Can the FDA accelerate clinical trial completion timelines through rapid review of Sponsor study data submitted from Physician Investigative Sites utilizing documented cGMP-like processes, completed under on-site, point-of-process completion, quality review systems?

Anton Lewis Usala, MD* and Neil DiSpirito, Esq.**

*Anton Lewis Usala, MD
CTMG, Inc.
1800 North Greene St., Suite B
Greenville, NC 27834
ausala@ctmginc.com
252-752-8553, ext. 114

**Corresponding author:
Neil DiSpirito, Esq.
Rumberger, Kirk & Caldwell, P.A.
300 South Orange Avenue (32801)
Post Office Box 1873
Orlando, FL 32802-1873
ndispirito@rumberger.com
407-872-7300
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I. INTRODUCTION

Good Manufacturing Practices (“GMPs”) were developed in other industries prior to the FDA requiring their use in safe production of medical products. The automotive, aviation, defense, and multiple other manufacturing industries all used GMP’s rigorous procedures with quality systems to assure their products performed as intended, according to specifications, 100% of the time.\(^1\) To achieve this goal, manufacturing processes are “design-reviewed,” meaning they are formulated with subject matter expert and operational implementation personnel input, to maximize efficiencies in achieving product specification goals. All materials and equipment are pre-qualified prior to their introduction into the assembly or service process, and point-of-process completion quality systems assure the product meets specifications prior to completion.

Medical products, both drugs and devices, did not initially require GMP production documentation, with the resultant failure to meet expected performance. The well documented inadvertent contamination of sulfa drugs with phenobarbital in 1941 (resulting in approximately 300 patient deaths), and failure to totally inactivate polio viruses in one vaccine batch in 1955 (resulting in approximately 60 inoculated patients developing the disease), led to the establishment of Federal GMPs Regulations for drugs (21 CFR Parts 210 and 211) and medical devices (21 CFR 820) in 1978.\(^1,2\)

GMPs are perhaps the most rigorous of “Good _______ Practices”, also generically referred to as “GxPs”. The meticulous design-reviewed processes are only effective because they are required to be conducted under point-of-process completion quality systems by the entity utilizing the process, to assure the processes are completed as intended.\(^3\)

All GxPs, except one, are required to have internal quality systems to assure completion of the processes occurs per plan. Pre-qualification/validation of raw materials and required services before either are entered into the process, with review of the data at the time is acquired, provide control over the outcome quality.

The final stage of drug and medical device development is the clinical trial, where experimental products are tested for the first time in human patients. Surprisingly, the only GxP involved with drug development that does not require detailed design-reviewed processes, specific for service implementation at specific locations, is Good Clinical Practice (“GCP”)\(^4\). The International Committee on Harmonisation (“ICH”) cGCPs list required steps Investigative Sites must follow,, but they lack requirement of detailed protocol-specific operational processes and quality system assurance that such processes are completed as intended, as the data is obtained at the Investigative Site, as is required for GMP in ICH Quality Guidances.\(^3\) Sponsor monitors review clinical trial visit data after the data is obtained, often weeks or months after the visit has occurred, for GCP compliance. However, such monitors are only effective in identifying data or procedures that were not completed as intended, and cannot provide certainty as to how the data was obtained, or whether it was faithfully and completely reported.\(^5\)
The cost of developing a new drug from discovery through FDA approval has increased from $100 million in 1975, to $300 million in 1987, to $1.3 billion by 2005. The costs of conducting Phase III clinical trials, the final phase before an approval decision can be rendered by FDA, have spiraled upward, and according to one analysis by the Manhattan Institute for Policy Research, are estimated to represent more than 90% of total drug/device development expense.

This article will examine the effect of current clinical trial regulations not requiring quality system control as the data is collected at Investigative Sites. We postulate this is the primary reason for submission of data to FDA that is often contradictory, spiraling drug development costs, and the documented doubling of Phase III study completion from forecast timelines. Examples of successful implementation of such quality systems at Physician Investigator Sites will demonstrate their effectiveness in increasing Site performance efficiencies, superior data quality enabling timely FDA approval decisions, and increased patient safety. Paradoxically, this cGMP-like approach with on-site quality systems to assure protocol-specific processes are completed as intended, will show dramatic decreases in clinical trial costs.

Such implementation of Investigative Site Quality Systems will not require changes in either the CFR or ICH GCPs. Rather, the economic benefit to Sponsors will allow market forces to drive emergence of Investigative Site quality systems and cGMP-like process development. A proposal to provide FDA accelerated review of study data, if acquired at Investigative Sites with documented design-reviewed processes implemented under on-site quality systems, will accelerate the paradigm shift to cGMP-like conduct in Clinical Trials.

II. BACKGROUND

A. The Clinical Trial Problem

Nationwide, multiple studies have shown 60-70% of physician investigator sites are under- or non-performing in enrolling patients and/or submitting allowable data for entry into statistical analysis, with 20-50% of all studies requiring additional “rescue site” activation to complete enrollment. Such inability to accurately forecast Investigative Site patient enrollment/retention results in both large increases in direct capital expenditures, as well as an average of doubling of forecast trial completion (and lost sales revenues secondary to these delays). Furthermore, as no on-site Quality Systems are required at the point of Physician Investigator/Patient interaction the Food and Drug Administration (FDA) must make decisions on the safety and efficacy of a new test article without the benefit of a complete data audit trail. These poor site metrics and data uncertainty result in excessive costs, delays to FDA submission, prolonged time to market, increased drug pricing, and an increasing number of drugs pulled from the market secondary to unrecognized significance of adverse events during Phases I-III.

Although all Pharmaceutical Company Sponsors (“Sponsors”) and their traditional Contract Research Organization agents (“CROs”) utilize selection and management tools to qualify Investigative Sites, as well as “after the fact” monitoring of site data, poor site metrics and unrecognized or unreliable
La attribution de l'article test à des événements adverses sérieux persiste. Le résultat a été moins de médicaments en développement clinique et le démantèlement de grandes compagnies pharmaceutiques à partir des projections de bénéfices non réalisées.

Aucun Sponsor ni leur partenaire traditionnel CROs ne peuvent opérationnellement gérer les cabinet médical pour mettre en œuvre les processus cGMP avec des systèmes de qualité qu'ils utilisent eux-mêmes à l'intérieur en raison des conflits d'intérêt. Les conflits sont évidents si le Sponsor fournit du personnel qui interacte avec l'Investigateur alors que les médecins conduisent des visites de recherche sur les patients. Cela peut injecter des informations de type pivotal biaisées affectant les conclusions finales de l'Investigateur concernant le rôle de l'article test dans l'occurrence de l'événement adverse.

### B. Effet de l'absence de processus cGMP et systèmes de qualité dans la conduite des essais cliniques à des sites d'investigation

Notamment, toutes les facettes de la nouvelle médication et procédés de dispositifs médicaux sont effectuées sous des contrôles rigoureux, planifiés et documentés (cGxP et Revue de qualité), *à l'exception* de l'ultime domaine de recherche clinique impliquant des patients humains. Toutes les autres facettes du développement pharmaceutique exigent de tels systèmes pour assurer le temps opportun, la qualité de la réalisation des tâches requises. Le cGxP de la FDA doit être mis en œuvre par les Sponsors sous des systèmes de qualité avec des actions corrigitives et préventives (CAPA) pendant les tests pré-cliniques pour assurer la crédibilité des données soumises, et pour assurer que la fabrication de tous les nouveaux médicaments est conforme aux procédures de processus retenus.

Ces systèmes requis sur place, où l'activité se produit, ne sont pas transposés à la phase de recherche clinique de l'évolution de l'article test.

Heureusement, ni les managers et surveillants des Sponsors/CRO clinicals ni les sites Investigateurs, n'ont d'expérience de conduite de la phase de recherche clinique en conformité avec des contrôles de processus cGMP et associés à des systèmes de qualité requis. Sans tels systèmes, il n'y a ni assurances que l'évolution du médicament se produit comme prévu, et que les données qui prouvent la sécurité et l'efficacité d'un produit peuvent avoir été compromises.


Le processus assurant la sûreté et le fonctionnement des produits pharmaceutiques et dispositifs médicaux est de manière internationale largement accepté pour la fabrication tel que décrit dans la Guide Tripartite Harmonisé ICH Q10.

Les définitions concernant les produits de qualité, leur planification et leur développement sont listées ci-dessous pour la production de qualité dans le document ICH Q10.
• **Quality**: The degree to which a set of inherent properties of a product, system or process fulfills requirements. (ICH Q9)

• **Quality Objectives**: A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

• **Quality Planning**: Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfill the quality objectives. (ISO 9000:2005)

• **Quality Policy**: Overall intentions and direction of an organization related to quality as formally expressed by senior management. (ISO 9000:2005)

A Quality System is therefore the organizational structure, responsibilities, procedures, processes and resources that together ensure the quality of a product or service. Problems result from the release of any product or any service without design-reviewed processes that have been authored by subject matter experts and implemented under effective Quality Systems. Effective Quality Systems are designed to provide continuous monitoring and Corrective and Preventive Action (CAPA) functions that enable solutions to close identified process/production gaps. Because of these design-reviewed processes and Quality System requirements, pharmaceuticals and medical devices entering clinical trials in the United States are the safest in the world.

The gap in clinical trials occurs between release of the Sponsor’s final, FDA-approved, Clinical Protocol (either IND for drugs/biologics or IDE for devices), and the conduct of the protocol at the Investigative Site. Without protocol-specific processes to translate protocol requirements into precise, discreet steps with onsite Quality Systems, complete with effective CAPAs to assure their completion, there is no credible evidence to assure that what was intended in the protocol was in fact done at the Investigative Site. After-the-fact monitoring cannot adequately assure how the data was obtained, or its credibility, if such quality-assured documentation is not present.

To compound this problem, monitoring personnel for clinical studies are now largely provided by Sponsor-contracted CROs whose monitors have no clinical certifications or medical licenses. Thus, the critical independent initial review of the data is performed by personnel without professional clinical education or degrees (example RN, MD, PharmD), who are supervised by Project Managers who also may not have clinical certifications or licensure. At the next step, data managers query incomplete entries that a monitor may have missed, but the context of the data is often lost. Incorrect interpretation of the data and missed adverse event relationships may result.

The recent number of approved pharmaceuticals requiring either post-approval warning labeling or removal from the market, results not from lack of quality in manufacturing or pre-clinical testing, but in the handling of clinical trial data supplied by Physician Investigative Sites. The FDA is aware of the data problems, and issued a Final Guidance for Industry—Investigator Responsibilities (October, 2009) to
more specifically delineate the responsibilities of both Sponsor and Investigator in conducting clinical trials, and further outline the need for a quality-based approach.10

III. IMPLEMENTATION OF cGMP-LIKE PROCESSES AND QUALITY SYSTEMS AT INVESTIGATIVE SITES

A. Requirements at the Investigative Site—Personnel

1. GMP process development requires personnel have appropriate background, training, education, and/or experience to implement a given process. The Principal Investigator (“PI”) is currently responsible for all aspects of his Site and staff in conducting each clinical trial protocol.

2. PIs are subject matter experts in the medical decision-making, procedures, and data interpretation. However, physicians do not receive training in design-reviewed process development, or quality system enforcement, unless they have worked in industry. As a result, medical researchers are unfamiliar with both process development and quality system integration.

3. PIs and Investigative Sites will require partnering with expert operational and quality system Business Associates (as defined by the HIPAA Omnibus Resolution Final Rule of 2013) for their site to utilize in conducting protocol requirements, as they currently do not have such expertise themselves. All medical decision making, review of data, medical procedures, and data interpretation must be completed by the PI and sub-investigators, but done so per design-reviewed, protocol-specific operational and quality systems implemented by qualified expert Business Associate personnel.

B. Requirements at the Investigative Site—ability and desire to integrate current site systems with design-reviewed cGMP-like operational processes, administered with real time, onsite quality systems to assure protocol requirements are completed as intended, and on time.

1. Physician Investigators are subject matter experts with the medical aspects of clinical trial protocol completion, but very few have industry experience in design-reviewed process development, or implementation under quality systems (cGMP training or experience).

2. Investigative Sites must have adequate patient numbers, the ability to embrace design-reviewed processes with completion enforced by real time quality systems provided by Business Associate subject matter experts, and the willingness to conduct the study with these systems in place.
C. Requirements for Business Associates providing validated cGMP-like processes and quality systems to the Investigative Site—the Site Specific CRO Model (SS-CRO)

1. As described in Rick Turner’s *New Drug Development: An Introduction to Clinical Trials*, (2nd Edition), Section 7.12, “Another New Paradigm: The Site-Specific CRO”, the Site Specific CRO (“SS-CRO”) model is a new paradigm that provides cGMP-like operational capabilities and quality systems, to maximize Investigative Site Performance, increase patient safety, and decrease clinical trial costs.\(^{11}\)

2. The SS-CRO provides a complementary, not a replacement, service for Sponsor/traditional CRO site qualification, materials accountability, and monitoring. Only a qualified Business Associate (as defined by the HIPAA Omnibus Final Rule, 2013) can have access to the required confidential Protected Health Information (“PHI”) to implement the detailed systems required to assist the Investigator with conducting the study. Neither the traditional CRO nor Sponsor can provide this service, or be present to assist the physician in acquiring original medical data, because of conflict of interest regulations.

3. A Site Specific CRO differs from the traditional CRO in that it signs Business Associate Agreements with the Investigative Sites, and per HIPAA rules, has access to the Physician’s confidential systems and patient PHI to assist the Site in conducting the clinical trial. The SS-CRO staff is present with the Physician Investigator as the patients are seen, to assure compliance with the protocol-specific systems. Real time layered quality systems assure the accuracy and full documentation of data conditions, in addition to identifying and eliminating barriers to each patient completing the “next protocol step.”

4. The SS-CRO model differs from the Site Management Organization (“SMO”) model in that cGMP-like processes implemented under layered quality systems, with personnel expertise to both create and implement these systems, are not found in the SMO model. The SMO model focuses on delegation of authority for clinical visits, regulatory submissions, and data acquisition. The focus of the SS-CRO model is to provide cGMP-like rigor to Investigative Sites, by providing comprehensive, quality based solutions via the following teams, to provide *Adaptive Investigative Site Management*:

a) **Protocol Feasibility Review Team**

   Main Tasks: “First Touch” protocol review to assess feasibility and operational barriers to patient enrollment and completion, identification of investigator and support expertise areas required to successfully conduct study
b) **Network Site Identification and Qualification Team**  
Main Tasks: Identify potential Site Capabilities for expertise required to conduct protocol; conduct Site Qualification Visits to assess integration ability of the Site’s operational processes with SS-CRO’s cGMP-like processes and Quality.

c) **Clinical Operations Team**  
Main Tasks: Create processes with subject-matter expert input and review to translate the protocol requirements into measurable steps, with Quality System check points to assure these steps are completed as intended; develop protocol process tools (source documents, action item checklists, vendor communication templates, etc.) with instruction to, and feedback from, those who will use the tools; Site instruction and material preparation; Coordinate Cross Functional review of Investigator Brochure (“IB”) and Protocol with SS-CRO Clinical, Quality, Operations, Regulatory and Finance Departments, and assign subject matter expert presentations on relevant protocol and IB topics; Coordinate detailed instruction of specific protocol procedures with Clinical Service Teams, and document individual proficiency; Coordinate protocol instruction from SS-CRO operations perspective to Physician Investigators and any Site staff.

d) **Standard Operating Procedures, Policies, and Infrastructure Quality Systems**  
Main Tasks: Identify relevant approved SOPs and Policies to be utilized in creation of protocol-specific systems, and assure adequacy to address any additional protocol specific system needs; Coordinate subject matter expert input involving any SOPs or Policies that need amendment for protocol-specific requirements, or introduce new SOP creation per SS-CRO policies; coordinate individual training confirmation with SS-CRO IT Department using electronic methods; Lead and coordinate Corrective and Preventive Action (CAPA) meetings to address identified gaps in completion of any approved process that requires subject matter discussion, documentation of specific circumstances, creation of draft resolution policies with editing, and passage through final approval and training processes; oversee and coordinate the validation of equipment, equipment calibration, lab testing preparation (if any), consumables, and other materials or procedures related to material support of
protocol requirements in conjunction with the SS-CRO Information Technology (“IT”) Department.

e) Clinical Quality Systems Team

Main Tasks: Create protocol specific quality system check points to assure each protocol specific process is completed as intended and on time; serve as reviewer for protocol-specific tool development, especially in creation of study source documents to assure all needed descriptions for data acquisition are recorded and verified; oversee the quality assurance review of completed study visit source documents and binders, conversion of reviewed and corrected study visit data from paper source to de-identified un-editable digital image and placement on server for remote access by authorized Sponsor monitors, and EDC data entry by Data Management; participate in the qualification visit process for new and existing sites; review and oversee lab results to notify PI Site of clinically significant values; Lead and coordinate activities of the Serious Adverse Event (SAE) Team.

f) Patient Enrollment Team

Main Tasks: Oversee development of I/E Pre-Screen Patient Data tool for Sponsor study, and submit to Clinical Quality and Clinical Operations teams for Quality Assurance Review; assemble lists of potential patients from Investigative Sites, and distribute to PI and sub-investigator members of pre-screening team; present progress of each patient at each site at the twice daily meetings, with information surrounding any barrier to next step completion through randomization; participate in CAPA meetings for creation and implementation of enrollment/retention barriers, and review of draft documents; coordinate weekly meetings regarding review and comment on any Enrollment Team policy adjustments designed to maximize Sponsor Study patient enrollment or retention, with the Internal Standard Operating Procedures, Policies, and Infrastructure Quality Systems Team.
g)  **Clinical Service Team**
Main Tasks: Coordinate SS-CRO Clinical Research Coordinator (CRC) training and understanding of Study Protocol and Investigator Brochure; participate in teaching of, and document CRC understanding of, protocol procedures requirements, and set up mock training sessions for SS-CRO and any required Investigator staff; review and coordinate training of Source Documents with Clinical Operations/ Clinical Quality Operations Teams after Cross Functional Review of Study Protocol; coordinate Mock run through of first patient consent/screen/randomization visits at investigative site prior to Site Initiation; oversee binder and study visit preparation, completed by SS-CRO Infrastructure Support, to assure required documents and materials are ready for CRC pick up prior to the next day visit; coordinate reminder calls with Patient Enrollment Team and document each patient has been called, reminded what if anything to do or bring in (i.e., come to visit in fasted state, bring all meds to visit, etc.), and obtain any interim medical history prior to visit (once consent has been signed); provide oversight with Clinical Operations, Clinical Quality Operations, and Quality System Teams of CRC visit conduct, Investigator document completion, and overall Investigative Site clinical timeline performance.

h)  **IT and HIPAA Assurance Team**
Main Tasks: Assure integrity and security of electronic devices, server connections, server performance, real time (every 30 second) server backup, and authorized remote connections to study data by Investigators, SS-CRO Personnel, Sponsor, and designated Sponsor monitors; oversee daily validation of SS-CRO’s 21 CFR Part 11 compliant process that converts all study paper documentation (completed source documents, regulatory documents, Sponsor and PI communications, etc.) to un-editable digital image; coordinate with Quality Systems (Clinical and Infrastructure) electronic placement of study documents; assign passwords to authorized personnel for Sponsor monitor remote real time access to patient study data; monitor SS-CRO electronic communications to assure HIPAA compliance with patient information for the Sponsor study; monitor and assure encryption of equipment used by personnel that may contain patient Protected Health
Information; provide emergency response to electronic equipment or electronic connection failure to assure SS-CRO study process completion per design-reviewed system timelines.

i) **Regulatory Team**

Main Tasks: Coordinate Sponsor PSQV, SIV, and Monitoring request dates with Network PI Sites; obtain current GCP training certification from study staff; coordinate review of Sponsor Informed Consent with ICF Review Team members, and submit suggested changes to Sponsor for review prior to Reg Pack submission; establish communication with Sponsor’s central IRB, and if necessary any local IRBs regarding Regulatory submissions; oversee and coordinate document submission with Sponsor Regulatory Packets; coordinate SS-CRO team and PI schedules for periodic Sponsor study discussions, and take minutes of meetings; participate in SAE team meetings, and coordinate PI document signings for submission to IRB and Sponsor; distribute IRB and Sponsor materials for PI review and signature, including safety reports.

j) **Finance/Accounting Team**

Main Tasks: Creation of Sponsor Study Systems Development and Continuous Quality System Review Budget and Payment terms, and link payment of these costs to enrollment deliverables; creation of Sponsor Study Visit Budget and Payment terms, and with invoicing for all Patient Completed Visits sent at the end of every month, with payment due every 30 days; oversee accuracy of study invoicing to represent only completed study visit procedures, and System Development/Continuous Quality System Review invoicing per enrollment block payment terms; document distribution of patient completed visit payments; oversee completion of financial documentation, tax forms, and other required financial instruments required for the Sponsor study; serve as Point of Contact for any budget, financial, or accounting issues for Sponsor, PI Site or Patients involved with the Sponsor study.
k) **Continuous Quality System Review Team**

Main Tasks: The overall task of the Continuous Quality System Review Team is to twice daily review the progress of every patient being considered for participation in the Sponsor Study, and assuring progression of each patient from pre-screening identification through randomization per protocol requirements and timelines. Any barriers to efficient progression to “the next step” as defined by SS-CRO Operational Processes (based on protocol requirements) are identified and solution tasks distributed to the best suited subject matter expert Team. Throughout the day, Action Item questions/progress/resolution are disseminated to each of the different Team Members, so that subject matter experts can contribute information or fine tuning of solutions, to assure each patient can progress to the next step as quickly as possible, with both individual and group solutions drafted, reviewed, and implemented as needed.

IV. **CGMP-LIKE PROCESSES WITH QUALITY SYSTEMS PROVIDED TO INVESTIGATOR SITES THROUGH A BUSINESS ASSOCIATE SS-CRO—CLINICAL TRIAL CASE HISTORY**

SS-CRO’s creation of detailed design-reviewed processes that translate Sponsor protocol requirements into discreet, measurable steps, whose successful completion is assured by SS-CRO’s continuous onsite quality system enforcement, has the characteristics of a disruptive innovation in clinical drug development. The following example of an SS-CRO managed study demonstrates the power of cGMP-like design-reviewed processes implemented under layered quality systems, in bringing a product to successful NDA completion, and full FDA Approval, that otherwise would have failed.

**CLINICAL TRIAL CASE HISTORY**

**Clinical Trial Indication:** Treatment of hypercholesterolemia in patients with statin-resistance or statin intolerance, at high risk for cardiovascular events

This case demonstrates the value of an SS-CRO’s providing Investigative sites with cGMP-like quality and operational systems as outlined in the previous section. The result of cGMP-like controls not only decreased direct clinical trial costs and enablement of sales revenue years earlier than if SS-CRO were not brought in, but also the value in identifying severe adverse events linked to products that all other investigative sites had missed. SS-CRO’s early recognition of this adverse event allowed effective remediation to occur, with correct identification of target patient indication, and eventual FDA approval.
**Case History Study Background**

1. Phase 3 study, requiring only 160 patients as patient indication was for select high risk group.

2. Approximately 80 non-SS-CRO sites brought up in U.S., unable to reach required patient enrollment numbers after 19 months.

3. SS-CRO was contacted after 20 months when study enrollment stalled at 115 of the 160 required patients had been enrolled.

4. After one week, SS-CRO analyzed protocol, created design-reviewed processes, and forecast enrolling remainder of patients (30) within 3 months of Site Initiation of 3 SS-CRO Network Sites.

5. Sponsor was concerned about the cost of bringing up 3 new sites, with one Site not having done a clinical trial before, and initially brought up only the two sites with research experience. SS-CRO demonstrated rapid patient identification and enrollment, and Sponsor activated the 3rd site four weeks later (who later become the 2nd highest study enroller).

6. Twelve weeks after the first two sites were initiated, and eight weeks after the third, SS-CRO completed enrollment of 30 patients, and the study enrollment was completed.

7. Three months after completing enrollment, SS-CRO noted approximately 1/3 of its sites’ patients experiencing severe, delayed skin sensitivity reactions (half of the patients received placebo, SS-CRO was blinded to treatment as were Investigators).

8. Despite having 80 other Investigative Sites participating prior to SS-CRO involvement, the Sponsor was unaware of this significant and pervasive adverse event.

9. SS-CRO contacted Sponsor directly, with rapid Sponsor intervention.

10. One SS-CRO patient who developed severe delayed skin reaction later died of rapid, fulminate hepatic failure.

11. Per SS-CRO SOPs, medical monitors, IRB, Sponsor and Sponsor’s traditional CRO were notified within four hours of SS-CRO becoming aware of patient death.

12. Sponsors met with SS-CRO by week’s end, reviewed data, and halted plans for FDA submission for current therapeutic indication. Upon breaking the blind, it was found that the patients that received test article and did not have any liver or delayed skin reactions were the patients that needed the therapy most. These patients were found to have homozygous familial hypercholesterolemia, resistant to statin medications, and at high risk for early cardiac events.

13. The Sponsor developed a small safety testing protocol based on SS-CRO’s data, and NDA was submitted for the altered therapeutic indication in 2012, with recommendation for approval received later that year, and full FDA approval received in January 2013.
Clinical Trial Case History Cost Analysis

1. Additional per patient cost of SS-CRO services over average of other 80 sites was approximately $5,000 more ($18,700 compared to $13,900 per enrolled patient).

2. SS-CRO reached study enrollment closure numbers within three months, saving Sponsor 6-10 months of further internal Sponsor burn rate.

3. Utilizing 8 SS-CRO sites at outset, study enrollment could have been completed within 6 months, again saving Sponsor 1.25 years of burn rate. Total SS-CRO site payment premium would be $5,000 more per patient or $750k for all 160 patients, but saving sponsor a net $3.7 Million, and several hundreds of millions realization of delayed sales revenues.

4. Identification of adverse event was critical for patient safety and potentially saved millions of dollars in drug recall, enabled successful understanding of event cause and appropriate indication, and resulted in eventual FDA Approval for related therapeutic indication.

### Phase III Case Study:

**Traditional System (TS) vs. Adaptive Site Management SS-CRO Performance**

<table>
<thead>
<tr>
<th></th>
<th>TS Sites</th>
<th>SS-CRO Sites</th>
<th>SS-CRO Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number Sites</td>
<td>80</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Enrollment/weeks</td>
<td>130 pts/77 weeks</td>
<td>30 pts/12 weeks</td>
<td>160 pts/24 weeks</td>
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<tr>
<td>Time to Enrollment Closure</td>
<td>23 months</td>
<td>3 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Adverse Event Recognition</td>
<td>Did not record delayed skin sensitivity</td>
<td>Noted extensive delayed skin reaction, and challenged CRO</td>
<td>Noted extensive skin reaction</td>
</tr>
<tr>
<td>Cost to enroll all patients</td>
<td>$10.1 million</td>
<td>$1.2 million</td>
<td>$5.4 million</td>
</tr>
</tbody>
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Enables launching 15 months earlier ~$450 million in incremental sales
V. SUGGESTED FDA GUIDANCE AMENDMENTS TO ACCELERATE VOLUNTARY CGMP PROCESS USE BY INVESTIGATIVE SITES

In summary, we submit that the effect of having cGMP-like, design-reviewed protocol-specific processes implemented with continuous quality system review at the Investigative Site, results in the following:

- More rapid and clinically relevant assessment of adverse events linked to new study drugs/devices
- Assurance of data integrity with complete audit trails documenting precisely the conditions patient data was obtained
- More efficient and less costly implementation of clinical trials, enabling more new drugs to be tested and more treatment alternatives available
- Reduction of Sponsor risk in allocating resources to clinical trials, and thereby encouraging investment in innovative therapeutic approaches

We propose the following two suggestions for consideration by Policy Makers at the Food and Drug Administration, to assist in the voluntary use of cGMP-like processes, and quality systems, at Investigative Sites.

**Suggestion #1:** Provide an accelerated study review OPTION to Sponsors if clinical trial data is obtained at investigative sites using internal Quality Systems demonstrated to meet FDA requirements (including effective CAPAs).

**Rationale:** Effective onsite quality processes will provide FDA with complete data audit trails, full documentation of patient medical history prior to and during study participation, and documentation of the basis for medical decision making. This will increase confidence in data credibility and enable the Agency to make safety and efficacy decisions with fewer outstanding questions, as well as further improving safety for existing accelerated paths.

Establishing requirements for effective Investigative Site processes linked to onsite point-of-process completion quality systems, may include documentation of:

A. Adequate understanding of required protocol procedures by involved parties, and documentation of involved personnel qualifications to conduct assigned procedures
B. Adequacy of supervision procedures regarding completion of intended protocol events
C. General approach to gap identification and resolution, including involved personnel, personnel qualifications, and timeline intervals for gap assessment, gap identifications, and gap resolution

D. Internal data assessment for query identification and resolution, and documentation procedures for query assessment and resolution

E. Clarity and adequacy of Adverse Event, Unanticipated Adverse Events, Serious Adverse Event, and Unanticipated Serious Adverse Event timelines and procedures

F. Adequacy and appropriateness of Physician Investigator involvement, including timelines, to demonstrate effective physician oversight and involvement with all medical decision-making, including but not limited to, appropriateness of patients selected for study participation, medical review of all study patient data, medical decision making regarding protocol study results, medical assessment as to relationship of adverse events to test article, and overall patient safety

**Suggestion #2:** Revise Form 1572 to give OPTION for Principal Investigator SS-CRO Business Associates to assume responsibility for operations and Quality Systems implementation, while maintaining PI responsibility for all medical decision making, medical procedures, and medical interpretation involved in study protocol completion.

**Rationale:** GxP systems require that assigned personnel possess subject matter expertise, or relevant background, training, experience or education to be responsible for given tasks. PIs are subject matter experts, with relevant training, experience, and education in the medical aspects of the protocol as described above, but not the effective implementation of Operational/Quality Systems.

**V. CONCLUSIONS**

The cGMP approach to drug and device manufacturing has demonstrated itself effective in assuring approved medical products conform to design-reviewed specifications, nearly 100% of the time. The lack of such quality-system based processes in clinical trials needs to be addressed at the Investigative Site level as this is the site where the protocol is conducted, and patient data obtained. Providing an option for accelerated FDA review for Sponsor Clinical Trials that utilize Physician Investigative Sites with documentation of such cGMP-like processes and quality systems, will have profound effects on patient safety, data integrity, predictability in clinical trial completion, decreased costs, and the ability of the market to make this a desired option, without further compulsory legislation.
Anton Lewis Usala, MD is a former pediatric endocrinologist, who is currently President and CEO of CTMG, Inc., a Site Specific CRO with offices in Raleigh and Greenville, NC. Dr. Usala founded several biotech companies, and brought products from discovery through FDA clinical trials where he noted that the rigorous quality systems required in the GLP and GMP portion of the drug development, were not required once his products reached the clinical trial phase at independent physician investigative sites.

Neil DiSpirito, Esq. is Special Counsel for FDA matters at the Firm of Rumberger, Kirk and Caldwell. Mr. DiSpirito’s practice focuses on FDA regulatory and compliance, new drug approval, worldwide business development, licensing, labeling issues, FDA and state enforcement, FDA litigation and a wide array of government and commercial matters affecting pharmaceutical and FDA regulated companies. Neil P. DiSpirito represents CTMG as legal counsel.
ENDNOTES


