Optimizing Site Start-Up in Oncology Trials:

Practical and Creative Strategies to Improve Cycle Time, Control Cost, and Maintain Quality

Alicia Keenan Williams
Sr. Project Manager

MedSource provides support for complex clinical trials. Whether a challenging therapeutic area or a sophisticated trial design, our highly experienced team excels at delivering results.
Focus on Site Start-up
“First Patient-In” Cycle Time by Therapeutic Area

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Average N</th>
<th>Pre-Visit to Contract/Budget Sent to Site</th>
<th>Contract Execution to Site Initiation</th>
<th>Contract/ Budget Sent to Site to Contract Execution</th>
<th>Site Initiation to First Patient in</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>335</td>
<td>4.3</td>
<td>3.6</td>
<td>1.3</td>
<td>3.5+</td>
</tr>
<tr>
<td>CNS/Neuroscience</td>
<td>652</td>
<td>3.5</td>
<td>3.9</td>
<td>2.2*</td>
<td>2.6+</td>
</tr>
<tr>
<td>Metabolics/Endocrine</td>
<td>234</td>
<td>3.6</td>
<td>0.8+</td>
<td>1.8</td>
<td>2.1</td>
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<tr>
<td>Infectious Disease</td>
<td>219</td>
<td>1.4+</td>
<td>2.6</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Phase II/III/IV Benchmark</td>
<td>1777</td>
<td>3.0</td>
<td>3.2</td>
<td>1.8</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Statistically significant, p ≤ 0.05
Top SSU Challenges

- **Delayed Schedule**
  - ~45 - 70% of trials experience study start-up delays
  - 2017 Tufts CSDD Benchmarking
    - SSU cycle time has increased, not decreased, over the past 10 years (by 1 full month)
  - Oncology site start-up (selection to activation): ranges from 3 - 12+ months, depending on type of site
  - Prolonged site start-up directly increases enrollment cycle time, decreasing number of months enrolling at target rate
  - Oncology trials typically exceed projected enrollment timeline by 71% (Tufts CSDD 2012)

- **Increased Costs**
  - JAMA Intern Med. 2017;177(11)
    - Median out of pocket cost to develop new cancer drug: $648mil (range, $157.3mil - $1.9bil)
    - Median time for cancer drug development: 7.3 years (range, 5.8-15.2yrs).
  - Median ~$250,000 direct costs per day of delay

- **Quality Risks**
  - Site start-up generates ~40% of the artifacts filed in the TMF
The Growing Complexities of Oncology Trials

Increasing protocol complexities and new paradigms in Oncology treatment, i.e. targeted therapies and Immuno-Oncology, have lead to:

- Lengthened scientific and regulatory reviews
- Additional Ex-US complications
  - GMOs highly regulated
- Additional budget/contract considerations
- Larger site study teams
- Increased volume of essential documents
- Additional training components
- New logistical challenges

**Increasing Protocol Complexity**

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scientific</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of Endpoints</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Total Number of Procedures</td>
<td>106</td>
<td>167</td>
</tr>
<tr>
<td>Proportion of Procedures that are ‘Non Core’</td>
<td>18%</td>
<td>31%</td>
</tr>
<tr>
<td><strong>Total Number of Eligibility Criteria</strong></td>
<td>31</td>
<td>50</td>
</tr>
<tr>
<td><strong>Operating</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of Countries</td>
<td>11</td>
<td>34</td>
</tr>
<tr>
<td>Total Number of Investigative sites</td>
<td>124</td>
<td>196</td>
</tr>
</tbody>
</table>
Best Practices that Lead to Success

• Leverage cost-efficient technology to facilitate real-time information sharing and transparency between stakeholders
  – Provides visibility to SSU KPIs and KRI
  – Includes detailed tracking of SSU milestones by sites
  – Supports proper sponsor oversight of outsourced projects
  – Prevents inefficiencies from duplication of tasks
  – Movement from organizational silos to ‘One Team’ approach

• Embrace trial planning and preparation
  – Movement from reactive to proactive approaches
  – ‘Quality by Design’ and inspection readiness
  – Development of clear and concise protocols to avoid amendments during site start-up
  – Projection of realistic goals (incorporate site activation projections into enrollment cycle time)

• Implement practical strategies to streamline each site’s critical path to activation
Information Sharing and Transparency
Improving Methods Through Technology

• Ongoing healthcare data analytics revolution
  – From paper-based to electronic processes
  – From single-point solutions to shared and cloud-based systems

• Automating clinical trials
  – EDC, IWRS, eTMF, CTMS, numerous cloud-based solutions

• Yet SSU cycle times have not improved and there’s little evidence of improved collaboration
  – Systems function in silos
  – Sites complain of technology overload, multiple logins
  – Complications and bottlenecks still exist, just now in a digital format

• The future
  – Block Chain
  – Collaborative integration, standardization, and knowledge sharing initiatives are underway
    (TransCelerate, etc.)
Visibility to Well Defined KPIs

- Projected vs. Actual Activations
- % Activations Complete
- Average Cycle Times:
  - Selection to Regulatory Pack Sent
  - Selection to CTA Templates Sent
  - CTA Templates sent to Full Execution
  - ICF Review
  - Section to Activation
- % Regulatory Submission Deadline Missed
# Detailed Site Start-up Tracking

<table>
<thead>
<tr>
<th>Site No.</th>
<th>PI Last Name</th>
<th>Site Selected</th>
<th>Reg Pack Sent to Site</th>
<th>Essential Document Collection Complete</th>
<th>Debarment Check</th>
<th>ICF Template Changed</th>
<th>ICF Template Finalized</th>
<th>SRC Submission</th>
<th>SRC Meeting</th>
<th>SRC Approval</th>
<th>IRB Submission</th>
<th>IRB Meeting</th>
<th>IRB Approval</th>
<th>IP Authorization</th>
<th>Contract Fully Executed</th>
<th>Site Binders Received</th>
<th>IP Received</th>
<th>Lab Kits Received</th>
<th>EDC Access</th>
<th>SIV Date</th>
</tr>
</thead>
</table>

**Date:** 1Mar2017
Case Study

• A familiar scenario: A small biotech with a promising drug candidate, high expectations, demanding timeline, and no experience with their product in the indication
  – Phase 1/2 Bladder Cancer study
  – Immuno-Oncology cancer vaccine requiring IBC review
  – Logistical complexities in start-up such as inspection of each site’s liquid nitrogen storage capabilities
  – Training for cryopreserved IP shipments
• Site activation cycle time prior to proper tracking/measuring of site and study level milestones and metrics:
  – Average 6.8 months
• MedSource SSU team assigned and site start-up measures implemented. Site activation cycle time reduced to:
  – Average 5.0 months
Trial Planning and Preparation
Building Efficiencies with Core Documents

- **Protocol**
  - Include time for key physician review from each country and operational review by a Project Manager and key site nurses/coordinators
  - Thoroughly vet eligibility criteria and be as specific as possible
  - Use clear and concise language to avoid lengthy Q&A during regulatory reviews
- **Subject-facing documents and tools**
- **Site Study Manuals/Binders (Lab, Imaging, Operations, IP), DMC Charter, Investigational Product SDS**
- **Regulatory pack templates**
  - Pre-populate with study-specific and site-specific information, where available
  - Provide the site a Regulatory Document Checklist (guidelines and requirements for all documents. i.e. name on 1572 must match medical license)
  - Avoid requirement for wet ink documents (not required by regulations or GCP)
- **Local IBC submission pack (as required)**
  - NIH OBA/RAC submission (Appendix M)
  - RAC outcome notification
  - NIH Reporting Delegation Letter template
CTA Template Development

- **Budget Template**
  - Include time for both a clinical and operations reviewer by local country experts
  - Customize by country and/or geographical region since FMV and SOC varies
  - Include standard fees, pass-throughs and overhead (Start-up, pharmacy set-up, professional, IRB/IBC, screen failures, record retention)

- **Contract Template**
  - Focus on the clauses that matter. Consider using TransCelerate’s CLEAR (common language evaluation and reconciliation) language for:
    - Confidentiality, Indemnification, Intellectual Property, Publication Rights, Subject Injury

- **Create site-specific budget and contract templates by referring to previously negotiated contracts with that site**
Operational Study Plans

- Project Plan
  - Roles and responsibilities in SSU

- Study Start-Up Plan
  - Country/region timelines and processes
  - ICF review process
  - IP release process

- Site Contracts Plan
  - CTA Playbook (negotiation parameters)
  - Country-specific considerations, i.e. ancillary agreements

- Communication Plan
  - SSU reports: define source, frequency of delivery, and content
  - Routine meetings: define attendance, frequency, and structure
  - Path of escalation at all stakeholders
Site Selection Planning

• Use of community based/private practice sites
  – May help achieve FPI by a target date
• Use of central IRB sites
  – Vet timeline of institutional IRB waivers that really provide no time benefit
• Use of SMOs (faster start-up, 6-12 weeks, but higher cost)
• Use the same sites, where possible, and transfer/replicate all knowledge and information
• Bundle central IRB with central IBC services, where applicable
  – Provider may be able to provide site list for fast-track IBC approval
Practical Strategies and Process Optimization
General Site Management Strategies

• Customize site management approach by site. Flexibility is key.
• Provide the site a single point of contact for regulatory and CTA negotiation if possible
• Utilize a tier system to prioritize sites for activation
• Utilize a regulatory review FAQ Log
• Limit correspondence. Be clear, concise, accurate, and intentional (use email templates for milestone communications)
• Ensure site is properly communicating internally and facilitate that if necessary, i.e. prompting ancillary departments reviews (pharmacy, radiology, lab, finance)
• In a prolonged site start-up, be mindful of study enrollment status and whether opening additional sites continues to make sense
Leveraging the Feasibility Survey

Use the feasibility survey as a launch pad for site start-up by collecting:

- Type of site and legal contracting entity
- Number of site locations and number of IP-dispensing locations
- Key site contacts (clinical, regulatory, contract, budget, etc.)
- Study supplies and IP shipment address
- IP traceability procedures and documentation
- Site’s experience with study systems
- Site-specific process and timeline for essential document collection, regulatory review(s), and CTA negotiation
  - Type of IRB/IBC, other committee/department review (sequential or parallel review)
  - Committee meeting schedules/calendar and submission deadlines
  - Timing for release of Approval Letter(s) and other administrative steps leading to internal activation
  - Use of wet-ink or e-signature and proper Part 11 compliance documentation
  - Ability to use sponsor’s CTA templates and/or if MSA is in place
  - Ability to begin start-up tasks immediately
  - Ability to conduct SIV prior to being activation-ready
The Site Kick-Off Call

• An introductory teleconference is critical
  – Sets the tone for the sponsor-site relationship
  – Sets expectation for accuracy, timeliness, and accountability
  – Results in site-specific, realistic critical path to activation, including a projected SIV date
  – Garners site buy-in and ownership of their start-up process

• Prior to the meeting
  – Review the feasibility survey, noting discrepancies or gaps in information.

• During the meeting
  – Outline the purpose and goal of the meeting
  – Express understanding of variables outside of site control
  – Discuss the process for making future adjustments to the projected timeline
  – Communicate commitment to providing the site support to meet their targets
  – Ask the right questions and dig deep to ensure an accurate timeline is projected
  – Obtain actual upcoming SRC, IRB/IBC meeting dates and submission deadlines
  – Project all approval and milestones dates, including the SIV date

• After the meeting
  – Circulate timeline via email to all key site contacts and request confirmation of accuracy
  – Follow-up in advance of all milestones
  – Investigate and document all missed milestones, including root cause
Questions?

Alicia Williams
Awilliams@medsource.com
References


