

**Enriched Enrollment Randomized Withdrawal
Design for Studies in Chronic Pain
FDA Anesthetic and Analgesic Drug Products
Advisory Committee Meeting**

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April 19, 2023



Declaration:

The opinions expressed in this presentation are my own and not those of the University of Pennsylvania or the FDA

Topics for This Presentation

1. Concept of enriched enrollment randomized withdrawal (EERW) studies compared to other study designs

1. Description

2. Advantages and disadvantages

3. Potential uses

2. Issues to consider

1. Internal validity

2. External validity (Generalizability)

3. Importance of inclusion/ exclusion criteria

3. Conclusions



Defining the Purpose of Any Clinical Study

- ▶ To answer a specific question
- ▶ Selection of design must focus on question to be answered (population, exposure, and outcome)
- ▶ No single study can answer all questions
- ▶ Every study has:
 - Advantages/ disadvantages
 - Underlying assumptions that must be understood to properly interpret the results
- ▶ EERW studies are no different

Diagram of Common Approaches to Randomized Clinical Trials (RCTs)

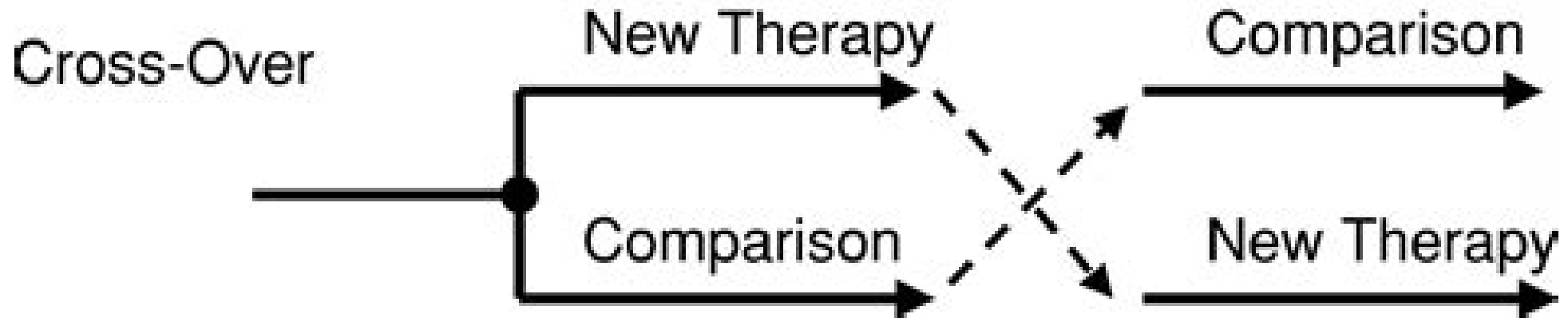
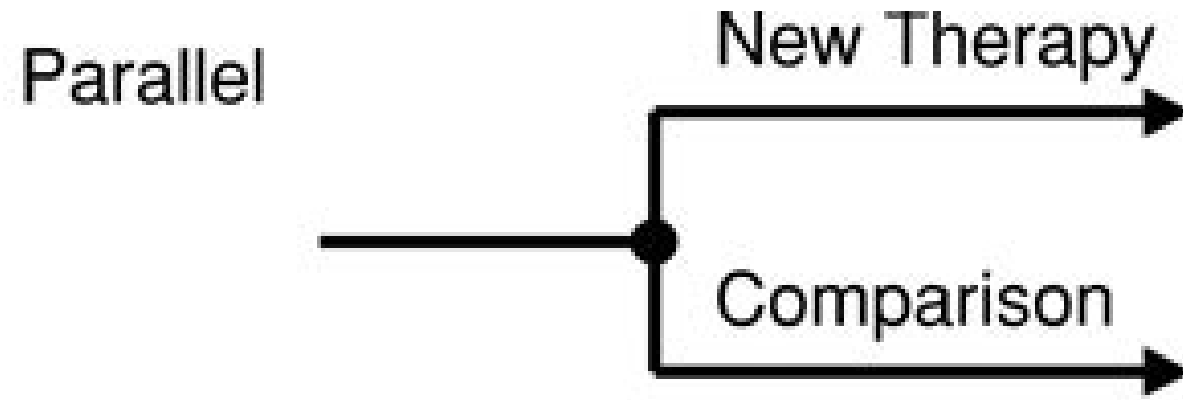
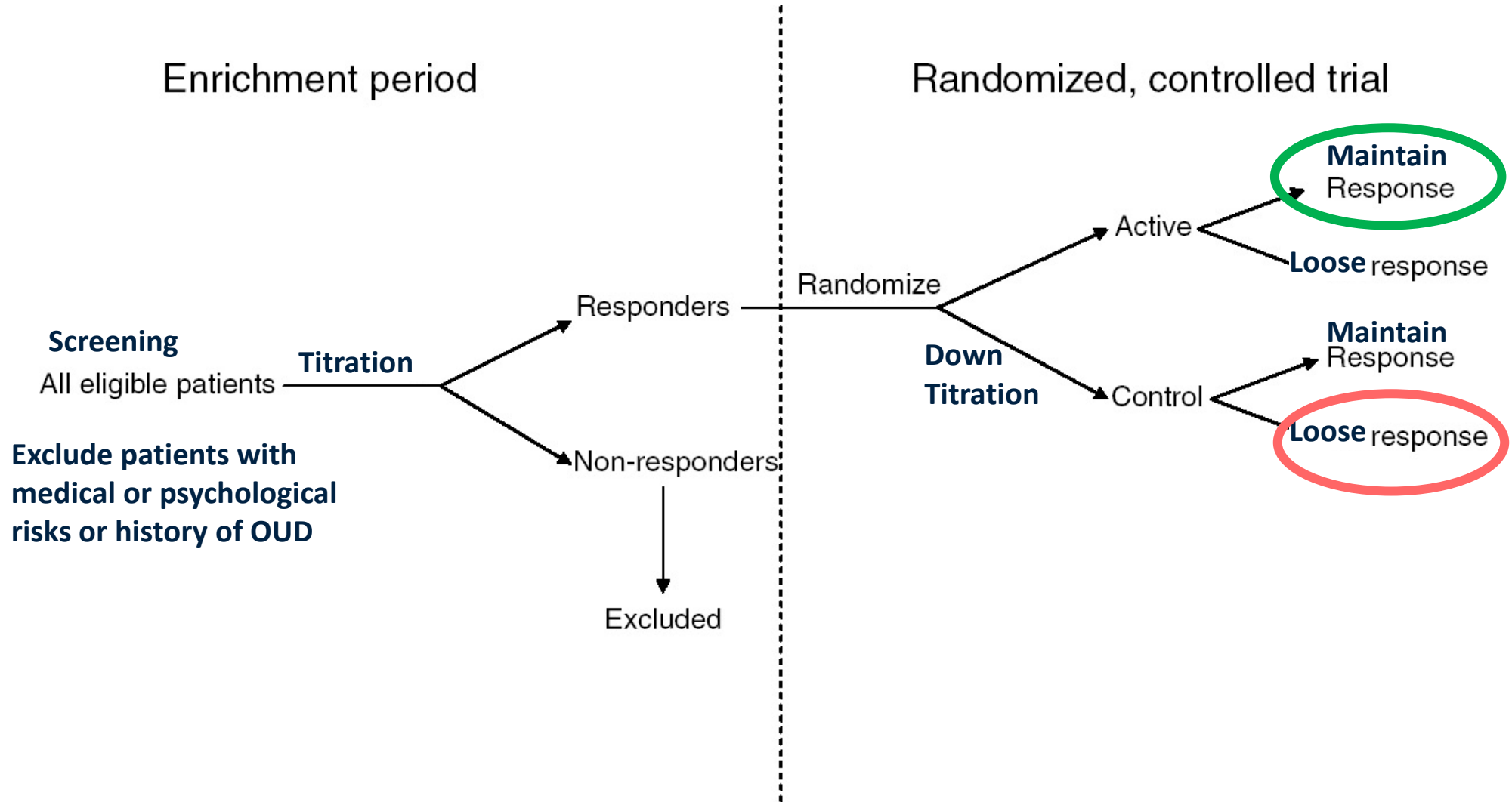
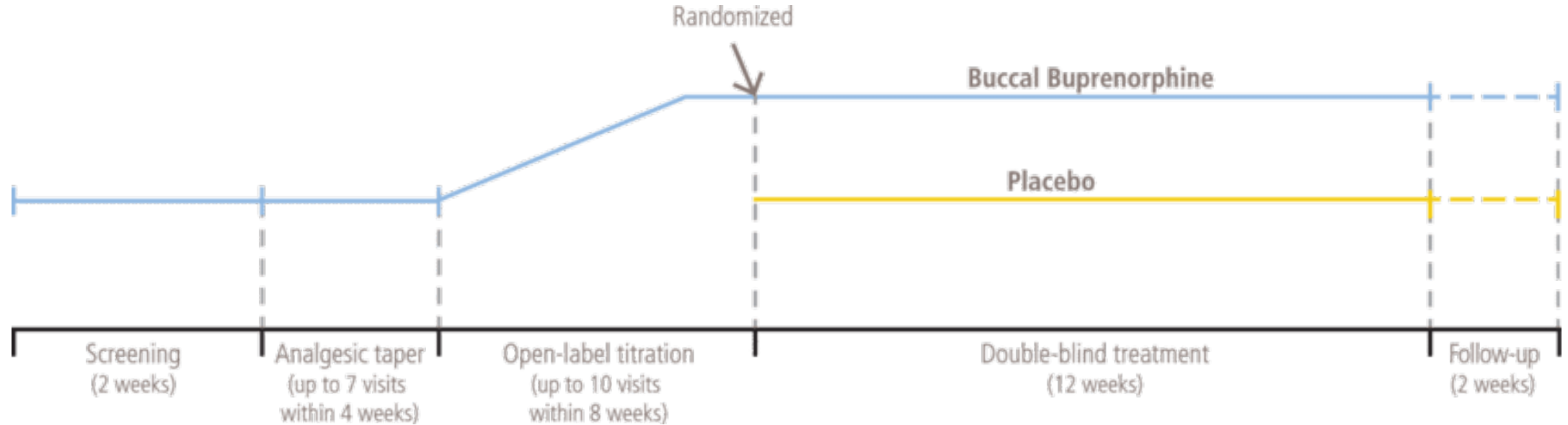


Diagram of EERW Studies



Buprenorphine Study Example



Effect Size Comparison of Pain RCT Types

▶ Parallel trials since 2007

– (49 trials, N=15,342, mean difference -0.66, 95% CI, -0.81 to -0.52)

▶ Trial before 2007 reported larger differences

– (22 trials, N=4274, mean difference -1.12, 95%CI, -1.37 to -0.92)

▶ Cross over trials all had larger differences

– (13 trials, N=1234, mean difference -1.19, 95% CI, -1.58 to -0.81)

▶ EERW trials (all since 2007) had larger differences

– (21 trials, N=7178, Mean difference -0.81 95%CI, -0.99 to -0.64)

Design Issues – All RCTs



General Clinical Trial Design Issues

- ▶ All clinical trials are designed to answer a specific question with defined limitations.
- ▶ Parallel RCTs – Randomization removes most baseline bias and confounding between groups
- ▶ Population homogeneity may limit broader generalizability
- ▶ Cross Over Trials (COTs) – Highly efficient with participant as their own control but have issues of carry over and time effects

Potential Problems with All RCTs

- ▶ Ethics – not ethical to randomize to many exposures
- ▶ Population selection (phenotype) and recruitment
- ▶ Limited patient willingness of patients to participate in a placebo controlled trial
- ▶ Randomization should be centralized
- ▶ Drop-outs/ Missing data
- ▶ Generalizability
- ▶ For pain studies – need to account for rescue use

Potential Problems with All RCTs (cont.)

- ▶ **Careful blinding to control group (placebo) exposure**
 - Intended to limit participant's expectation of effect
 - More effective if participant and study staff are unaware of group and timing of potential placebo exposure
 - Unblinding from side-effects is an issue
- ▶ **Blinding is not always possible – e.g. surgical trials**
- ▶ **Lack of blinding changes the comparison groups to:**
 - Treated **WITH** knowledge of treatment
 - Untreated **WITH** knowledge of untreated status

What Does Enriched Enrollment Mean



Definition of Enrichment – Clinical Care

- ▶ Differential diagnosis in clinical care is a process to select patients based on history, exam, and laboratories to enrich the likelihood of finding the etiology of the signs and symptoms
- ▶ Even then treatment of patients often involves some degree of trial and error, carefully following the patient's response.
- ▶ Example: Hypertension – patients on initial therapy are followed for response and side-effects.
 - But not every treatment works in every patient.
- ▶ Trial and error is a common approach to the treatment of pain

Definition of Enrichment – Study Population

- ▶ **Every prospective study uses an enriched population**
 - Example: study of angina therapy - enroll only patients with pain related to heart function not all chest pain
 - Example: study of antibiotics for URI symptoms – since viral etiology is most likely cause, enroll patients for antibiotics only if symptomatic therapies not working
- ▶ **Homogeneity of the population improves likelihood of finding an effect but reduces generalizability**
- ▶ **EERW – Enriches the population by identifying increased likelihood of ability to respond to study drug**

Need for Enrichment in Pain Studies

- ▶ Current ability to identify specific pain etiologies is limited
- ▶ Example: Chronic low back pain –
 - Etiology could be nerve, bone, muscle, or connective tissue
 - Muscle spasm can be predominant pain but derived from any of these etiologies
 - Factors that facilitate nociceptive input, transmission to the brain, or perception of that input can vary significantly
 - Thus, any clinical trial CLBP involve a heterogeneous group
- ▶ EERW studies identify a population with the phenotype to potentially respond to treatment if a true effect exists

Design Issues – EERW Studies



EERW Study Design Issues

- ▶ EERW studies are like parallel RCTs with some advantages which include:
 - Potentially less issues with recruitment since we treat all subjects.
 - Population selection is specific for patients with phenotype that increased likelihood of responding to the study drug
 - Titration period leads to less missing data after randomization
- ▶ Generalizability is an issue, but less of a problem if selection of the population is consistent with usual clinical practice
- ▶ There may be some potential issues during drug taper to placebo after randomization

EERW Study Design Issues (cont.)

- ▶ Run-in titration period help prevent study drop outs and are consistent with clinical practice
 - Excludes participants likely to be unable to tolerate treatment - similar drug trial in clinical practice
 - Handles high variability in participant response to treatment by titrating to an effective dose – similar to titration in clinical practice
 - Run-in periods are important as test of participant's willingness to complete study procedures reducing dropouts

EERW Study Design Issues (cont.)

- ▶ **Generalizability is an issue but...**
 - Similar issue occur with standard parallel studies if population is selected to be homogenous.
 - May be less of a practical issue if selection criteria for the study population is consistent with usual clinical practice
 - Titration to an effective dose with tolerable side-effects does mimic clinical practice
- ▶ **Possible carryover effects similar to cross-over studies**
 - Better design for short acting drugs (such as analgesics)

EERW Study Design Issues (cont.)

- ▶ Potential withdrawal symptoms during drug taper to placebo
 - Blinded withdrawal is less problematic than open withdrawal
 - Randomizing the time of starting taper can reduce expectation of transition effects
 - Allow reasonable use of rescue throughout the study
 - Extend observation period on stable dose after titration to allow for patients to experience natural variation in pain and use of rescue
 - Randomize timing of transition to placebo over a few weeks so patients do not know when they are being transitioned

EERW Study Design Issues (cont.)

- ▶ Potential withdrawal symptoms during drug taper to placebo
 - Ensure careful blinding of patient and study personnel
 - Measuring withdrawal symptoms (COWS and SOWS) throughout the trial is important to understand potential unblinding
 - Carefully collect specific reasons for any drop-outs
 - Consider offering “return to previous active medication dose ”to patients rather than dropping out

Potential Uses of EERW Study Design

- ▶ EERW studies are randomized assessments of the continued benefit of a drug over time in a population of patients who have demonstrated an initial response.
- ▶ Has the potential to be used for multiple assessments over time if appropriate by returning patients to study drug between assessments.
- ▶ An advantage is that although patients know they will be randomized to placebo at some point they also know they will return to study drug following the placebo period – encourages staying in study

Potential Issues for EERW Design

- ▶ The primary outcome should be pain levels and patient report of loss of efficacy (PGIC or related measure)
- ▶ If there are only a small number of dropouts the study becomes a true cross-over design increasing power
- ▶ If not, then each randomized withdrawal period will continue to be an internally valid study of patients remaining in the study.

Conclusions

- ▶ The EERW study is a validated and well documented design for assessing continued efficacy in patients demonstrating drug benefit without serious side effects similar to the use of drugs in clinical practice
- ▶ EERW studies answer the question of whether there is a group of patients in a population who respond to a drug therapy and lose the effect when withdrawn

Conclusions (cont.)

- ▶ EERW studies do not inform us about the results of the exposure of a larger less select population
- ▶ But...
 - The screening process for admission to the titration period is identical to that used in most other RCT study designs
 - The titration period does provide data about the success of and rate of side effects in the population enrolled and exposed to the drug
- ▶ The EERW study design is useful in the proper setting

Questions/ Comments?

