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Operational Efficiency Working Group Final Report

"Compressing the Timeline for Cancer Clinical Trial Activation"

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March 10, 2010

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

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Operational Efficiency Working Group (OEWG)

- Clinical Trials and Translational Research 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

- Composition: *63 clinical trial stakeholders: All 10 Cooperative Group Chairs, 8 Cancer Center Directors, Statisticians, Community Oncologists, FDA, CMS, Protocol Specialists, and NCI Clinical Trials Leadership*

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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
- Cancer Center Activation of Cooperative Group Trials
- NOT: Industry-sponsored trials; OHRP-related issues, CMS coverage

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OEWG Accomplishments

- Developed commitment to new target timelines for steps in trial activation
- Developed new process maps for trial activation
- Developed recommendations and associated implementation plans to achieve target timelines
- Established firm dates to terminate protocol development if all issues are not resolved
- Developed resources to support implementation

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Cooperative Group Phase III Trials

- Current State
- OEWG Target Timeline
- Recommended Process Improvements

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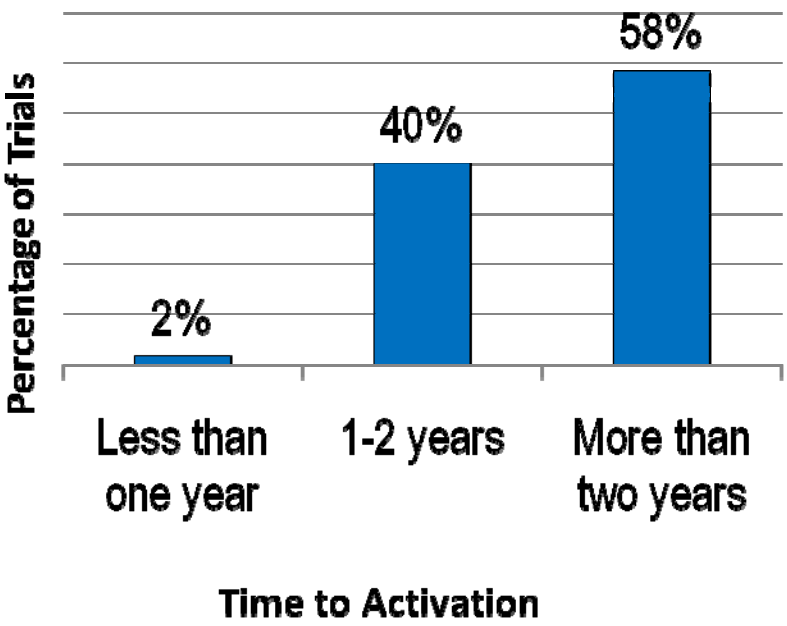
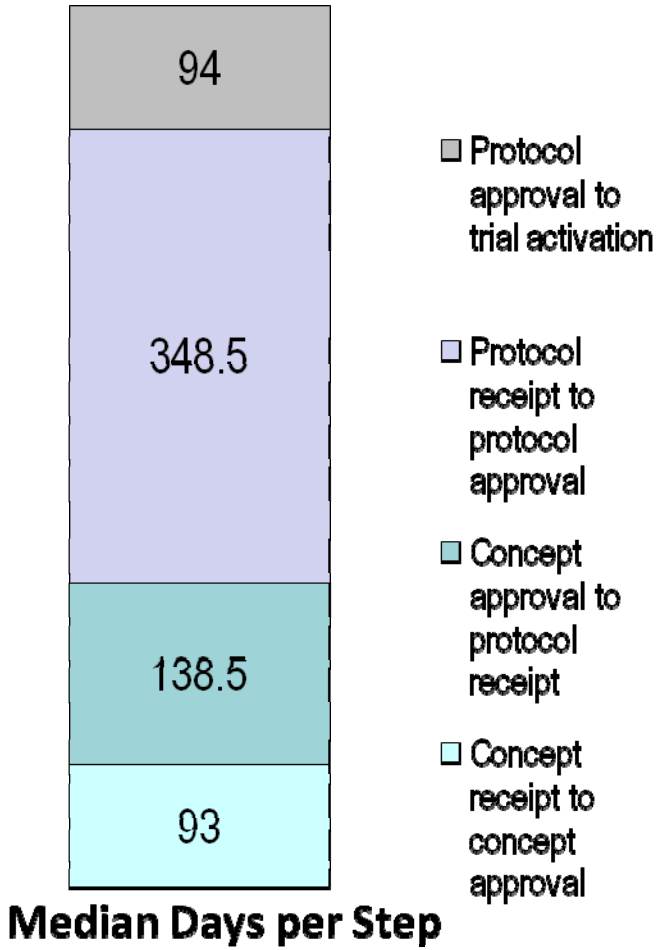
Time to Activation – Current State
Cooperative Group Phase III Trials (2006 – 2008)





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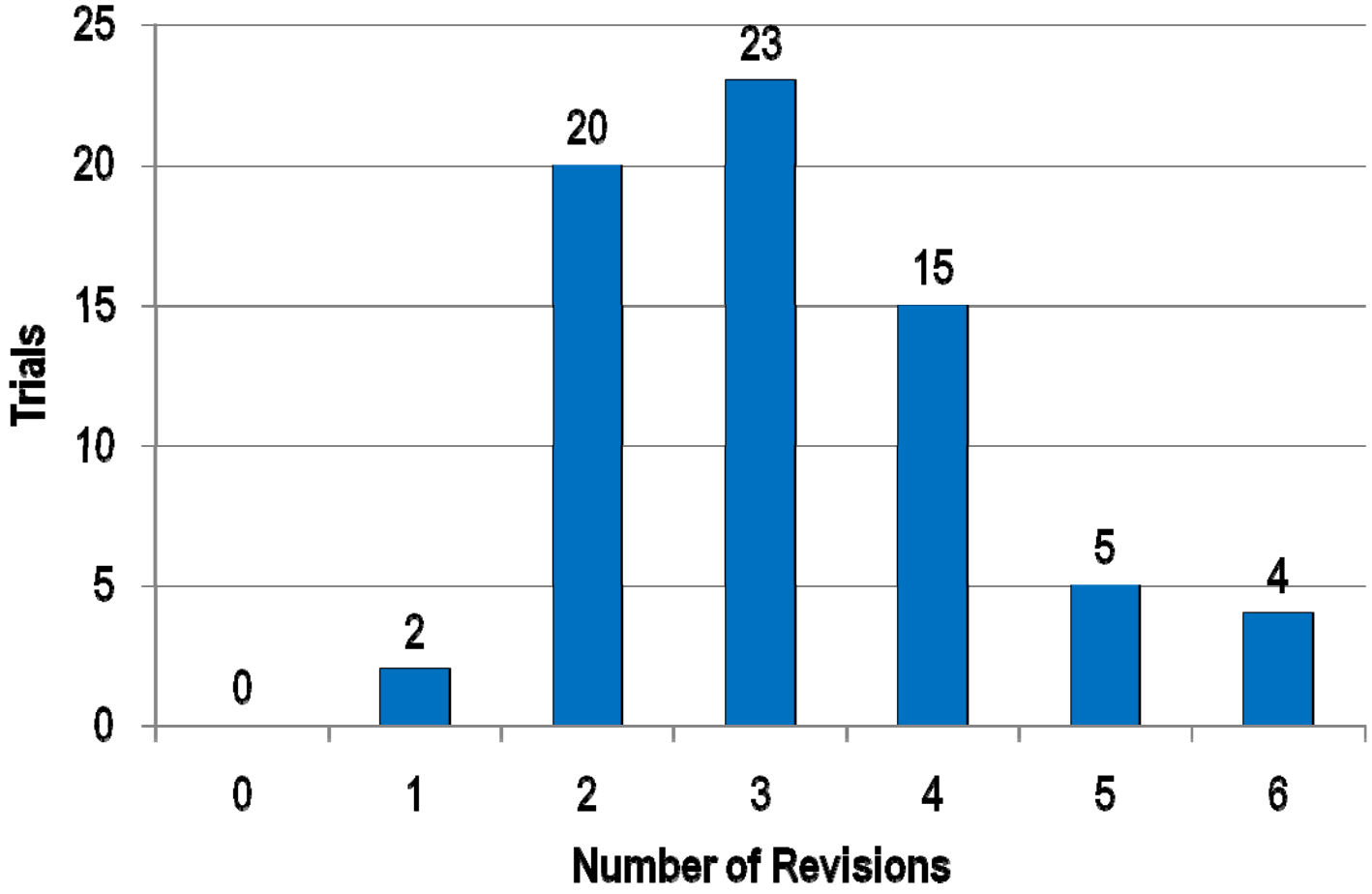
Review/Revision of Phase III Protocols (2006 – 2008)



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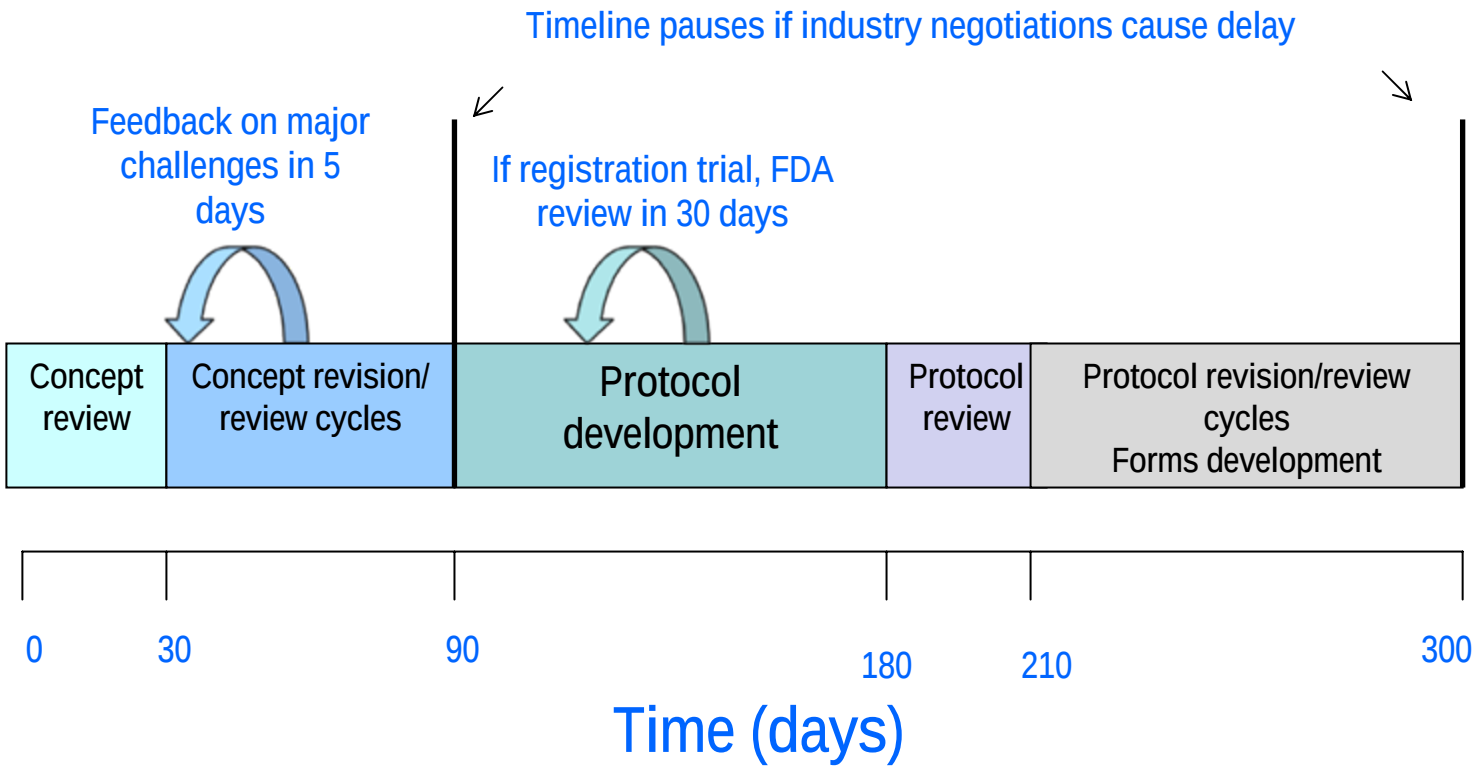
OEWG Target Timeline – 300 days



Timeline excludes IRB, contracting, drug supply

Protocol terminated if not activated in two years

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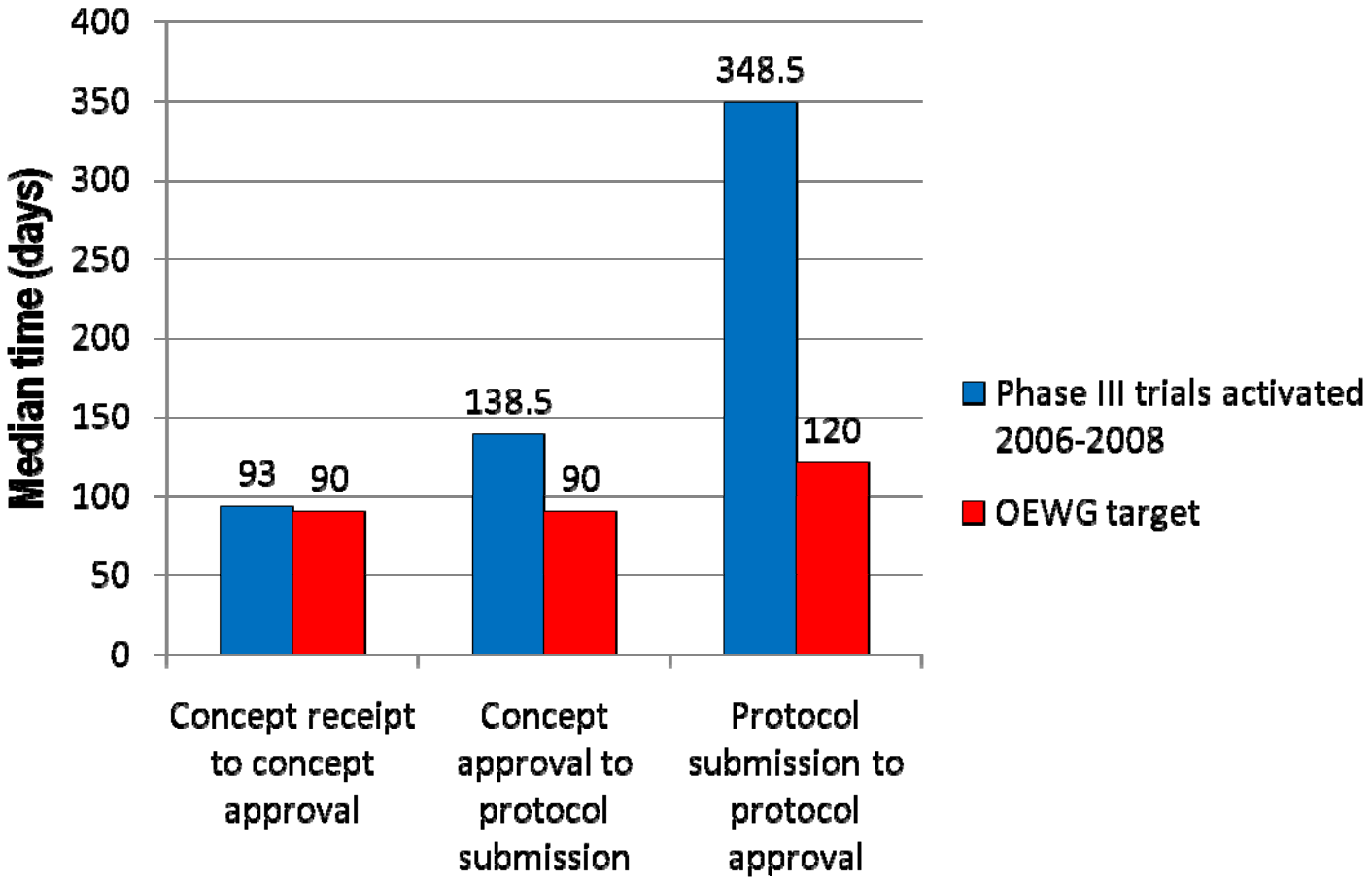
Time to Trial Activation
Current vs OEWG Target



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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IDB Early Drug Development Phase II Trials

- Current State
- OEWG Target Timeline
- Recommended Process Improvements

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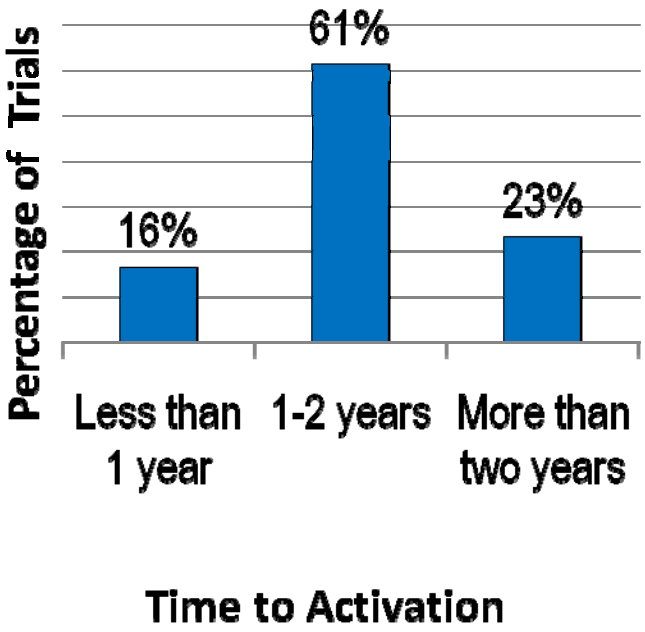
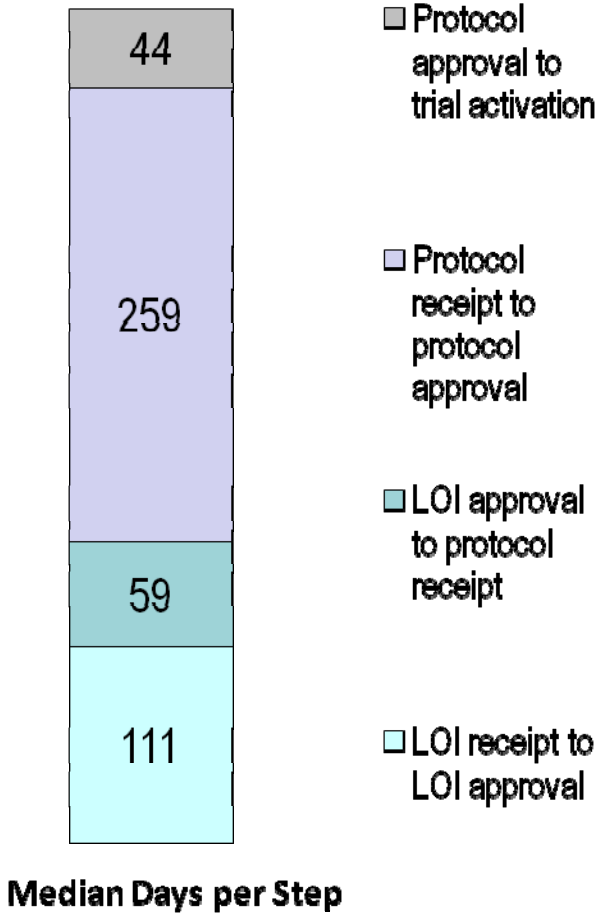
Time to Activation - Current State
N01 and Cooperative Groups (2006-2008)





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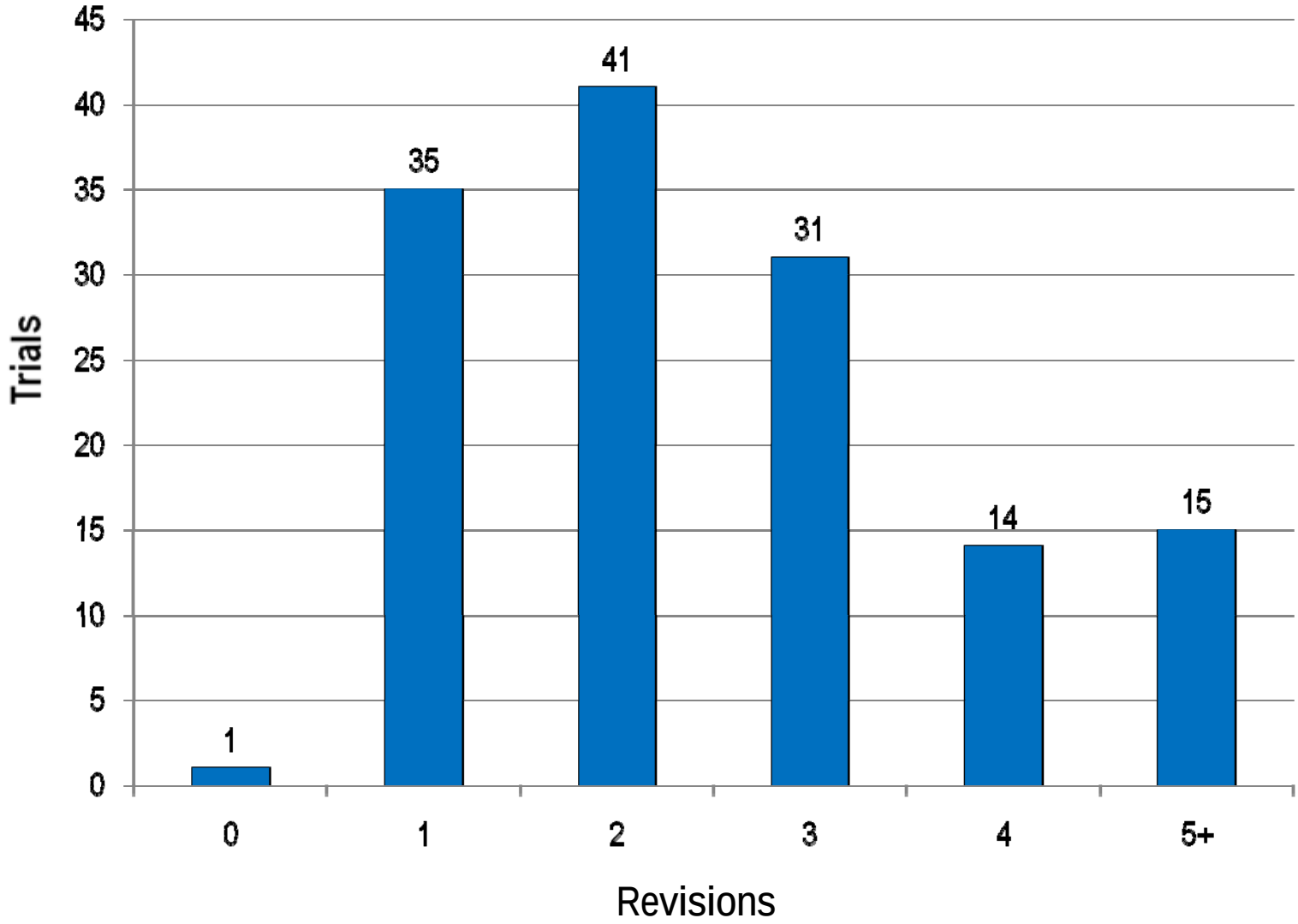
Review/Revision of Protocols N01 and Cooperative Groups (2006-2008)



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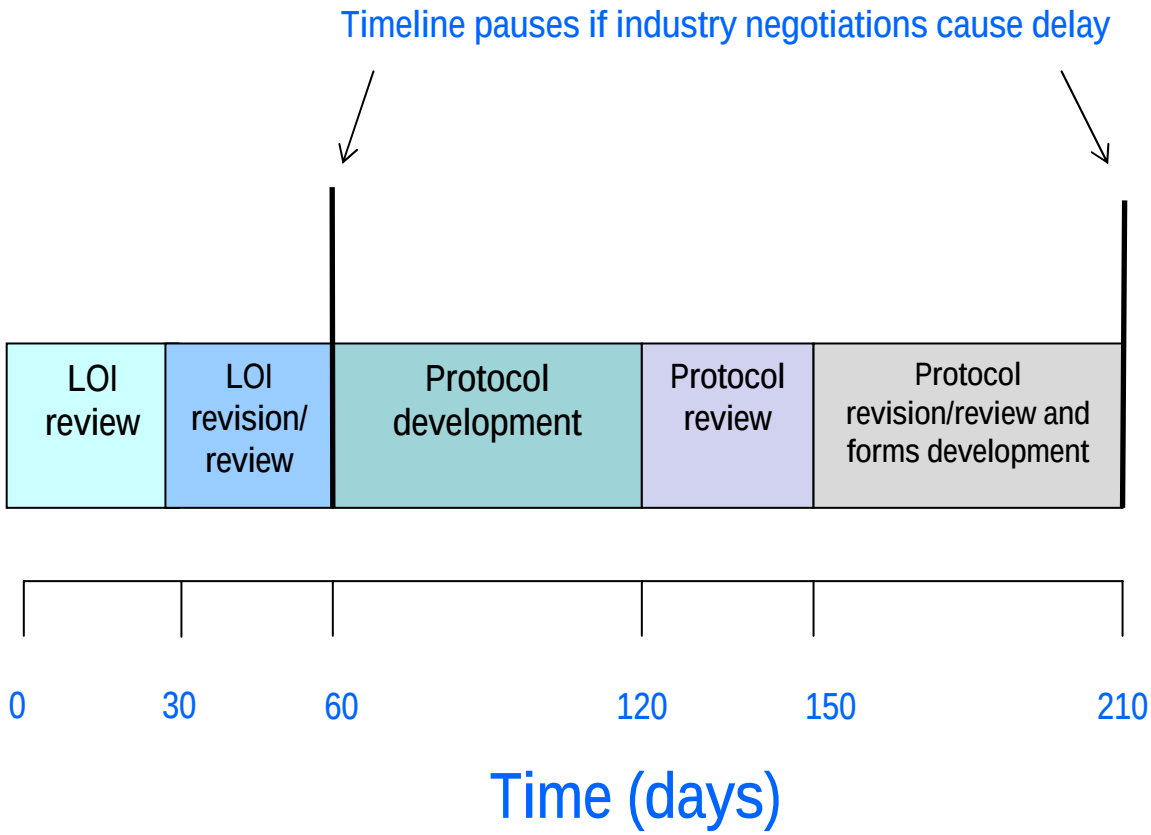
OEWG Target Timeline – 210 days



Timeline excludes contracting, drug supply, IRB, FDA

Protocol terminated if not activated in 18 months

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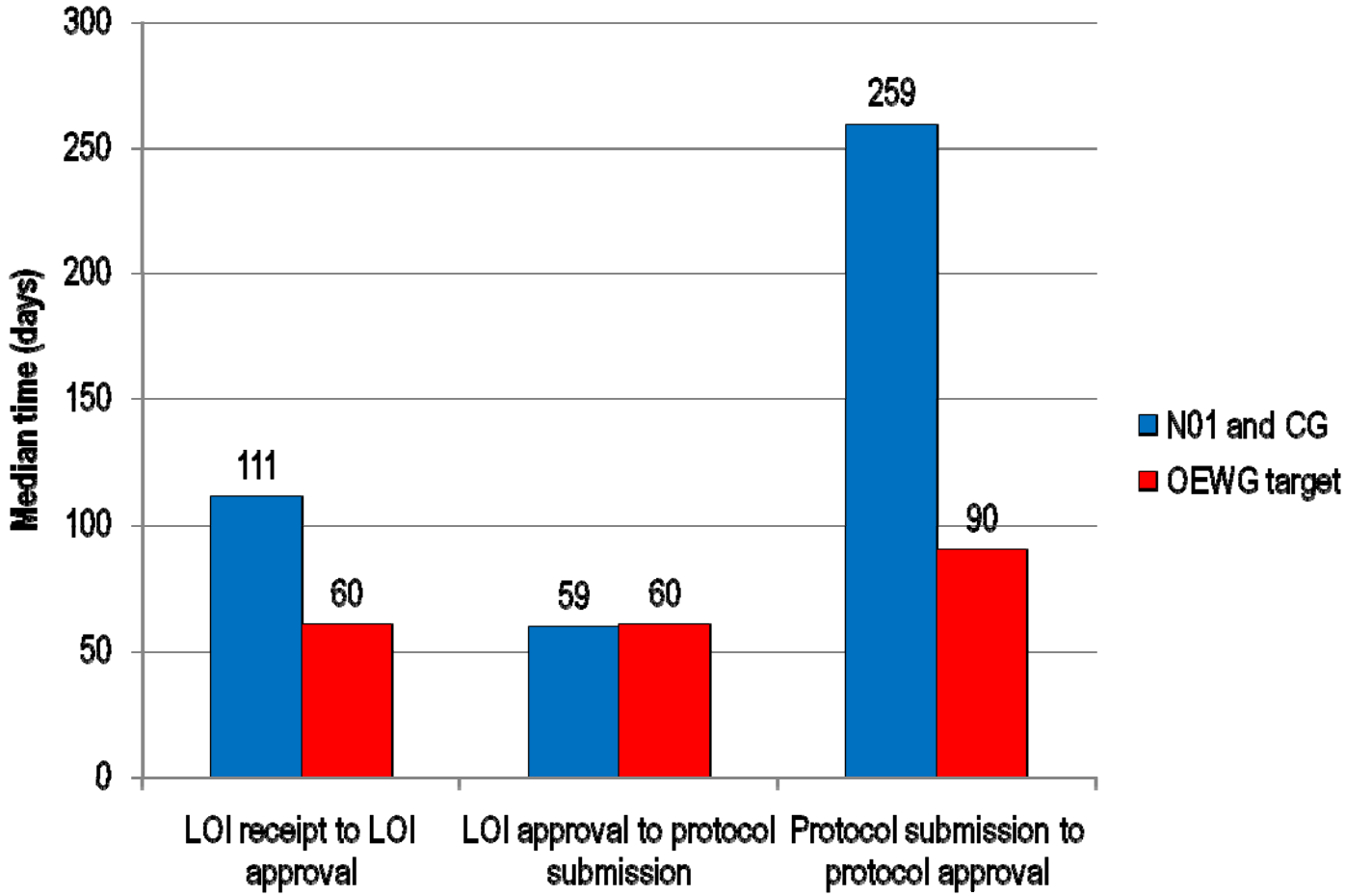
Time to Trial Activation
Current vs OEWG Target



Current median time includes IRB approval and industry negotiations

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Early Drug Development Phase II Trial Activation Process Improvement

Recommendation 5: 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 6: Collaborative Group/N01/CTEP process for LOI and protocol revision

Implementation Plan

- Direct, coordinated interactions to resolve issues (within 14 days of LOI 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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Cancer Center Investigator Initiated Trials

- OEWG Target Timeline
- Recommended Process Improvements

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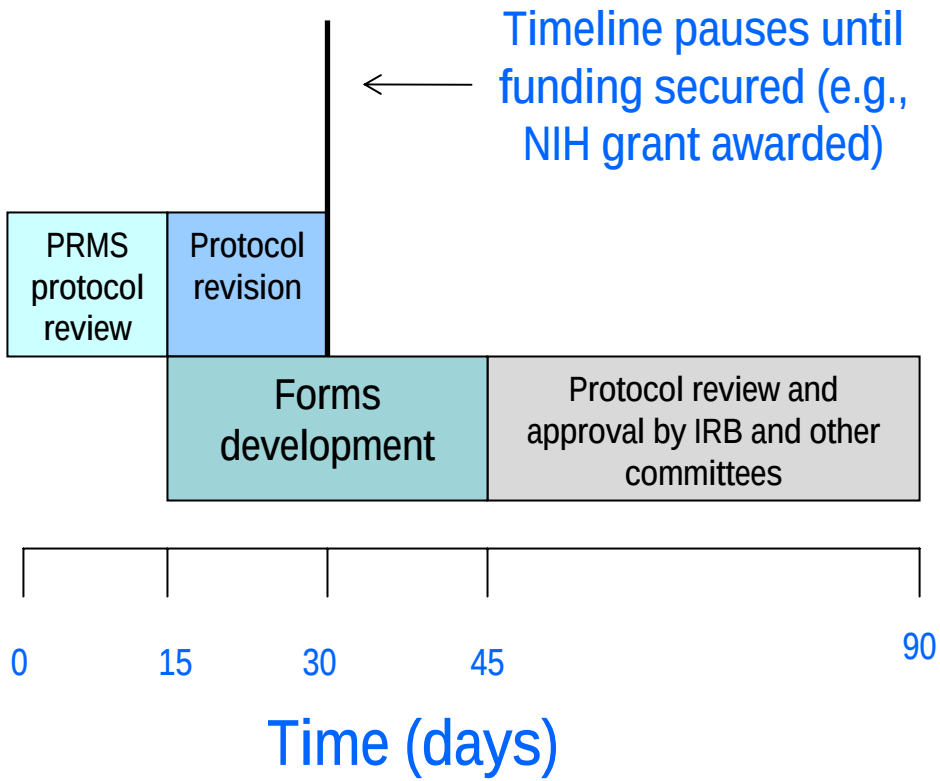
OEWG Target Timeline – 90 days



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 7: 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 8: Streamline university contracting and financial review processes

Implementation Plan

- System level
  - Educate universities on NCI START (Standard Terms of Agreement for Research Trials) clauses (http://ccct.nci.nih.gov)
  - Develop standardized clauses for other types of agreements
  - Collaborate with CTSA program to streamline processes
- Institution level activities
  - Educate stakeholders on NCI START clauses
  - 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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Process Improvements Applicable across Trial Categories

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

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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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Enhanced Biomarker Funding/Capabilities

Goal: Facilitate rapid activation of trials involving critical biomarker studies

Recommendation 10: 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: Done
- Support 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: Underway
- Develop standards for qualifying sites to conduct imaging studies associated with clinical trials: Underway

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Cancer Center Trial Prioritization

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

Recommendation 11: 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

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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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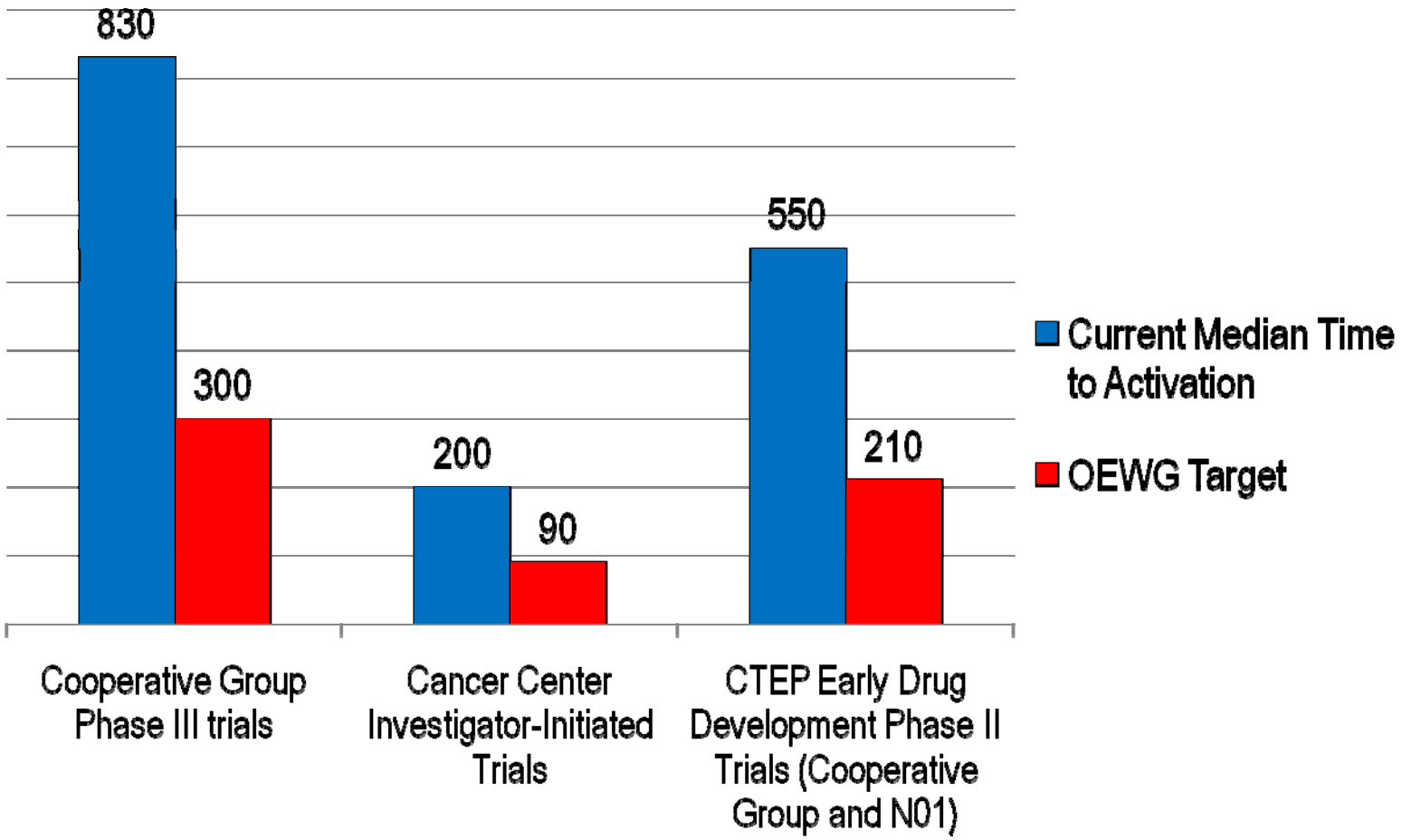
Targets Aggressive But Necessary



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 Recommendations: Implementation

- Develop Cooperative Group and Cancer Center Action Plans
  - Administrative supplements awarded to all ten Cooperative Groups
    - Develop action plans
    - Hire additional staff
    - Acquire and deploy project management tools
  - Administrative supplement requests in review for NCI-designated Cancer Centers: 48 applications
- CTEP action plan to be initiated for new concepts and LOI's April 1, 2010; OEWG implementation kickoff meetings March 23rd for Phase I/II Investigators and March 24th for Coop Groups
  - Revised LOI and protocol processing
  - Revised templates and AE reporting tables
  - Transparent timeline tracking system: "Who has the concept/protocol?"
  - Cancer Center action plans: Working Groups (Phase I/II trials)
  - Coop Group models and action plans

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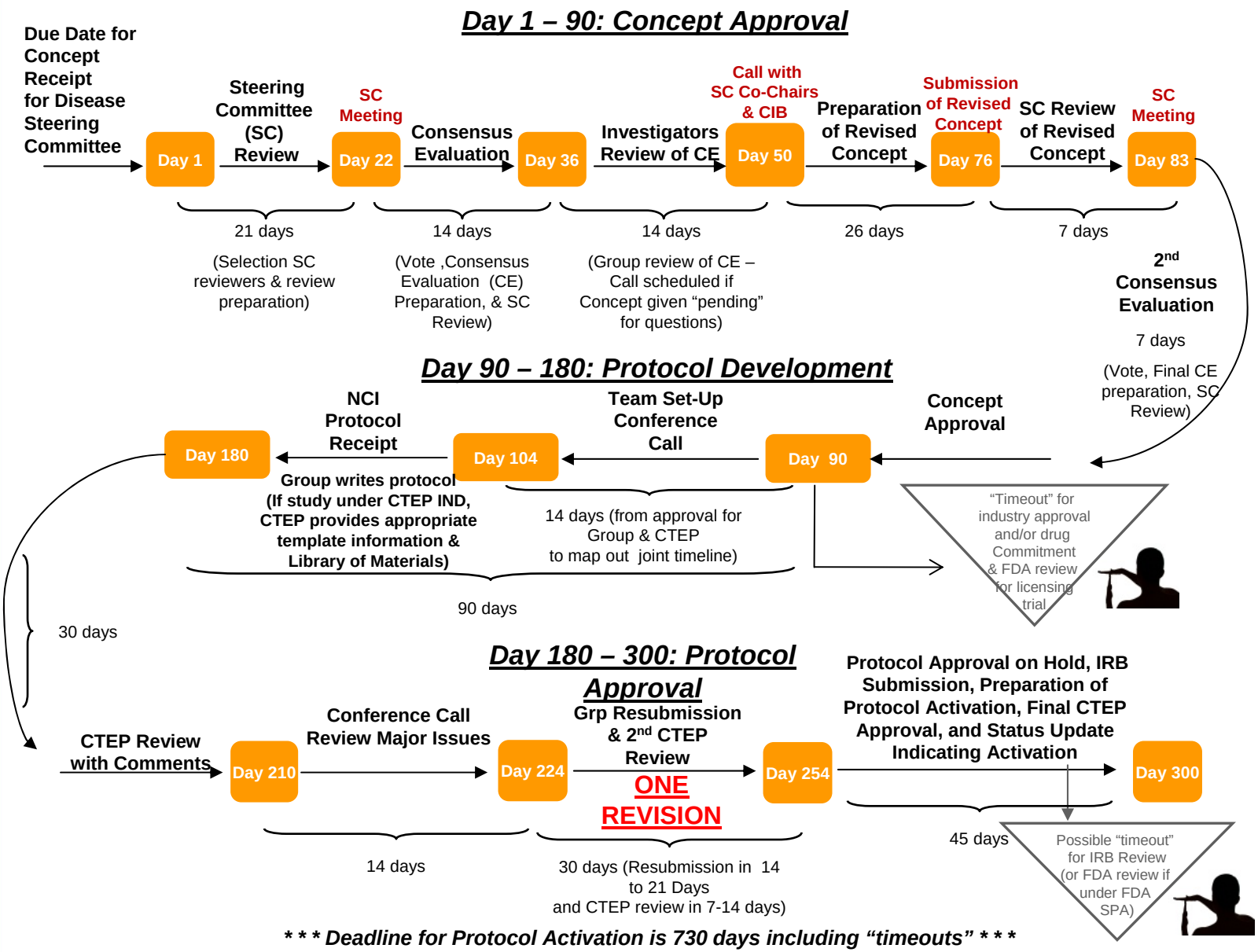
Phase 3 Timeline



**** * * Deadline for Protocol Activation is 730 days including "timeouts" * * ****

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OEWG Recommendations: Implementation (2)

- Firm Termination Deadlines Beginning January 2011
  - 24 months for Phase III
  - 18 months for Phase II
- FY 2011 and beyond
  - Routine collection and reporting of timeline performance
  - Incentives for Cooperative Groups, Cancer Centers, CTEP, and DCP to meet the target timelines
  - Long term support for efficiency initiatives
- **Vision:** Coordinated, interactive processes for timely development, review, revision and approval of all NCI-supported clinical trials

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OEWG Next Steps

Launch OEWG Phase II addressing rate of accrual and time to trial completion

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Appreciation

Thanks to:

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

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CTAC Requested Action

Motion to accept the recommendations of the Operational Efficiency Working Group report

Phase 3 Timeline – Modification if No Existing Steering Committee

Day 1 – 90: Concept Approval

NCI Receipt of Concept in Disease with With No Existing Steering Committee → **Day 1**

CTEP CRM Review With External Reviewers → **CRM Meeting** → **Day 36**

35 days
(Selection external reviewers & review preparation)

Consensus Evaluation → **Day 43**

7 days
(Consensus Evaluation (CE) Preparation)

Investigators Review of CE → **Call with CTEP (CIB, IDB)** → **Day 50**

7 days
(Group review of CE – Call scheduled if Concept given "pending" for questions)

Preparation of Revised Concept → **Submission of Revised Concept** → **Day 76**

26 days

CRM Review of Revised Concept → **CRM Meeting** → **Day 83**

7 days

2nd Consensus Evaluation

7 days

(Final CE preparation)

Day 90 – 180: Protocol Development

Concept Approval → **Day 90**

Team Set-Up Conference Call → **Day 104**

14 days
(from approval for Group & CTEP to map out joint timeline)

NCI Protocol Receipt → **Day 180**

Group writes protocol (If study under CTEP IND, CTEP provides appropriate template information & Library of Materials)

90 days

"Timeout" for industry approval and/or drug Commitment & FDA review for licensing trial

30 days

Day 180 – 300: Protocol Approval

CTEP Review with Comments → **Day 210**

Conference Call To Review Major Issues → **Day 224**

14 days

Group Resubmission & 2nd CTEP Review → **Day 254**

30 days
(Resubmission in 14 to 21 Days and CTEP review in 7-14 days)

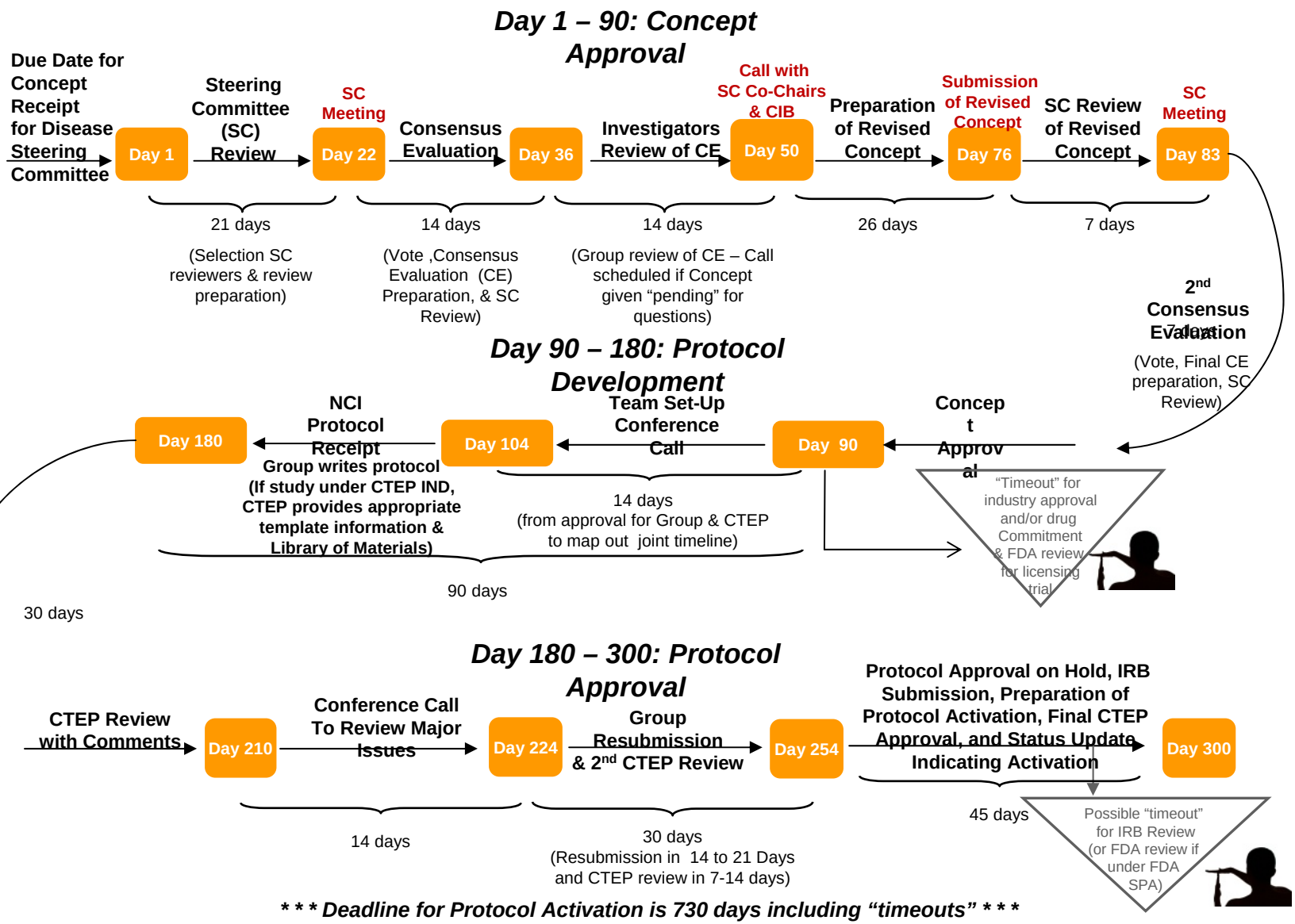
Protocol Approval on Hold, IRB Submission, Preparation of Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation → **Day 300**

45 days

Possible "timeout" for IRB Review (or FDA review if under FDA SPA)

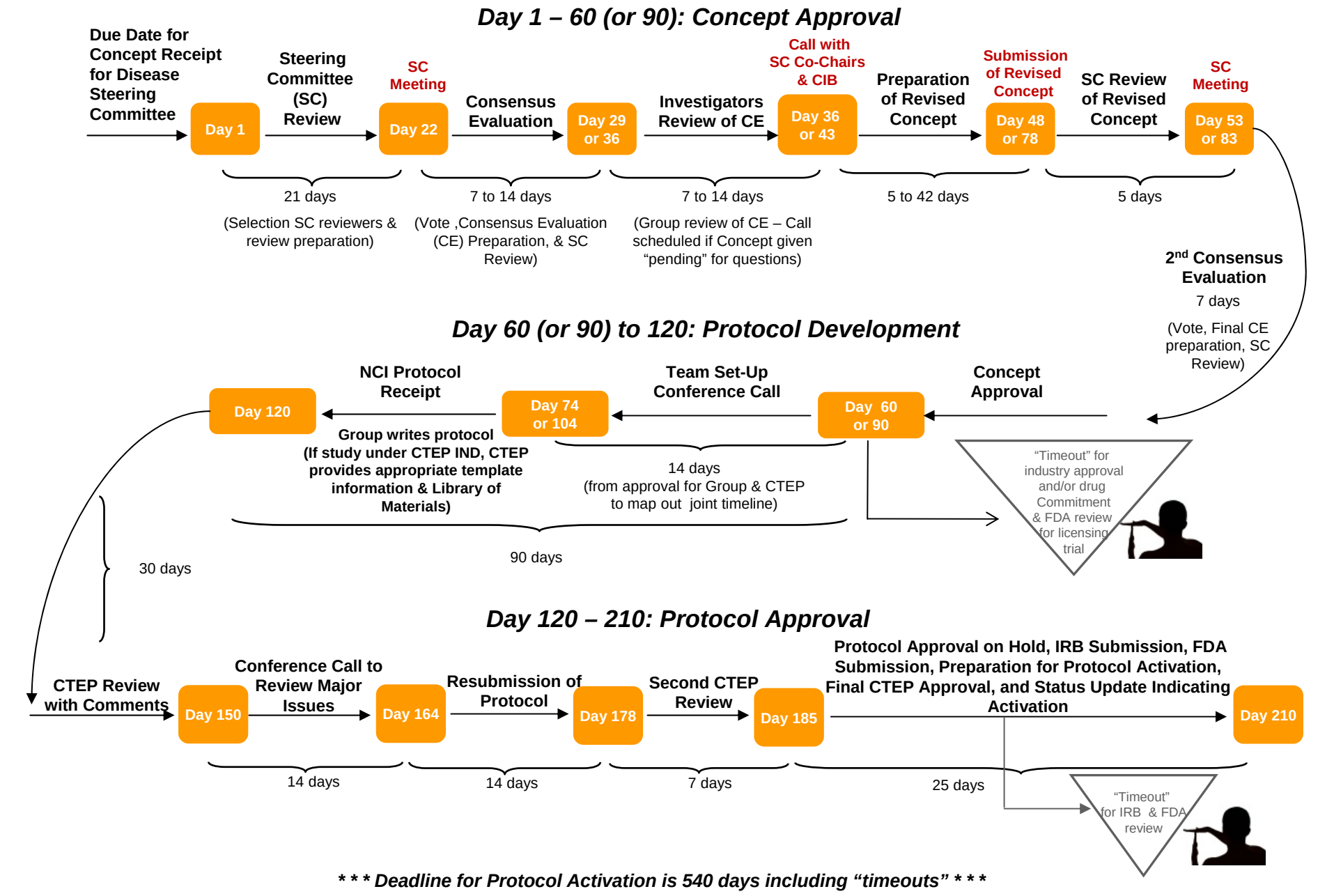
**** * * Deadline for Protocol Activation is 730 days including "timeouts" * * ****

Phase 3 Timeline – Steering Committee Evaluation

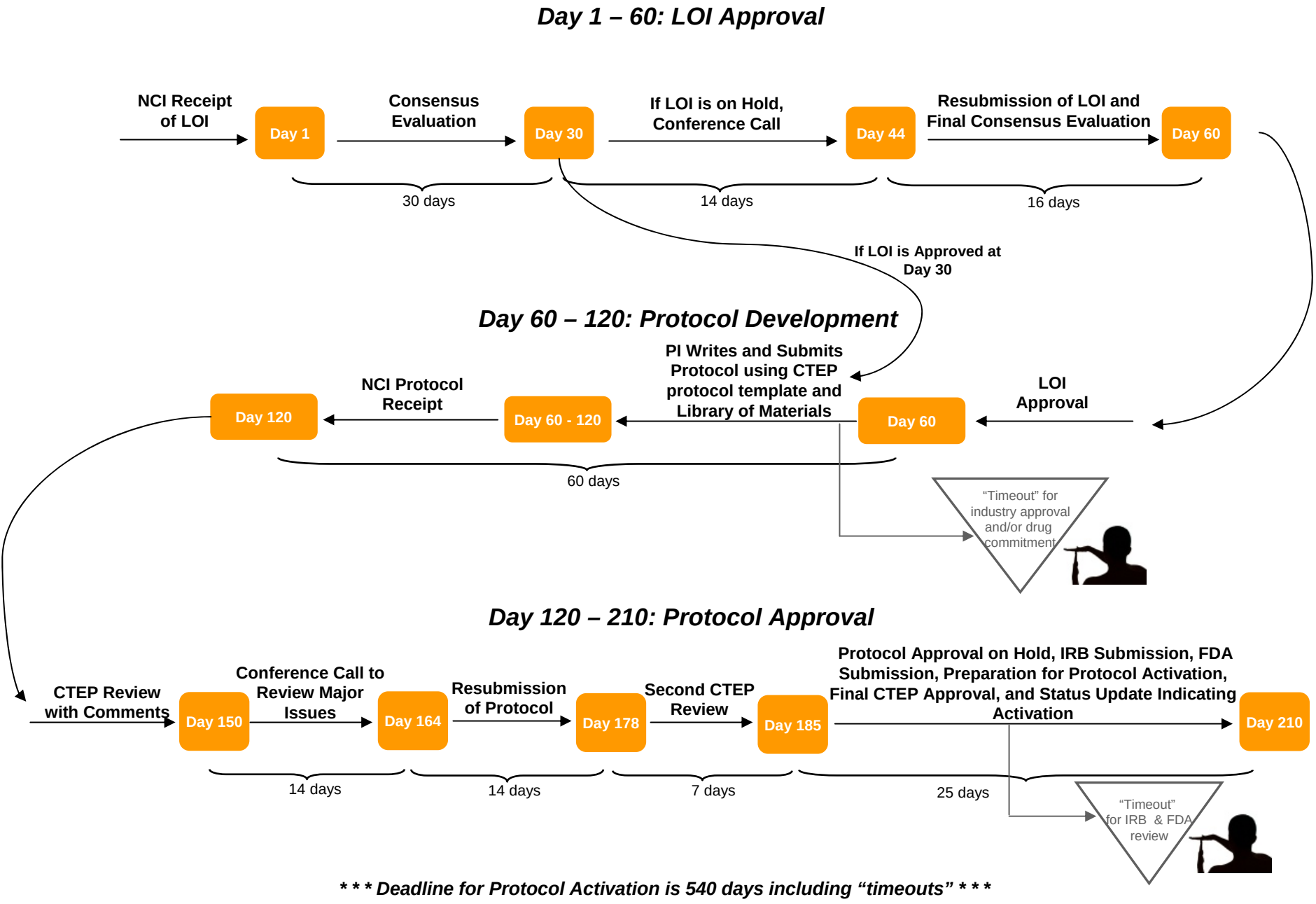


*** Deadline for Protocol Activation is 730 days including "timeouts" ***

Phase 2 Timeline – Steering Committee Evaluation

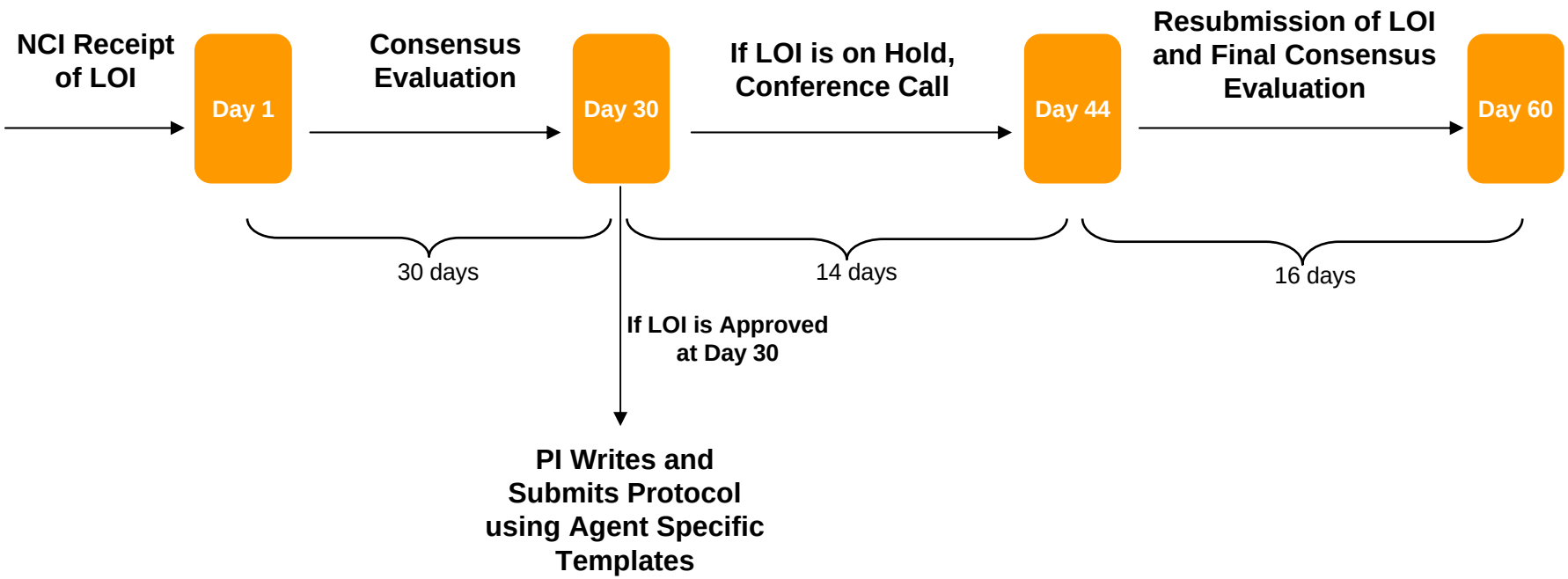


Phase 1/2 Timeline: Unsolicited LOI's



**** * * Deadline for Protocol Activation is 540 days including "timeouts" * * ****

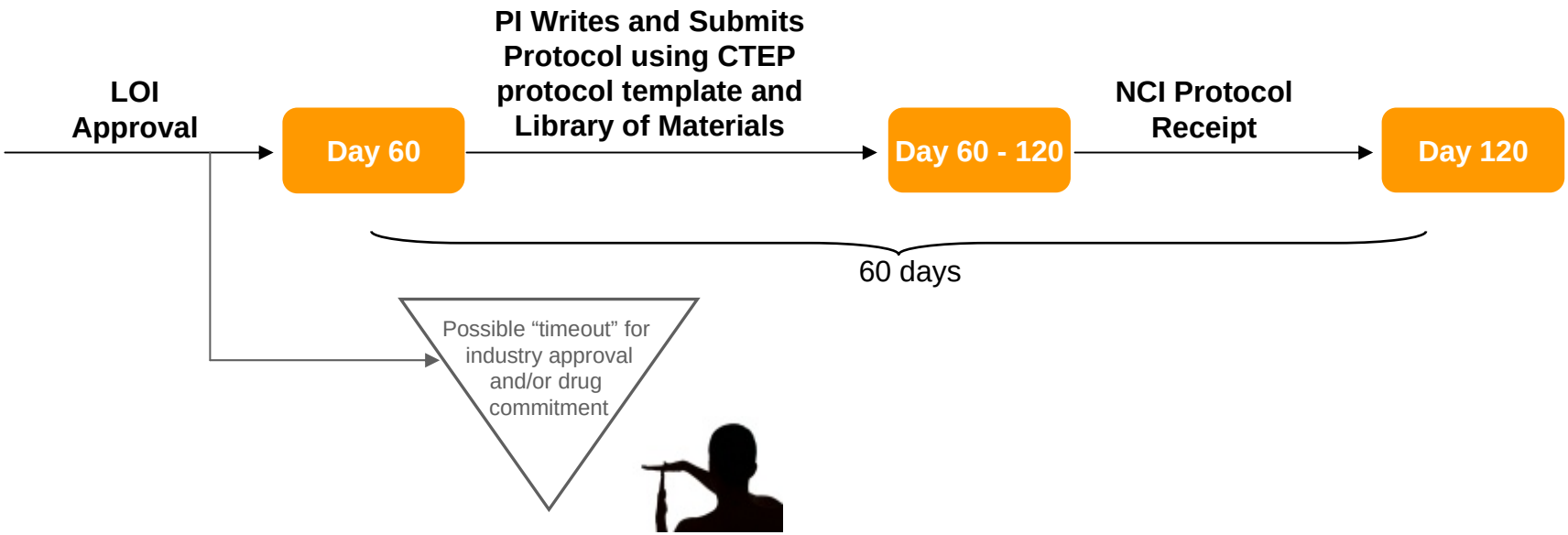
Day 1 – Day 60:
LOI Approval



Day 1 – Day 60:
LOI Approval

- Timeline begins on the receipt of the LOI by NCI
- If the LOI receives a pending approval, a conference call will be held within two weeks of the consensus review to discuss any issues and/or questions.
- The revised LOI must be submitted within 30 days to complete the revision process and gain approval.
- If the LOI is rejected, the PI has the right to request review of the decision through a rapid arbitration process.
- Once an LOI is approved, it is sent to the industry partner. The timeline is in “timeout” until the industry partner approves the LOI and commits a supply of the investigational agent.

Day 60 – 120:
Protocol Development



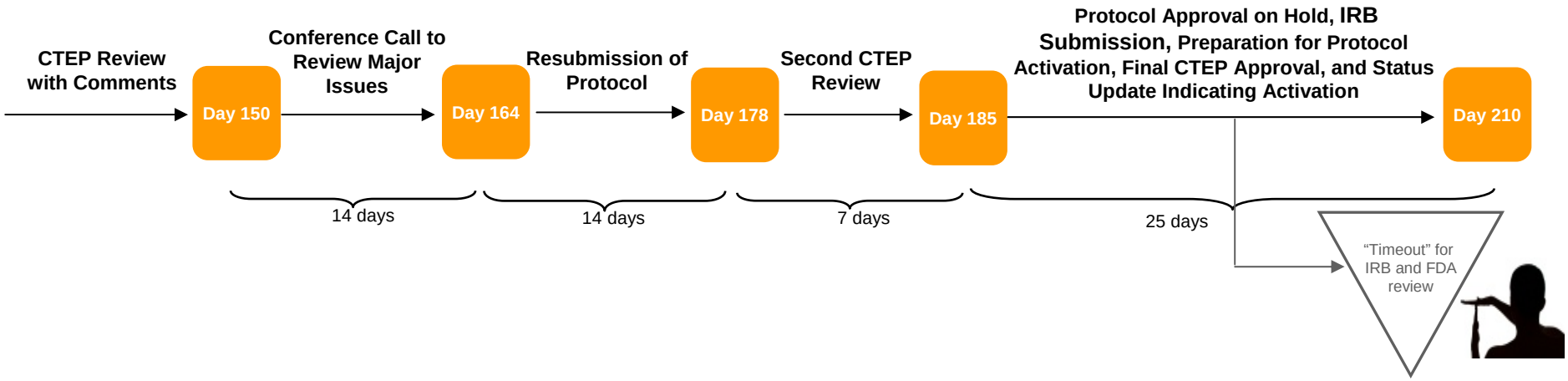
Day 60 – Day 120:
Protocol Development

- Once a LOI has approval, there is a “timeout” for industry review. The timeline restarts once industry approves LOI and commits supply of investigational agent.

- The PI should write the protocol using the protocol template and the CTEP library of materials as references.

- Protocols must be submitted to CTEP within 60 days of LOI approval (not including timeout for industry approval of LOI).

Day 120 – Day 210:
Protocol Approval



**** * * Deadline for Protocol Activation is 540 days including "timeouts" * * ****

Day 120 – Day 210:
Protocol Approval

- Within the first 30 days after protocol receipt, the protocol will be discussed at PRC, the Consensus Review will be compiled and the review sent to the PI.

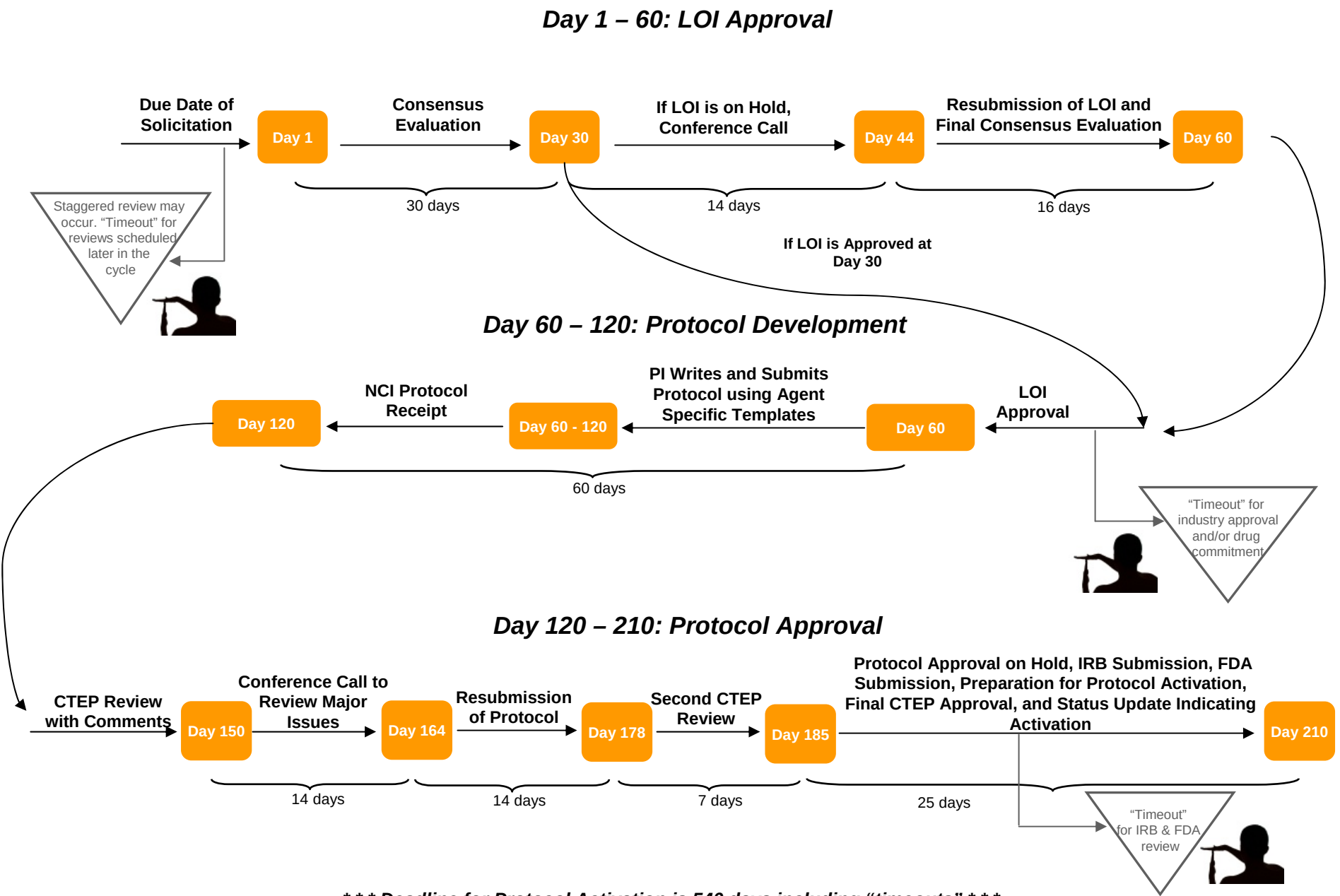
- If the status is pending, there will be a conference call held with CTEP and the PI to discuss any critical issues two weeks after the Consensus Review is sent.

- The PI has two weeks to resubmit the protocol, which will then be reviewed by CTEP the following week.

- Once the protocol is given a status of approval on-hold, the PI has 25 days to complete the IRB submission and other activation preparations. A "timeout" will be granted during this period for IRB approval.

- A protocol is activated once the status update of "open to enrollment" is received at CTEP.

Phase 1/2 Timeline: Mass Solicitation



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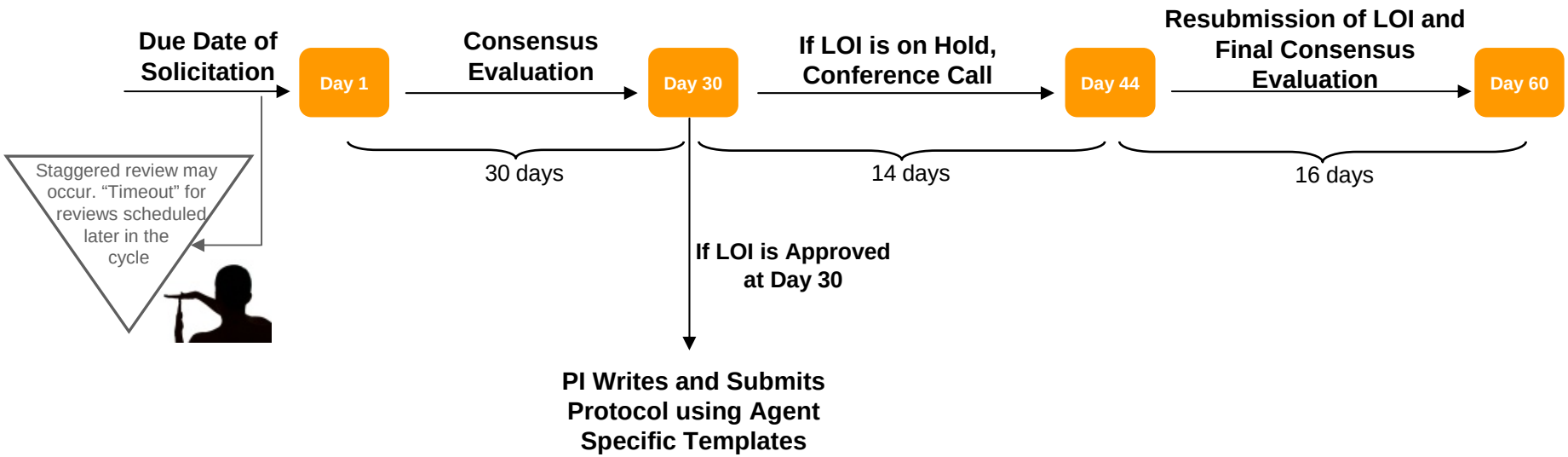
Day 1 – Day 60:
LOI Approval



Day 1 – Day 60:
LOI Approval

- Timeline begins on the due date of the solicitation.
- If a large number of LOI's are received, a staggered review will occur in groups of 20-30. For LOI's that are scheduled for review later in the cycle, the timeline will be in a scheduled "timeout."
- If the LOI receives a pending approval, a conference call will be held within two weeks of the consensus review to discuss any issues and/or questions.
- The revised LOI must be submitted within 30 days to complete the revision process and gain approval.
- If the LOI is rejected, the PI has the right to request review of the decision through a rapid arbitration process.
- Once an LOI is approved, it is sent to the industry partner. The timeline is in "timeout" until the industry partner approves the LOI and commits a supply of the investigational agent.

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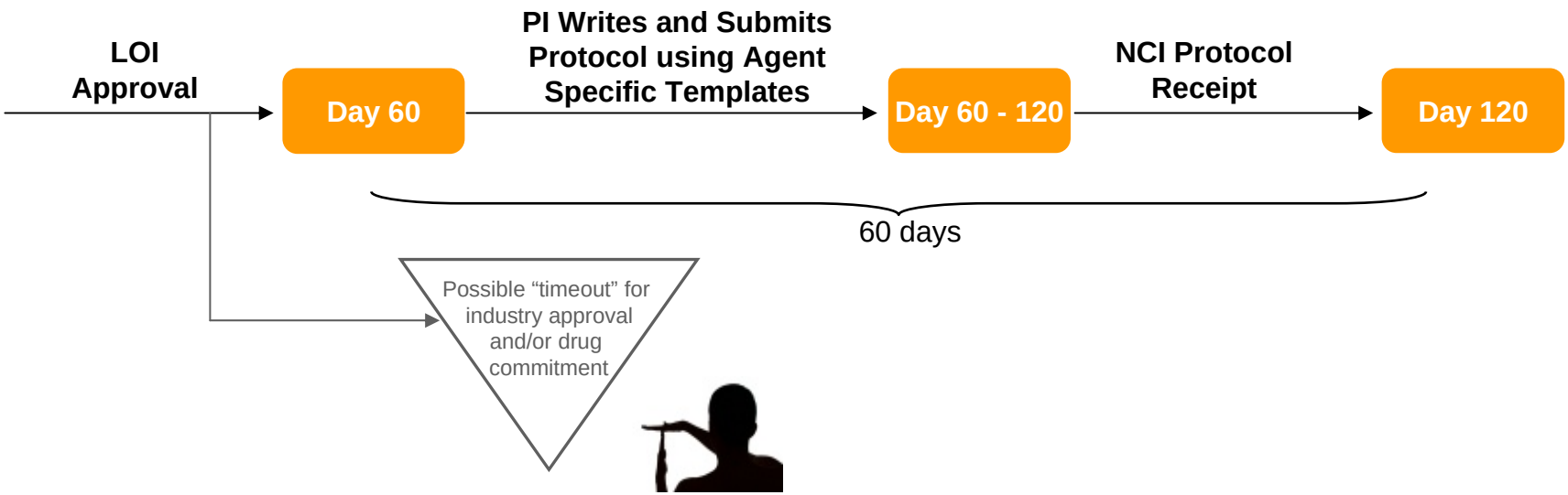
Protocol Development



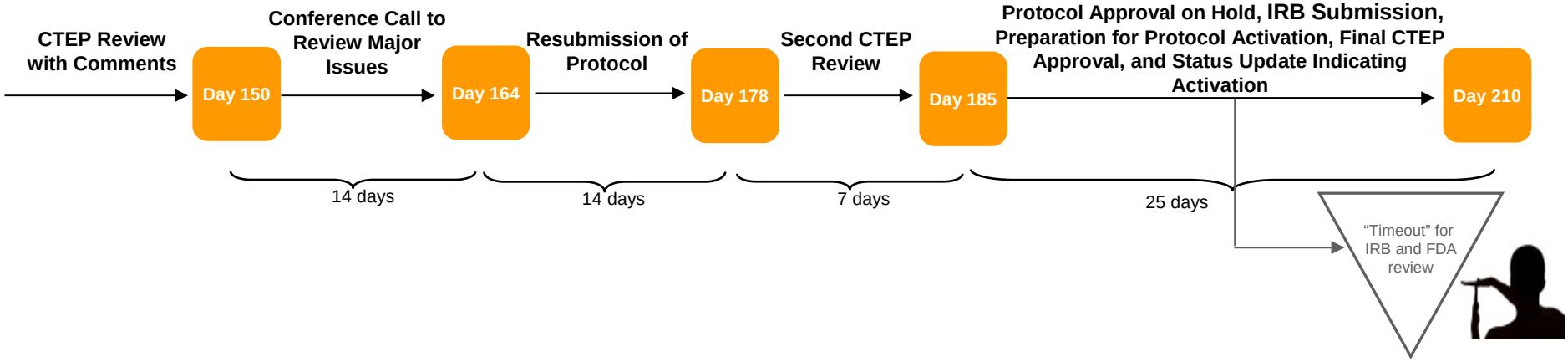
Day 60 – Day 120:
Protocol Development

- Once a LOI has approval, there is a “timeout” for industry review. The timeline restarts once industry approves LOI and commits supply of investigational agent.

- The PI should write the protocol using the agent specific templates provided by CTEP.

- Protocols must be submitted to CTEP within 60 days of LOI approval (not including timeout for industry approval of LOI).

Day 120 – Day 210:
Protocol Approval



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Day 120 – Day 210:
Protocol Approval

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- If the status is pending, there will be a conference call held with CTEP and the PI to discuss any critical issues two weeks after the Consensus Review is sent.

- The PI has two weeks to resubmit the protocol, which will then be reviewed by CTEP the following week.

- Once the protocol is given a status of approval on-hold, the PI has 25 days to complete the IRB submission and other activation preparations. A "timeout" will be granted during this period for IRB approval.

- A protocol is activated once the status update of "open to enrollment" is received at CTEP.