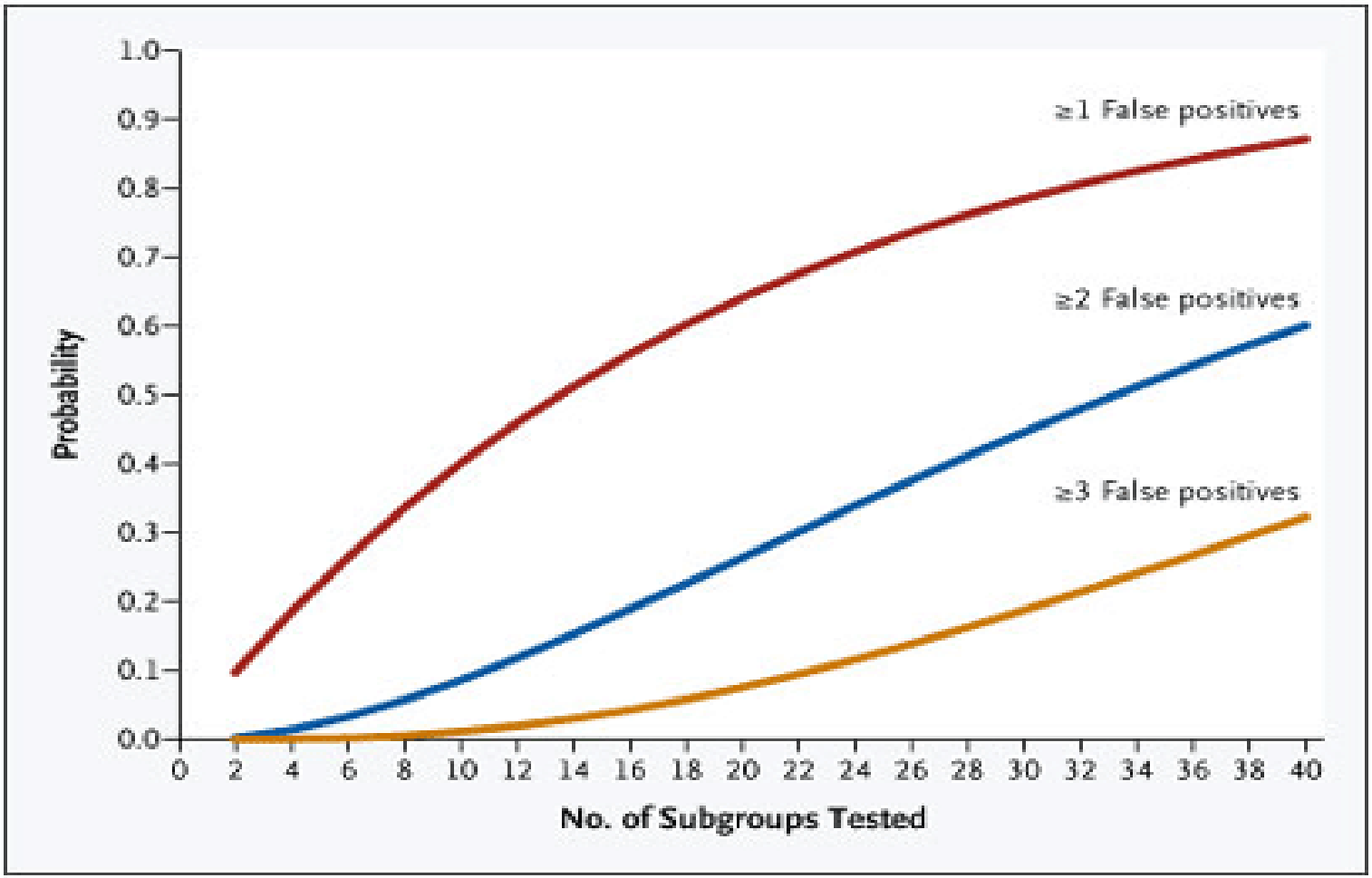
1. Subgroup of subjects that are independent of any unique pathophysiology associated with or at increased risk for the index disease or primary efficacy endpoint (evaluating for curiosity)
2. Subgroup of subjects with unique pathophysiology that might matter to the treatment effect

- These two groups should be treated separately when controlling for false positives
- For the subgroup that might matter to the treatment effect, it is advised to have a pre-specified expected treatment effect prior to data unblinding

Subgroup Analysis

- A positive trial driven by one region/country/site, negative everywhere else is still positive
- A negative trial but with a strongly positive subgroup is still negative.
- Careful about multiplicity when studying many subgroups for a possible claim

Probability that multiple subgroup analyses will yield at least one (red), two (blue), or three (yellow) false positive results



Lagakos SW; NEJM 2006; 354: 1667-1669

Population: Key Messages

- Data analysis should be conducted on the ITT or mITT population
- ITT population should be selected to optimize the treatment effect of the intervention
  - Caution: label may be restricted to the ITT population if selection was based on narrow severity spectrum, rather than the broader population with various levels of index disease severity in the market
- Be cognizant about regression to the mean when enrolling subjects
- Be cognizant about subgroup categories as pertains to a group that matters to a treatment effect
- A positive subgroup in the setting of a negative trial does not constitute a basis for a claim
- Testing too many subgroups will produce a false positive result. Subgroup analyses are inconclusive

INTERVENTION
(PROTOCOL DESIGNS)

A Word About Blinding: Open or Blind

Open Label trials

- Everyone knows which patient is receiving which treatment
- May be randomized (controlled) or uncontrolled

Open Label Trials

- Pros:
  - Easier to conduct, especially when blinding is not feasible
  - Useful when comparing two approved drugs of similar characteristics, where each drug can be equally prescribed
  - Useful in long term extension trials to evaluate safety or persistence of effect
- Cons:
  - Possibility of bias (patients or investigator may have pre-conceived notion of safety/efficacy that might impact judgement)

A Word About Blinding: Open or Blind

Blinded trials

- Neither investigator nor patient has knowledge about which treatment is being given
- Element of a randomized trial

Blinded Trials

- Pros:
  - Attenuates potential bias in efficacy endpoint assessment (if subjective) and attribution of adverse event to drug (*e.g., if you are concerned about drug safety, knowing a subject is on the drug when experiencing an adverse event may result in assigning causality to drug*)
- Cons:
  - More costly: (e.g., more complicated logistical design in terms of randomized code generation, blinded study drug kit design, distribution of study drug kits, treatment assignment, monitoring for study drug allocation assignment)

Types of Blinded Strategies

Blinded Strategies

Single blinded, double blinded, double-blinded-double dummy

Single Blinded

- Subject has no knowledge what is being given, but investigator does

Double Blinded

- Neither investigator nor subject knows what is being administered

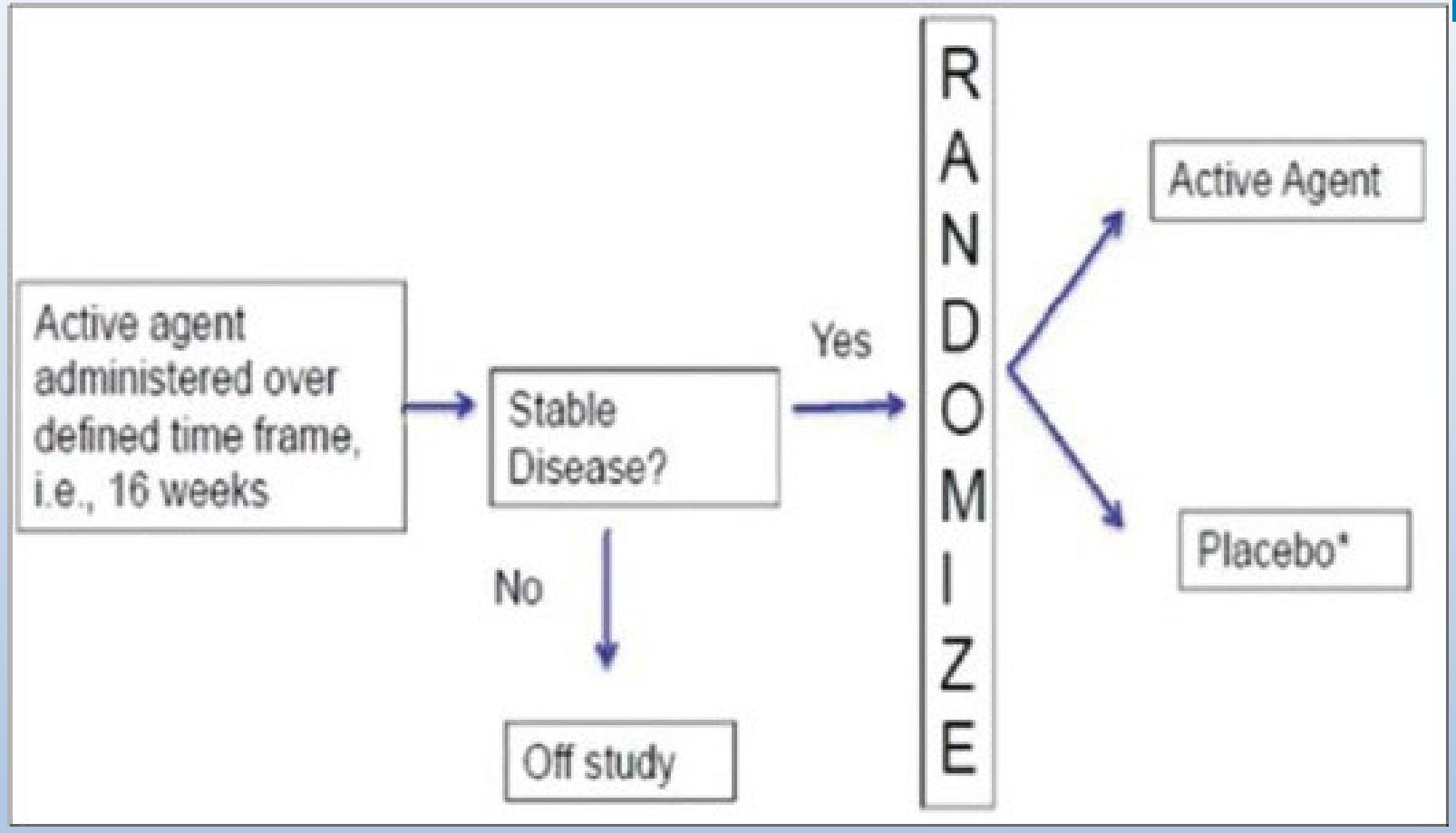
Double-blinded double-dummy

- Same as double blinded but each arm in 2-arm study has different posology (e.g., pill vs IV). In this case, both dosage forms have a placebo mirror

A Word About Randomization

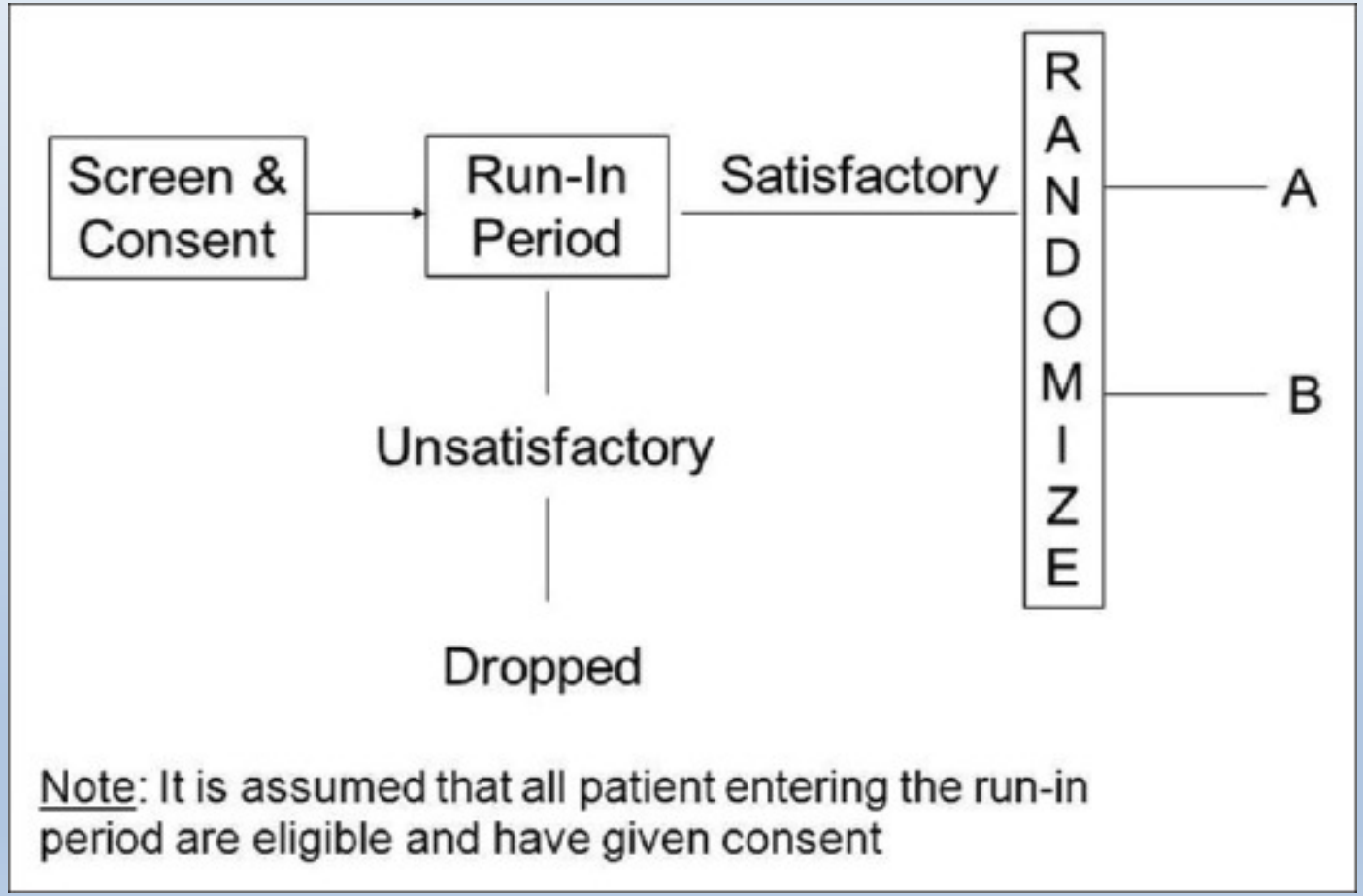
- Attenuates influence of covariates on the primary efficacy endpoint:
  - Important to assess the effect of the intervention on the primary efficacy endpoint while minimizing the affect of confounders on the primary efficacy endpoint by balanced distribution of confounders in the arms

Randomized Parallel Trial



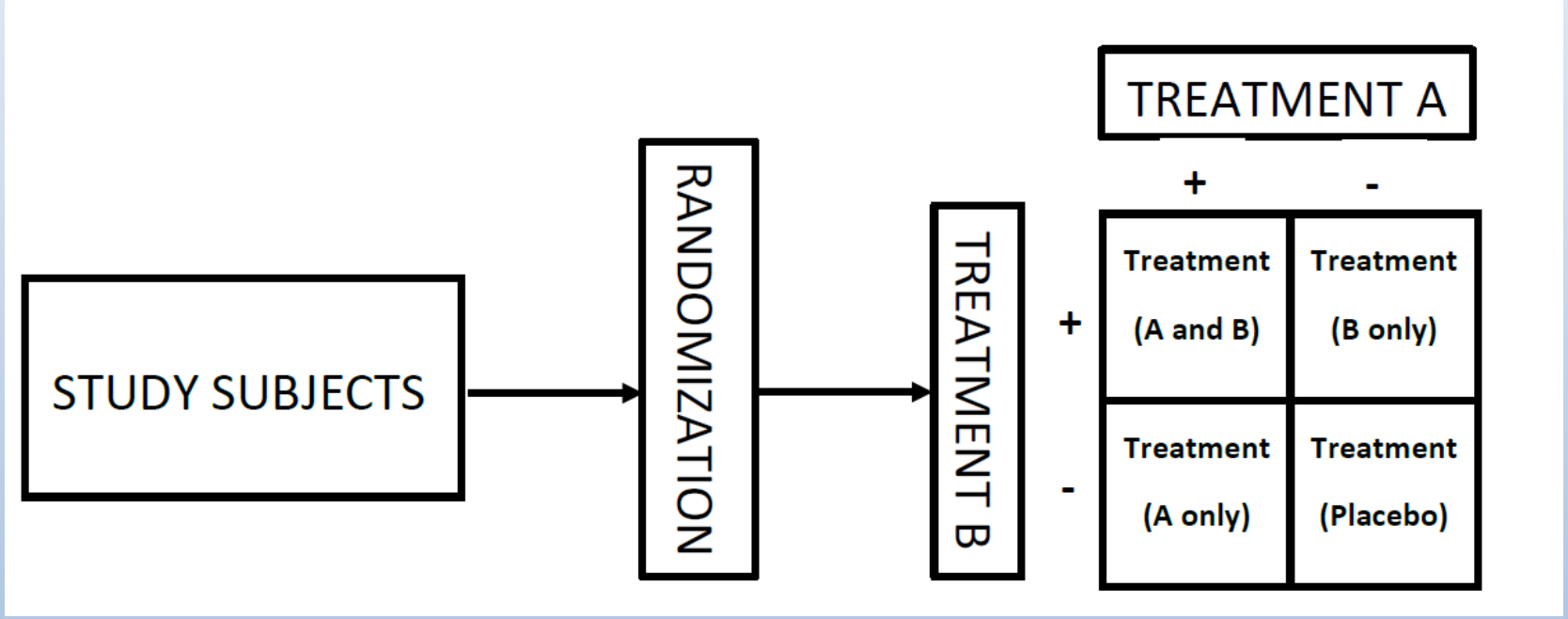
- * could be active comparator
- Usual approach to evaluate superiority or non-inferiority.
- Screening for stable disease is a strategy to increase probability of detecting a treatment effect: enrolling very sick and unstable patients may cause the drug to appear ineffective (i.e., extreme enrichment).

Randomized Parallel Trial



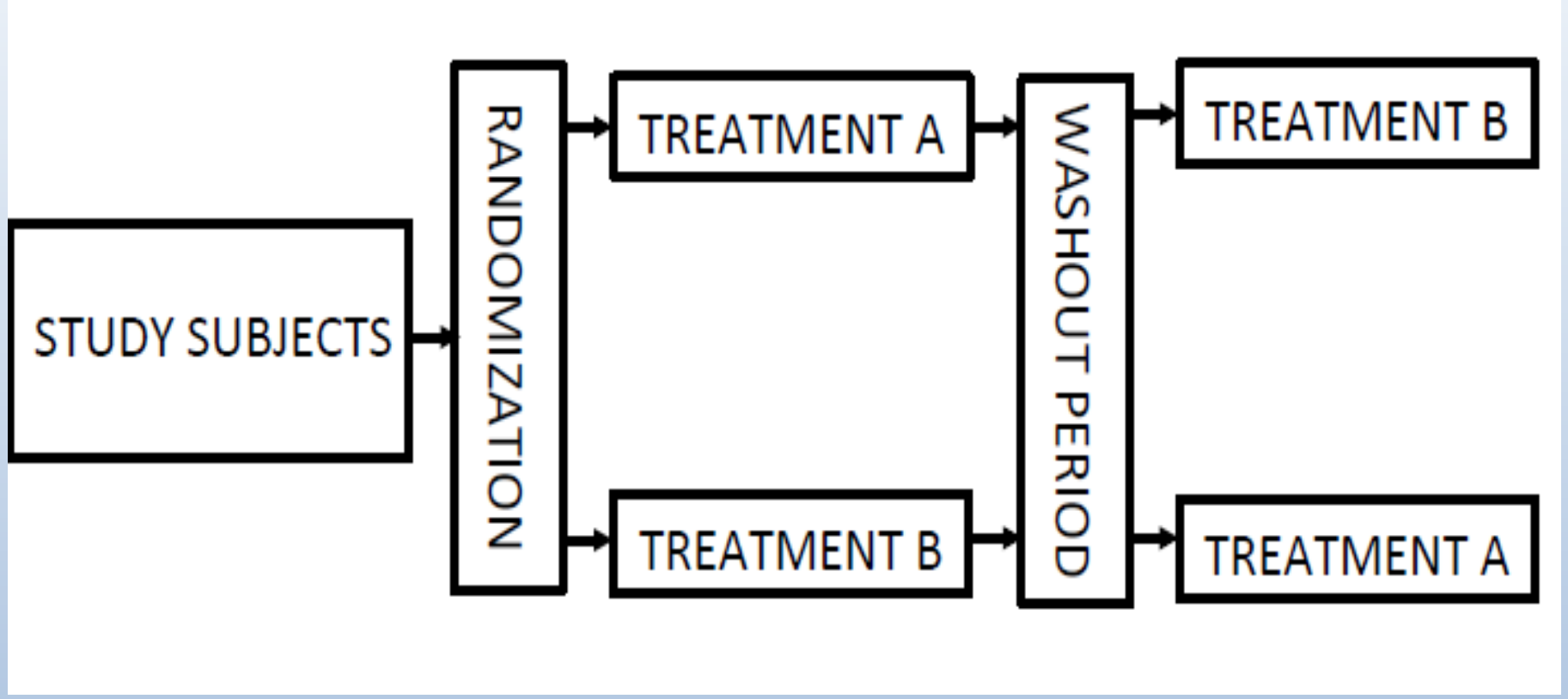
Run-in period, usually involving placebo or drug, evaluates compliance or toleration; can involve like-drug discontinuation, e.g., hypertension drug

Factorial Trial



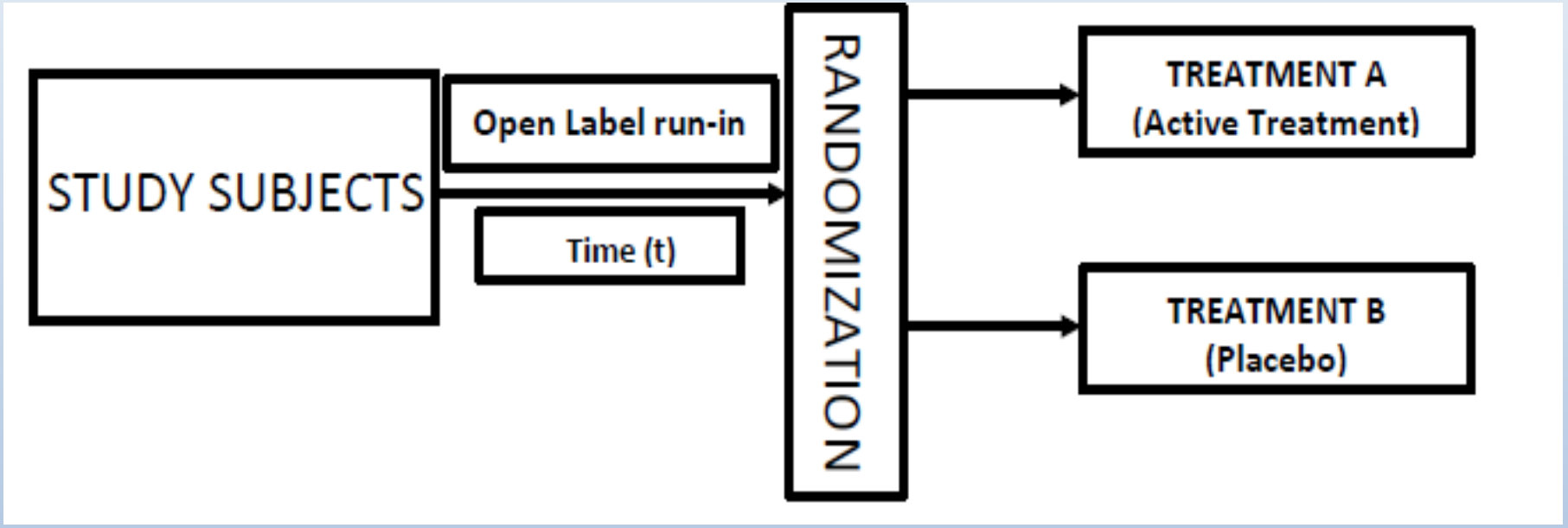
Trial Hypothesis: Drug combination is superior to individual drug components

Cross-Over Trial



- Usually a Phase 1 PK trial short term trial design (i.e., 2 weeks); lowers sample size.
- Crossover trials allow the response of a subject to treatment A to be contrasted with the same subject's response to treatment B.
- **Removing patient variation** in this way makes crossover trials potentially more efficient than similar sized, parallel group trials in which each subject is exposed to only one treatment.

Randomized Placebo-Controlled Withdrawal



The primary efficacy endpoint is relapse of symptoms following withdrawal of drug. This trial design has been used for hypertension and pericarditis trials.

Persistence of effect and disease modification can be tested with this design

Design: Key Messages

- Pick the right protocol design to fit the program hypothesis
- Gold standard: randomized double-blind clinical trial:
  - Attenuates influence of confounding covariates
  - Minimizes potential for bias

Factors to Consider in Designing Trials

- Characteristics of the Disease
  - Understanding the drug's mechanism of action and the pathophysiology of the disease
- Study Objectives / Hypothesis
  - Hypothesis maps to primary efficacy endpoint
- Primary Efficacy Endpoint
  - For a registrational trial, must be based on the feel-function-survive paradigm

Factors to Consider in Designing Trials

- Timeframe / Duration
  - Duration of treatment and follow-up time should coincide with duration of treatment requirement to distinguish a treatment effect
  - Caution: the longer the trial, greater possibility of drop-out. Must have subject-retention plan as part of design

Factors to Consider in Designing Trials

- Trial Logistics
  - Streamline execution of trial and acquisition of data from site → CRO → sponsor databank; maintain blindness. Need a data migration plan (*usually a sponsor responsibility where instructions should be clear to investigators → if not, speak up*)

Factors to Consider in Designing Trials

- Ethical Considerations
  - Ensure patient safety (major reason for clinical hold)
  - Maintain GCP/ICH-E6 compliance (*i.e., ethical and scientific quality standard for designing, conducting, recording, and reporting human trials; key GCP issue: informed consent*)
  - Need a safety monitoring plan and trial stopping criteria. If sponsor does not have one --> inquire about it

- Patient Convenience
  - Do not create hardship for enrolled subjects (e.g., excessive travel, subjects bearing cost-especially for adverse events (speak up if the protocol creates hardships)

Factors to Consider in Designing Trials

- Statistical Considerations
  - Inter and Intra subject variability: treatment effect should be discernable above subject variability on the feel-function-survival paradigm
  - The sample size should be aligned with the prespecified criteria for success (e.g., accepting a 5% chance of committing a type 1 error and a 20% chance of committing a type 2 error unless otherwise agreed to—based on rarity of disease)
  - *Speak up if the protocol is not clear on this*

- Clinical Meaningfulness
  - Treatment effect should be large enough to have a net benefit for patients

Factors to Consider: Key Messages

- When considering a protocol at your site, make sure the primary efficacy endpoint is one that you and enrolling patients deem important-if not, speak up
- Ensure the treatment and follow-up timeframe is coincident with treatment duration required to discern a clear treatment effect
- Ensure the protocol has an adequate safety monitoring plan, subject retention plan, subject retention plan and data migration plan
- Ensure proper informed consent (hide nothing!)—interact with your IRB

OUTCOME
PRIMARY AND SECONDARY ENDPOINTS

Primary Endpoint

- Defined as the specific clinical effect you wish to test (e.g., reduce mortality, stroke and heart attack).

- The statistical analysis plan and sample size focuses on obtaining interpretable results and being able to draw conclusions regarding the primary endpoint.

Primary Endpoint

- PEP can be a single variable: MORTALITY.
- PEP can also be a composite endpoint of several components
- Important to ensure that each component of the proposed composite PEP have similar degrees of clinical importance.
  - E.g., *Death, Stroke, Heart Attack*; or *Death, Stroke, Hair-loss*

As an investigator, worth knowing

Secondary Endpoints

- Secondary endpoints are of interest but do not constitute the basis of trial design
- Sometimes, a clinically meaningful endpoint (i.e., mortality) is designated as secondary and the trial is powered for it; the primary endpoint is excessively powered
- Mention of secondary endpoints in the label depends on whether they were part of a pre-specified alpha conservation strategy
- Sometimes, a mortality benefit even outside of the alpha conservation strategy may provide sufficient clinical meaningfulness to warrant a label claim

Leeway of Phase 2 and the rigor of Phase 3

- Phase 2:
  - More flexibility in primary endpoint selection (e.g., biomarkers or putative surrogates) to inform on safety profile and posology to phase 3

- Phase 3:
  - Primary endpoint must be clinically meaningful within the feel-function-survive paradigm

Outcome: Key Messages

- The primary efficacy endpoint leading to a claim should be clinically meaningful within the feel-function-survive paradigm
- When analyzing the results of the trial evaluating a composite endpoint of several components, consider the impact of individual component endpoints going in different directions

SUMMARY / CONCLUSION

Summary

Design

- As an investigator / clinical trialist, YOU are responsible to
  - Ensure the trial satisfies the statutory requirements pursuant to CFR 312.126
  - Maintain knowledge on regulatory requirements to safeguard your patients when enrolling them in a clinical trial

Summary

Population

- Do not enroll very sick subjects (during enrichment) where the drug may be ineffective
- Do not enroll a minimally sick ITT population whereby the drug may not have a discernable treatment effect
- Be cognizant about regression to the mean when enrolling subjects
- Use your clinical knowledge if you think the protocol eligibility criteria are enrolling subjects at the tail ends of variability at baseline, thus potentially impacting results

Summary

Interventions

- Focus on patient safety by ensuring existence of and adherence to an adequate safety monitoring plan
- Understand the data migration plan and the subject retention plan and adhere to it to minimize missing or corrupt data
- Keep control of your site: maintain vigilance over the research team and identify/correct issues expeditiously

Summary

Outcome

- If you as investigator serve on a steering committee, you should ensure the primary efficacy endpoint is clinically meaningful (i.e., based on feel-function-survival) and discernable by the subject above normal variability of disease presentation)

Conclusion

- **ASK THE SPONSOR if you have any questions**

- YOU, the investigator, have a significant say in the trial design. Investigator meetings are designed to ensure the protocol is consistent with the clinical practice paradigm

- YOU, the Investigator, are responsible for your patients enrolled in the trial (safety, informed consent, trial with a clinically meaningful outcome, data management at your site)

- YOU, the Investigator are ultimately changing the practice paradigm for the better by bringing into the market a drug that you will have contributed to demonstrating a beneficial treatment effect

Thank you for your service to society!

Challenge Question 1

If a sponsor wishes to include the primary and a series of secondary efficacy endpoints in the label, it is incumbent on the sponsor to develop a hierarchical analysis plan for testing each endpoint by pre-specified order to avoid committing type 1 errors:

A. True

B. False

Challenge Question 2

Which of the following are true?

A. A global trial is considered positive if the entire population (intention-to-treat) met the prespecified criteria for success even if subjects in the USA did not show a benefit.

B. Attempts to determine specific subgroups for which the drug will benefit the most in order to better guide health care practitioners may increase the probability of committing a type 1 error.

C. A positive trial that is driven by only one region of the world (i.e., Russia / Ukraine), but negative everywhere else, disqualifies that trial from having met the evidentiary standard.

D. Choices A, B, and C are correct

E. Choices A and B are correct

F. Choices B and C are correct