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Operational Efficiency Working Group

Clinical Trials Advisory Committee Report

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Bethesda, MD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

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Operational Efficiency Working Group Background

- **Clinical Trials Working Group (CTWG) Report Operational Efficiency Initiative 2**

  Identify the institutional barriers that prolong the time from concept approval to accrual of first patient, and develop solutions for overcoming these barriers

- **Clinical Trials Advisory Committee (CTAC) Charge**

  Establish an Operational Efficiency Working Group (OEWG) to recommend strategies and implementation plans for reducing the time for activation of Cooperative Group and Cancer Center trials

- **Focus is on timeliness of trial activation**

  Trial quality being addressed by several other CTWG and CTAC initiatives

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OEWG Membership
63 Clinical Trial Stakeholders

- 10 Cooperative Group Chairs
- 8 Cancer Center Directors
- Clinical Investigators
- Statisticians
- Protocol/Trial Specialists
- Community Oncologist
- NCI Clinical Trials Leadership and Staff
  - DCTD, CTEP, DCP, CCR, NCICB, CCCT, Cancer Centers
- Pharma/Biotech
- Patient Advocates
- FDA
- CMS
- CTSU

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Trial Categories Addressed by OEWG

- Cooperative Group Phase III Trials
- Cancer Center Investigator Initiated Trials
- IDB Early Drug Development Phase II Trials
  - N01 Contract Holders
  - Cooperative Groups

(Post-meeting note: Phase I trials, including U01, are also addressed by OEWG.)

- Cancer Center Activation of Cooperative Group Trials

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Topics Outside OEWG Purview

- Industry sponsored trials
- OHRP regulated issues
- CMS coverage determinations
- State laws and requirements
- Congressional funding mandates

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OEWG Deliberations

- Agreement on key barriers to timely trial activation
- Commitment to achieve new target timelines for steps in trial activation
- Developed new process maps for trial activation
- Identified external factors outside of NCI or investigators' control that delay activation
- Developed recommendations and associated implementation plans to achieve target timelines
- Established firm dates to terminate protocol development if all issues are not resolved

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Cooperative Group Phase III Trials

- **Current State**
- **OEWG Target Timeline**
- **Recommended Process Improvements**

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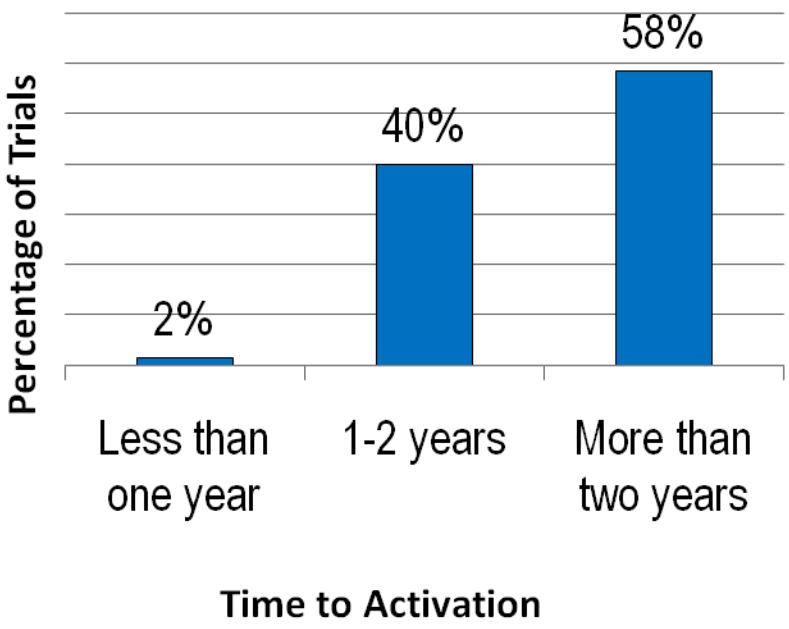
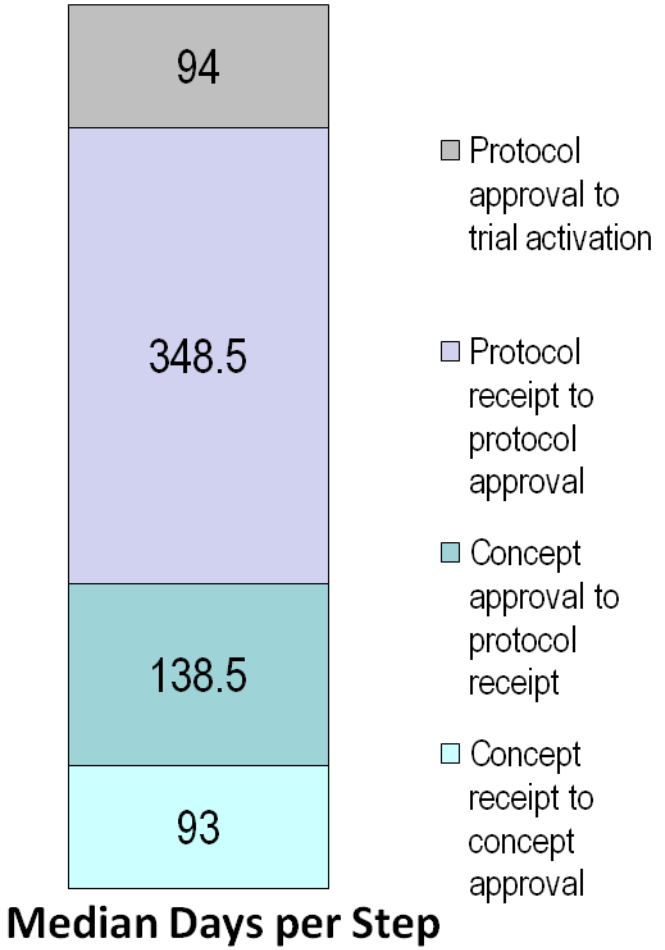
Time to Activation – Current State
Cooperative Group Phase III Trials (2006 – 2008)





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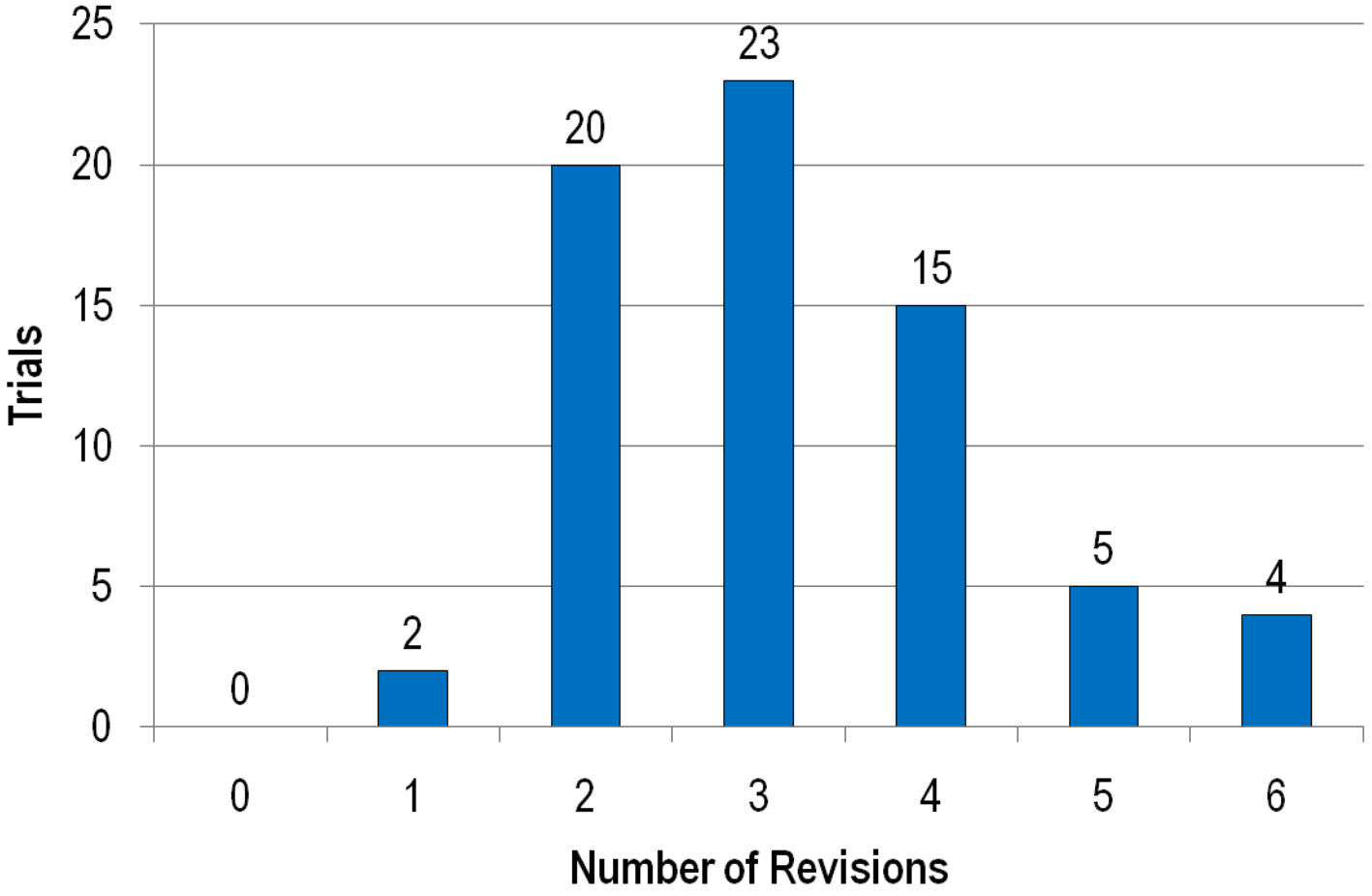
Review/Revision of Phase III Protocols (2006 – 2008)



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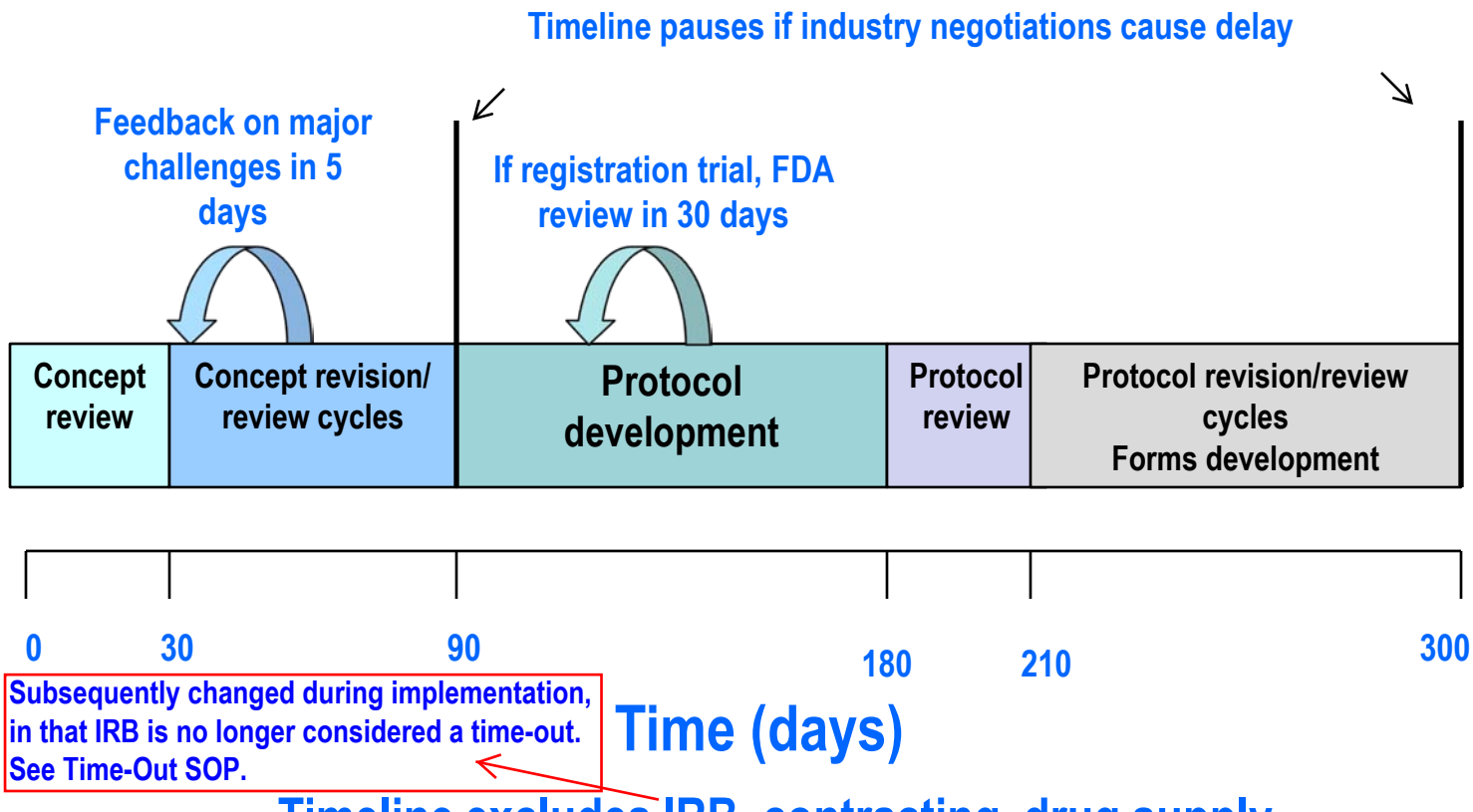
OEWG Target Timeline – 300 days



Subsequently changed during implementation, in that IRB is no longer considered a time-out. See Time-Out SOP.

Timeline excludes ~~IRB~~, contracting, drug supply

Protocol terminated if not activated in two years

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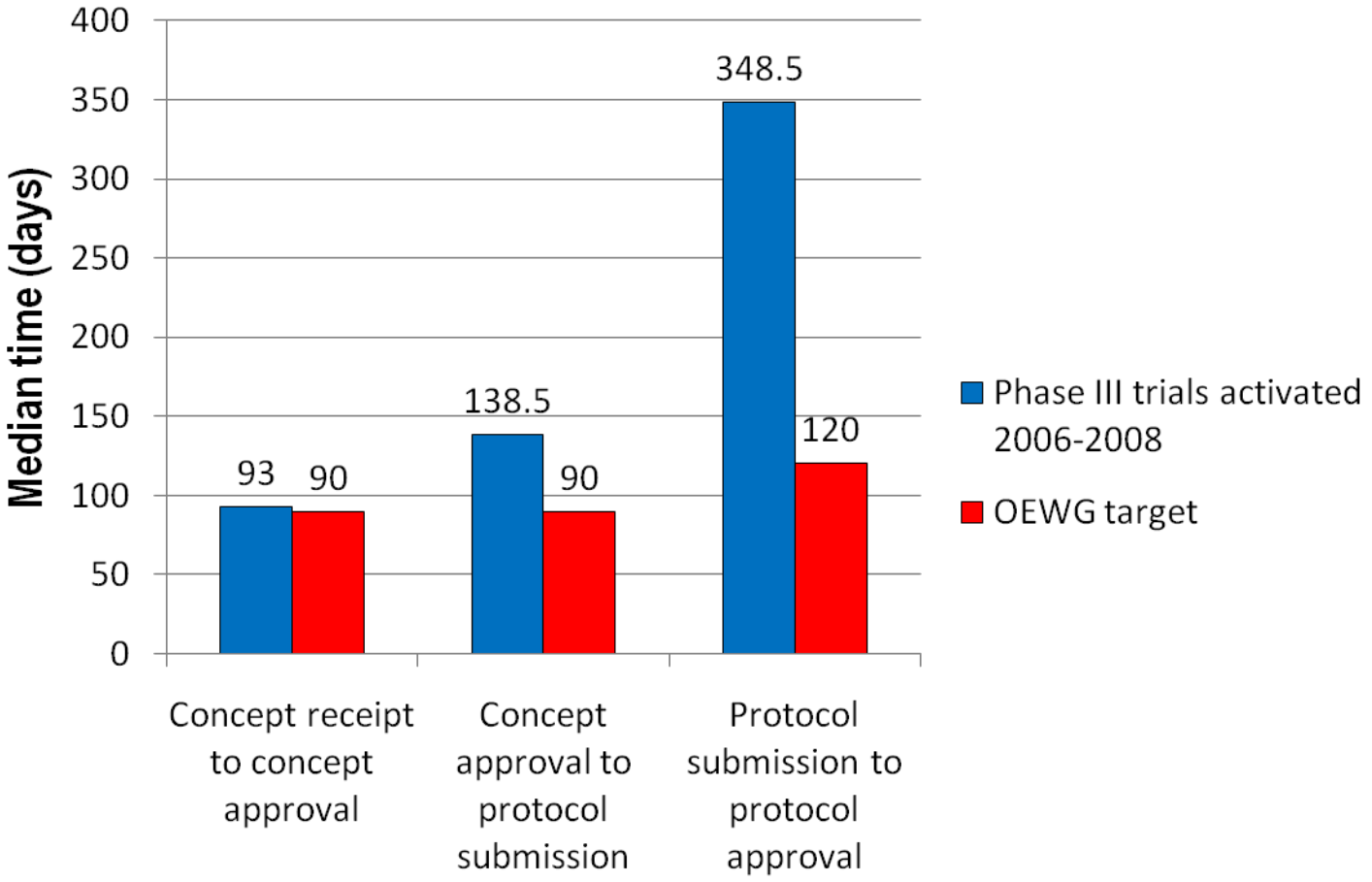
Time to Trial Activation
Current vs OEWG Target



Current median time includes CIRB approval, industry negotiations, and FDA approval

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Cooperative Group Process Improvement

Recommendation 1: Group-specific Action Plan to achieve OEWG target timeline

Implementation Plan

- **Potential staffing changes**
  - **Physician Senior Protocol Officers**
  - **Non-physician Trial Development Managers**
  - **Specialist medical writers**
- **Trial development steps performed in parallel**
- **Direct, coordinated interactions to resolve issues**
- **Project management/protocol tracking tools**

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Cooperative Group Process Improvement

Recommendation 2: CTEP Action Plan to achieve OEWG target timeline

Implementation Plan

- **Project Managers**
  - **Manage overall protocol review, revision and approval process**
  - **Facilitate interactions between CTEP and the Groups**
- **Coordinated NCI scientific review to identify all issues at time of initial concept review**
- **Prompt communication of critical issues in advance of formal written reviews**
- **Streamlined methods for communicating comments**
- **Distinguish advisory comments from those requiring response**
- **Project management/protocol tracking tool**

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Cooperative Group Process Improvement

Recommendation 3: Collaborative Group/CTEP process for concept and protocol revision

Implementation Plan

- **Direct, coordinated interactions to resolve issues**
- **High priority given for devoting time to issue resolution**
- **Fundamental aspects of study design resolved at concept stage**
- **Interactions at protocol stage focused on mechanics of completing a protocol embodying an agreed concept**
  - **Prompt communication and resolution of major differences**
  - **Minimal time spent discussing non-critical differences of opinion**
  - **Minimization of time and effort for routine or pro forma revisions**
- **Rapid arbitration for any issues not resolved quickly**

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Cooperative Group Process Improvement

Recommendation 4: Develop approaches to reward performance against timelines

Implementation Plan

- **Establish comprehensive, reliable system for reporting timeline performance for each step in trial activation**
- **Collect timeline performance data for at least one year and assess accuracy and value of the data and reports**
- **Analyze performance data by individual Groups and across the Group system compared to target timelines**
- **Joint Group/NCI deliberations concerning**
  - **Linking incentives to Group-specific timeline performance**
  - **Incorporating performance against timeline targets in Subcommittee H review**
- **CTEP to include timeline performance in its annual staff performance evaluations**

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Cancer Center Investigator Initiated Trials

- **OEWG Target Timeline**
- **Recommended Process Improvements**

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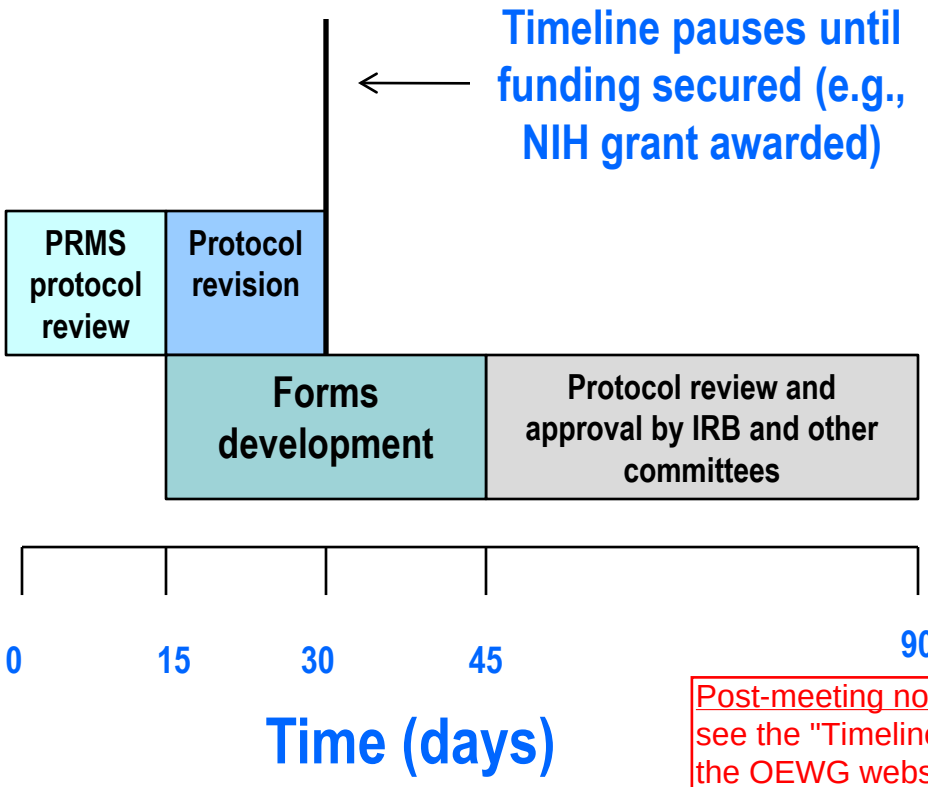
OEWG Target Timeline – 90 days



Post-meeting note: Please see the "Timeline Charts" on the OEWG website for the actual timelines implemented.

Timeline excludes writing of protocol, contracting, institutional financial review, drug supply

Performance benchmark for trial activation = 180 days

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Cancer Center Process Improvement

Recommendation 5: Center-specific Action Plan to achieve OEWG target timeline

Implementation Plan

- **Potential Action Plan Elements**
  - Specialist medical writers
  - Direct coordinated interactions to resolve differences
  - Project management /protocol tracking tool
- **Center-Specific Timeline Targets**
  - OEWG target modified to reflect specific Cancer Center environment
  - Targets analyzed for reasonableness by Cancer Center Directors/NCI
  - Timeline data reported annually against target
  - Centers performing below expectations report annually on actions taken
- **Funding Sources**
  - Explicitly allow use of CCSG funds for protocol development
  - Provide supplemental funds to implement Action Plan

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Cancer Center Process Improvement

Recommendation 6: Streamline university contracting and financial review processes

Implementation Plan

- **System level**
  - Educate universities on NCI Standardized Clauses for Clinical Trial Agreements
  - Develop standardized clauses for other types of agreements
  - Collaborate with CTSA program to streamline processes
- **Institution level activities**
  - Educate stakeholders on NCI Standardized Clauses for Clinical Trial Agreements
  - Establish master agreements with individual companies
  - Consider use of non-federal funds for university legal/contracting staff devoted to Cancer Center trials
  - Direct interactions among Center/university/hospital staff to resolve issues

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IDB Early Drug Development Phase II Trials

- Current State
- OEWG Target Timeline
- Recommended Process Improvements

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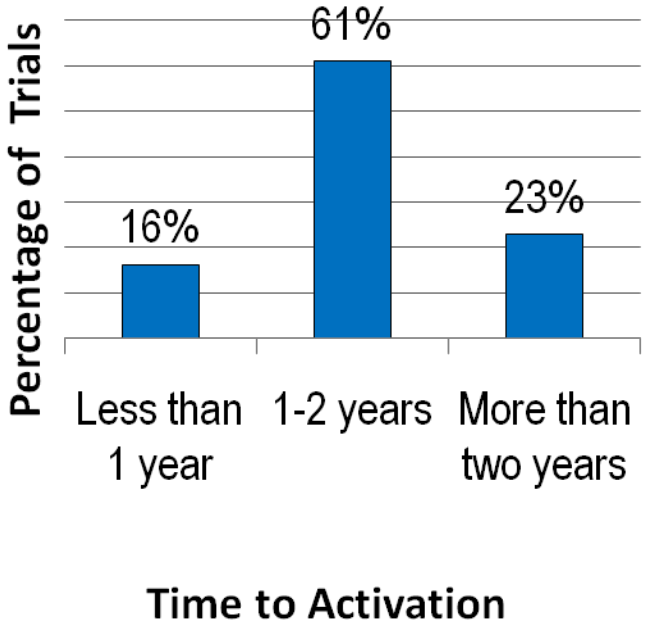
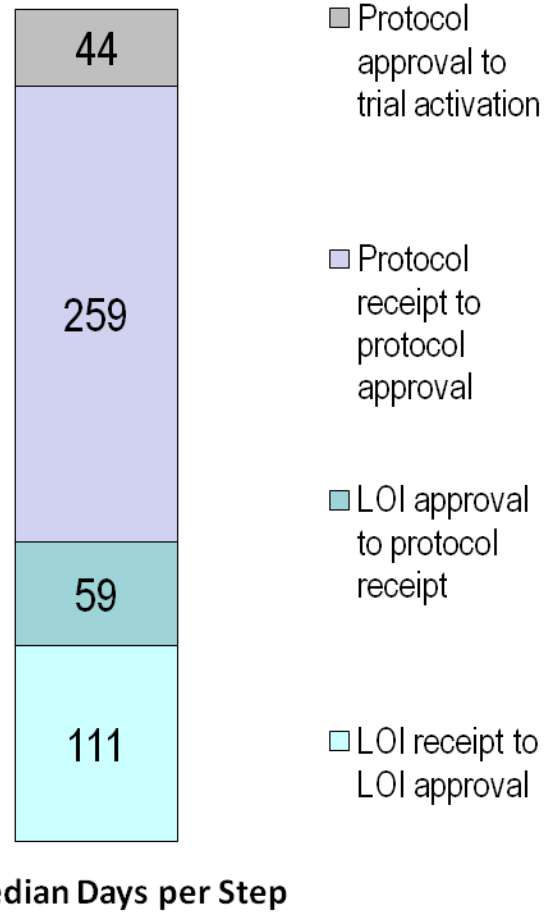
Time to Activation - Current State
N01 and Cooperative Groups (2006-2008)



Time to Activation



Median Days per Step

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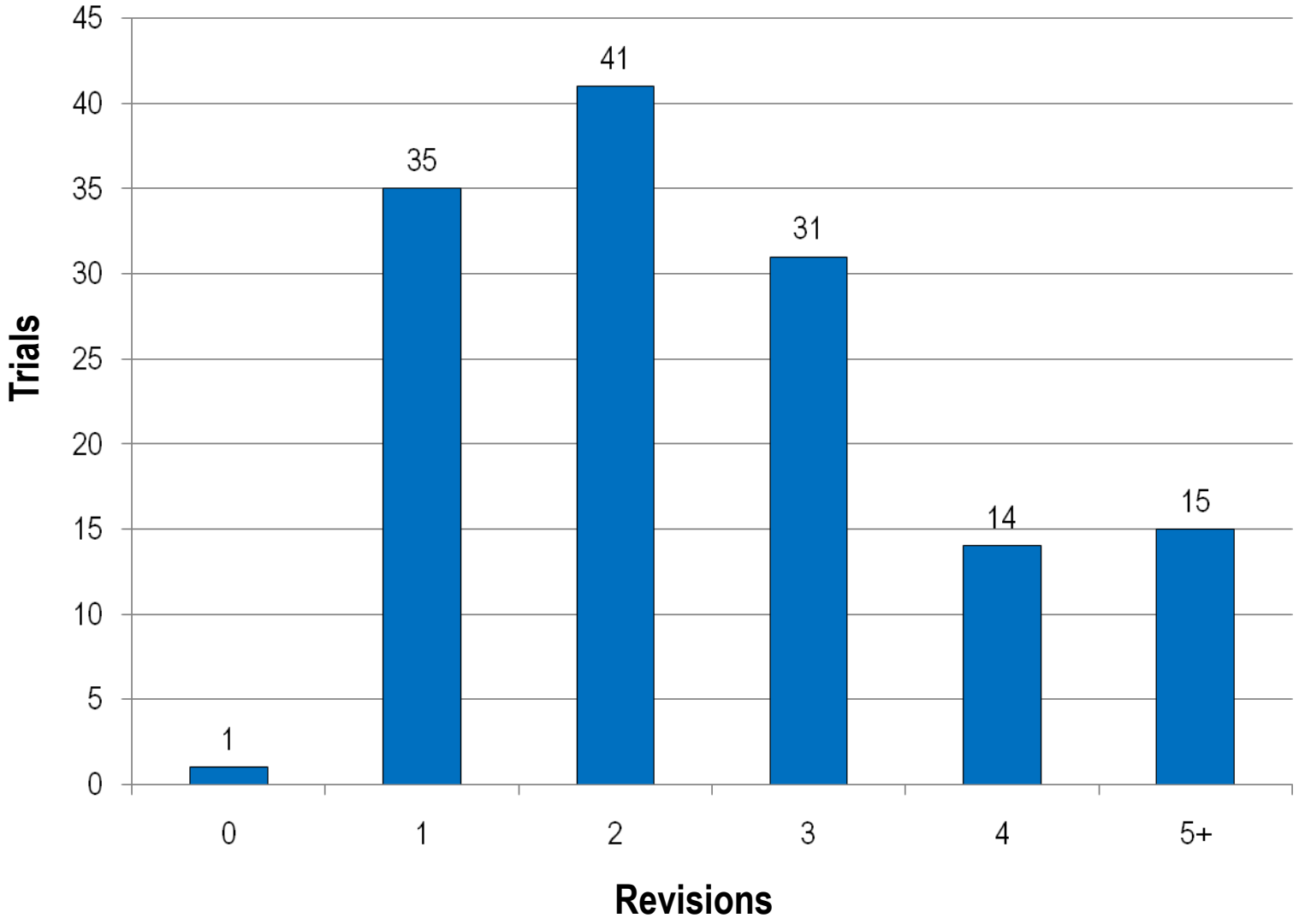
Review/Revision of Protocols N01 and Cooperative Groups (2006-2008)



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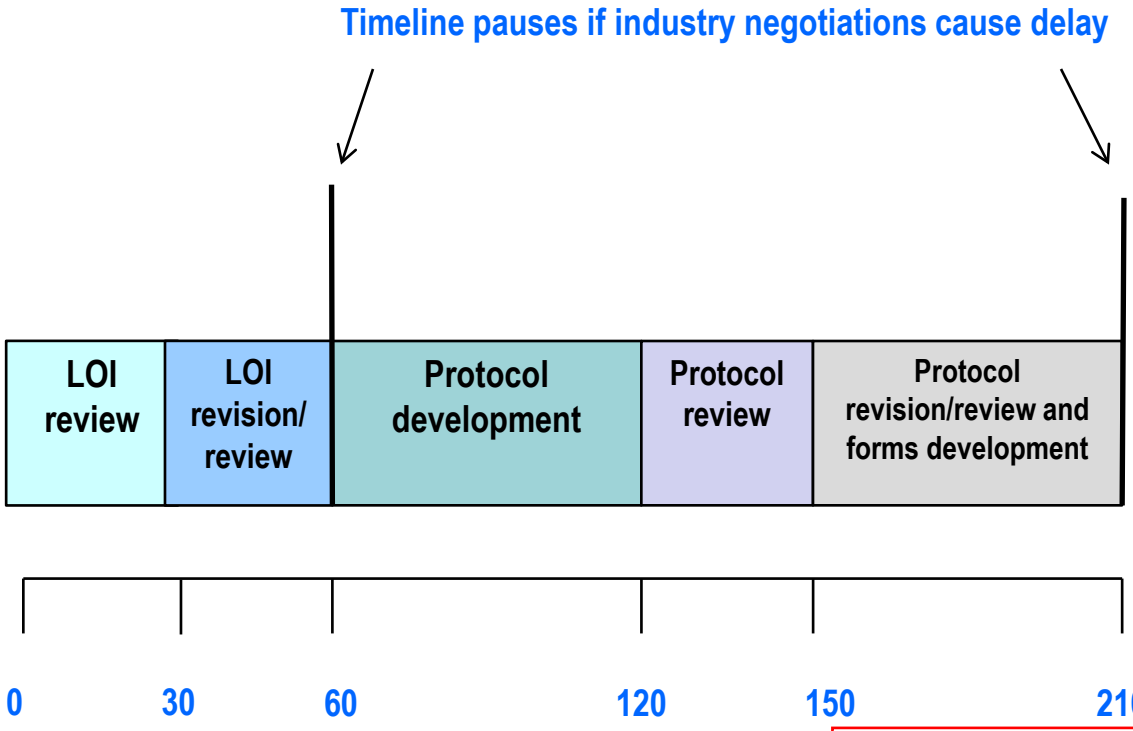
OEWG Target Timeline – 210 days



Subsequently changed during implementation in that IRB is no longer considered a time-out. See Time-Out SOP.

Timeline excludes contracting, drug supply, ~~IRB~~, FDA

Protocol terminated if not activated in 18 months

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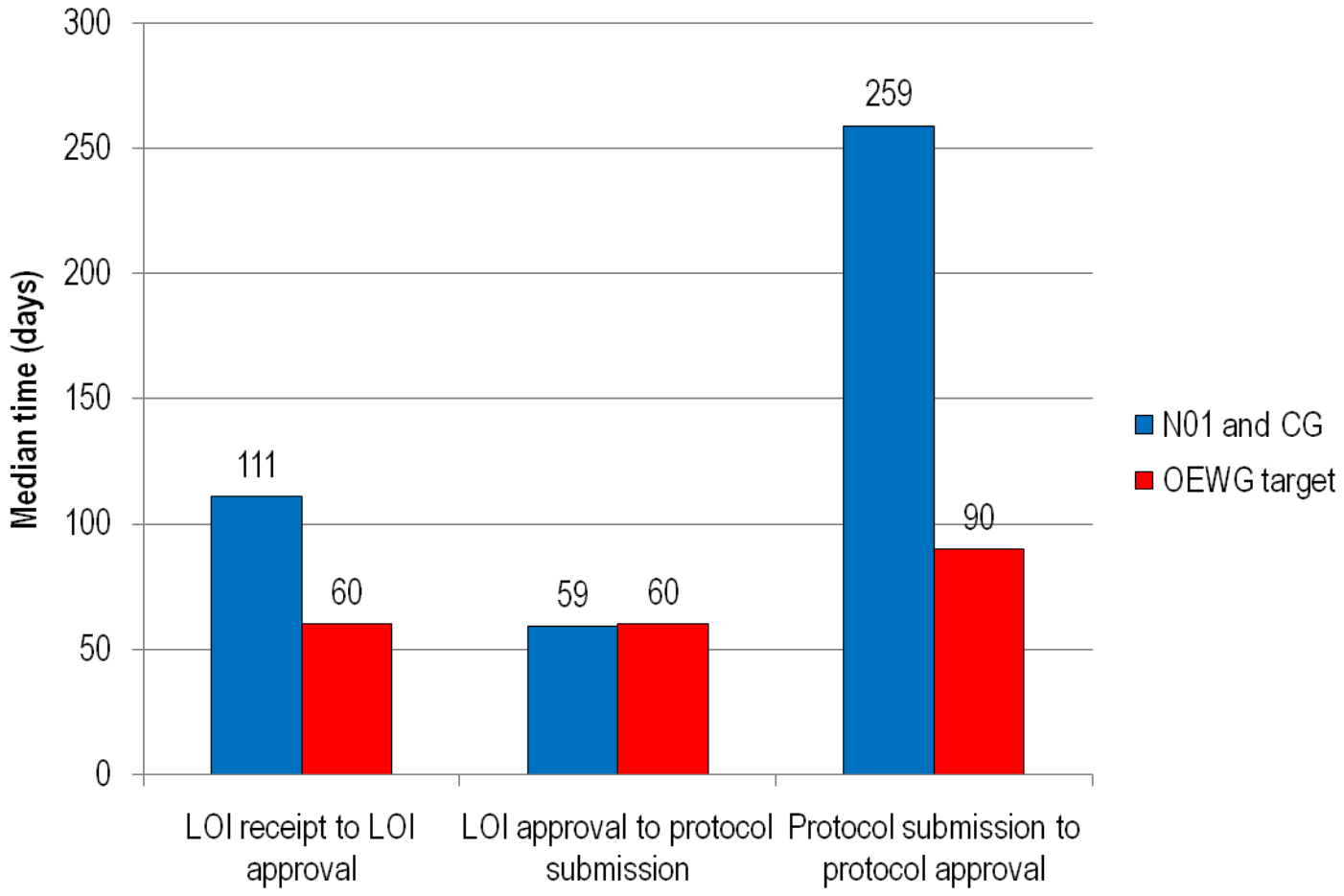
Time to Trial Activation
Current vs OEWG Target



Current median time includes IRB approval and industry negotiations

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Early Drug Development Phase II Trial Activation Process Improvement

Recommendation 7: CTEP Action Plan to achieve OEWG target timeline

Implementation Plan

- **Project Managers**
  - **Manage overall protocol review, revision and approval process**
  - **Facilitate interactions among CTEP, PIs and industry**
- **Teleconferences to resolve issues for "on hold" LOIs**
- **Prompt communication of disapprovals in advance of review letter**
- **Streamlined methods for communicating comments**
- **Distinguish advisory comments from those requiring response**
- **Project management/protocol tracking tools**

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Early Drug Development Phase II Trial Activation Process Improvement

Recommendation 8: Collaborative Group/N01/CTEP process for LOI and protocol revision

Implementation Plan

- **Direct, coordinated interactions to resolve issues (within 14 days of LOI review)** **(Post-meeting note: CTEP will set up calls within 14 days of review.)**
- **High priority on devoting time to issue resolution**
- **Fundamental aspects of study design resolved at LOI stage**
- **Interactions at protocol stage focused on mechanics of completing a protocol embodying an agreed LOI**
  - **Prompt communication and resolution of major differences**
  - **Minimal time spent discussing non-critical differences of opinion**
  - **Minimization of time and effort for routine or pro forma revisions**
- **Rapid arbitration for any issues not resolved quickly**

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Process Improvements Applicable across Trial Categories

- **Standardization of Tools and Templates**
- **Cancer Center Trial Prioritization**
- **Enhanced Biomarker Funding and Capabilities**

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Standardization of Tools and Templates

Goal: **Facilitate rapid assembly of protocols**

Recommendation 9: **Form working group involving NCI, Group and Center staff to coordinate standardization efforts**

Implementation Plan

- **Compile inventory of protocol templates, data elements, case report form modules, etc. from Groups, Centers and NCI**
- **Analyze inventory to identify current standards, best-in-class products, redundant development efforts and unmet needs**
- **Analyze status and output of existing standardization efforts**
- **Identify tools and templates where standardization is mandatory and those where recommended or optional**
- **Identify needed standards for interoperability**
- **Develop a coordinated process for implementing standards**

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Cancer Center Trial Prioritization

Goal: **Optimize use of resources by reducing the number of protocols in development**

Recommendation 10: **Perform rigorous review of clinical trial concepts in advance of protocol development**

Implementation Plan

- **Concept review process specified in CCSG guidelines**
  - **Approval/disapproval by disease group or Center-wide**
  - **Uniformity of reviews across diseases**
  - **Content of a concept document**
  - **Criteria by which concepts are reviewed**
- **NCI should not mandate the specific process or criteria**
- **Applicable to all trials – investigator initiated, Cooperative Group and N01** **(Post-meeting note: Phase I trials, including U01, are also addressed by OEWG.)**

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Enhanced Biomarker Funding/Capabilities

Goal: **Facilitate rapid activation of trials involving critical biomarker studies**

Recommendation 11: **Enhance funding and capabilities for use of biomarkers in NCI-funded clinical trials**

Implementation Plan

- **Expand the Biomarker, Imaging and Quality of Life Studies Funding Program (BIQSFP) to large randomized Phase II trials**
- **Create program to fund biomarker studies for early-phase trials**
- **Require clinical trial concepts/LOIs to describe proposed integral or integrated biomarker studies**
- **Provide funding for development, validation, and conduct of clinical grade assays**
- **Develop standards for qualifying sites to conduct imaging studies associated with clinical trials**

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Process Improvements to Enhance Overall Clinical Trials Program

- **Robust OEWG discussion of several improvements in the NCI clinical trials program not directly linked to activation time**
  - **Cancer Center Participation in Cooperative Group Trials**
  - **Cancer Center Clinical Trials Strategic Review**
  - **Clinical Research Mentorship and Training**
- **Developed recommendations and implementation plans for improvements in each of these areas**

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Process Improvements to Enhance Overall Clinical Trials Program

- **Enhance Cancer Center Participation in Cooperative Group Trials**
  - Cooperative Group leadership and accrual part of CCSG review criteria
  - NCI officially recognizes investigators for leadership in the design and conduct of Cooperative Group trials
  - Enhance the stability and size of accrual funding
  - Create incentives for institutions to include Cooperative Group accrual as a "service" criterion for tenure and promotion
- **Cancer Center Clinical Trials Strategic Review**
  - Requirement for Comprehensive Cancer Centers
  - Allocate clinical trial resources based on scientific/clinical advances, basic/translational/clinical research strengths and patient population
- **Enhance Clinical Research Mentorship and Training**
  - Flexibility in use of CCSG funds for mentorship and training
  - Clinical research training required for Comprehensive Cancer Centers
  - Create new training awards, programs and tools

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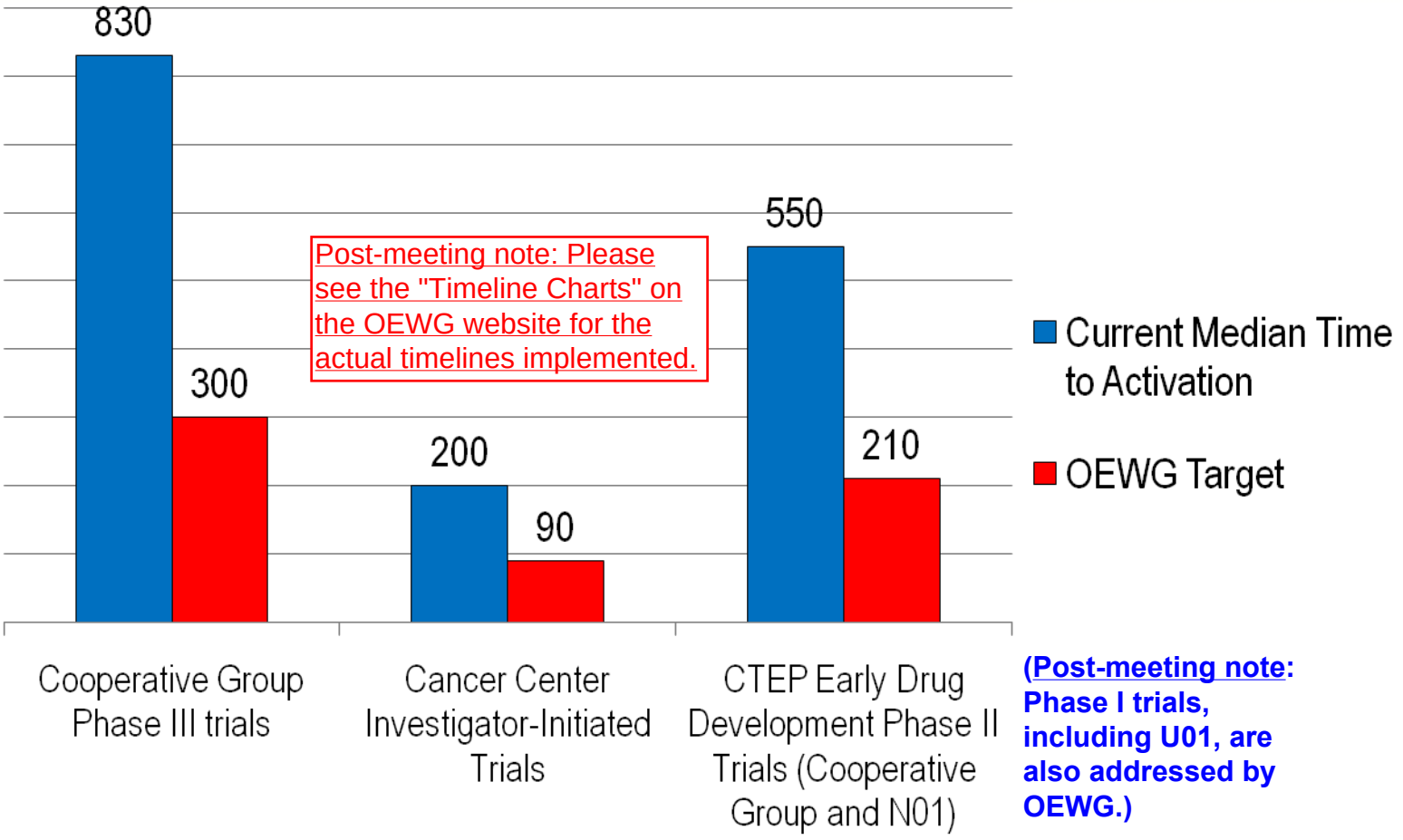
Targets Aggressive But Necessary



(Post-meeting note: Phase I trials, including U01, are also addressed by OEWG.)

Current median time includes IRB approval, industry negotiations, and FDA approval

Commitment will result in significant progress but success will not be fully achieved without incremental funding

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OEWG ARRA Funding and Beyond

- **ARRA Administrative Supplements**
  - Develop Cooperative Group, Cancer Center, NCI Action Plans
  - Dedicated protocol development staff (protocol writers, trial development managers, etc)
  - Acquisition and deployment of project management/protocol tracking software tools
- **Firm Termination Deadlines Beginning January 2011**
  - 24 months for Phase III
  - 18 months for Phase II (Post-meeting note: Phase I trials are also addressed by OEWG.)
- **Long Term**
  - Economic incentives for Cooperative Groups and Cancer Centers to meet the target timelines

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OEWG Next Steps

- **Prepare Phase I OEWG Final Report**
- **Launch OEWG Phase II addressing rate of accrual and time to trial completion**

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OEWG Ultimate Vision

Coordinated, collaborative, interactive processes for timely development, review, revision and approval of all NCI-supported clinical trials

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Appreciation

Thanks to:

- **OEWG members**
- **NCI professional staff**
- **Science Technology Policy Institute: Judy Hautala, Oren Grad, Brian Zuckerman**