Study Start-Up Timelines: Identifying Challenges & Opportunities for Change

EXECUTIVE SUMMARY

With medical product development continuing to last up to 10 years and costing hundreds of millions of dollars, the lengthiness of the study start-up (SSU) process has become a key issue for many stakeholders across the clinical trials ecosystem. As such, the Clinical Trials Transformation Initiative (CTTI) considered whether it should begin a project to address this issue.

Budget and contract delays have long been a major problem in SSU. The Start-up Time and Readiness Tracking (START) study by Tufts Center for Study of Drug Development reported that nearly 11% of sites selected are never activated primarily due to budget and contract issues.[1] CenterWatch's 2019 Financial and Operating Benchmarks survey noted that contract and budget negotiations remain the biggest SSU headache for sites.[2] This was confirmed in exploratory conversations, where CTTI repeatedly heard the need to improve budget and contract processes.

Although CTTI decided not to pursue a formal project on SSU, the findings—detailed in this report—may provide an opportunity for other organizations and stakeholders to continue the conversation on remodeling the SSU process and, therefore, simplifying a complex area that is vital to the success of a clinical trial.

Methods

SSU is a broad category ranging from site feasibility to site activation and often takes six months or more to complete.[1] CTTI's literature scan (see appendix) and corresponding multistakeholder conversations revealed that activities specifically related to budgets and contracts are one of the biggest contributors to SSU delays. Thus, for purposes of this research, CTTI focused on the opportunity to improve budget and contract negotiations.

CTTI first formed a multistakeholder working group consisting of individuals from patient advocacy groups, industry, government, IRBs, and academic institutions. The group helped develop interview questions, provided feedback on the literature scan, and explored potential project opportunities.

To better assess the SSU landscape, CTTI conducted an informal literature scan and held in-depth conversations with eight sites and sponsor groups. These activities helped to identify current barriers, assess existing tools and resources, and understand the strengths and limitations of improvement initiatives.

The landscape assessment was followed by a face-to-face working group meeting to discuss the findings and explore future opportunities. The findings from the literature scan, in-depth discussion with sites and sponsors, and working group discussions highlighted challenges and improvement efforts in SSU.

Findings

1. Budget and contract delays

Several process, infrastructure, and motivational factors impede timely budget and contract negotiations:

- A general lack of uniformity is a key factor, delaying efficiency in both contracts and budgets. For example, the language in clinical trial contracts and clinical trial agreements (CTAs) varies considerably among sponsors and may be subject to different interpretation. Indemnification, intellectual property, publication rights, participant injury, and confidentiality continue to be contentious topics, often delaying timelines in order to reach an agreement. For budgets, inconsistencies exist with the interpretation of fair market value (FMV), which is influenced by factors such as geography and study complexity. There are also too many parties involved, with no central point of contact, making delays inevitable.
- Further complicating the issue is the variability of infrastructure and resources among organizations. Limited or inexperienced staff, personnel turnover, and the lack of investment in streamlining technology can influence how efficient (or not) the process is.
- Motivational factors may also influence budget and contract negotiation timelines. Having a key opinion leader in a trial or participating in a "blockbuster" trial are potential motivators for a site or sponsor to agree to a less-than-ideal budget or contract provisions. Despite motivational interests, sites often reported feeling underpaid for their time and resources, while sponsors reported experiencing unintended administrative costs, overhead fees, and/or additional expenses outside the intended protocol budget from sites. Ultimately, these motivations can affect how quickly a budget and contract agreement is reached.
- Of note, a previous CTTI project, **Investigator Community**, touched on improving budget processes as a means to retain investigators in clinical trials.

2. Streamlining efforts

Budget and contract agreements are time-consuming yet critical. They protect sites and sponsors from unanticipated financial liability, strengthen the relationships between them, and ensure compliance with federal regulations. Ideally, budgets and contracts would be finalized simultaneously. However, many sites still handle this in a sequential manner, working through the budget before the contract. Despite the many delay factors, streamlining efforts to improve SSU efficiency exist. Groups such as the Model Agreements and Guidelines International (MAGI), the Society for Clinical Research Sites (SCRS), and Accelerated Research Agreements have developed contract templates with standardized language aimed to improve clinical trial contract review and negotiation timelines. Grant management and workflow systems and document exchange portals allow tracking of document status and reduce document duplicity.

3. Barriers to adoption of improvement initiatives

CTTI explored barriers to adoption of these initiatives through informal conversations with organizations such as MAGI and SCRS and during the working group meeting. Contract barriers include that the standard language in existing templates is perceived as "too sponsor-friendly," and the initiatives have had a hard time getting buy-in from those who make legal and financial decisions for the organization. Impediments to budget initiatives include variability in costs and disagreements over "fair" compensation, as well as the lack of time or incentive to implement a new process. Last, initiatives often require appropriate implementation funds that are not available.

After considering the findings, the working group determined that streamlining clinical trial budgets would be more feasible and have a greater potential impact than streamlining contracts. These best practices would focus on three topic areas:

- Infrastructure and resource needs to streamline the budget process (e.g., appropriate staff training, use of technology, workflow)
- Communication and transparency (e.g., cost justifications, ways to standardize fair market value)
- Budget review and negotiation methods (e.g., identifying and interpreting standard of care, consideration of pre-negotiated rates)

These topics are not exhaustive, and CTTI encourages other interested organizations to consider additional issues for which to develop best practices.

Conclusion

CTTI decided to pursue other projects but acknowledges the importance of continuing the conversation on improving budget and contract processes in SSU, and hopes that this report will motivate others to continue the search for sustainable solutions to improve SSU efficiency.

References

1. Lamberti MJ. **Assessing Study Start-up Practices, Performance, and Perceptions Among Sponsors and Contract Research Organizations**. Therapeutic Innovation & Regulatory Science. January 11, 2018.
2. CenterWatch. **2019 Financial & Operating Benchmarks**.

Appendix: Resources Used in CTTI's Literature Review

Title	Year	First Author	Source	Link
The Training Challenges in Billing and Research Compliance	2019	Willenberg KM	ACRP	**https://acrpnet.org/2019/03/12/the-training-challenges-in-billing-and-research-compliance/**
Why Fair Market Value Is Not One Number	2019	Goldfarb NM	Journal of Clinical Research Best Practices	**https://www.magiworld.org/resources/journal/2317_Physician.pdf**
Financial Barriers to Site Sustainability, Patient Experience and Overall Study Success	2019	NA	SCRS	**https://myscrs.org/learning-campus/white-papers/** (sign in required)
Assessing Study Start-up Practices, Performance, and Perceptions Among Sponsors and Contract Research Organizations	2018	Lamberti MJ	Therapeutic Innovation & Regulatory Science	**https://journals.sagepub.com/doi/full/10.1177/2168479017751403**

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Analytics and Metrics Help Pinpoint Costs of Study Start-Up	2018	Morgan C	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/analytics-and-metrics-help-pinpoint-costs-study-startup (copy and paste URL into your browser)
The Hidden Costs of Clinical Trial Agreement Negotiations	2018	Florez M	Orthopedic Design and Technology	https://www.odtmag.com/issues/2018-05-01/view_columns/the-hidden-costs-of-clinical-trial-agreement-negotiations
The Case For Plain-Language Contracts	2018	Burton S	Harvard Business Review	https://hbr.org/2018/01/the-case-for-plain-language-contracts
Molasses in Study Start Up Efficiencies	2018	Morgan C	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/molasses-study-startup-efficiencies (copy and paste URL into your browser)
Clinical Trial Agreements: Do You Understand All the Important Terms in the Contract?	2018	Redfearn S	CenterWatch	https://www.centerwatch.com/articles/12616-clinical-trial-agreements-do-you-understand-all-the-important-terms-in-the-contract
Three Clinical Trial Agreement Standard Templates	2018	Kulkarni, D	Journal of Clinical Research Best Practices	https://www.magiworld.org/Journal/2018/1804_CTA_Templates.pdf
Study Start-Up Obstacles at an Academic Medical Center and How to Overcome Them	2016	Agriesti J	ACRP	https://acrpnet.org/2018/04/17/study-start-obstacles-academic-medical-center-overcome/
Accelerating Study-Start Up: The Key to Avoiding Trial Delays	2017	N/A	ACRP	https://acrpnet.org/2017/02/01/accelerating-study-start-up-the-key-to-avoiding-trial-delays/
Site Payments and Reimbursements: A Global Perspective	2017	NA	SCRS	https://myscrs.org/learning-campus/white-papers/ (sign in required)
Site Budget Development and Payment Systems: A Call for Transparency from Clinical Research Sites	2017	NA	SCRS	https://myscrs.org/learning-campus/white-papers/ (sign in required)
What is Fair Market Value?	2017	Goldfarb NM	Journal of Clinical Research Best Practices	https://www.magiworld.org/resources/journal/2148_FMV.pdf

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Clinical Trial Contracts: Language and Limitations	2017	Pfeiffer JP	Pharmaceutical Outsourcing	https://www.pharmoutsourcing.com/Featured-Articles/336113-Clinical-Trial-Contracts-Language-and-Limitations/
Are Clinical Research Sites a Dying Paradigm?	2017	Morgan C	Drug Discovery and Development	https://www.rdmag.com/article/2017/08/are-clinical-research-sites-dying-paradigm
Collaboration in Action: Measuring and Improving Contracting Performance in the University of California Contracting Network	2017	Tran T	Research Management Review	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6029617/
9 Essential Components of a Clinical Trial Agreement	2017	Sampat K	Clinical Trials Arena	https://www.clinicaltrialsarena.com/news/9-essential-components-of-a-clinical-trial-agreement-5885280-2/
Budget, Contract Negotiations Greatest Causes of Clinical Trial Delays, New Report Shows	2017	Huggins M	ACRP	https://acrpnet.org/2017/01/26/contract-negotiations-greatest-cause-clinical-trial-delays-new-report-shows/
4 Villains That Can Delay Your Clinical Trial Agreement (CTA) and How to Defeat Them	2017	Araujo DS	Clinical Leader	https://www.clinicalleader.com/doc/villains-that-can-delay-your-clinical-trial-agreement-cta-and-how-to-defeat-them-0001
Three Questions	2017	Goldfarb NM	CenterWatch	https://www.centerwatch.com/articles/13638
A Single Center Analysis of Factors Influencing Study Start-up Timeline in Clinical Trials	2017	Krafcik BM	Future Science OA	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674216/
Honey, I Shrunk the Contract: How Plain English Is Helping GE Keep Its Business Humming	2017	Kloberdanz K	GE Reports	https://www.ge.com/reports/keep-simple-plain-english-helping-ge-keep-business-humming/
CLEAR (Common Language Evaluation and Reconciliation)	2016	NA	SCRS	https://myscrs.org/learning-campus/white-papers/ (sign in required)
Site Payment	2016	NA	SCRS	https://myscrs.org/learning-campus/white-papers/ (sign in required)
FMV and the Market Failure in Clinical Research	2016	Goldfarb NM	Journal of Clinical Research Best Practices	https://www.magiworld.org/resources/journal/1901_Market_Failure.pdf

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Challenges With Research Contract Negotiations in Community-Based Cancer Research	2016	Thompson MA	Journal of Oncology Practice	https://ascopubs.org/doi/pdf/10.1200/JOP.2016.010975
Budget Management and Forecasting for Clinical Trials	2016	NA	Bioclinica	http://www.bioclinica.com/assets/Uploads/fls-budget-management-and-forecasting-for-clinical-trials-white-paper.pdf
New Benchmarks for Trial Initiation Activities	2016	Lamberti MJ	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/new-benchmarks-trial-initiation-activities (copy and paste URL into your browser)
How to Negotiate Study Budgets	2016	Goldfarb N	Journal of Clinical Research Best Practices	https://www.magiworld.org/Journal/2016/1608_Budget_Negotiation.pdf
Site Contracts from Weeks to Months: Results From KMR Group's Site Contracts Study	2016	NA	BioSpace	https://www.biospace.com/article/releases/site-contracts-from-weeks-to-months-results-from-kmr-group-s-site-contracts-study-/
Recommendations for Strategic Recruitment Planning	2016	NA	Clinical Trials Transformation Initiative	https://www.ctti-clinicaltrials.org/projects/recruitment
Developing and Negotiating a Study Budget	2016	Fallon D	Premier Research	https://premier-research.com/perspectivesdeveloping-negotiating-study-budget-2/
Management of Clinical Trial Agreements: Current Practices of Investigators in the United States	2015	Pfeiffer JP	Therapeutic Innovation & Regulatory Science	https://doi.org/10.1177/2168479014551645
MAGI's New 11-Page Model CTA Template	2015	Goldfarb NM	Journal of Clinical Research Best Practices	https://www.magiworld.org/Journal/2015/1512_MAGI_CTA.pdf
Cycle Time Metrics for Multisite Clinical Trials in the United States	2013	Abbott D	Clinical Trials	https://journals.sagepub.com/doi/pdf/10.1177/2168479012464371
Observational Study of Contracts Processing at 29 CTSA Sites	2013	Kiriakis J	Clinical and Translational Science	https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12073
Streamline and Improve Study Start-Up	2013	Schimanski C	Applied Clinical Trials	https://search.proquest.com/docview/1439272534?pq-origsite=gscholar
Addressing Ever-Rising Cost in Conducting Clinical Trials	2013	NA	Covance	https://www.covance.com/content/dam/covance/assetLibrary/infographics/Xcellerate%20Challenger%20Infographic-2014.pdf

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Negotiating Effective Clinical Trial Agreements and Study Budgets with Research Sites	2013	NA	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/negotiating-effective-clinical-trial-agreements-and-study-budgets-research-sites (copy and paste URL into your browser)
Benchmarking the Study Initiation Process	2012	Lamberti MJ	Therapeutic Innovation & Regulatory Science	https://journals.sagepub.com/doi/full/10.1177/2168479012469947
Clinical Trial Agreement Negotiations	2012	Rijswijk-Trompert M	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/clinical-trial-agreement-negotiations (copy and paste URL into your browser)
Negotiating for Success: Navigating the Contracting Process for an Exemplary Research Program	2010	Baer AR	Journal of Oncology Practice	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835476/
CTMS Can Provide Business Intelligence for Sites	2010	Snyder A	Applied Clinical Trials	http://www.appliedclinicaltrialsonline.com/ctms-can-provide-business-intelligence-sites (copy and paste URL into your browser)
Development of Clinical Trial Agreement Principles	2010	Moldofsky M	Drug Information Journal	https://search.proquest.com/docview/744367835?https://www.nclive.org/cgi-bin/nclsm?rsrc=413&pq-origsite=360link
Project Zero Delay: A Process for Accelerating the Activation of Cancer Clinical Trials	2009	Kurzrock R	Journal of Clinical Oncology	https://ascopubs.org/doi/full/10.1200/JCO.2008.21.6093
Invisible Barriers to Clinical Trials: The Impact of Structural, Infrastructural, and Procedural Barriers to Opening Oncology Clinical Trials	2006	Dilts DM	Journal of Clinical Oncology	https://ascopubs.org/doi/full/10.1200/JCO.2005.05.0104?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry	2005	Mello MM	New England Journal of Medicine	https://www.nejm.org/doi/full/10.1056/NEJMsa044115
Negotiating a Stronger Clinical Trial Agreement and Budget		NA	Forte Research Systems	http://cdn2.hubspot.net/hub/216272/file-522866688-pdf/Negotiations_eBook.pdf