Accrual Quality Improvement Program (AQuIP) Update 2017

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Objectives

- The Problem of Clinical Trial Accrual
- About AQuIP
  - AQuIP Purpose, Objectives and Goals
  - AQuIP Components
- Summary Data
- Improving Accrual Rate Projections
- Lessons Learned
The Problem of Clinical Trial Accrual

• Impact of inadequate accrual rates
  • Scientific
  • Economic
  • Ethical
  • Public Health
• Complex interplay of multiple factors
  • Agent
  • Endpoint
  • Cohort
  • Design – eligibility, study burden
  • Unrealistic projections
Projected Recruitment Rates
Consortia 2003

Only 28% of trials (14 of 50) achieved more than 50% of projected accrual
Accrual Quality Improvement Program (AQuIP)

Careful planning
+ Continuous analytic monitoring
+ Evidence-based interventions

Achieve Accrual Projections
AQuIP Purpose and Objectives

• Purpose
  • A comprehensive multi-dimensional program designed to support, document, monitor, understand and improve clinical trial accrual activities in order to foster ethical and efficient conduct of early phase clinical chemoprevention research, proper stewardship of public funds and significant scientific progress.

• Objectives
  • Short-term – To collect unique data points for systematic analysis of accrual activities and effectors in real-time to enable continuous quality improvement
  • Long term -To apply lessons learned to design practicable clinical trials with realistic accrual projections
AQuIP Goals

• Enhanced accrual reports
• Collaborative Continuous Quality Improvement (CQI)
  • Monitor and improve early and often together
• Realistic recruitment rate projections by consensus
• Accrual zones for evaluation and early intervention
• Consortia Accrual Review and Enhancement (CARE) Team - Think Tank
• Develop model for accrual prediction with standardized metrics
Components of AQuIP

• Recruitment and Retention Adherence (RRA) Plan
• AQuIP Toolkit and Education
• Online Accrual Reporting System (OARS)

• Monthly AQuIP Zone Monitoring Report
• Think Tank
• DCP Helpdesk
Accrual Zones
Evaluate often & Improve Continuously

<table>
<thead>
<tr>
<th>Color</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green:</td>
<td>≥ 90%                         Celebrate and Share what worked</td>
</tr>
<tr>
<td>Amber:</td>
<td>&lt; 90% and ≥75%                Corrective action plan based on Accrual Report review</td>
</tr>
<tr>
<td>Yellow:</td>
<td>&lt;75%, but still &gt; Red Zone     Corrective action plan approval by leadership</td>
</tr>
<tr>
<td>Red:</td>
<td>&lt;25% at end of 1st quarter&lt;br&gt;&lt;25% at end of 2nd quarter&lt;br&gt;&lt;50% at end of 3rd quarter</td>
</tr>
</tbody>
</table>

Journaling
Tells the study story

Analyze impact of study specific and administrative events against accrual rates to show impact.
<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples of unexpected issues (Journal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staff issues</td>
<td>S.C. has too many studies, staff on vacation, morale</td>
</tr>
<tr>
<td>Logistics related to clinic</td>
<td>Scheduling, location</td>
</tr>
<tr>
<td>Competing studies</td>
<td>Same cohort, Name the study</td>
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<tr>
<td>Time of year</td>
<td>National or religious holidays, snowbirds issue, weather</td>
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<tr>
<td>Local events</td>
<td>Hospital, clinic promotion, educational event</td>
</tr>
<tr>
<td>Begin strategy/material</td>
<td>New brochure, mailing, new ad</td>
</tr>
<tr>
<td>Study on hold</td>
<td>FDA clinical hold, dose escalation/analysis</td>
</tr>
<tr>
<td>Event Categories</td>
<td>Examples of unexpected events (Journal)</td>
</tr>
<tr>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Study issues</td>
<td>Any amendment- eligibility; procedures</td>
</tr>
<tr>
<td></td>
<td>Misunderstood eligibility</td>
</tr>
<tr>
<td></td>
<td>Adding site</td>
</tr>
<tr>
<td></td>
<td>Main referring physician moves</td>
</tr>
<tr>
<td></td>
<td>Analysis capability</td>
</tr>
<tr>
<td></td>
<td>Drug publicity</td>
</tr>
<tr>
<td>P.O. sites issues</td>
<td>Delayed opening d/t subcontracts, Local IRB</td>
</tr>
<tr>
<td></td>
<td>Staffing change</td>
</tr>
<tr>
<td></td>
<td>Consent translation</td>
</tr>
<tr>
<td></td>
<td>Accrual limits per subcontract</td>
</tr>
<tr>
<td></td>
<td>Scheduling</td>
</tr>
<tr>
<td>PI issues</td>
<td>Change in PI, vacation, too busy, commitment</td>
</tr>
</tbody>
</table>
Interventions

• Broaden eligibility criteria
• Add accrual sites
• Staff education
• Sponsor – site communication
• Add strategies
• Check staff morale
• Get feedback from sites
AQuIIP summary data
## Participant Candidate Trajectory: Contacted/ Consented/ Started Study Agent

<table>
<thead>
<tr>
<th></th>
<th>May 2015</th>
<th>January 2017</th>
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<tbody>
<tr>
<td>Studies</td>
<td>12</td>
<td>22</td>
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<tr>
<td>Reports</td>
<td>87</td>
<td>281</td>
</tr>
<tr>
<td>Months per study</td>
<td>4-30</td>
<td>1-32</td>
</tr>
<tr>
<td>Participants contacted</td>
<td>2892</td>
<td>4368</td>
</tr>
<tr>
<td>Consented participants</td>
<td>631</td>
<td>3075</td>
</tr>
<tr>
<td>Started study agent</td>
<td>391</td>
<td>863</td>
</tr>
</tbody>
</table>

### Bar Graphs

**May-15**
- Studies: 12
- Participants contacted: 2892
- Consented participants: 631
- Started study agent: 391

**Jan-17**
- Studies: 22
- Participants contacted: 4368
- Consented participants: 3075
- Started study agent: 863

7/5/2017
## Contacted: Started Agent (Mean 6:1)

<table>
<thead>
<tr>
<th>Study</th>
<th>Contacted</th>
<th>Started Agent</th>
<th>Ratio</th>
<th>Study</th>
<th>Contacted</th>
<th>Started Agent</th>
<th>Ratio</th>
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<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>24</td>
<td>2</td>
<td>13</td>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>249</td>
<td>95</td>
<td>2.5</td>
<td>14</td>
<td>11</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>5</td>
<td>4</td>
<td>15</td>
<td>1282</td>
<td>53</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>9</td>
<td>5</td>
<td>16</td>
<td>138</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>627</td>
<td>58</td>
<td>10</td>
<td>17</td>
<td>130</td>
<td>97</td>
<td>1.3</td>
</tr>
<tr>
<td>6</td>
<td>213</td>
<td>93</td>
<td>2</td>
<td>18</td>
<td>149</td>
<td>146</td>
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<td>7</td>
<td>327</td>
<td>74</td>
<td>4.5</td>
<td>19</td>
<td>27</td>
<td>17</td>
<td>1.5</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>6</td>
<td>33</td>
<td>20</td>
<td>122</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>0</td>
<td>N/A</td>
<td>21</td>
<td>264</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>0</td>
<td>N/A</td>
<td>22</td>
<td>190</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>11</td>
<td>216</td>
<td>44</td>
<td>4</td>
<td>23</td>
<td>21</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>8</td>
<td>7</td>
<td>24</td>
<td>27</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
## Recruitment Strategies Categories

Select all that apply.

- Protocol Staff Recruitment
- Existing Database
- U.S. Postal Service Email
- Telephone Calls
- Referral
- Non-Digital Mass Media
- Digital Media
- Community Contacts
- Patient Issues/Concerns
- Other
## Recruitment strategies

<table>
<thead>
<tr>
<th>Newspaper Advertisement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic Schedules</td>
</tr>
<tr>
<td>PI</td>
</tr>
<tr>
<td>Site Coordinator</td>
</tr>
<tr>
<td>Recruitment designee</td>
</tr>
<tr>
<td>Brochure</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Co-PI</td>
</tr>
<tr>
<td>Patient registries</td>
</tr>
<tr>
<td>Script calls</td>
</tr>
<tr>
<td>Research Nurse</td>
</tr>
<tr>
<td>Path Report</td>
</tr>
<tr>
<td>Craig’s List</td>
</tr>
<tr>
<td>Flyer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Newsletter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Another study participant</td>
</tr>
<tr>
<td>Mailing list</td>
</tr>
<tr>
<td>TV ad</td>
</tr>
<tr>
<td>Returned Call</td>
</tr>
<tr>
<td>Other dept. referral</td>
</tr>
<tr>
<td>O.R. schedules</td>
</tr>
<tr>
<td>CT.gov</td>
</tr>
<tr>
<td>Study Website</td>
</tr>
<tr>
<td>Radio Ad</td>
</tr>
<tr>
<td>Institutional Website</td>
</tr>
<tr>
<td>Site website</td>
</tr>
<tr>
<td>FB</td>
</tr>
</tbody>
</table>
Recruitment Strategies for Participants Contacted

- F1 - Newspaper Advertisement: 1045
- B2 - Clinic Schedules: 1026
- A1 - Principal Investigator (specify name in comments): 608
- A4 - Site Coordinator (specify name in comments): 575
- A3 - Recruitment Designee (specify name in comments): 323
- F4 - Brochure: 303
- J1 - Other (please specify in comments): 244
- A2 - Co-Principal Investigator (specify name in comments): 190
- B1 - Participant Registries: 161
- D2 - Script Call: 135
- A5 - Research Nurse (specify name in comments): 131
- B4 - Pathology Reports: 106
- G4 - Craig’s List: 101
- F5 - Flyer: 69
- C4 - Newsletter: 64
- E3 - Another Study Participant: 54
- C3 - Mailing List: 49
- F2 - TV Advertisement: 47
Tracking recruitment strategies helps identify both effective and ineffective approaches.
Recruitment Strategies Of Participants On Intervention

- Protocol Staff: 51%
- Existing Database: 19%
- Advertisement: 13%
- Telephone: 8%
- Social Media/Web: 1%
- Referral: 3%
- Other: 3%
- Mail: 2%
Reason Consent NOT Signed or Study Intervention NOT Started Categories

Select all that apply.

- ELIGIBILITY CRITERIA NOT MET
- LOGISTICS
- STUDY RELATED ISSUES
- PARTICIPANT ATTITUDE AND CONCERN
- Other
Detailed breakdown of Reasons Not.

- Eligibility-related reasons are the most common.
“Reasons Not” For Those Participants Contacted But Not Consented

- Eligibility: 59%
- Other: 29%
- Study Design: 5%
- Participant Attitude/Concern: 2%
- Logistics: 5%
Reasons Not Contacted Participants Not Consented or Not Starting Study Agent

- Eligibility, 1898 (56.3%)
- Study Design, 179 (5.3%)
- Participant Attitude/Concern, 98 (2.9%)
- Other, 964 (28.6%)
- Logistics, 231 (6.9%)
Age Breakdown for Participants on Study Intervention

- 9-21 yrs: 19%
- 22-50 yrs: 14%
- 51-65 yrs: 41%
- 66+ yrs: 26%
More Sites Doesn’t Necessarily Mean Better Accrual

The best accruing studies fall within the 2-4 site range.
73% of trials (15 of 21) achieved greater than 50% of projected accrual.
AQuIP - Accrual Quality Improvement Program
AQuIP Data to Inform Protocol Design and Recruitment Planning
Study Characteristics that Affect Accrual

- Cancer risk of cohort
- Agent
- Route
- Duration (months)
- Frequency
- Toxicity
- Solid vs Hollow organ

- Study Design
  - Strict eligibility criteria
  - Common med excluded
  - Randomized
  - Placebo
  - # visits
  - Non-SOC invasive procedures
  - Pre-surgical window
  - Pharmacokinetics
### Study Factor Score Table

<table>
<thead>
<tr>
<th>Score →</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factor↓</strong></td>
<td>Cohort - cancer risk</td>
<td>Lifestyle</td>
<td>IEN low-grade non-dysplastic; HCV non-cirrhotic</td>
<td>Ulcerative colitis; dysplasia; pre-renal transplant</td>
<td>Inherited genetic; Transplant scheduled cirrhotic</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td>IM/ EP</td>
<td>Inhal</td>
<td>Oral</td>
<td>Topical</td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>&gt; 6</td>
<td>&gt;3 to &lt;6</td>
<td>&gt;1 to &lt;3</td>
<td></td>
<td>&lt; 1</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td>&gt; QD</td>
<td></td>
<td></td>
<td>QD</td>
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<tr>
<td><strong>Toxicity</strong></td>
<td>Cytotoxic or targeted</td>
<td>Investigational or hormonal</td>
<td>RX needed (not cytotox, vaccine)</td>
<td>Approved vaccine</td>
<td>OTC</td>
</tr>
<tr>
<td><strong>Common med</strong></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td>No</td>
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<tr>
<td><strong>Pharmacokinetics</strong></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Randomized</strong></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
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<tr>
<td><strong>Placebo</strong></td>
<td>yes</td>
<td>yes</td>
<td></td>
<td>no</td>
<td></td>
</tr>
<tr>
<td><strong># visits</strong></td>
<td>&gt; 9</td>
<td>&gt; 6 to &lt; 9</td>
<td>&gt;3 to &lt;6</td>
<td>2 or 3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Non-SOC invasive procedures</strong></td>
<td>Solid organ biopsy</td>
<td>Bronchoscopy</td>
<td>GI scope; Oral biopsy</td>
<td>Optional or none</td>
<td></td>
</tr>
<tr>
<td><strong># of eligibility criteria</strong></td>
<td>31-35</td>
<td>26-30</td>
<td>21-25</td>
<td>13-20</td>
<td></td>
</tr>
<tr>
<td><strong>Pre-surgical window</strong></td>
<td>Yes</td>
<td></td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Study Characteristics Scores Affect Accrual
Protocol A uses a toxic intervention targeting a high-risk population. We’ve collected a few other attributes of this study in the slider bars below. Our model predicts that the study will meet 40% of its projected monthly accrual.
To improve accrual, we try lowering the number of visits and the agent duration. However, our model predicts only a slight improvement from these changes, as these characteristics tend to have only a small impact on accrual.
In this last example, we make slight adjustments to the eligibility limitations and agent frequency. These factors have a larger impact on accrual, and improve our predicted accrual to 90%.
Lessons Learned

Prediction is very hard, especially about the future - Yogi Berra

• Stuff happens
• Accrual rates vary throughout the course of the study depending on number of sites open, slower starts
• More sites planned can throw off the projection if sites are delayed in opening
• Factor in planned accrual “holds” in recruitment plans and projections
• Beware of strict eligibility criteria
• Interaction of factors – one factor can cancel out the effects of another
• Consider:
  • Physician champion
  • Workload/staffing
  • Patient registries
  • Experience of staff
  • Fatal flaws
• Getting your help with the AQuIP Feasibility Index
Thank you

- AQuiP Operations Team
- Anne Ryan
- Maggie House
- Liz Walsh
- Jeffry Liu
- Daniel Molina
- Christina Russo

- Eva Szabo
- Leslie Ford
- DCP GI and Other Cancers Research Group
- DCP Consortium Program Staff

- DCP Consortium Investigators and Staff
QUESTIONS? Comments?
Factor: Accrual Association Slides
Agent Duration Score

Average Rate Metric vs. Agent Duration Score

End note:
Study Characteristics 3-2-17
Method:
(check number)
Agent Route Score

Average Rate Metric vs. Agent route score
Randomized Score

Average Rate Metric vs. Randomized score

Randomized score
Clinic Visit Score

Average Rate Metric vs. Clinic visit score

Clinic visit score
Type of Invasive Procedure Score

Average Rate Metric vs. type of invasive procedure score

Average Rate Metric

type of invasive procedure score
Pre-surgical Window Score

Average Rate Metric vs. Pre-surgical window score

Pre-surgical window score

Average Rate Metric

1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Common Drug Excluded Score

Average Rate Metric vs. Common drug excluded score

Common drug excluded score

Average Rate Metric

0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
2.2

1
2
3
4
5