Optimizing Site Start-Up in Oncology Trials:

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

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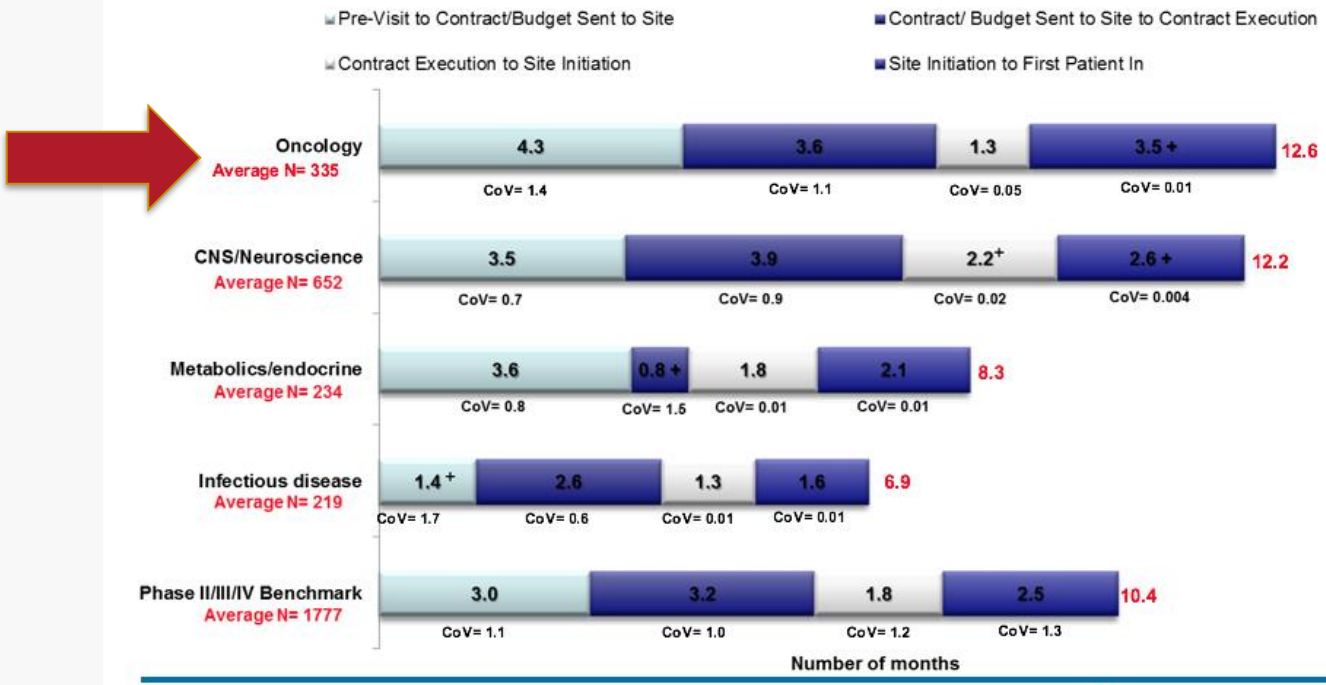
MedSource provides support for complex clinical trials. Whether a challenging therapeutic area or a sophisticated trial design, our highly experienced team excels at delivering results.

Focus on Site Start-up

“First Patient-In” Cycle Time by Therapeutic Area



+ Statistically significant, p ≤ 0.05

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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

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The Growing Complexities of Oncology Trials

Increasing Protocol Complexity

	A Typical Phase III Protocol	2002	2012
Scientific	Total Number of Endpoints	7	13
	Total Number of Procedures	106	167
	Proportion of Procedures that are 'Non Core'	18%	31%
	Total Number of Eligibility Criteria	31	50
Operating	Total Number of Countries	11	34
	Total Number of Investigative sites	124	196

Source: Tufts CSDD

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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

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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 KRIs
  - 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

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Information Sharing and Transparency

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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.)

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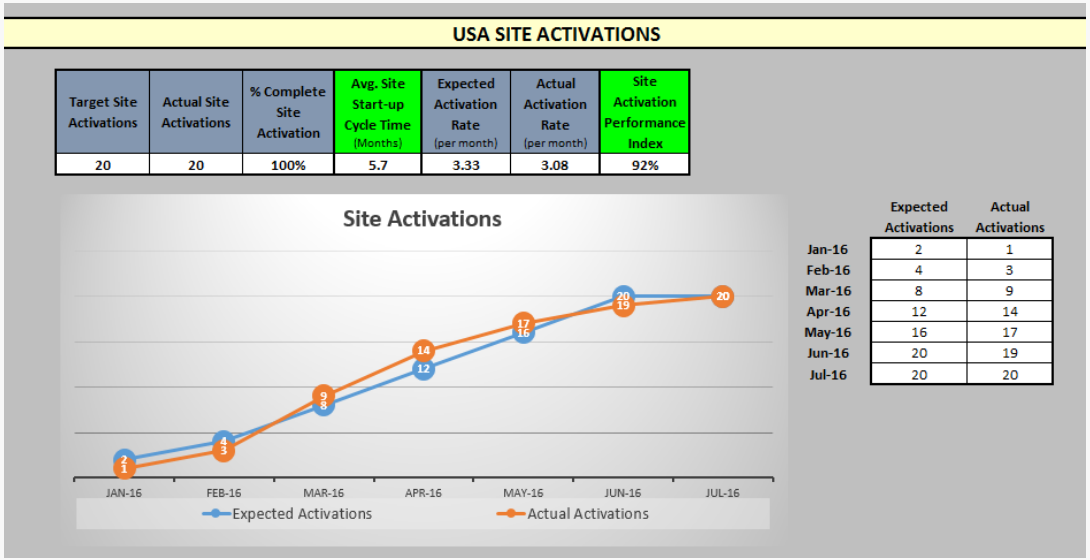
Visibility to Well Defined KPIs



- 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

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Detailed Site Start-up Tracking

Date: 1Mar2017		REGULATORY													CTA	SUPPLIES			ACTIVATION	
Site No.	PI Last Name	Site Selected	Reg Pack Sent to Site	Essential Document Collection Complete	Debarment Check	ICF Template Tracked Changed	ICF Template Finalized	SRC Submission	SRC Meeting	SRC Approval	IRB Submission	IRB Meeting	IRB Approval	IP Autorization	Contract Fully Executed	Site Binders Received	IP Received	Lab Kits Received	EDC Access	SIV Date
101	Black	20-Sep-2016	21-Sep-2016	9-Dec-2016	24-Nov-2016	10-Oct-2016	23-Oct-2016	NA	NA	NA	29-Oct-2016	17-Nov-2016	1-Dec-2016	18-Jan-2017	17-Jan-2017	7-Jan-2017	27-Jan-2017	11-Jan-2017	26-Jan-2017	14-Jan-2017
102	Doe	20-Sep-2016	21-Sep-2016	4-Feb-2017	4-Nov-2016	2-Oct-2016	7-Oct-2016	1-Oct-2016	21-Oct-2016	23-Oct-2016	15-Oct-2016	13-Jan-2017	20-Jan-2017	5-Feb-2017	4-Feb-2017	22-Jan-2017	9-Feb-2017	22-Jan-2017	10-Feb-2017	11-Feb-2017
103	Williams	20-Sep-2016	21-Sep-2016	17-Feb-2017	7-Dec-2016	16-Oct-2016	2-Nov-2016	11-Nov-2016	8-Dec-2016	10-Dec-2016	11-Nov-2016	29-Dec-2016	17-Feb-2017	18-Feb-2017	17-Feb-2017	17-Feb-2017	18-Feb-2017	17-Feb-2017	29-Jan-2017	17-Feb-2017
104	Davis	20-Sep-2016	21-Sep-2016	15-Mar-2017	15-Feb-2017	15-Oct-2016	28-Oct-2016	29-Oct-2016	18-Nov-2016	25-Nov-2016	15-Dec-2016	3-Feb-2017	28-Feb-2017	28-Feb-2017	27-Feb-2017	9-Mar-2017	9-Mar-2017	9-Mar-2017	7-Mar-2017	15-Mar-2017
105	Smith	9-Oct-2016	10-Oct-2016	13-Jan-2017	14-Jan-2017	28-Nov-2016	2-Dec-2016	15-Oct-2016	25-Oct-2016	15-Nov-2016	22-Dec-2016	21-Jan-2017	3-Mar-2017	17-Mar-2017	16-Mar-2017	15-Mar-2017	15-Mar-2017	15-Mar-2017	23-Mar-2017	22-Mar-2017
106	Johnson	20-Sep-2016	21-Sep-2016	8-Mar-2017	15-Feb-2017	15-Oct-2016	28-Oct-2016	29-Oct-2016	18-Nov-2016	25-Nov-2016	15-Dec-2016	3-Feb-2017	23-Feb-2017	4-Apr-2017	3-Apr-2017	1-Apr-2017	1-Apr-2017	1-Apr-2017	5-Apr-2017	7-Apr-2017
107	Jones	20-Sep-2016	21-Sep-2016	30-Oct-2016	26-Oct-2016	22-Apr-2017	25-Apr-2017	7-Oct-2016	NA	29-Jan-2017	26-Apr-2017	12-May-2017	12-May-2017	27-May-2017	26-May-2017	25-May-2017	25-May-2017	25-May-2017	8-Jun-2017	8-Jun-2017

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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

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Trial Planning and Preparation

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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

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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

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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

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Practical Strategies and Process Optimization

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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?

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