Activating & Opening Oncology Clinical Trials: A Process & Timing Study

David M. Dilts, PhD, MBA
Director & Professor, Engineering Management Program, School of Engineering
Professor, Owen Graduate School of Management
Co-Director, Center for Management Research in Healthcare (cMRHc.org)

Alan B. Sandler, MD
Associate Professor of Medicine, Division of Hematology/Oncology
Medical Director, Thoracic Oncology Program
Director, Vanderbilt-Ingram Cancer Center Affiliates Network
Co-Director, Center for Management Research in Healthcare (cMRHc.org)
Thank you to the study sites
Method

Part I: Process Mapping
• Extensive visits at each site to document processes, loops and decisions:
  • Say…..: What they say they do
  • Should: What policies and procedures say they should do
  • Do……: What study chart reviews show they actually do
• Creation of process map

Part II: Process Timing
• Identify calendar time for total process and major steps, and potential influencers of the time

Part III: Accrual Data
• Investigate actual accrual results of the studies

Detailed Process Maps

CCC-1

31.6 ft x 3.5 ft in 8pt font

CCC-2

37.1 ft x 3.5 ft in 8pt font
## Process Counts

### Comprehensive Cancer Centers

<table>
<thead>
<tr>
<th>Process Counts</th>
<th>CCC-1*</th>
<th>CCC-2</th>
<th>CCC-3</th>
<th>CCC-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Process Steps</td>
<td>117</td>
<td>374</td>
<td>345</td>
<td></td>
</tr>
<tr>
<td>Working Steps</td>
<td>64</td>
<td>292</td>
<td>272</td>
<td></td>
</tr>
<tr>
<td>Decision Points</td>
<td>53</td>
<td>61</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Processing Loops</td>
<td>-</td>
<td>31</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Stopping Points</td>
<td>19</td>
<td>21</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

### Process Steps by Type of Trial

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>CCC-1*</th>
<th>CCC-2</th>
<th>CCC-3</th>
<th>CCC-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator Initiated</td>
<td>-</td>
<td>180</td>
<td>234</td>
<td></td>
</tr>
<tr>
<td>NCI Initiated</td>
<td>-</td>
<td>131</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Cooperative Group Initiated</td>
<td>-</td>
<td>77</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Industry Initiated</td>
<td>-</td>
<td>144</td>
<td>169</td>
<td></td>
</tr>
</tbody>
</table>
## Activation & Opening Time

### Phase III Cooperative Group Trials

@ Cooperative Groups and Comprehensive Cancer Centers (CCC)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB</td>
<td>13</td>
<td>784</td>
<td>537</td>
<td>1130</td>
</tr>
<tr>
<td>ECOG</td>
<td>28</td>
<td>808</td>
<td>435</td>
<td>1604</td>
</tr>
<tr>
<td>CCC- 1</td>
<td>58</td>
<td>120</td>
<td>27</td>
<td>657</td>
</tr>
<tr>
<td>CCC- 2</td>
<td>3</td>
<td>252</td>
<td>139</td>
<td>315</td>
</tr>
<tr>
<td>CCC- 3</td>
<td>4</td>
<td>122</td>
<td>81</td>
<td>179</td>
</tr>
<tr>
<td>CCC- 4</td>
<td>178</td>
<td>116</td>
<td>21</td>
<td>836</td>
</tr>
</tbody>
</table>

**Notes:**
- Receipt by Group or AMC to activation or opening
- Time is calendar days, not work days
- These are lower bounds because only survivors were investigated
- Total time to open a study is the addition of Group time + CCC time
Days from Concept to Open
Investigator Initiated Trials (IIT)

<table>
<thead>
<tr>
<th>Comprehensive Cancer Center</th>
<th>n</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC-1</td>
<td>37</td>
<td>211</td>
<td>113</td>
<td>498</td>
</tr>
<tr>
<td>CCC-2</td>
<td>9</td>
<td>315</td>
<td>139</td>
<td>541</td>
</tr>
<tr>
<td>CCC-3</td>
<td>5</td>
<td>451</td>
<td>230</td>
<td>750</td>
</tr>
<tr>
<td>CCC-4</td>
<td>25</td>
<td>243</td>
<td>107</td>
<td>908</td>
</tr>
</tbody>
</table>
Total Processes to Open a Cooperative Group Study

Cooperative Group Processes

- Concept Development: 117 days
- Protocol Development: 447 days
- Protocol Review: 180 days
- IRB Completion: 100 days
- Grant Development: 90 days
- IRB Review: 7 days
- Informed Consent Development: 60 days
- Formal Budget Development: 90 days
- Final Contract Signing: 20 days
- Study Activation: 90 days

Median: 784 to 808 days*
Range: 435-1604 days

Comprehensive Cancer Center Processes

- LOI and Protocol Development (including Industry Sponsor review):
- Preliminary Budget Assessment:
- IRB Review:
- Regulatory Requirements:
- FDA Review:
- Formal Budget Development:
- Contracts Negotiations:
- Final Contract Signing:
- Study Activation:

Median: 116 to 252 days*
Range: 21-836 days

* Depending Upon Site, based on the Phase III trials studied
Example Of The Flow:

**E1301**

<table>
<thead>
<tr>
<th></th>
<th>Concept Review Days</th>
<th>Protocol Review Days</th>
<th>Total Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Chair</td>
<td>49</td>
<td>122</td>
<td>171</td>
</tr>
<tr>
<td>Cooperative Group</td>
<td>59</td>
<td>340</td>
<td>399</td>
</tr>
<tr>
<td>CTEP</td>
<td>98</td>
<td>184</td>
<td>282</td>
</tr>
<tr>
<td>CIRB</td>
<td>n/a</td>
<td>123</td>
<td>123</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>206</strong></td>
<td><strong>769</strong></td>
<td><strong>975</strong></td>
</tr>
</tbody>
</table>
Time From Concept Receipt toActivation

Phase III Therapeutic Studies activated through CTEP 1/2000 – 6/2007†

By year
# Actual Accrual Per Trial Ranges

**Comprehensive Cancer Centers**

<table>
<thead>
<tr>
<th>Accrual Per Trial</th>
<th>CCC-1</th>
<th>CCC-2</th>
<th>CCC-3</th>
<th>CCC-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20.6%</td>
<td>25.7%</td>
<td>27.7%</td>
<td>34.4%</td>
</tr>
<tr>
<td>1-4</td>
<td>33.0%</td>
<td>32.3%</td>
<td>30.3%</td>
<td>31.3%</td>
</tr>
<tr>
<td>5-10</td>
<td>19.3%</td>
<td>16.1%</td>
<td>22.7%</td>
<td>18.0%</td>
</tr>
<tr>
<td>11-15</td>
<td>11.0%</td>
<td>7.3%</td>
<td>8.4%</td>
<td>4.3%</td>
</tr>
<tr>
<td>16-20</td>
<td>3.7%</td>
<td>3.7%</td>
<td>3.4%</td>
<td>5.3%</td>
</tr>
<tr>
<td>&gt;20</td>
<td>12.4%</td>
<td>15.0%</td>
<td>7.6%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>
ECOG Phase III Accrual Performance

Phase III ECOG Studies Closed to Accrual (n=15*): Ratio of Actual Accruals vs. Expected Accrual

- All phase III studies activated and closed to accrual between 1/2000 – 7/2006
- Color Code:
  - red: studies taking greater than the median time to open
  - blue: studies taking less than the median time to open
  - gray: studies closed due to reasons other than poor accrual
Initial Quick-Fix Recommendations

• Immediately start collecting & analyzing data
• “Just Say No”
  • Eliminate “entitlement culture”
• Stop tweaking
  • “Two strikes and you’re out”
• Say what you mean & mean what you say
Simulation Results

* Simulation period defined over a period of 5 years (1825 Calendar Days)
* Note: Axes on the Timing Distribution Graphs are different
Initial **Long Term** Recommendations

- Start with a clean sheet of paper
- Develop and utilize standards
  - i.e., vary in critical scientific issues, not in administrative processes
- Use Focused Phase III Teams
Next Steps

- NCI intramural clinical trials program being studied
- CTAC Working Group forming
  - Results have been presented to Cancer Centers and Cooperative Groups
  - Collaboration and participation in the Working Group solicited
- Goal – cut clinical trial activation time in half