OEWG Timeline Analysis for CTEP Trials

Presentation to the Clinical Trials and Translational Research Advisory Committee

July 12, 2017

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Objectives

1. Review of OEWG Report Goals and Timelines
2. Comparison of Reviews and Timelines Pre- and Post-OEWG
3. In-Depth Look at Recent Trials
4. Next Steps and Questions

Background: OEWG Report

- Operational Efficiency Working Group (OEWG) established in December 2008 under CTAC
  - Established in response to issues identified in the 2005 Clinical Trials Working Group Report to the National Cancer Advisory Board
  - **First objective:** identify barriers to timely trial activation in the NCI system and solutions to improve timelines moving forward
  - **Second objective:** identify strategies to increase percentage of trials that reach their accrual targets in a timely fashion

Background: Original OEWG Timelines

- To reduce the time for CTEP Phase II early drug development trial activation, the OEWG set **a target of 210 days** to complete the steps under CTEP/IDB and extramural control – LOI review, protocol development, protocol review, and forms development.
  - The timeline excludes industry negotiations, arranging drug supply, and IRB and FDA approval.
  - However, the OEWG also set **a "drop-dead" date of 18 months by which all external issues must be resolved**.
  - If a protocol based upon an LOI submitted to CTEP is not activated within an 18-month period, it will be terminated.

- Phase III trials:
  - Target of **300 days** for steps under CTEP and Group control
  - Drop-dead date of **24 months** for resolution of all issues, including those controlled by industry partners or IRBs

Report of the CTAC Operational Efficiency Working Group. March 2010. https://www.cancer.gov/about-nci/organization/ccct/steering-committees/concept-submission-guidelines/OEWG-Report.pdf

Background: 2010 and 2012 Timelines

- OEWG tracking for Target Timelines began with all LOIs and Concepts received after 4/1/2010
- Absolute Deadlines were decreased on 4/5/2012
  - Last protocol under the old timelines was activated March 21, 2014

	Target 2010-2012	Absolute 2010-2012	Target 2012-Present	Absolute 2012-Present
Phase 1 and 2 LOIs	210 days	540 days	210 days	450 days
Phase 1/2 and 2 Concepts	240 days	540 days	210 days	450 days
Phase 3 Concepts	300 days	730 days	300 days	540 days

OEWG Stages and Milestones

1) LOI/Concept Approval

- Initial LOI/Concept Consensus Evaluation
  - LOI / Concept OEWG Start Date
  - CTEP Program Review Committee (PRC) Review
  - LOI / Concept Approved
- Follow-Up Consensus Evaluations and LOI/Concept Approval
  - Revised LOI / Concept Submitted
  - LOI / Concept Approved

2) Protocol Authoring

- Protocol Development
- Protocol Receipt

3) Protocol Development

- Initial Protocol Consensus Evaluation
  - PRC Review
  - Revised Protocol Submitted
- Follow-Up Protocol Consensus Evaluations
  - Revised Protocol Submitted

4) Protocol Approval and Activation

- Protocol Approved
- Amendment Receipt, Review, and Approval
- Protocol Active

Key Question

- How do trials after implementation of the OEWG timelines compare to trials before the OEWG timelines?
  - Time to activation
  - Median days per stage of the trial development process

Methods

Extracted data on OEWG stages and milestones for protocols with:

- Timeline data tracked in CTEP systems, including data on LOI/concept
- Activation dates 2012-2017, with two trial groupings by activation date:
  - Trials activated **7/1/2012 – 6/30/2014:** post-OEWG but largely before the launch of the NCTN and ETCTN (2 years)
    - Includes trials under both old and new deadlines
    - Last protocol under the old timelines was activated March 21, 2014
  - Trials activated **7/1/2014 – 6/30/2017:** post-OEWG and after the launch of the NCTN and ETCTN (3 years)
    - Only includes trials under the new deadlines

Methods

407 protocols activated July 2012 – June 2017 with timeline data

- Removed 35 trials that were phase “other” / non-treatment (n=20) or had no or inconsistent LOI or concept data (n=15)
- Analyzed 372 protocols

- For comparisons to pre-OEWG trials, used information from the March 2010 OEWG Report[1]
- Conducted additional analyses of:
  - More recently activated studies
  - Protocols that did not activate

1. Report of the CTAC Operational Efficiency Working Group. March 2010. https://www.cancer.gov/about-nci/organization/ccct/steering-committees/concept-submission-guidelines/OEWG-Report.pdf

Comparison Results

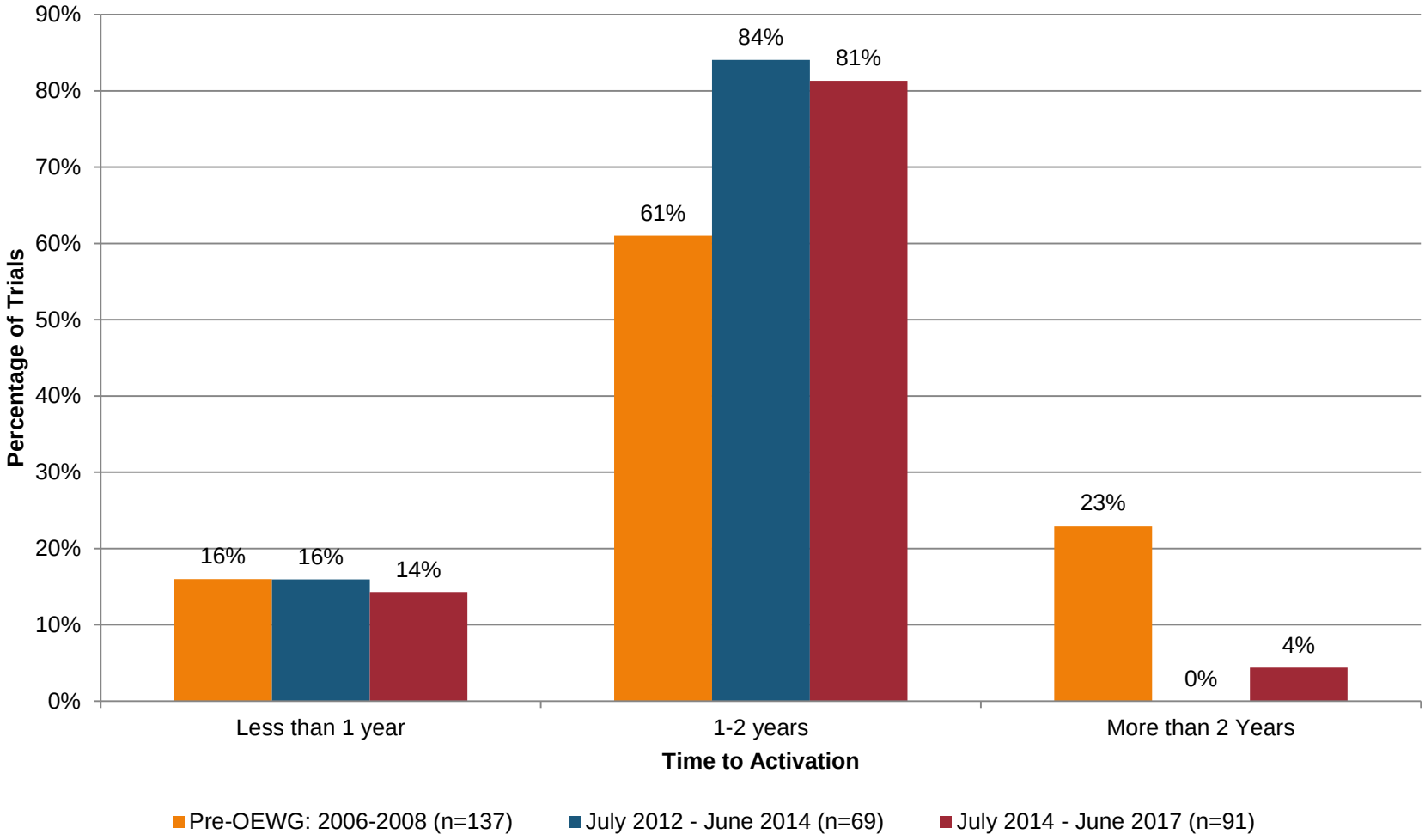
Included Trials by Phase and Activation Time Period

	Pilot	I	I/II	II	II/III	III	Total
July 2012 – June 2014	7	58	16	69	5	18	**173**
July 2014 – June 2017	5	57	9	91	9	28	**199**
Total	**12**	**115**	**25**	**160**	**14**	**46**	**372**

Included Trials by Lead Org and Activation Time Period

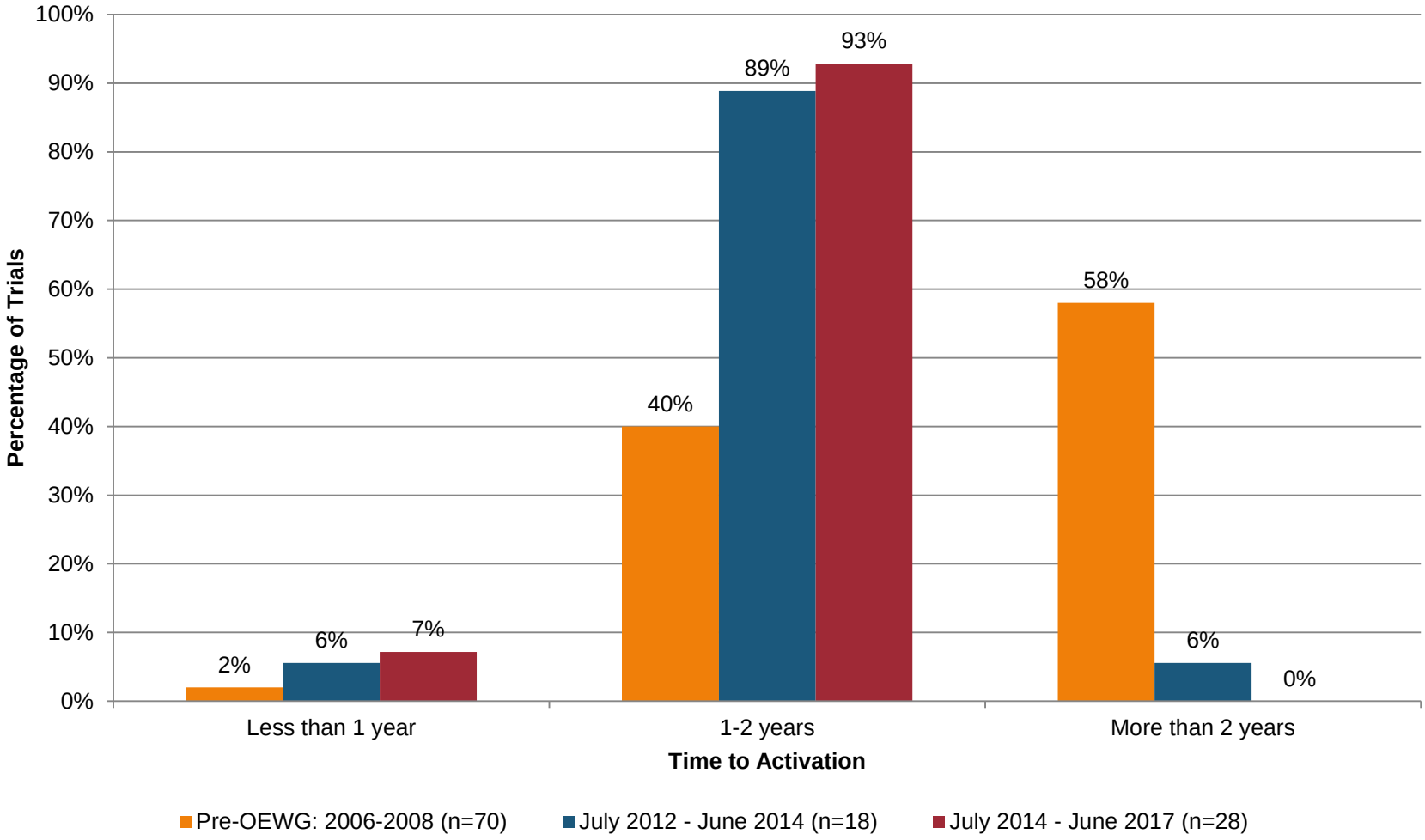
	Group / NCTN	ETCTN / Related Program	Cancer Center / Institution	Clinical Center	Consortia / Other Network	Total
July 2012 – June 2014	74	4	59	12	24	**173**
July 2014 – June 2017	93	54	12	11	29	**199**
Total	**167**	**58**	**71**	**23**	**53**	**372**

Comparing Time to Activation Pre- and Post-OEWG
Phase 2 Trials



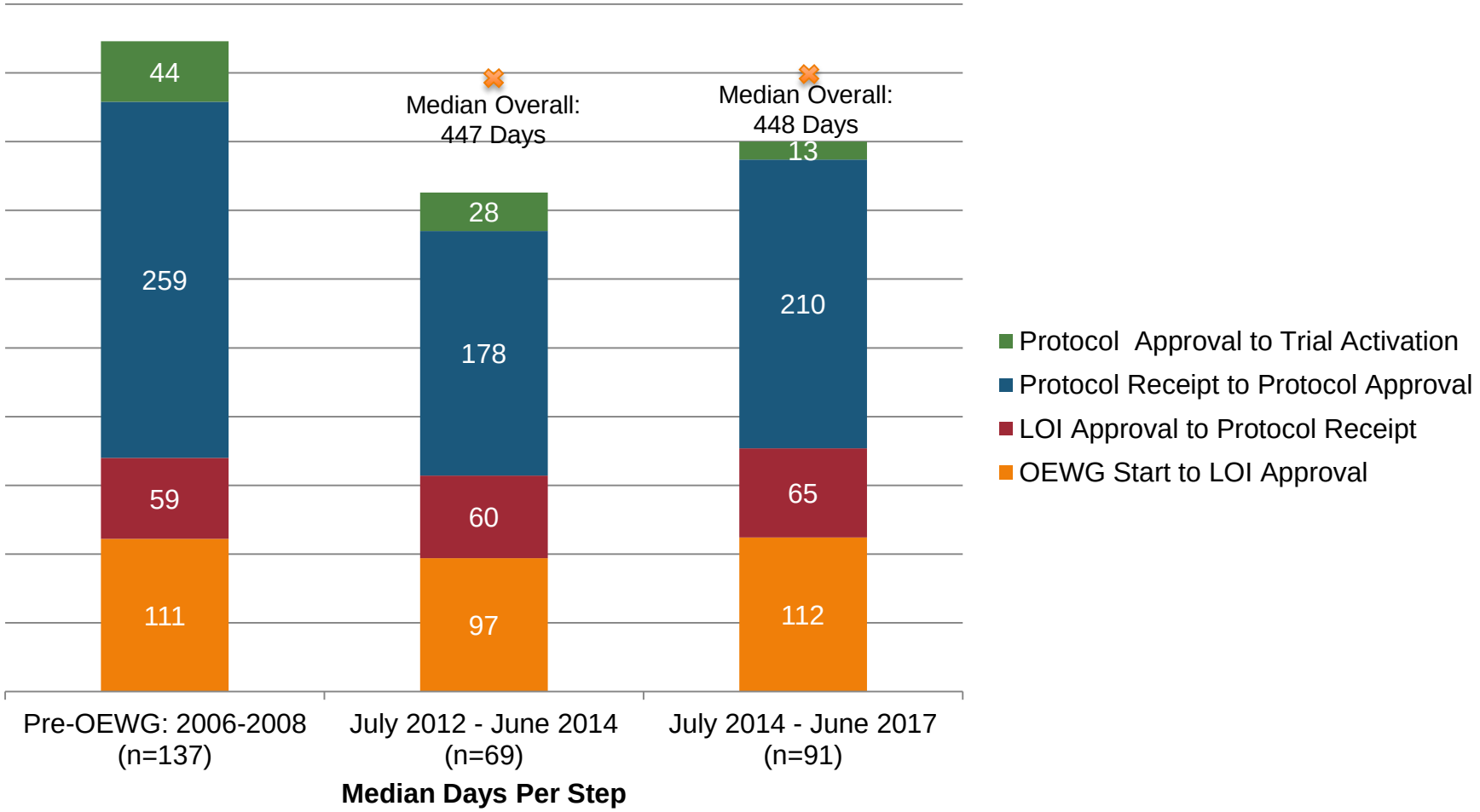
Pre-OEWG: Information from CTEP CDUS database on 137 CTEP Phase II trials activated 2006-2008 as reported in 2010 OEWG report. Post-OEWG: 160 phase II trials with complete OEWG information.

Comparing Time to Activation Pre- and Post-OEWG
Phase 3 Trials



Pre-OEWG: Information from CTEP CDUS database on 70 Phase III trials activated 2006-2008 as reported in 2010 OEWG report. 67 were Cooperative Group trials, plus one study each from NCIC, PACCT, and BMTCTN. Post-OEWG: 46 Phase 3 trials.

Comparing Median Days Per Step Pre- and Post-OEWG Phase 2 Trials



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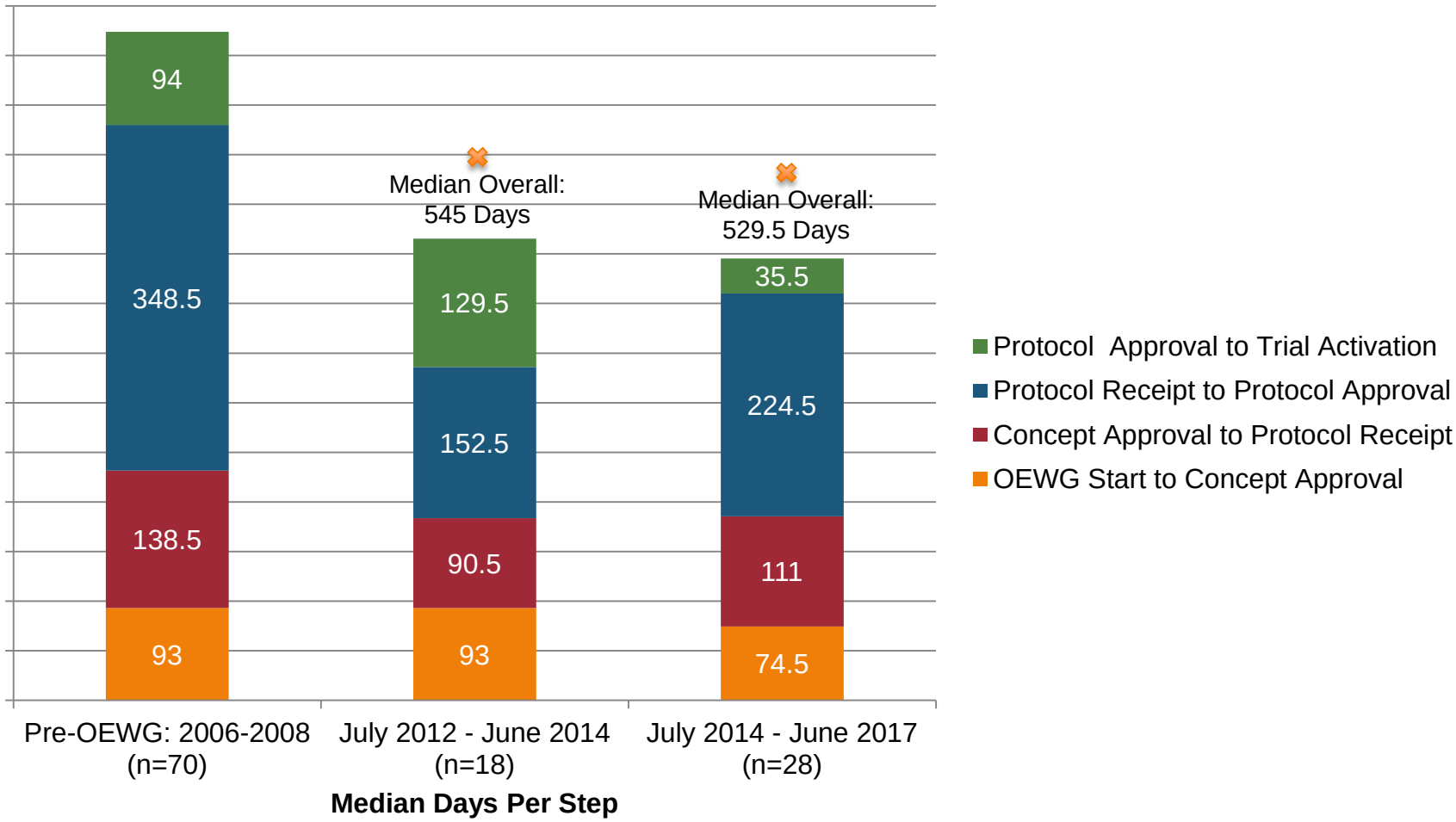

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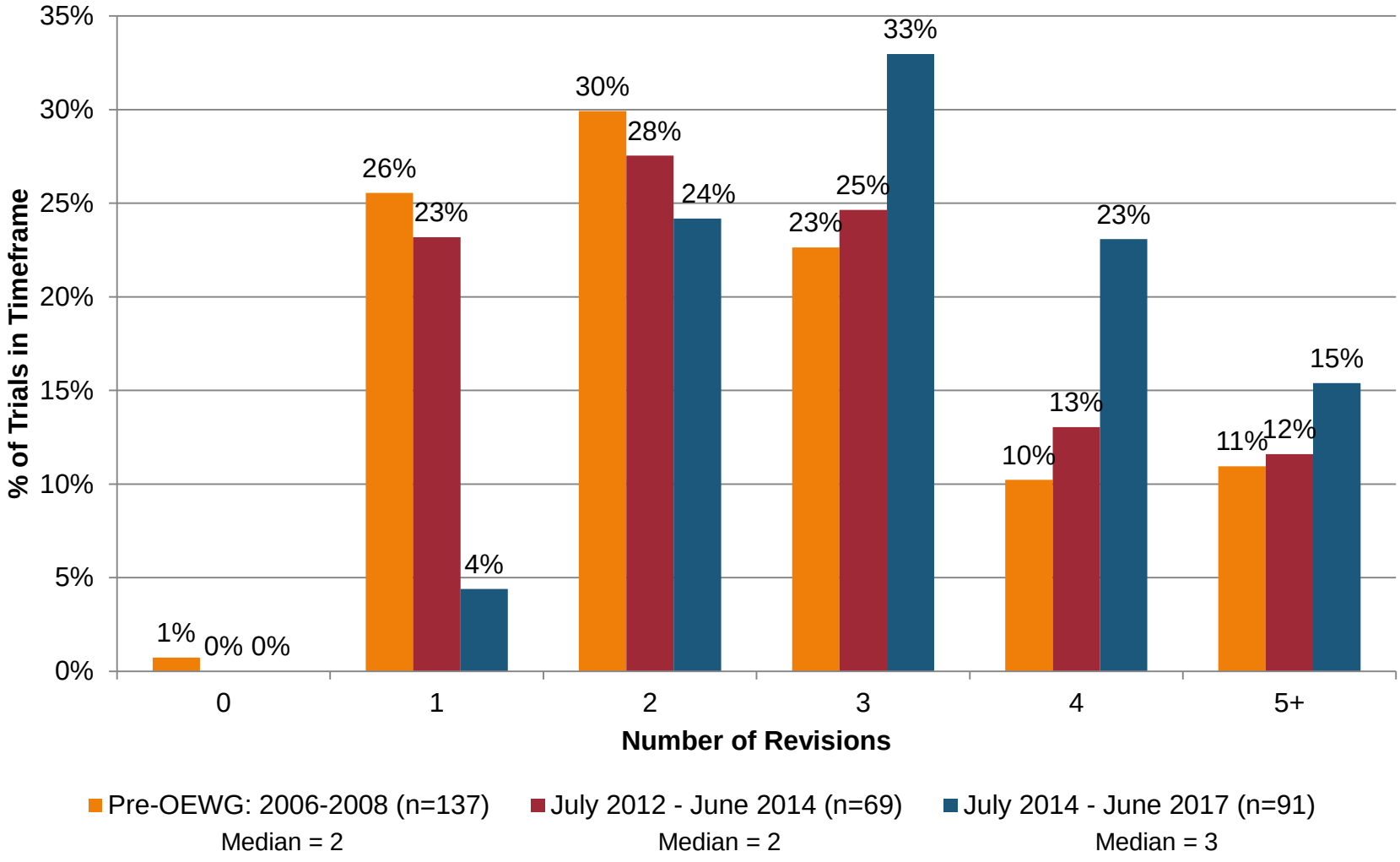
Comparing Number of Revisions Pre- and Post-OEWG Phase 2 Trials



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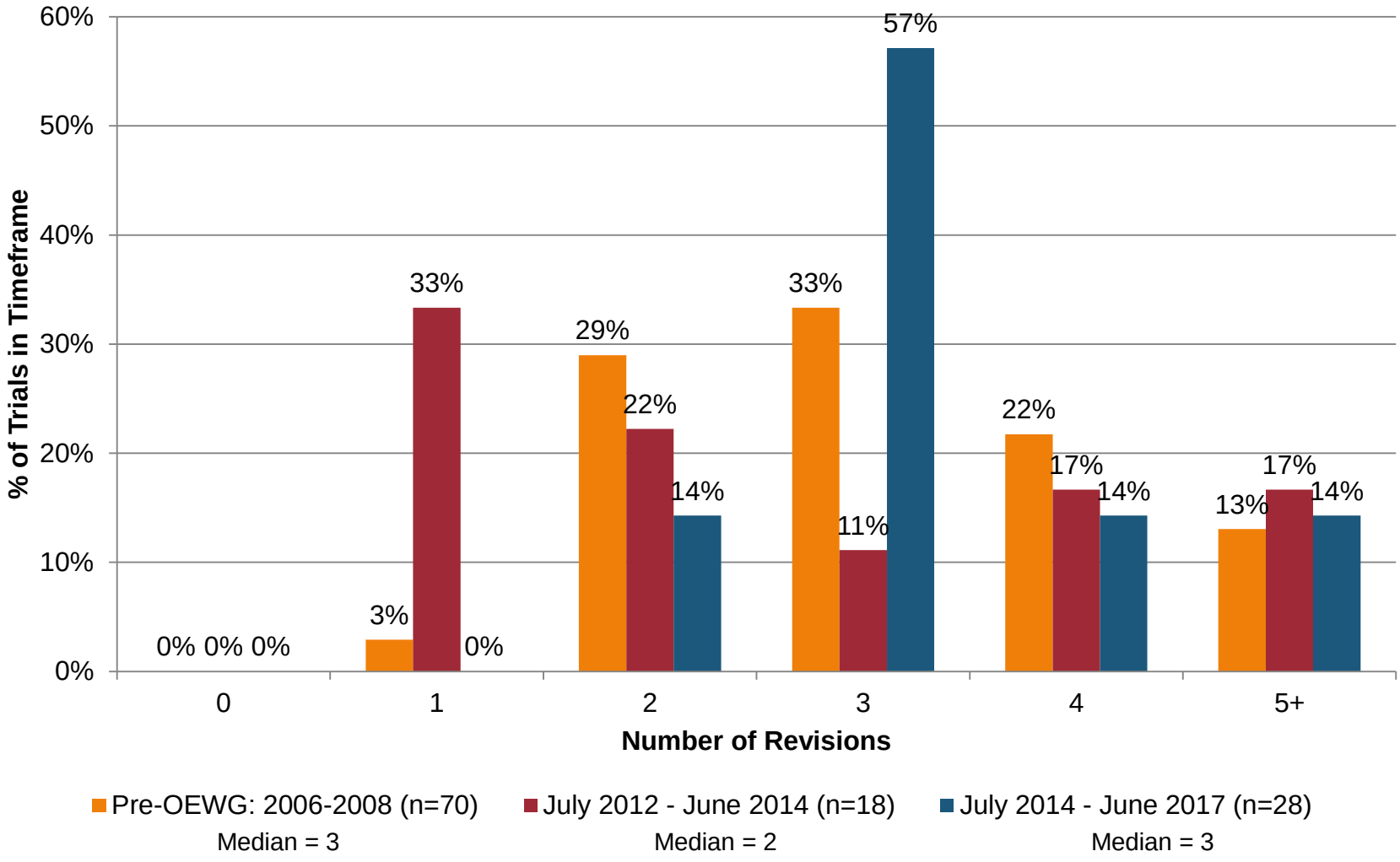

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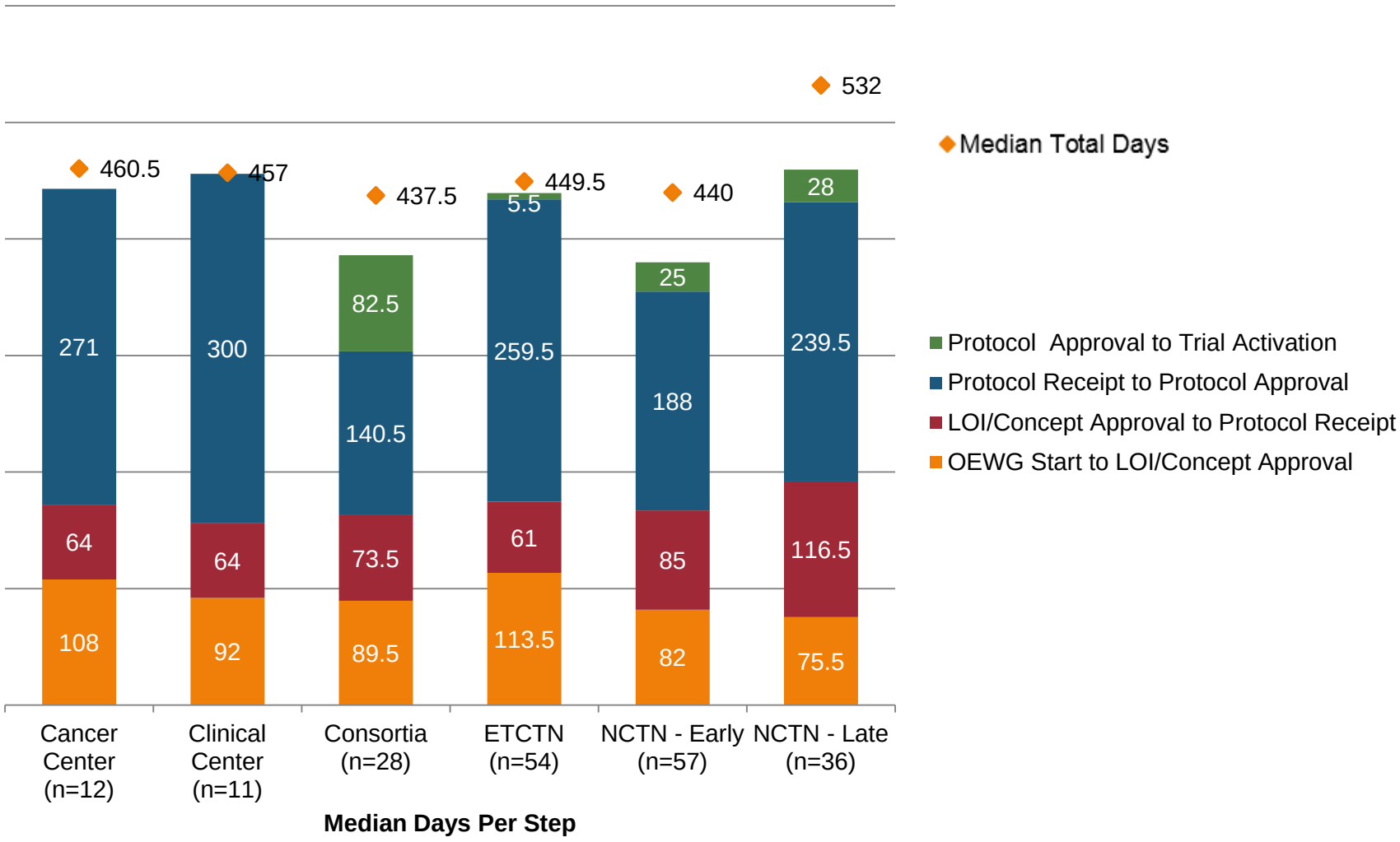
Overall Results

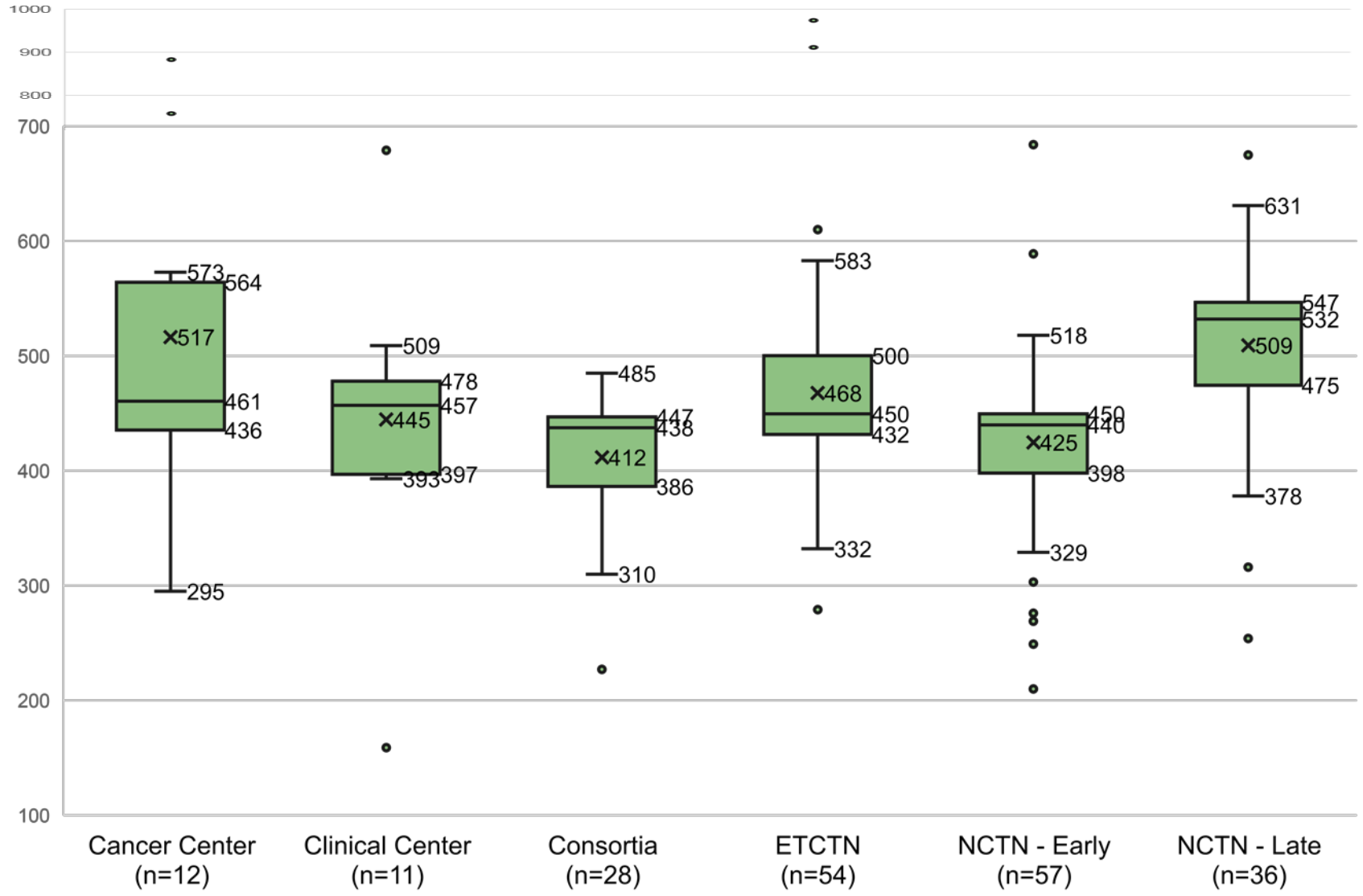
July 2014 – June 2017

Median Days for OEWG Stage by Lead Organization Type and Phase Grouping, 2014-2017



N=198; omitting 1 consortia phase III trial

Box and Whisker Plot: Total Time to Activation by Lead Org Grouping, 2014-2017



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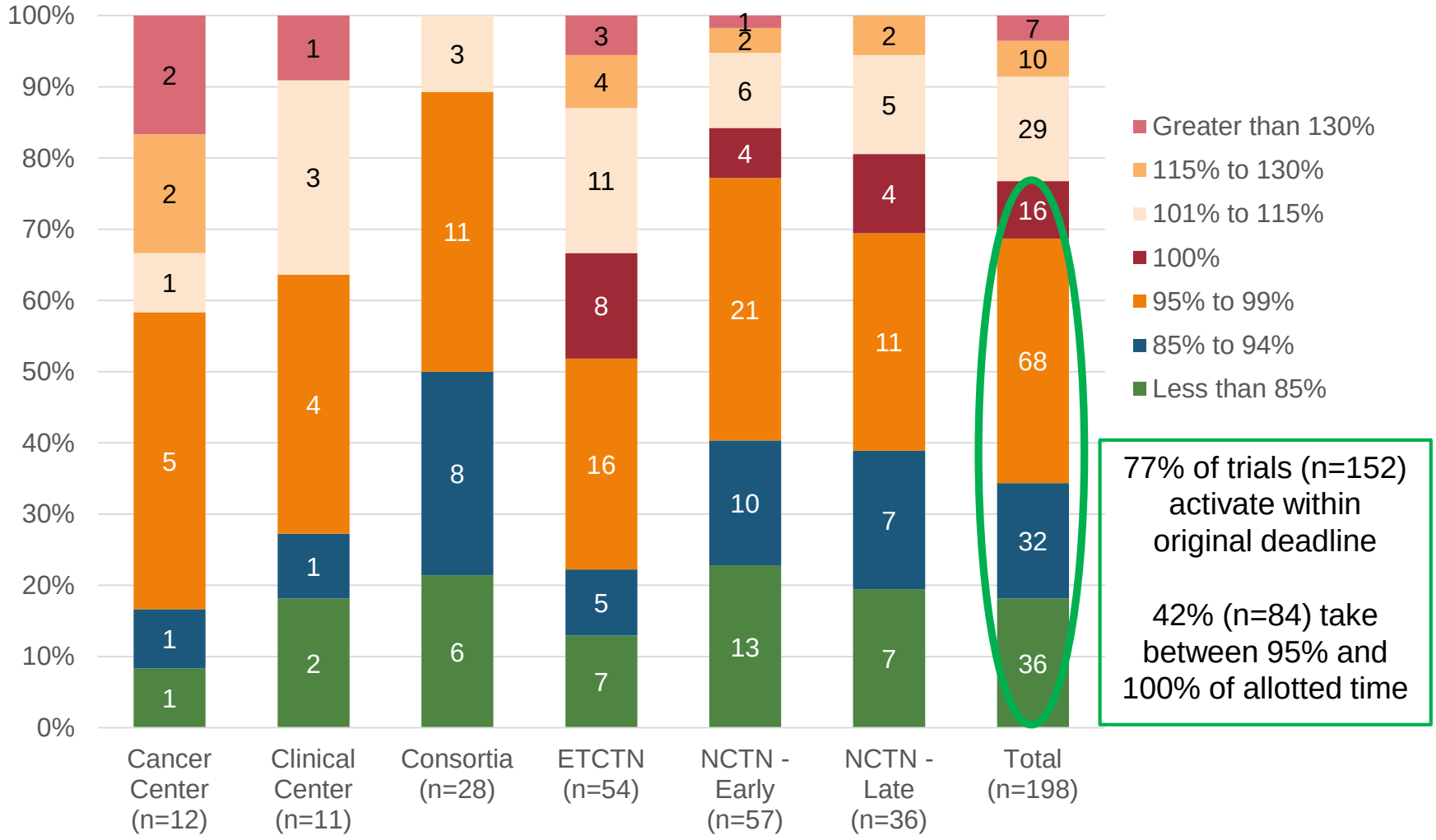
Percent of Original OEWG Deadline* for Trials by Lead Organization Type and Phase Grouping, 2014-2017



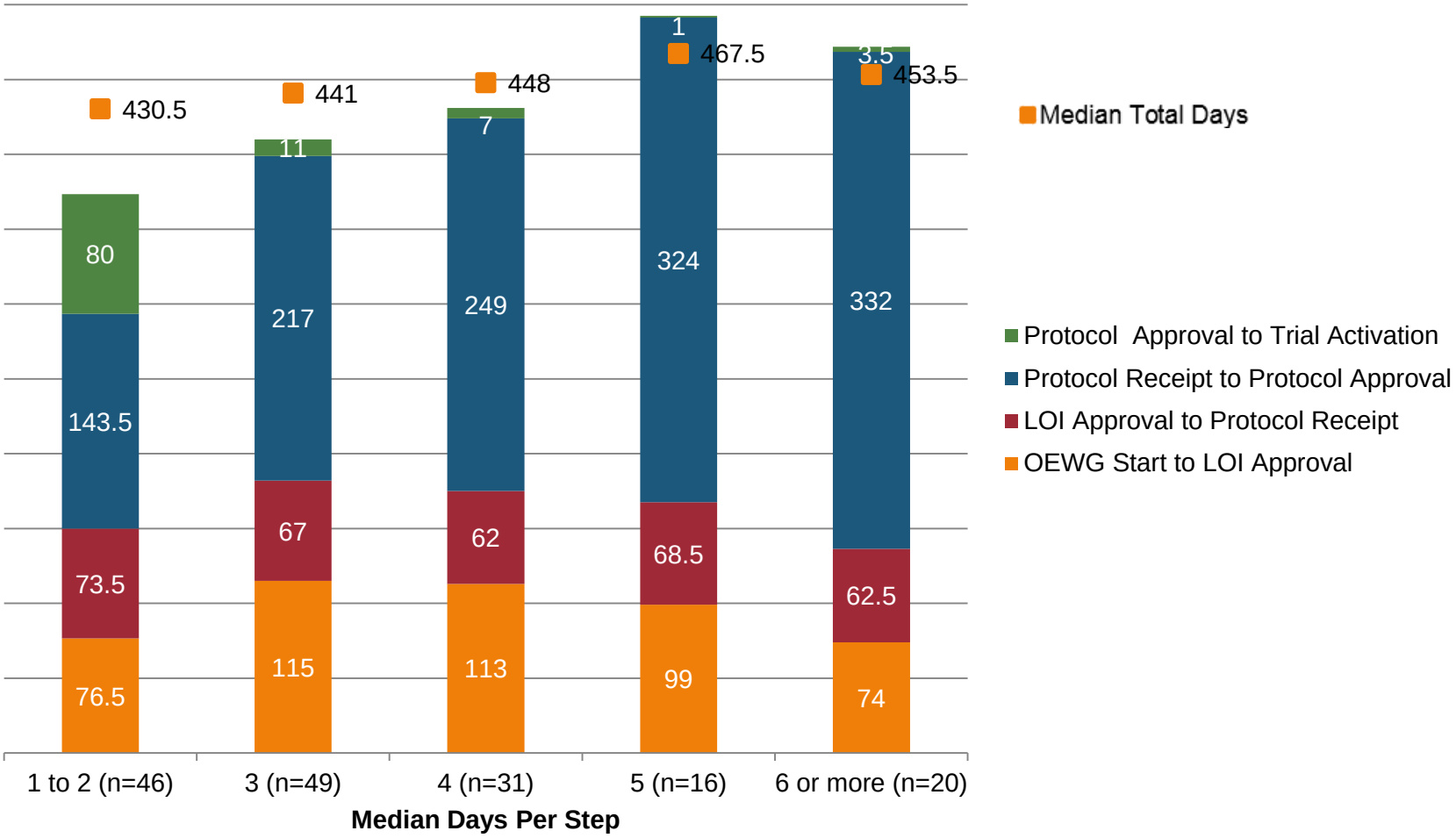
*Automatic extension of 16 days for government shutdown added to 35 trials
N=198; omitting 1 consortia phase III trial, 97% of original deadline

Common Reasons for Deadline Extensions

- Additional study component added or design changed
- Delay in drug dosing decisions or production
- NCI resource issues:
  - Backup due to other studies in CIRB or steering committees
  - Change in CIRB and network systems requirements
- Precision medicine study coordination
- Regulatory issues, e.g. late decisions to try for registration or require an IND
- Lead organization administrative issues

- Combination of factors that contribute to a rush at the deadline

Median Days for OEWG Stage by Number of Revisions, Early Phase Trials, 2014-2017



Limitations and Discussion

Limitations

- Potential bias due to studies withdrawn because they were expected to exceed OEWG deadline
  - This analysis only includes protocols that have been activated – trials that were withdrawn or disapproved are not included
  - Difficult to say conclusively why a study was withdrawn, but a brief review of LOIs, Concepts, and Protocols withdrawn after they are at least 100 days into their OEWG timeline suggests that the most common reasons for withdrawal are changes in the science
- Potential timing bias
  - If trials are grouped based on when their OEWG timeline **started**, then we risk underrepresenting how long the process takes, unless we wait long enough to allow the trials that take the longest to activate
    - This makes it harder to assess recent trials
  - This analysis grouped trials based on when they actually **activated**
    - This allowed us to look at trials activated through 2017

Next Steps and Questions for CTAC

- Expect different reasons for trial activation delays based on trial design and lead organization
  - Consortia & NCTN have centralized offices while ETCTN does not

- Analysis of ETCTN trial activation times identified additional support for protocol development as a potential facilitator
  - CTEP is developing a support mechanism to assist with the protocol authoring and revision process for ETCTN trials
  - Plan to evaluate the effect on trial timelines

- Strong tendency to work to the deadline across trials
  - Should deadlines be shortened?
  - Are there other analyses we should conduct?

Questions?

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