Rare Bootcamp™

Rare Disease Clinical Trial Design

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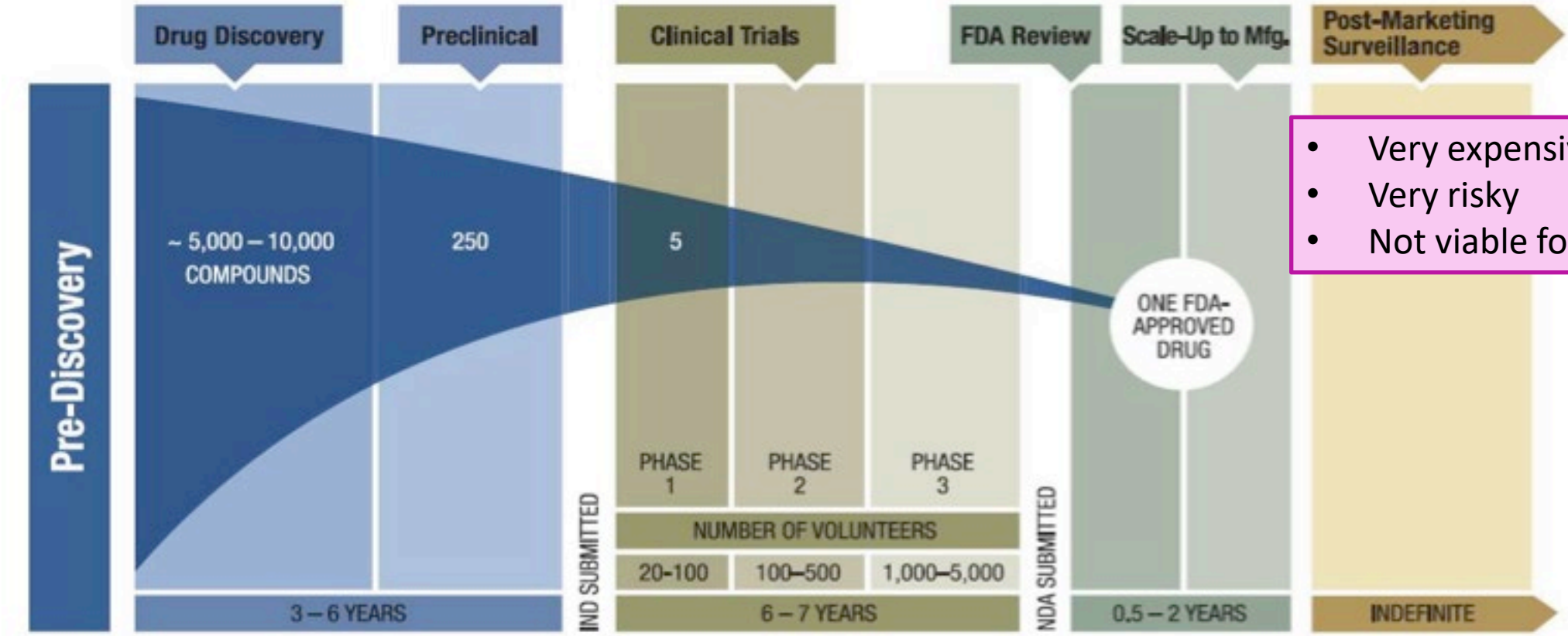
Traditional Drug Development is not Practical for Rare Diseases



- Very expensive
- Very risky
- Not viable for rare diseases

Rare Disease Drug Development has Unique Challenges and Opportunities

Challenges

- Limited understanding of disease natural history
- Limited clinical study or regulatory experience
- Development strategy can be very different
- The combination of unknowns can paralyze decision-making and delay programs
- Learning without preparation and insight can result in stress, time delays and drug failure
- Difficulties in powering a study with small sample sizes

Opportunities

- Clear disease biology, often with a single gene defect, simplifying drug discovery and shortening preclinical testing timelines
- Highly motivated patients and families
- Phase I and II can usually be combined
- Regulatory agencies may be open to novel and surrogate efficacy endpoints
- Payers may accept higher per-patient treatment costs due to small patient population
- Expedited regulatory review

Challenges can be Overcome with Dynamic Development

- Learn as you progress through development stages
  - Be humble and open to discovering the truth
  - Be willing to challenge well-established facts
  - Seek knowledge from patients and study data, not just advisory boards
  - Start with patient interviews, disease burden surveys, and clinical survey studies
- Invent when necessary to create the right tools or strategy
  - Be irreverent toward precedent
  - Take a bold and creative approach to study design, endpoints, and statistics when necessary
  - Invent only what needs to be invented – this is always more work and time consuming, but benefits will be long lasting and can improve probability of success
- Hedge by opening multiple paths to win and manage risk
  - Learn and adapt from your data, be ready to change course
  - Anticipate risks and create hedges
  - Open multiple paths to win

Pillars of the Ultragenyx Dynamic Development Model

All stakeholders have needs that must be met

Who	What they need	How you can give it to them
Patients and their families	• Access to life-changing therapy as soon as possible	• Listen and learn how the disease affects their lives • Design practical clinical trials that **measure what really matters to patients**
Physicians, Key Opinion Leaders (KOLs)	• Authorship on publications • Research funds • Ability to treat their patients with new therapies	• Advisory boards • Involve them in study design, especially eligibility criteria • Selection as investigators in clinical trials
Regulators (FDA, EMA, etc)	• To protect patients and approve drugs only after convincing data show a favorable risk-benefit	• **Educate them** about the disease • **Frequent meetings** to align on development strategy, including efficacy endpoints • Bring patients to meetings
Payers (Insurance companies, HMOs, Public Health Insurance, etc.)	• Attenuate spiraling healthcare costs	• **Collect data that can show reduced healthcare costs** for patients if the therapy works
Study Sponsor, including company shareholders	• Investments in drugs that have the potential to grow the business	• Establish proof-of-concept ASAP • Demonstrate high unmet need • **Shortest possible development timelines**

What are approvable efficacy endpoints?

A clinically meaningful change in the way a patient **feels**, **functions**, or **survives**

- Dr. Robert Temple, FDA

A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought **to predict clinical benefit**, but is not itself a measure of clinical benefit.

-FDA Overview of Accelerated Approval

It turns out that what is really bothering the patient and what is really bothering the doctor can be radically different things….patients are true experts in their disease.

- Dr. Janet Woodcock, FDA

The FDA doesn't have to get to 100% certainty between an accelerated approval endpoint and a clinical endpoint

-Dr. Peter Marks, FDA

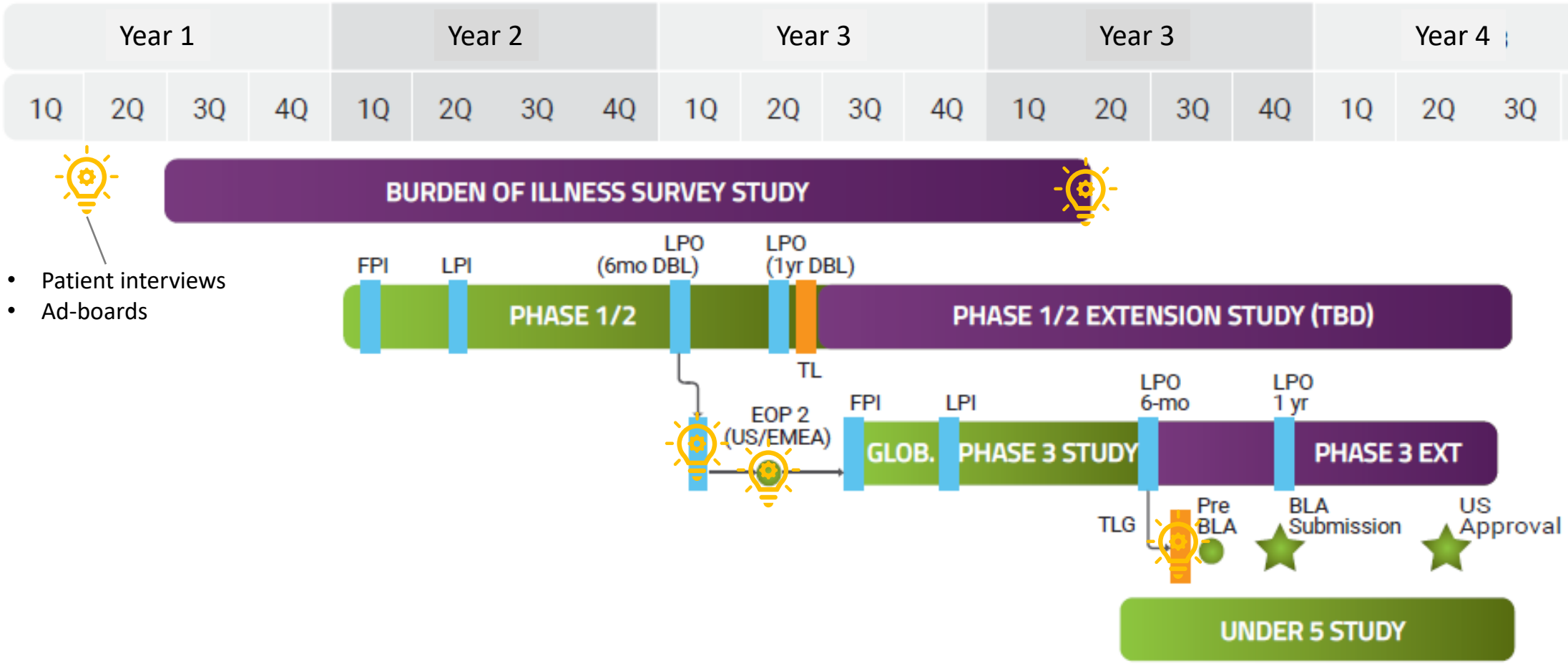
Important considerations in efficacy endpoint selection

- What are the key clinical manifestations of the disease across the life span?
- Are there disease features that most or all patients have in common?
- Are there other more common diseases with similar features?
- What is the impact of these features on how a patient “feels and functions”?
- What is the most bothersome aspect of the disease?
- What are patients’ expectations for treatment?
- What do you expect to change with treatment?
- What subset of patients is most likely to show benefit from treatment in a clinical trial?
- How long will it take to show improvement?
- Are there established biochemical markers that predict long-term outcomes?

How to pick efficacy endpoints

- Identify potential endpoints during preclinical phase by gathering as much information as possible from patients
- Evaluate many potential endpoints in phase I/II
  - Phase II is for learning, phase III is for verifying
  - Phase II design should be creative and adaptive
- Evaluate as broad of a patient population as possible in phase I/II
- Pair primary clinical physiologic (intermediate) endpoints with complementary secondary functional patient-reported outcomes (PROs)
- Use continuous variables whenever possible
  - Avoid dichotomous variables such as responder analyses
- Consider a novel biomarker as a primary endpoint
- A multi-domain responder index may be needed when disease manifestations are highly variable

Keep learning and aligning with regulatory agencies throughout the drug development process



Key Considerations in Study Design

1. What is the purpose of the study?
    - A first exploration without any chance of filing?
    - A phase 2 learn study that is potentially fileable?
    - A pivotal phase 3 study for approval?
2. How will the dose and treatment regimen be defined and managed?
    - Fixed dose regimen?
    - Adaptable dose regimen based on pharmacodynamic assessments?
    - Adaptable according to key safety or efficacy endpoints?
3. What is the control group strategy?
4. Who is the included population?
    - Must have treatable disease that is measurable in the allotted time frame
    - Broad enough array of population to understand heterogeneity and reversibility
    - Consider age, gender, genetics, severity of disease, severity of a given endpoint, and probability of benefit.
    - Consider also that some populations are difficult to measure, such as patients <5 years or old patients that are very severe and very few in number – these populations can be studied in nonqualifying companion studies

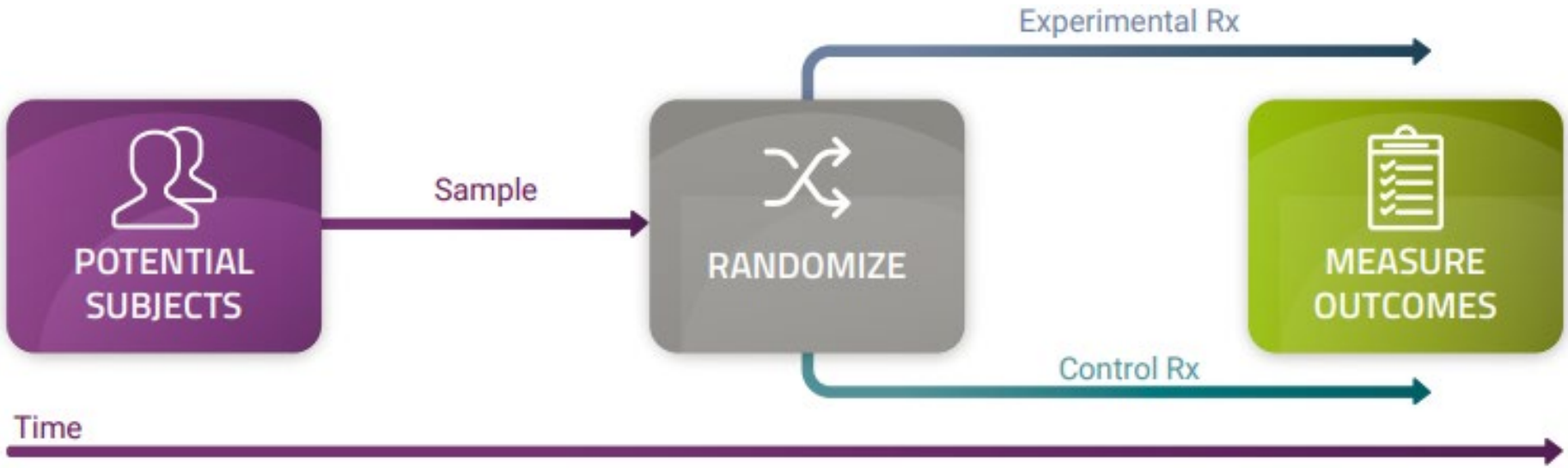
Type 1 and Type 2 Error

1. Null hypothesis (H_0): the drug doesn't work
2. Collect data and perform a statistical test to evaluate if the data are compatible with the null hypothesis → p value
   - p-value is the probability that the data are compatible with the null hypothesis
   - p-value generally must be < 0.05 to reject the null hypothesis (the drug works)

- Type 1 error occurs if you reject a null hypothesis that is actually true (you conclude that the drug works, even though it doesn't)
- Type 2 error occurs if you fail to reject the null hypothesis even though it is wrong (you conclude that the drug doesn't work, even though it does)

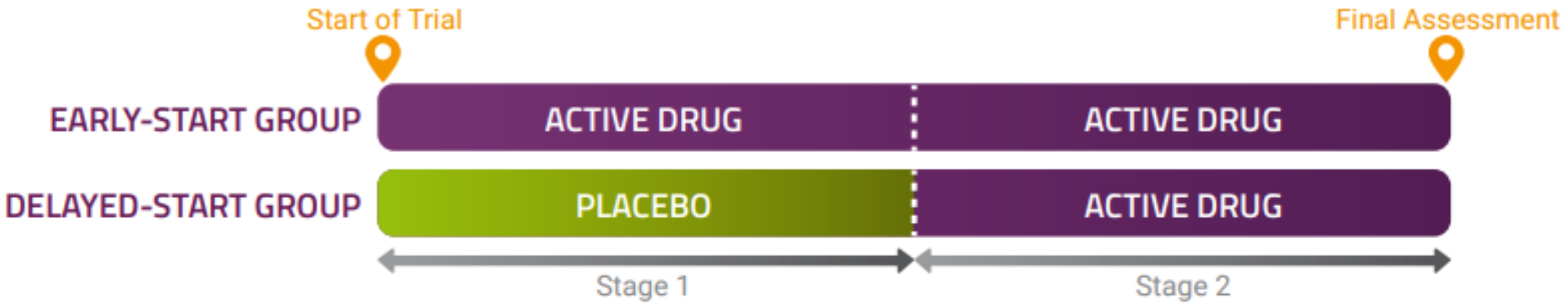
- Type 1 error is controlled by selecting the appropriate statistical methods given the study design, and minimizing bias in the study
- Type 2 error is controlled by ***powering*** the study appropriately: making sure you have enough patients that your p-value will be <0.05 if the effect size is as big as you anticipate. This requires some statistical modeling and assumptions about effect size and how much noise will be in the data

Randomized Controlled Trial



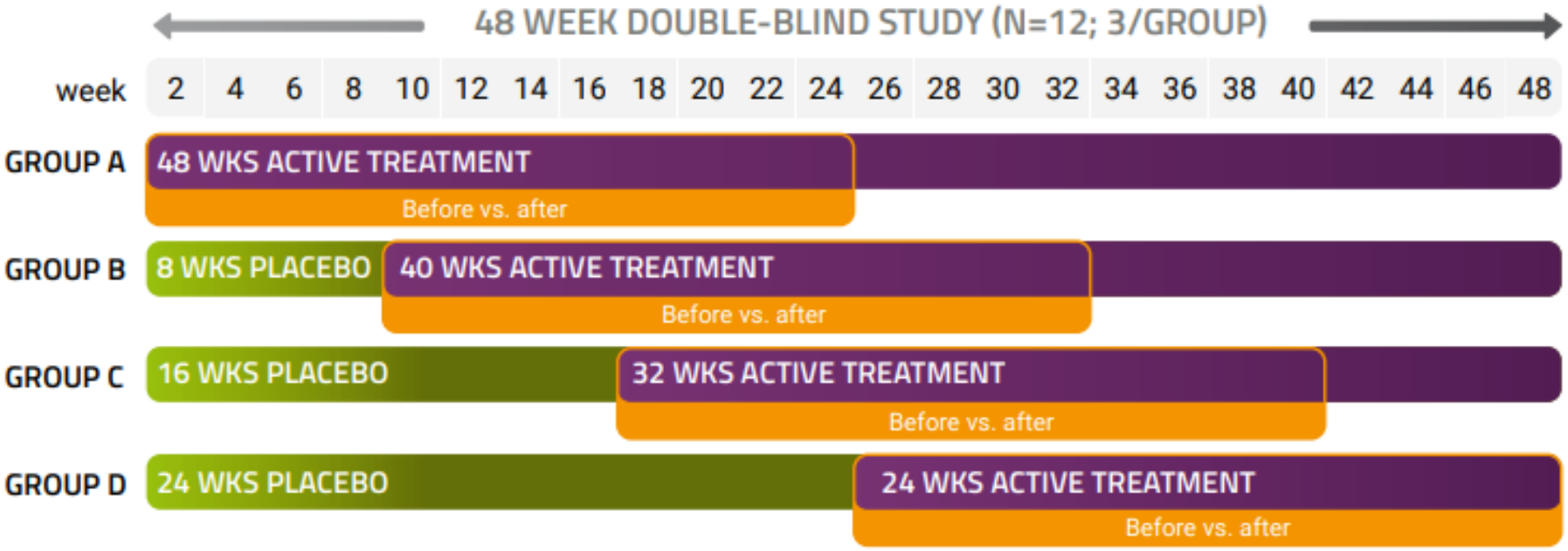
- Minimizes bias, especially when double-blind
- Most favored by global regulatory authorities and payers
- Can be difficult to power in rare diseases where sample sizes are small
- Sometimes blinding of treatment allocation is impossible
- Interim analysis can be used for sample size re-estimation without sacrificing power

Randomized Delayed Start



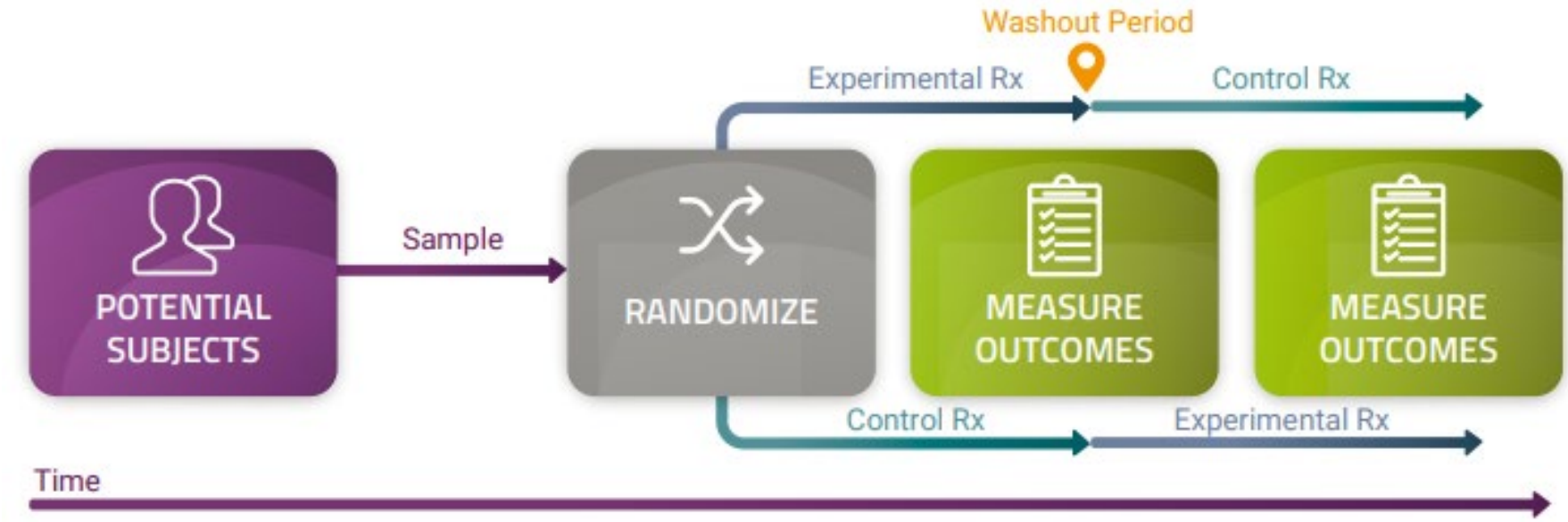
- Stage 1 may be a R/DB/PC trial
- Ensures all subjects eventually have access to study drug, facilitating recruitment
- Helpful for drugs whose effects develop slowly over time
- The results in Stage 2 can help determine whether the treatment has long-term benefits
- The short amount of time spent on placebo can underestimate the treatment effect, resulting in larger sample size requirements
- Susceptible to dropouts during the placebo phase, which may limit the interpretation to Stage 1 data.

Blind Start Trial



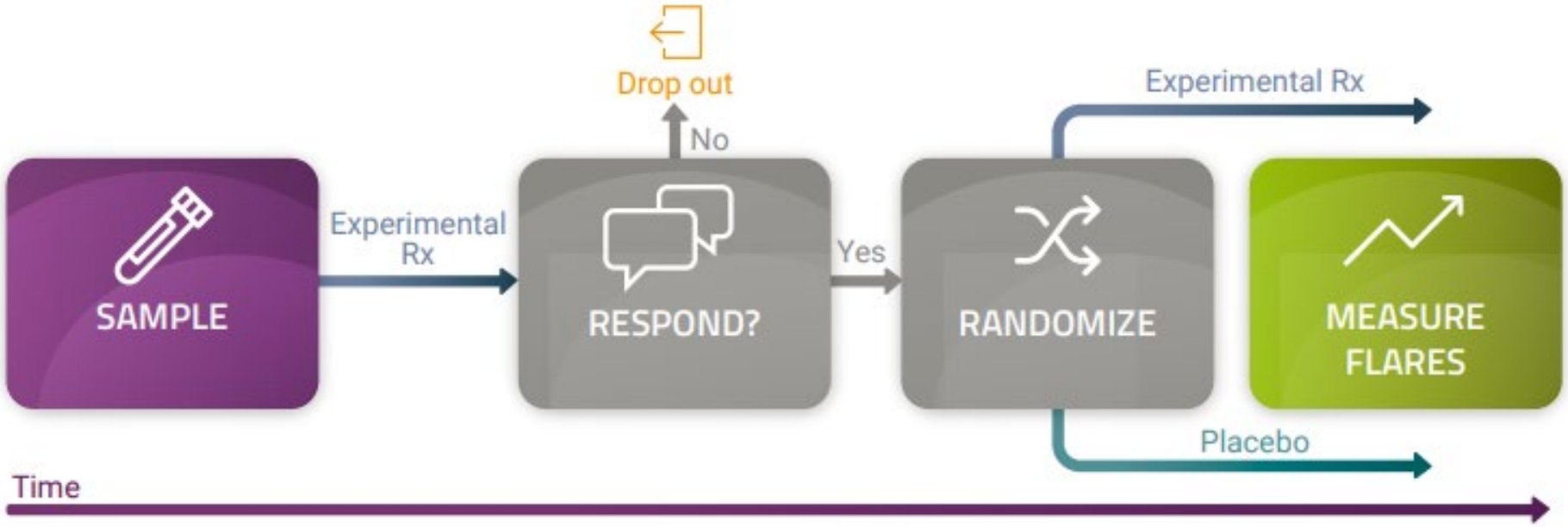
- A fancy type of randomized delayed-start trial
- Increases power for detecting effects when there are small sample sizes
- Creates better retention of blinding than a single delayed start design
- Results from before and after treatment and/or placebo are compared within subject and between groups

Double Crossover Trial



- Maximum use of subjects for data generation and within-patient comparisons
- You must already know the duration of treatment needed to show efficacy, the timeframe for carry-over effects to disappear, and the placebo effect size
- Best-suited for biochemical endpoints that respond rapidly

Randomized Withdrawal Trial



- Useful when response rate is modest and dose must be titrated for each subject
- Useful if there is a large placebo effect
- Treatment period must be long enough to reach a new stable state
- Requires crisp loss of effect when treatment is removed
- Difficult to assess long-term safety without safety comparator arm
- May result in missing data if patients drop out prematurely due to disease flares

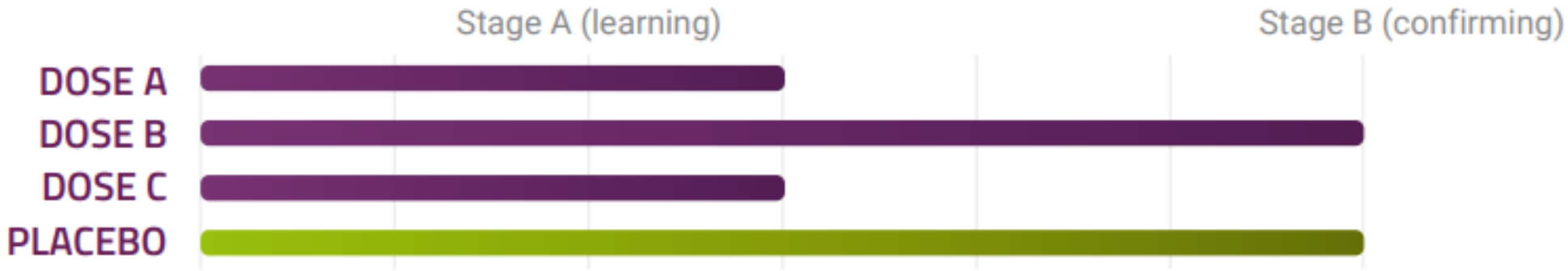
N of 1 Trial

- Power can be created with very small sample size if the response correlates with treatment
- Subject acts as their own control, confounding and variance are minimized.
- Provides highly personalized data on whether a given intervention works for a particular subject
- The patient has to know they will also be taken off the treatment several times
- Meta-analysis of n-of-1 trials is limited by heterogeneity of outcomes in individual trials.
- Share the same limitations as cross-over trials.
- Require validated, repeatable measures of treatment effects, such as biomarkers.

Non-controlled Open-Label Trial

- Vulnerable to placebo effect
- Outcomes are typically compared to a robust natural history study with similar patient characteristics
- Generally not accepted by regulatory agencies except in diseases where survival is known to be very poor and life-saving effects are clear

Seamless and Adaptive Trials



- Both stages are conducted in a single protocol. As the data from Stage A are analyzed and a dose is selected, that dose along with the placebo group are brought forward with new set of patients.
- The biggest advantage is savings in the operational activities
- Requires adequate drug supply and a mature manufacturing process early in development

Summary

- A dynamic development strategy is key to finding a path forward to approval
  - Learn throughout the process and be ready to change course
  - Invent when needed – challenge precedents and dogma
  - Hedge your bets – pursue multiple endpoints in parallel
- Consider needs of all stakeholders
- Learn as much as possible from patients and partner with them
- When possible, measure how a patient feels, functions, and survives
- Meet with regulators frequently, and educate them
- The selection of study design depends on disease characteristics, patient characteristics, response pattern, duration of effect, expected recruitment rate
- Use continuous variables when possible
- Develop novel endpoints when necessary (which is often the case)

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