Operational Efficiency Working Group
Final Report

“Compressing the Timeline for Cancer Clinical Trial Activation”

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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
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
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
Cooperative Group Phase III Trials

- Current State
- OEWG Target Timeline
- Recommended Process Improvements
Time to Activation – Current State
Cooperative Group Phase III Trials (2006 – 2008)

Percentage of Trials

<table>
<thead>
<tr>
<th>Time to Activation</th>
<th>Median Days per Step</th>
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<tr>
<td>Less than one year</td>
<td>Protocol approval to trial activation</td>
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<tr>
<td>1-2 years</td>
<td>Protocol receipt to protocol approval</td>
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<tr>
<td>More than two years</td>
<td>Concept approval to protocol receipt</td>
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- 2% of trials took less than one year
- 40% of trials took 1-2 years
- 58% of trials took more than two years

Number of Revisions

<table>
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<th>Trials</th>
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<tr>
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OEWG Target Timeline – 300 days

- Concept review
- Concept revision/review cycles
- Protocol development
- Protocol review
- Protocol revision/review cycles
- Forms development

Timeline pauses if industry negotiations cause delay

Feedback on major challenges in 5 days

If registration trial, FDA review in 30 days

Timeline excludes IRB, contracting, drug supply

Protocol terminated if not activated in two years
Time to Trial Activation
Current vs OEWG Target

Current median time includes CIRB approval, industry negotiations, and FDA approval
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
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
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
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
IDB Early Drug Development Phase II Trials

• Current State

• OEWG Target Timeline

• Recommended Process Improvements
Time to Activation - Current State
N01 and Cooperative Groups (2006-2008)

Percentage of Trials

- Less than 1 year: 16%
- 1-2 years: 61%
- More than two years: 23%

Time to Activation

- Protocol approval to trial activation
- Protocol receipt to protocol approval
- LOI approval to protocol receipt
- LOI receipt to LOI approval

Median Days per Step

44
259
59
111
OEWG Target Timeline – 210 days

Timeline pauses if industry negotiations cause delay

- LOI review
- LOI revision/revision
- Protocol development
- Protocol review
- Protocol revision/review and forms development

Timeline excludes contracting, drug supply, IRB, FDA

Protocol terminated if not activated in 18 months
Time to Trial Activation

Current vs OEWG Target

Current median time includes IRB approval and industry negotiations

Current median time includes IRB approval and industry negotiations
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
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
Cancer Center Investigator Initiated Trials

- OEWG Target Timeline
- Recommended Process Improvements
OEWG Target Timeline – 90 days

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

Performance benchmark for trial activation = 180 days
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
**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
Process Improvements Applicable across Trial Categories

- Standardization of Tools and Templates
- Enhanced Biomarker Funding and Capabilities
- Cancer Center Trial Prioritization
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
**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**
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
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
Targets Aggressive But Necessary

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

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

- Cooperative Group Phase III trials: 830 days current median time vs. 300 days OEWG target
- Cancer Center Investigator-Initiated Trials: 200 days current median time vs. 90 days OEWG target
- CTEP Early Drug Development Phase II Trials (Cooperative Group and N01): 550 days current median time vs. 210 days OEWG target

National Cancer Institute
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
Phase 3 Timeline

**Day 1 – 90: Concept Approval**
- **Day 1**: Due Date for Concept Receipt for Disease Steering Committee
- **Day 2**: Steering Committee (SC) Meeting
- **Day 3**: SC Meeting
- **Day 36**: Investigators Review of CE
- **Day 50**: Call with SC Co-Chairs & CIB
- **Day 76**: Preparation of Revised Concept
- **Day 90**: SC Review of Revised Concept
- **Day 93**: SC Meeting
- **Day 99**: SC Meeting
- **Day 104**: Team Set-Up Conference Call
- **Day 180**: NCI Protocol Receipt
- **Day 254**: Protocol Approval

**Day 90 – 180: Protocol Development**
- **Day 180**: Group writes protocol (if study under CTEP IND, CTEP provides appropriate template information & Library of Materials)
- **Day 210**: CTEP Review with Comments
- **Day 224**: ONE REVIEW
- **Day 300**: Protocol Approval on Hold, IRB Submission, Preparation of Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation

**Day 180 – 300: Protocol Approval**
- **Day 210**: Conference Call Review Major Issues
- **Day 224**: Grp Resubmission & 2nd CTEP Review
- **Day 254**: ONE REVISION

**Possible “timeout” for IRB Review (or FDA review if under FDA SPA)**

**Deadline for Protocol Activation is 730 days including “timeouts”**
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
Launch OEWG Phase II addressing rate of accrual and time to trial completion
Thanks to:

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

Day 1
- NCI Receipt of Concept in Disease with No Existing Steering Committee

Day 36
- CTEP CRM Review with External Reviewers

Day 43
- CRM Meeting
- Consensus Evaluation

Day 50
- Investigators Review of CE

Day 76
- Call with CTEP (CIB, IDB)
- Preparation of Revised Concept

Day 83
- Submission of Revised Concept

Day 1 – 90: Concept Approval

Day 180
- NCI Protocol Receipt

Day 104
- Team Set-Up Conference Call

Day 90
- Concept Approval

Day 210
- CTEP Review with Comments

Day 224
- Conference Call to Review Major Issues
- Group Resubmission & 2nd CTEP Review

Day 254
- Protocol Approval on Hold, IRB Submission, Preparation of Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation

Day 300
- Possible “timeout” for IRB Review (or FDA review if under FDA SPA)

**Deadline for Protocol Activation is 730 days including “timeouts”**

Day 90 – 180: Protocol Development

Day 180
- Group writes protocol (If study under CTEP IND, CTEP provides appropriate template information & Library of Materials)

Day 104
- Team Set-Up Conference Call

Day 90
- Concept Approval

Day 210
- CTEP Review with Comments

Day 224
- Conference Call to Review Major Issues

Day 254
- Group Resubmission & 2nd CTEP Review

Day 300
- 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

**Day 1 – 90: Concept Approval**

- Day 1: Due Date for Concept Receipt for Disease Steering Committee
- Day 2: Steering Committee (SC) Review
  - 21 days
  - (Selection SC reviewers & review preparation)
- Day 22: SC Meeting
- Day 36: Consensus Evaluation
  - 14 days
  - (Vote, Consensus Evaluation (CE) Preparation, & SC Review)
- Day 50: Investigators Review of CE
  - 14 days
  - (Group review of CE – Call scheduled if Concept given “pending” for questions)
- Day 76: SC Review of Revised Concept
  - 26 days
- Day 83: SC Meeting

**Day 90 – 180: Protocol Development**

- Day 104: Call
  - 14 days
  - (from approval for Group & CTEP to map out joint timeline)
- Day 180: NCI Protocol Receipt
  - Group writes protocol
  - (If study under CTEP IND, CTEP provides appropriate template information & Library of Materials)

**Day 180 – 300: Protocol Approval**

- Day 210: CTEP Review with Comments
  - 14 days
- Day 224: Conference Call To Review Major Issues
  - 14 days
- Day 254: Group Resubmission & 2nd CTEP Review
  - 30 days
  - (Resubmission in 14 to 21 Days and CTEP review in 7-14 days)
- Day 300: Protocol Approval
  - 45 days
  - Possible “timeout” for IRB Review (or FDA review if under FDA SPA)

**2nd Consensus Evaluation**

(Vote, Final CE preparation, SC Review)

* * * Deadline for Protocol Activation is 730 days including “timeouts” * * *
Phase 2 Timeline – Steering Committee Evaluation

Day 1 – 60 (or 90): Concept Approval

Day 1
Due Date for Concept Receipt for Disease Steering Committee

Day 2
Steering Committee (SC) Review

Day 22
SC Meeting

Day 29 or 36
Consensus Evaluation

Day 36 or 43
Investigators Review of CE

Day 48 or 78
Preparation of Revised Concept

Day 53 or 83
Submission of Revised Concept

Day 60 (or 90) to 120: Protocol Development

Day 60 or 90
Concept Approval

Day 120
NCI Protocol Receipt

Day 124
SC Meeting

Day 126
Group writes protocol (If study under CTEP IND, CTEP provides appropriate template information & Library of Materials)

Day 150
Conference Call to Review Major Issues

Day 164
CTEP Review with Comments

Day 165
“Timeout” for industry approval and/or drug commitment & FDA review for licensing trial

Day 178
Second CTEP Review

Day 185
Resubmission of Protocol

Day 189
Second CTEP Review with Comments

Day 200
Protocol Approval on Hold, IRB Submission, FDA Submission, Preparation for Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation

Day 210
“Timeout” for IRB & FDA review

* * * Deadline for Protocol Activation is 540 days including “timeouts” * * *
Phase 1/2 Timeline: Unsolicited LOI’s

**Day 1 – 60: LOI Approval**

- NCI Receipt of LOI
- Consensus Evaluation
- If LOI is on Hold, Conference Call
- Resubmission of LOI and Final Consensus Evaluation

**Day 60 – 120: Protocol Development**

- Day 120
- NCI Protocol Receipt
- Day 60 - 120
- PI Writes and Submits Protocol using CTEP protocol template and Library of Materials
- LOI Approval

**Day 120 – 210: Protocol Approval**

- Day 150
- Conference Call to Review Major Issues
- Day 164
- Resubmission of Protocol
- Day 178
- Second CTEP Review
- Day 185
- Protocol Approval on Hold, IRB Submission, FDA Submission, Preparation for Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation

***Deadline for Protocol Activation is 540 days including “timeouts”***
Day 1 – Day 60: LOI Approval

- **Day 1**: NCI Receipt of LOI
- **Day 30**: Consensus Evaluation
- If LOI is on Hold, Conference Call
  - 14 days
- **Day 44**: Resubmission of LOI and Final Consensus Evaluation
  - 16 days
- If LOI is Approved at Day 30
  - PI Writes and Submits Protocol using Agent Specific Templates
  - 30 days

Day 60
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

- **LOI Approval**
- **Day 60**: PI Writes and Submits Protocol using CTEP protocol template and Library of Materials
- **Day 60 - 120**: Possible "timeout" for industry approval and/or drug commitment
- **Day 120**: NCI Protocol Receipt

60 days
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

**Day 1 – 60: LOI Approval**

- Day 1: Consensus Evaluation
- Day 30: If LOI is on Hold, Conference Call
- Day 44: Resubmission of LOI and Final Consensus Evaluation

**Day 60 – 120: Protocol Development**

- Day 120: NCI Protocol Receipt
- Day 60 - 120: PI Writes and Submits Protocol using Agent Specific Templates
- Day 60: LOI Approval

**Day 120 – 210: Protocol Approval**

- Day 150: Conference Call to Review Major Issues
- Day 164: Resubmission of Protocol
- Day 178: Second CTEP Review
- Day 185: Protocol Approval on Hold, IRB Submission, FDA Submission, Preparation for Protocol Activation, Final CTEP Approval, and Status Update Indicating Activation

**Deadline for Protocol Activation is 540 days including “timeouts”***
Day 1 – Day 60:
LOI Approval

Due Date of Solicitation

Day 1 – Consensus Evaluation

Day 30 – If LOI is on Hold, Conference Call

Day 44 – Resubmission of LOI and Final Consensus Evaluation

Staggered review may occur. "Timeout" for reviews scheduled later in the cycle.

If LOI is Approved at Day 30

PI Writes and Submits Protocol using Agent Specific Templates

30 days

14 days

16 days
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.
Day 60 – 120: Protocol Development

LOI Approval → Day 60

PI Writes and Submits Protocol using Agent Specific Templates → Day 60 - 120

NCI Protocol Receipt → Day 120

Possible "timeout" for industry approval and/or drug commitment

60 days
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

*** 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.