OEWG Timeline Analysis for CTEP Trials

Presentation to the Clinical Trials and Translational Research Advisory Committee

July 12, 2017
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
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
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

<table>
<thead>
<tr>
<th></th>
<th>Target 2010-2012</th>
<th>Absolute 2010-2012</th>
<th>Target 2012-Present</th>
<th>Absolute 2012-Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 and 2 LOIs</td>
<td>210 days</td>
<td>540 days</td>
<td>210 days</td>
<td>450 days</td>
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<tr>
<td>Phase 1/2 and 2 Concepts</td>
<td>240 days</td>
<td>540 days</td>
<td>210 days</td>
<td>450 days</td>
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<tr>
<td>Phase 3 Concepts</td>
<td>300 days</td>
<td>730 days</td>
<td>300 days</td>
<td>540 days</td>
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</table>
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

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Comparison Results
# Included Trials by Phase and Activation Time Period

<table>
<thead>
<tr>
<th></th>
<th>Pilot</th>
<th>I</th>
<th>I/II</th>
<th>II</th>
<th>II/III</th>
<th>III</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>July 2012 – June 2014</td>
<td>7</td>
<td>58</td>
<td>16</td>
<td>69</td>
<td>5</td>
<td>18</td>
<td>173</td>
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<tr>
<td>July 2014 – June 2017</td>
<td>5</td>
<td>57</td>
<td>9</td>
<td>91</td>
<td>9</td>
<td>28</td>
<td>199</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>12</strong></td>
<td><strong>115</strong></td>
<td><strong>25</strong></td>
<td><strong>160</strong></td>
<td><strong>14</strong></td>
<td><strong>46</strong></td>
<td><strong>372</strong></td>
</tr>
</tbody>
</table>
## Included Trials by Lead Org and Activation Time Period

<table>
<thead>
<tr>
<th></th>
<th>Group / NCTN</th>
<th>ETCTN / Related Program</th>
<th>Cancer Center / Institution</th>
<th>Clinical Center</th>
<th>Consortia / Other Network</th>
<th>Total</th>
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<tbody>
<tr>
<td>July 2012 – June 2014</td>
<td>74</td>
<td>4</td>
<td>59</td>
<td>12</td>
<td>24</td>
<td>173</td>
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<tr>
<td>July 2014 – June 2017</td>
<td>93</td>
<td>54</td>
<td>12</td>
<td>11</td>
<td>29</td>
<td>199</td>
</tr>
<tr>
<td>Total</td>
<td>167</td>
<td>58</td>
<td>71</td>
<td>23</td>
<td>53</td>
<td>372</td>
</tr>
</tbody>
</table>
Comparing Time to Activation Pre- and Post-OEWG Phase 2 Trials

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

Comparing Median Days Per Step Pre- and Post-OEWG Phase 3 Trials

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

Comparing Number of Revisions Pre- and Post-OEWG
Phase 3 Trials

Overall Results
July 2014 – June 2017
Median Days for OEWG Stage by Lead Organization Type and Phase Grouping, 2014-2017

- **Protocol Approval to Trial Activation**: 460.5 days (Cancer Center), 457 days (Clinical Center), 437.5 days (Consortia), 449.5 days (ETCTN), 440 days (NCTN - Early), 28 days (NCTN - Late)
- **Protocol Receipt to Protocol Approval**: 271 days (Cancer Center), 300 days (Clinical Center), 82.5 days (Consortia), 259.5 days (ETCTN), 188 days (NCTN - Early), 116.5 days (NCTN - Late)
- **LOI/Concept Approval to Protocol Receipt**: 108 days (Cancer Center), 92 days (Clinical Center), 73.5 days (Consortia), 61 days (ETCTN), 85 days (NCTN - Early), 75.5 days (NCTN - Late)
- **OEWG Start to LOI/Concept Approval**: 64 days (Cancer Center), 64 days (Clinical Center), 140.5 days (Consortia), 25 days (ETCTN), 25 days (NCTN - Early), 239.5 days (NCTN - Late)

**Median Total Days**: 532 days

N=198; omitting 1 consortia phase III trial
Box and Whisker Plot: Total Time to Activation by Lead Org Grouping, 2014-2017

N=198; omitting 1 consortia phase III trial
Percent of Original OEWG Deadline* for Trials by Lead Organization Type and Phase Grouping, 2014-2017

77% of trials (n=152) activate within original deadline
42% (n=84) take between 95% and 100% of allotted time

*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

Median Days Per Step:
- Protocol Approval to Trial Activation
- Protocol Receipt to Protocol Approval
- LOI Approval to Protocol Receipt
- OEWG Start to LOI Approval

Median Total Days:
- 430.5
- 441
- 448
- 467.5
- 453.5

Median Days:
- 1 to 2 (n=46): 80
- 3 (n=49): 143.5
- 4 (n=31): 73.5
- 5 (n=16): 76.5
- 6 or more (n=20): 74

- 3 (n=49): 217
- 4 (n=31): 249
- 5 (n=16): 324
- 6 or more (n=20): 332
- 3 (n=49): 67
- 4 (n=31): 62
- 5 (n=16): 68.5
- 6 or more (n=20): 62.5
- 4 (n=31): 11
- 5 (n=16): 99
- 6 or more (n=20): 74
- 3 (n=49): 1
- 4 (n=31): 3.5

MH: 24
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?