



ETCTN

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

Insights for the ETCTN: An analysis of Corrective Action Plans (CAPs) for early phase trials

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Presented at: 25th regular meeting of the NCI Clinical Trials and Translational Research Advisory Committee (CTAC)

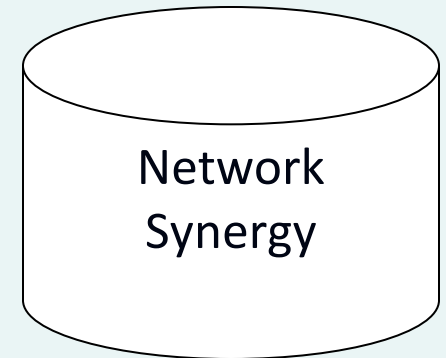
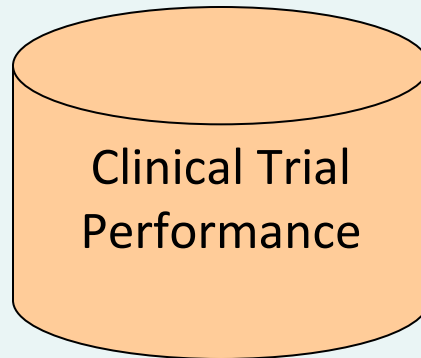
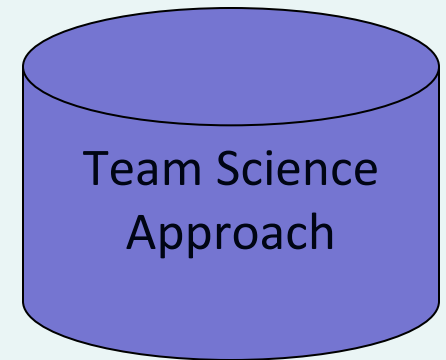
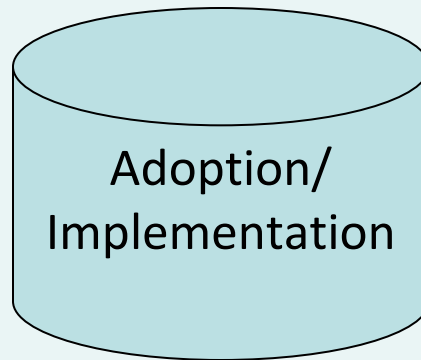
Wednesday, November 12, 2014

3-Year Process Evaluation of ETCTN

Goals:

- Document ETCTN's implementation
- Identify course corrections if needed
- Provide data to guide decision making for program's subsequent funding cycle

Assess Four Key ETCTN Domains



ETCTN Process Evaluation Tasks

- Task 1: Quarterly Data Review
- Task 2: Archival Baselines
- Task 3: Annual Field Survey
- Task 4: Annual Network Analysis
- Task 5: Annual In-depth Interviews
- Task 6: Drug Development Plan Milestone Review

IOM Consensus Goals for a Transformed System

1. Incorporate innovative science and trial design
2. Improve trial prioritization, selection, support & completion
3. Ensure participation of patients & physicians in the system
4. Improve speed & efficiency of development and conduct of trials

NCTN: Protocol development: Reported in: Abrams JS et al, *J Natl Cancer Inst* (2013) 105 (13): 954-959

Accrual guidelines: Update presented to CTAC (3/12/14) by Drs. Meg Mooney & Ed Korn



Analysis of Corrective Action Plans (CAPs)

Background

- 2010: As part of OEWG, CTEP began tracking post-activation activities for early phase trials
 - Provide support to Investigational Drug Branch (IDB) investigators regarding their trial portfolios
- For trials with slow accrual, CTEP requests a Corrective Action Plan (CAP) from Study PI
 - CAP to be completed and returned within 2 weeks
 - Identify reasons and possible actions to increase accrual

2010 OEWG Guidelines

CTEP requests a Corrective Action Plan (CAP) from PI if:

Phase 1

- After Quarter 2, is accruing less than 50% of the projected accrual rate during active enrollment

Phase 2

- After 3 quarters a trial is enrolling less than 50% of projected accrual rate (for the last 2 quarters)

Goal/Objectives of CAPs Analysis

Goal: Identify accrual challenges for early phase trials & provide guidance for the new ETCTN

Objectives:

1. Categorize slow accrual reasons/actions provided in CAPs
2. Document metrics of CAP trials, including:
 - Trial duration
 - Monthly accrual rates
 - Minimum accrual goals
 - Primary scientific objectives

Sample

CTEP held IND studies active between:
August 2011 - February 2013

Total studies in timeframe: 327

- 150 CAP requests sent (46% of total)
- 135 eligible for analysis (41% of total; 90% of CAPs)

Methods

1. Content Analysis of CAP reasons/actions for low accrual
2. Analysis of CAP trial timelines and accrual data, by Phase
3. Worked with IDB to code closed CAP trials for whether or not met primary scientific objectives

A faded, light gray background graphic consisting of four stylized human figures arranged in a circle, holding hands. The figures are simple, with circular heads and angular bodies. The overall image has a soft, ethereal quality.

Description of Trials in CAPs Analysis

Trial Phase and Focus

Trial Phase:

- Phase 1: 51% (n=69)
- Phase 2: 49% (n=66)

Adult vs. pediatric

- Adult: 88% (n=119)
- Pediatric: 8% (n=11)
- Both: 4% (n=5)

Activation/Status

Median trial activation date: October 15, 2010

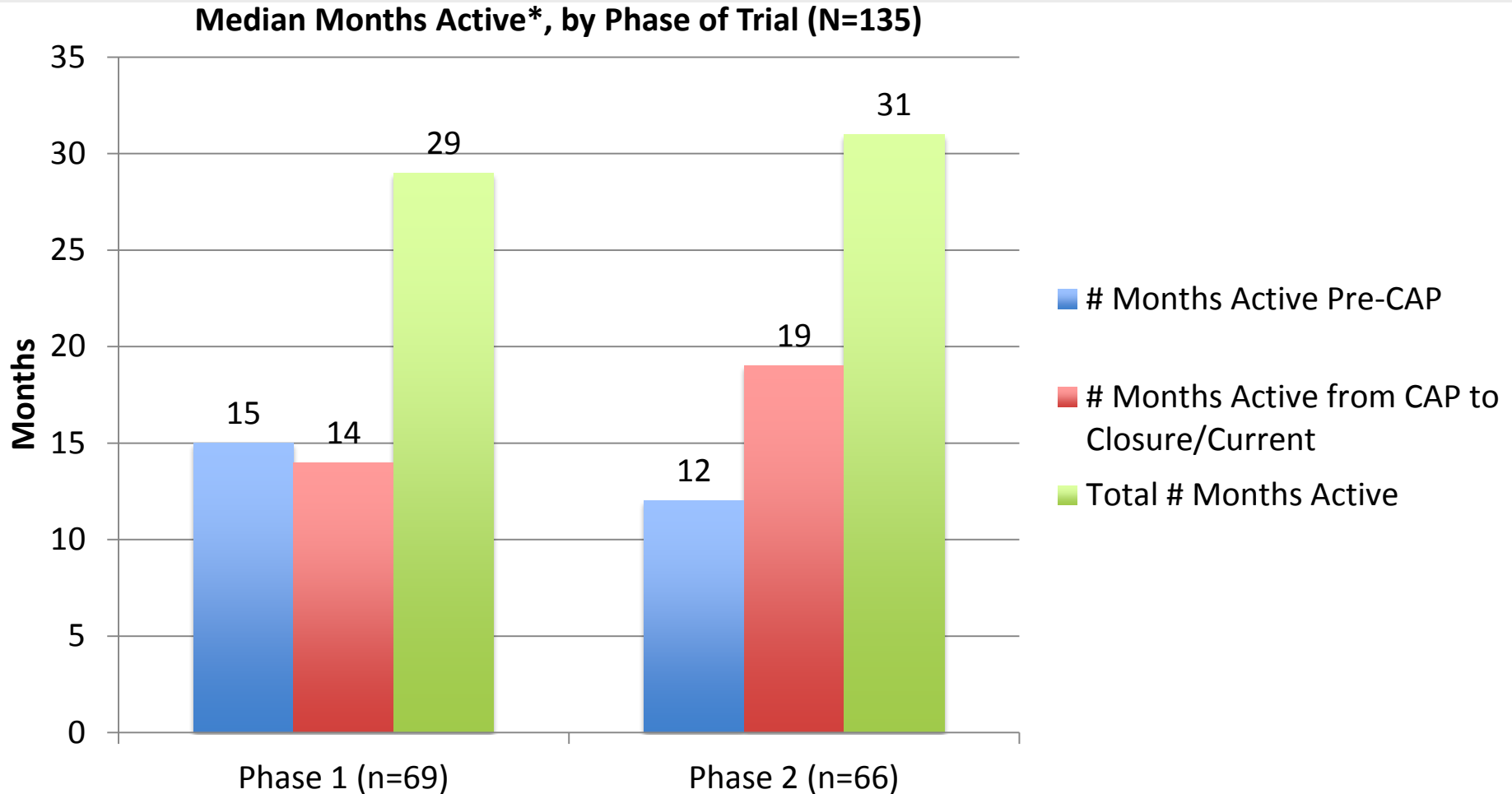
Trial Status (as of 2/24/14)

- 30% active
- 70% closed to accrual



Duration & Accrual for CAP Trials

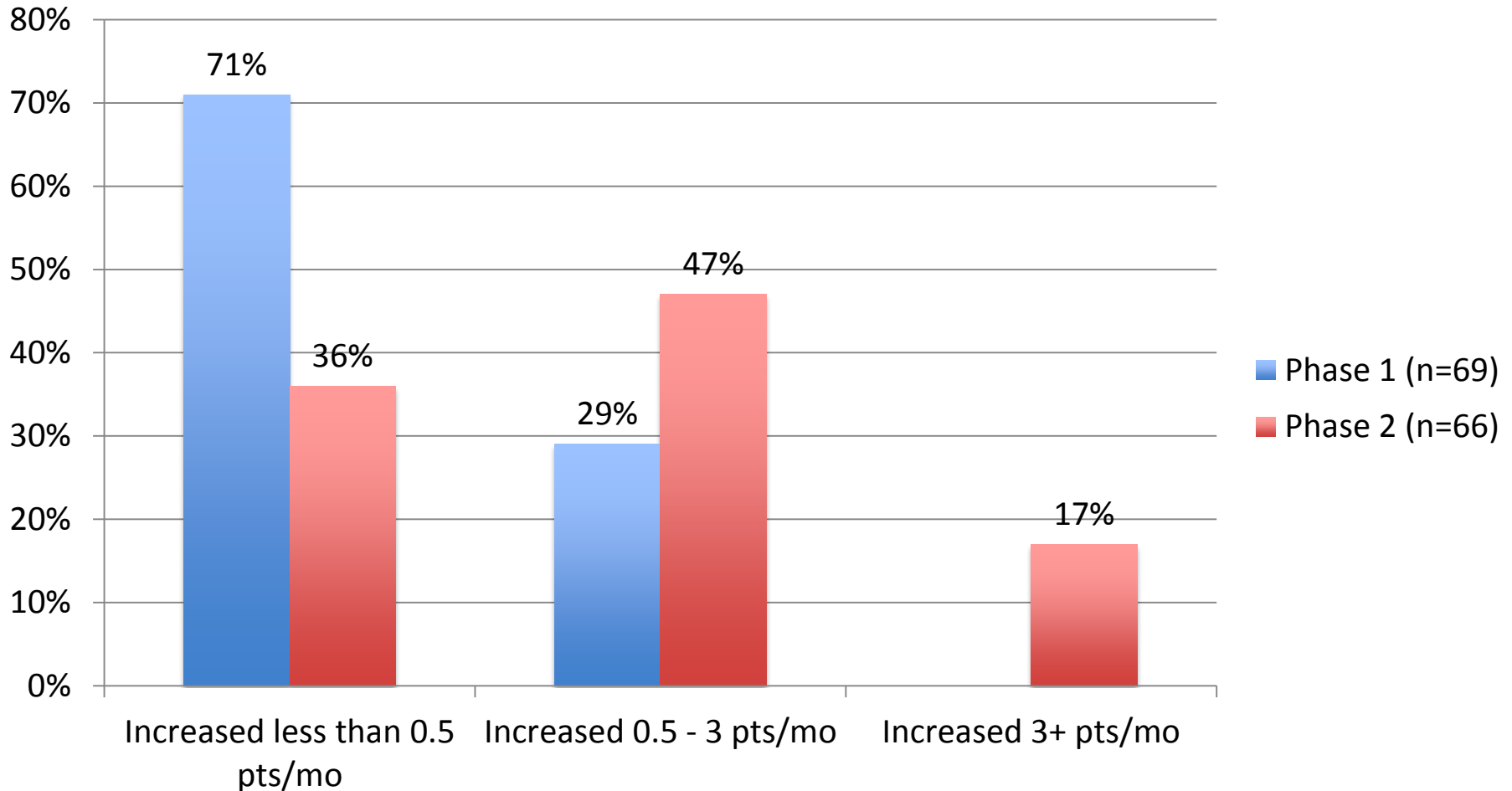
Duration of CAPs Trials, by Phase



*Months active were adjusted for temporary closures; 30% of trials were still active at analysis

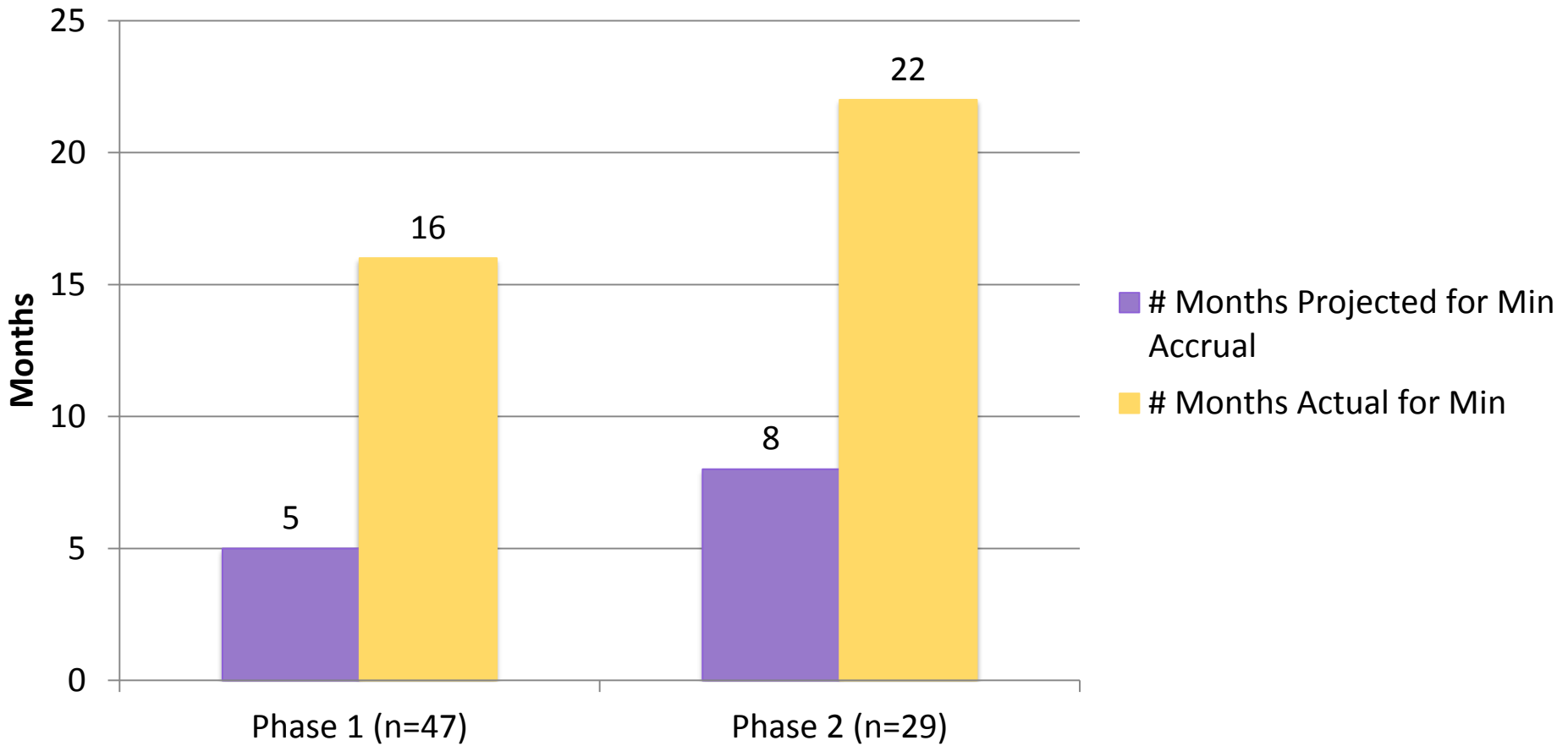
Monthly Accrual Rate Change Pre-Post CAP

Accrual Rate Change from Pre-Cap to Post-CAP, by Phase (N=135)



Time Needed to Meet Minimum Accrual

Projected vs. Actual # Months to Reach Min Accrual, by Phase (median scores, N=76)



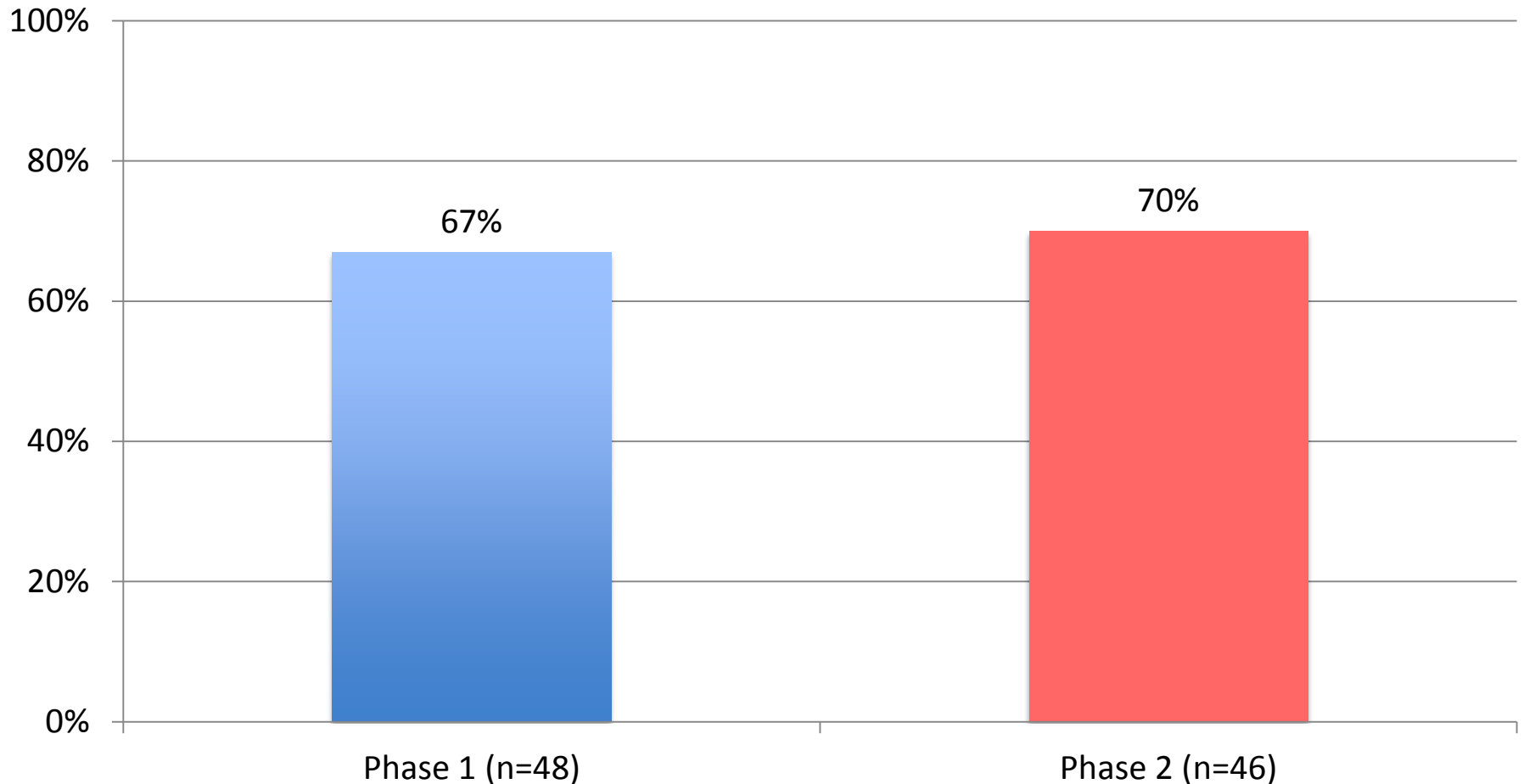
*Of Phase 1 trials: 1 reached min early, 1 on-time; Of Phase 2 trials: 2 reached min early, 1 on-time

The background features a large, faint, light-gray graphic of four stylized human figures arranged in a circle, holding hands. Each figure is composed of a circular head and a triangular body with a pointed bottom, creating a continuous loop. The figures are positioned at the top, bottom, left, and right of the central text area.

Achieving Primary Scientific Objectives among Closed CAP Trials

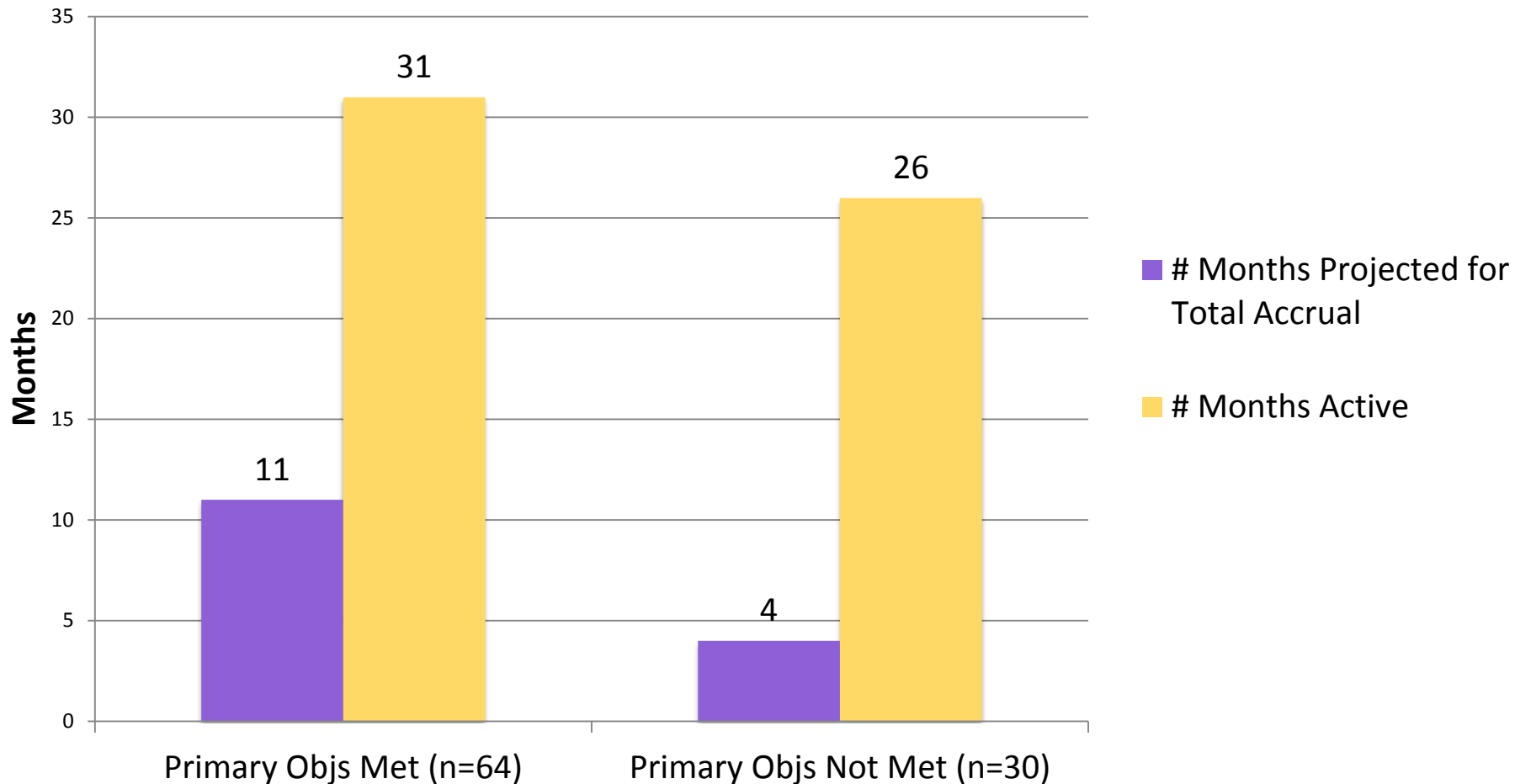
Percent Meeting Primary Scientific Objectives, by Phase

Percent of Closed CAPs Trials Meeting Primary Sci Objectives, by Phase (N=94)



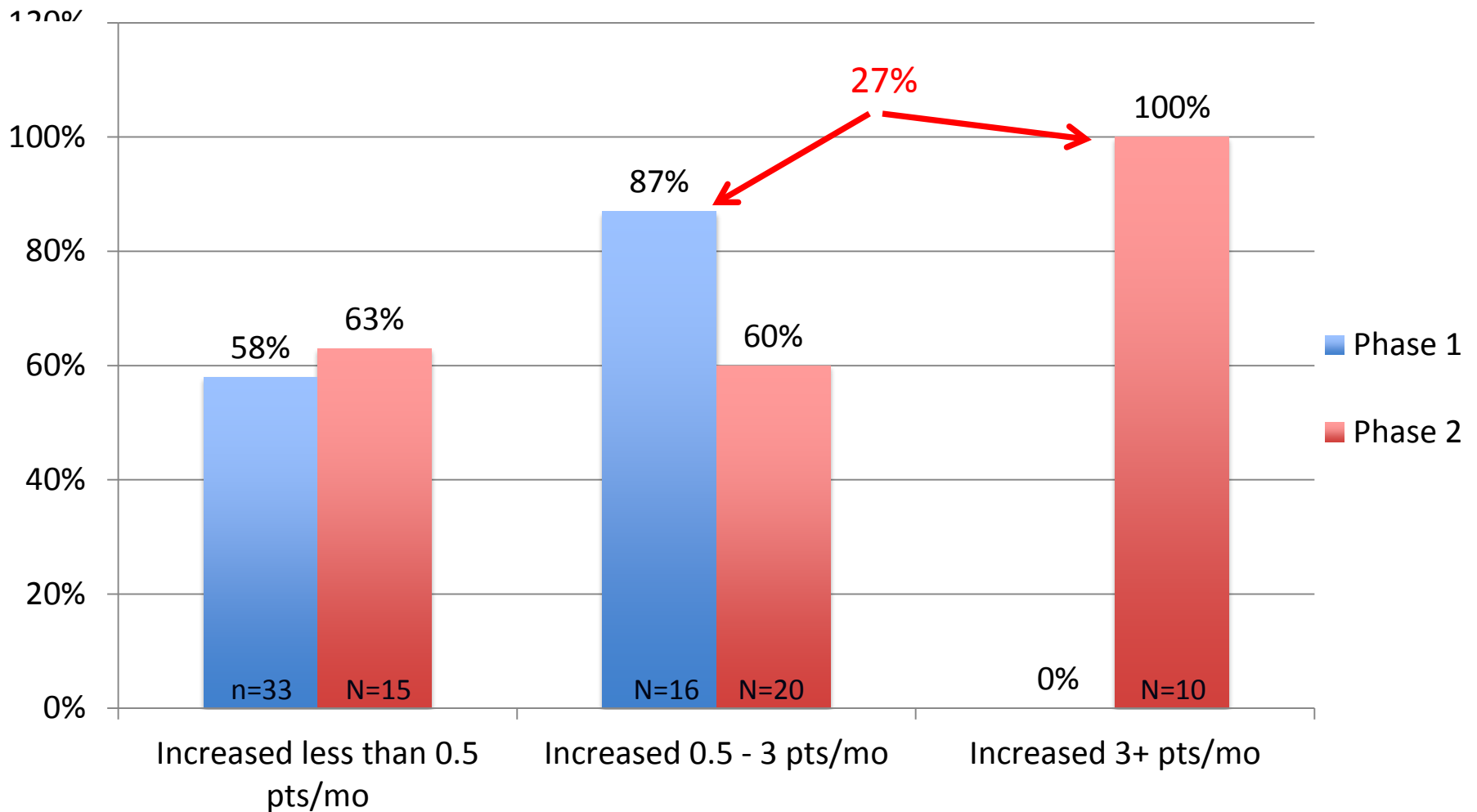
Projected vs. Actual Time Open to Meet Scientific Objectives

Months Open by Primary Sci Objectives Met, Closed Trials (median scores, N=94)



Accrual Rate Change and Primary Scientific Objectives

Percent of Closed CAPs Trials that Met Prim Sci Objs, by Rate Change & Ph (N=94)

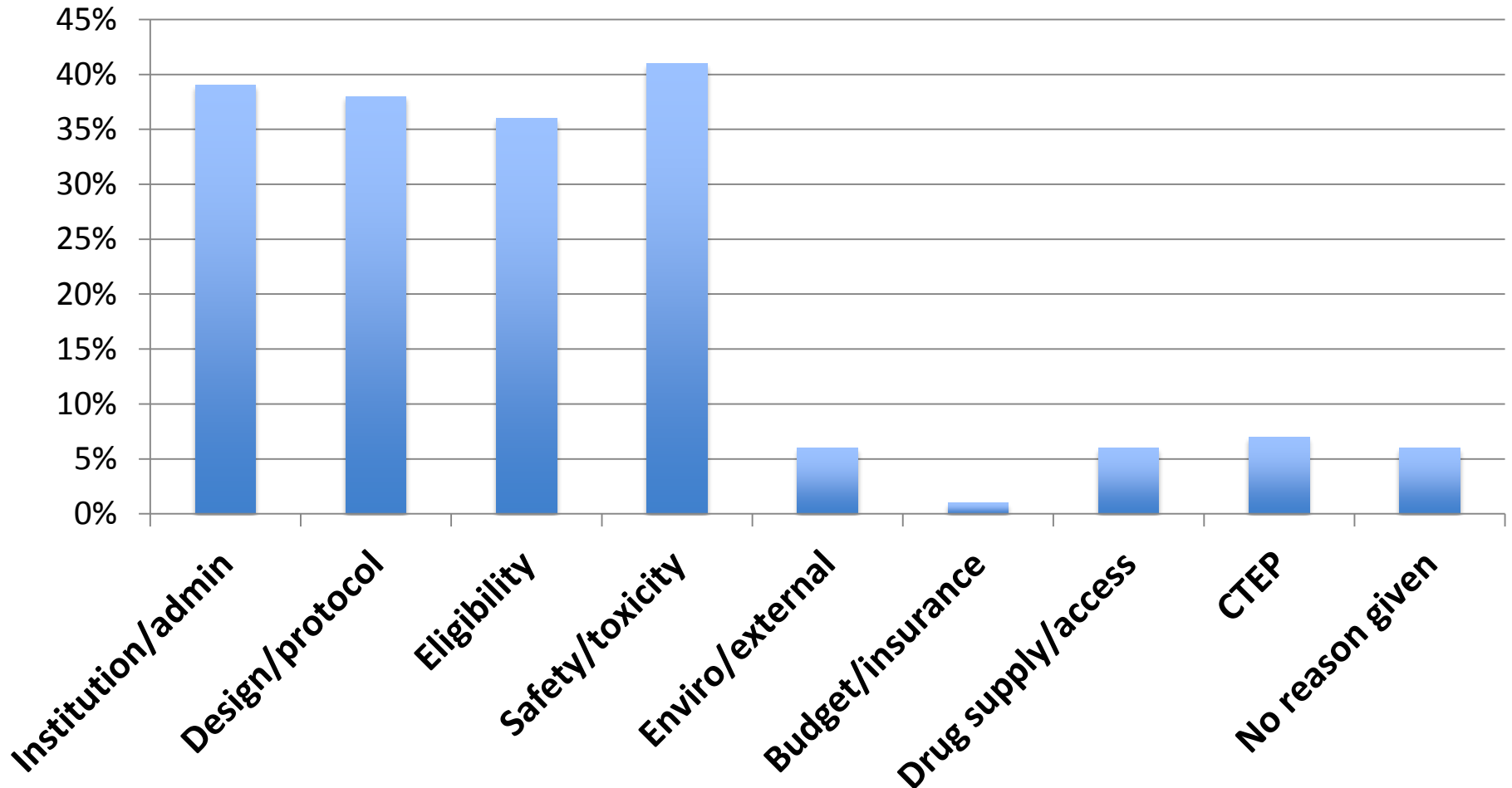


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Slow Accruing Reasons Identified in CAPs

Phase 1: CAPs Slow Accrual Reasons

Percent of Ph1 Trials Reporting Slow Accrual Reasons (N=69)



Phase 1 -- Summary of Reasons

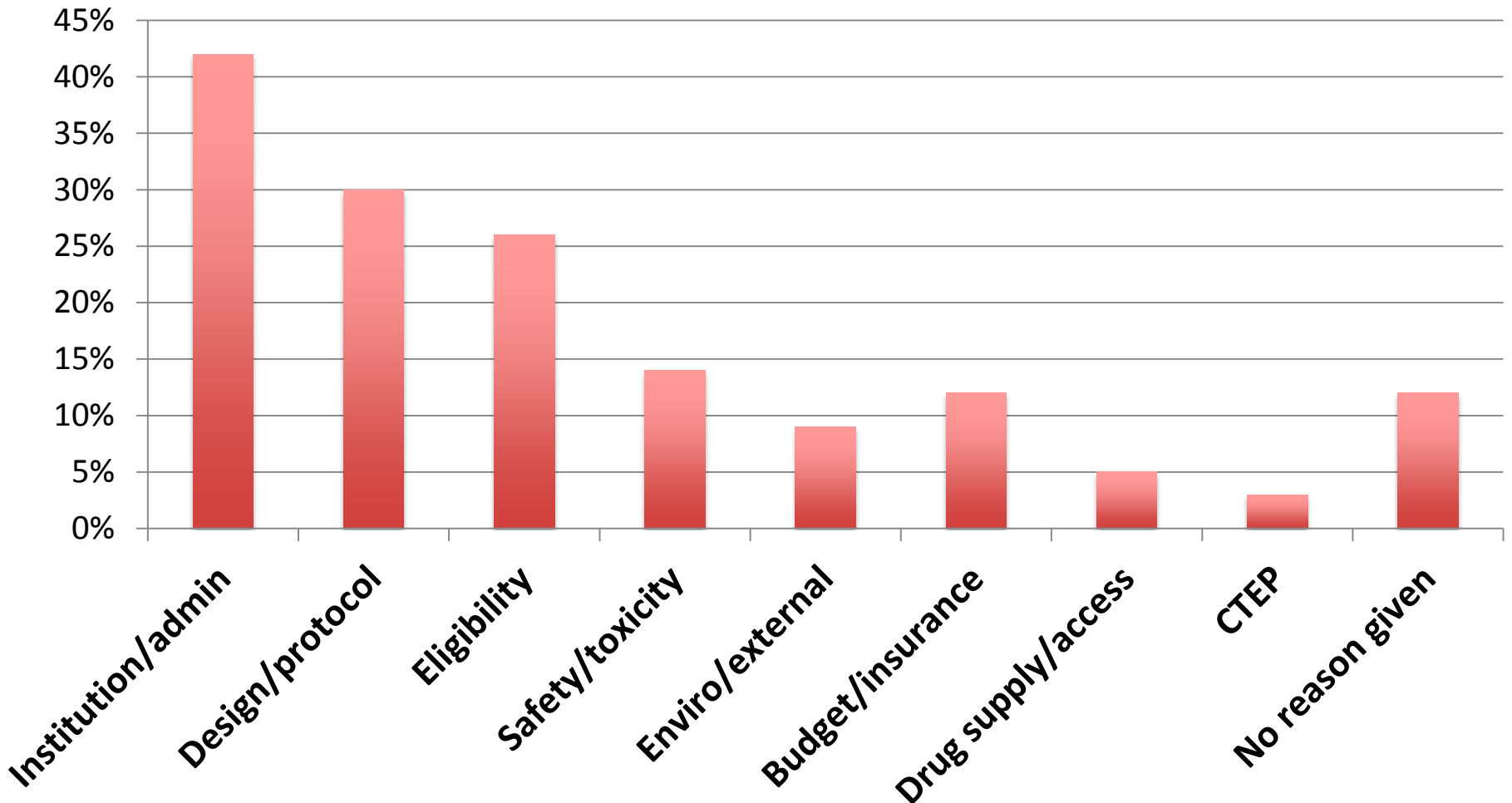
56% of trials had 2+ reasons given

If we remove “safety” reasons:

- 74% still have at least one other reason for slow accrual:
 - Strict eligibility
 - Delays in staffing/management issues
 - High screen failure
 - Extended IRB delays

Phase 2: CAPs Slow Accrual Reasons

Percent of Ph2 Trials Reporting Slow Accrual Reasons (N=66)



Phase 2 -- Summary of Reasons

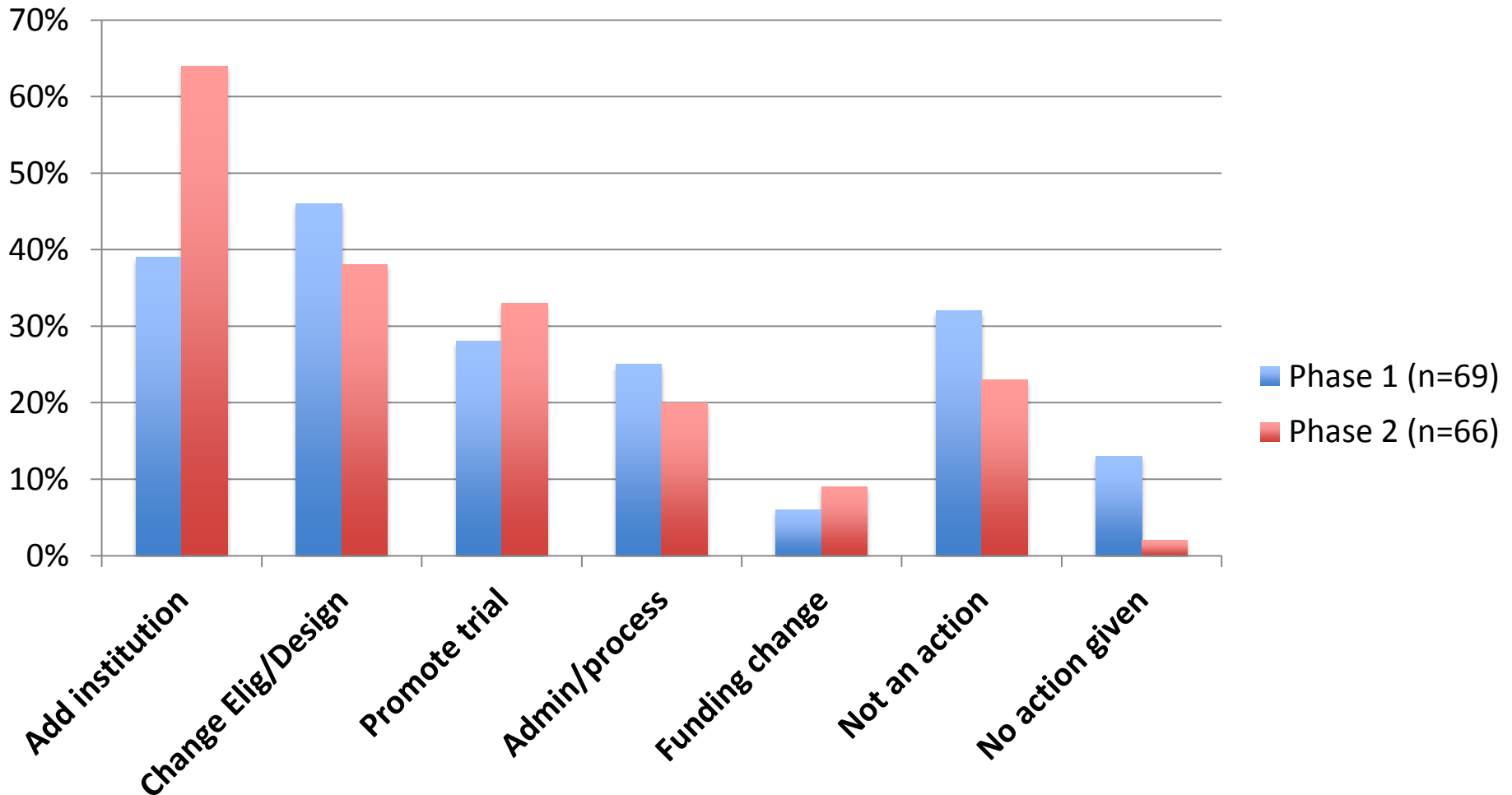
- 40% of trials has 2+ reasons for slow accrual:
 - Extended IRB delays
 - Strict eligibility
 - Planned sites not activated



**Proposed Corrective Actions
in CAPs to Address Slow Accrual**

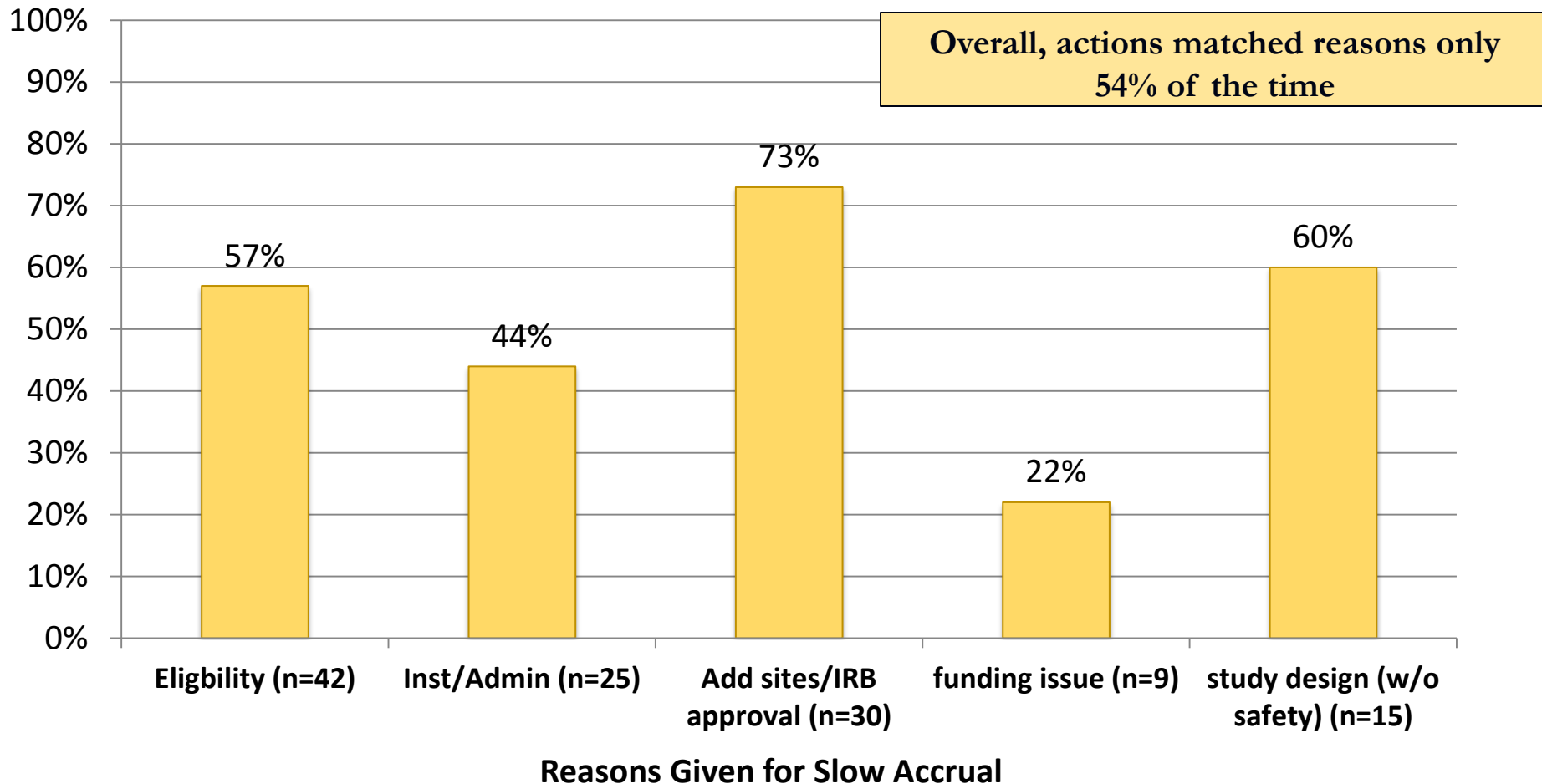
Proposed Corrective Actions, by Phase

Percent of Trials Reporting Actions to Address Accrual, by Phase



Comparison of Specific Reasons vs. Actions

Percent Where Corrective Actions Matched Reasons for Slow Accrual





Summary

Time Open and Minimum Accrual Goals

- CAP trials were open median of 30 months
- Trials meeting their minimum accrual goals took about 3x longer than projected
 - Regardless of phase of trial

Meeting Trials' Primary Scientific Objectives

- Of closed trials, over two-thirds met their primary scientific objectives
 - Trials meeting their objectives took 3x times longer than projected
 - Trials not meeting their objectives took 6x longer than projected (to close)

Monthly Accrual Rates

- 27% of all closed trials had an accrual rate increase associated with a greater likelihood of meeting their primary scientific objectives
 - Phase 1:
All those with even a modest increase (0.5+ pts/mo)
 - Phase 2:
All those that had substantial increase (3+ pts/mo)

Reasons/Actions to Improve Accrual

- Phase 1 trials:
 - Safety delays dominated
 - 74% of trials had at least one reason beyond “safety”
- Phase 2 trials
 - Institutional/Administrative reasons topped the list
- Just over half (54%) of actionable reasons matched the proposed corrective actions

Recommendations for ETCTN Trials

1. Provide more realistic accrual projections.
2. Define and implement an accrual plan early in trial's development (i.e., decrease need for a CAP).
3. Aim to better match corrective actions with slow accruing reasons, when feasible.

ETCTN Poised to Address Accrual Challenges

ETCTN model should address many accrual concerns raised in this CAP analysis:

- **CIRB** → reduce IRB delays & accelerates site activation
- **Access to entire network** → more sites accruing patients
- **Team approach** → improve quality of science & commitment to trial completion

Next Steps

1. Developing CAP coding sheet based on this analysis to:
 - Standardize collection of reasons/actions for slow accrual
 - Develop statistical algorithms for evidence-based decision-making for trial closure due to slow accrual
2. Continue CAPs analysis as part of the larger 3-year ETCTN process evaluation
 - Analysis moving forward also will include non-CAP trials

Questions to CTAC

1. Are there recommendations regarding the ETCTN program evaluation moving forward?
2. Are there ways the CAPs analysis can be enhanced moving forward?

Other questions/concerns from CTAC?

Thank You

- Kate DiPiazza
- Percy Ivy
- James Zwiebel
- Jeff Abrams
- Andrea Denicoff
- Steve Freidman
- IDB Senior Investigators
- Investigators & Study Teams who submitted CAPs



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