

Stop the pain: Tips for increasing patient retention and decreasing missing data in analgesia clinical trials

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Agenda

- Overview of landscape of pain program issues
- Strategies for Success
 - ✓ Program development
 - ✓ Study execution
 - ✓ Analysis
- Considerations for Ongoing Programs

The Pain Paradigm

“We've seen over the years that analgesic [pain] clinical trials frequently fail, and often with drugs that we know work. When opioids that have been known to be effective for hundreds of years are put in clinical trials, we can't get a positive result...It has become clear to the entire pain community that there are design problems with the trials, making it difficult to accurately evaluate whether drugs work or not.”

Bob Rappaport

Director of the Division of Anesthesia, Analgesia, and Addiction Products

FDA Center for Drug Evaluation and Research

ACRP Wire 24NOV2011

How does this affect your development program?

FDA Re-evaluating
ongoing programs

FDA not
recommending
specific methods

Must identify
approvable
endpoints

Affects
operational
execution

Requires complex
statistical
methods

Impacts results

Case Study

- Acute Pain Program; NDA submission
- Original imputation method: LOCF/BOCF hybrid
- FDA requested new imputation method on a new trial prior to submission of NDA
- Sponsor chose a new method in alignment with the NAS report

Situation



- Proactive planning led to excellent trial implementation and enrollment
- No communication with FDA about the new analysis
- Acceptability of new analysis unclear
- Approval potentially at risk

Implications



NAS Report



National Academy of Sciences convened experts to address this issue



Issued report July 2010 which describes problem and possible solutions



With no FDA guidance, report being used as a reference for possible solutions

NAS Report Recommendations

Have a plan
and put it in
the protocol

Reduce
dropouts

Keep collecting
information on
dropouts

Don't use
LOCF

Use Sensitivity
Analyses

Reasons Subjects Dropout



Insufficient
pain relief



Side
effects



Frequency
of visits



Study
burden



Need for
rescue
medication



Dropout Rates

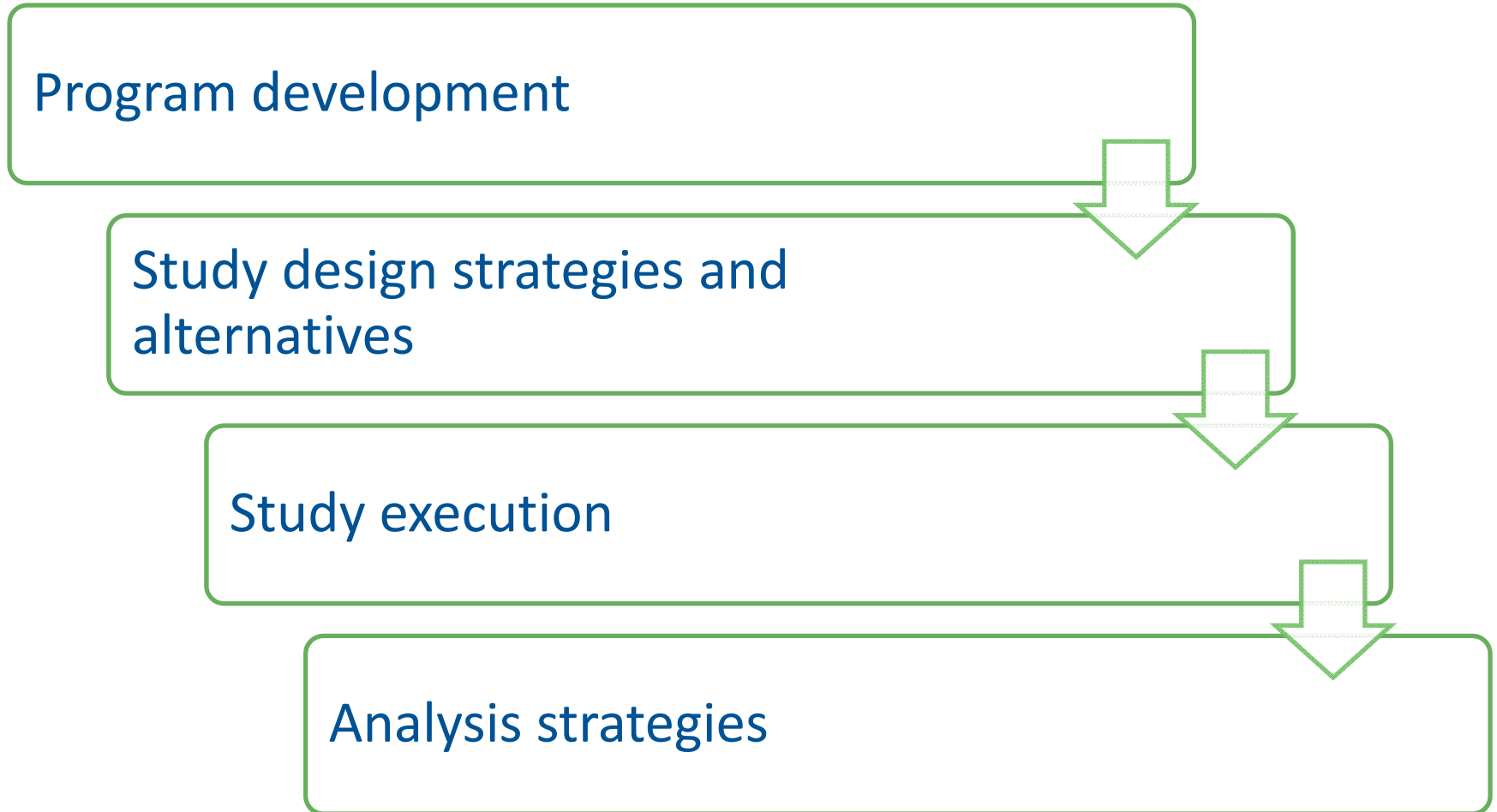
>20%

Chronic
pain studies

5-40%

Short term
pain studies

Program Strategies



Program Development Strategies

Start with
the end in
mind

Plug-in to the
FDA Pain
Division



Draft desired
label

Strategize trial
implementation

Study Design Strategies

Consult experts
and practitioners

Keep assessments
simple

Consider adaptive
designs

Examine potential
endpoints

Consider PROs

Plan for missing
data

Conduct detailed
site feasibility

Consider current
practice in
planned countries

Study Design: Endpoints



Composite Endpoints

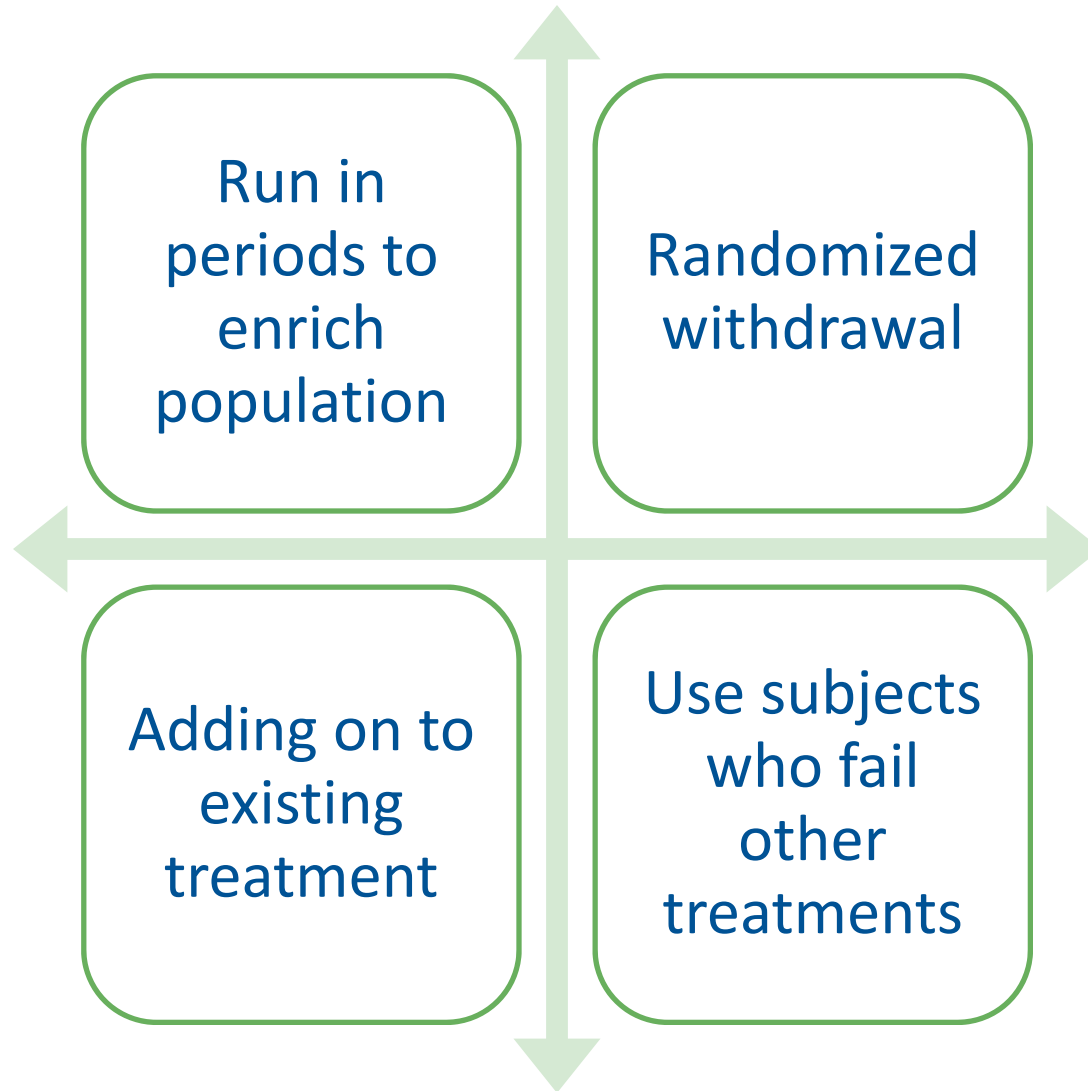


Time to rescue medications



Categorical Responders
Analysis

Study Design: Alternatives



Study Execution: Site Management



Site
selection is
critical



Focused
site staff
training



Proactive
planning
to reduce
dropouts

Subject Retention Strategies

Subject contact during study
Preferences

Reminders

Personal



Use technology
Apps

Diaries

Social Media

Monitoring & Data Management



Monitoring plan is important



EDC/ePRO can alert you to missing data trends more quickly



Cross-functional communication is critical



Real-time and continuous assessment of missing data



NAS recommends continued data capture on subjects that dropout

Analysis Strategies

Define:

- a statistically valid analysis for the primary endpoint using reasonable assumptions for the missing data

Perform:

- a sensitivity analysis on the primary endpoint

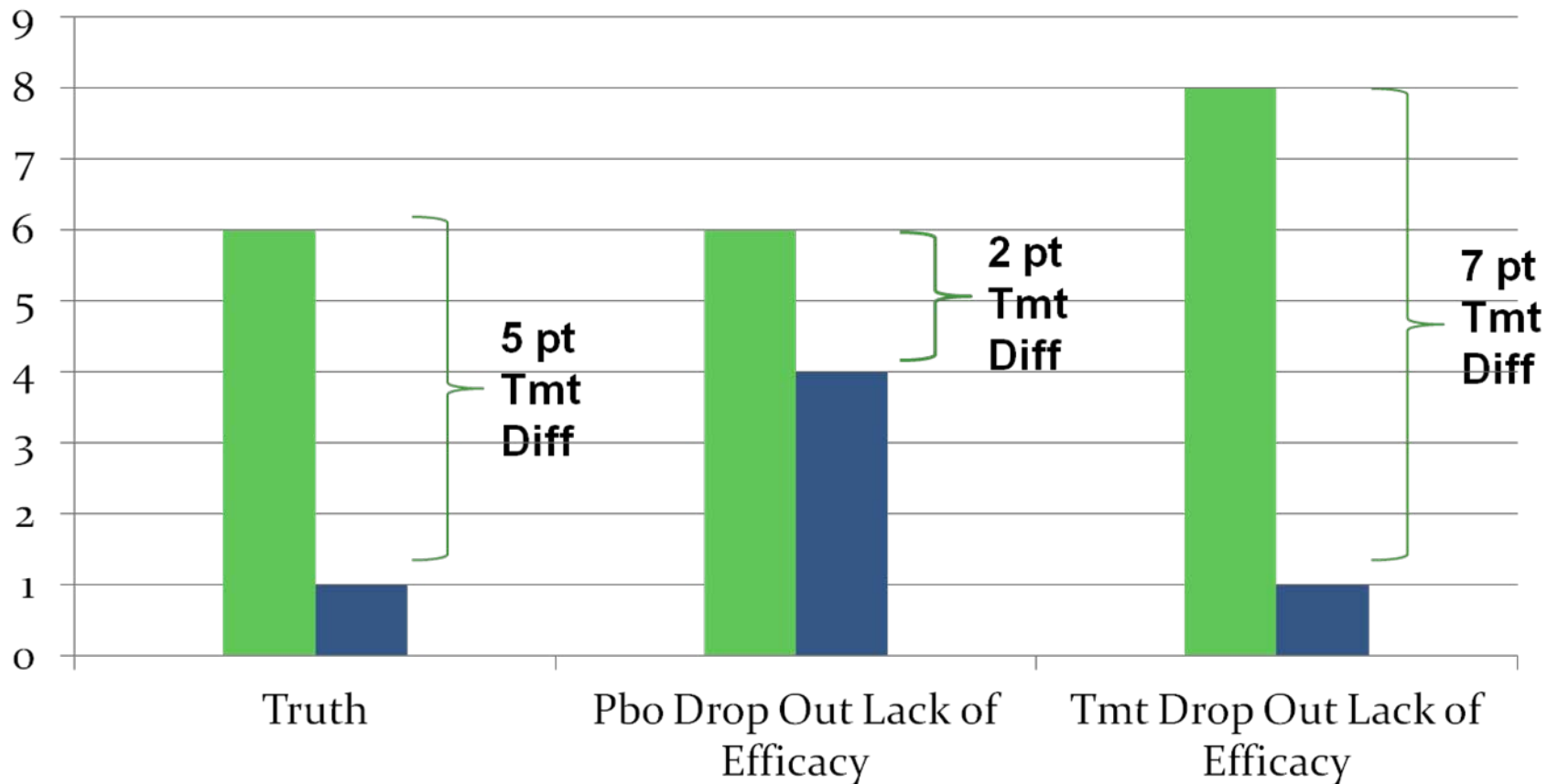
Support:

- use secondary endpoints to support conclusions about the primary

A dramatic, stormy sky with a large, dark, swirling cloud formation over a road. The sky is filled with dark, heavy clouds, and a large, dark, swirling cloud formation, resembling a storm or a large-scale weather phenomenon, dominates the upper half of the image. The road below is a two-lane asphalt road with white dashed lines, stretching into the distance. The overall atmosphere is dark and ominous.

**Missing Data Can Destroy the
Estimate of your Treatment Effect**

Potential Bias from Missing Data



Assessing Risk of Missing Data



Not all missing data is a problem



If <5% of your subjects drop out, it won't affect your results



If dropouts are random, it's also not a problem



Look for imbalance in missing data

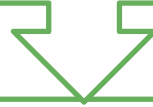
Historic Missing Data Strategies

- Standard parallel arm fixed dose studies
- Remove subjects from study when they go off study drug
- “LOCF”: Last Observation Carried Forward

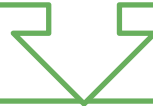


LOCF: Issues

Theory: Pain is reduced over time, so an earlier score will be higher and that this will lead to a “conservative” estimate



May be conservative for an individual estimate, **but** it may over or under estimate the overall treatment effect



We don't know what would happen to the treatment effect if we had the missing data



Considered a “single imputation method”

Analysis: Sensitivity Analysis

Basic principle is that you consider a variety of imputation methods, including extreme cases

- All missings are failures
- All missings are successes
- Worst case: success for placebo, failure for treatment
- LOCF

Compare results/conclusions to get a range of possible answers

Sensitivity Analysis Example

Primary Endpoint

- Change in VAS from baseline to 12 weeks in chronic pain

Assumption

- Missing data is random, do a longitudinal analysis

Sensitivity Analysis

- Calculate the same estimates and p-values, but use other methods
- Methods to use: LOCF, Multiple Imputation, Pattern Mixture

Analysis: Pattern Mixture Models

- Very useful for sensitivity analyses
- Impute values based on observed data and the “pattern” of missingness
- Can be based on *when* subject drops out or *why* a subject drops out

Considerations for Ongoing Programs

Reanalysis of all Phase III studies or just the ones
FDA requests?

- How do we make them consistent for the submission?

Does this affect your timelines?

- Complex analyses
- Multiple studies

How to present original analyses vs. new
analyses?

Summary

- ✓ Overview of missing data issues
- ✓ Program development strategies
- ✓ Study design strategies and alternatives
- ✓ Study execution
- ✓ Analysis strategies

Q & A