



## Investor Awareness for Effective Clinical Development: The Tie between Clinical Development and ROI.

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### Overview

In the past 25 years, the clinical trial processes for developing new drugs have grown increasingly complex. The nature of the therapies being investigated has increased the difficulty of the procedures being conducted, and competition for trial subjects has resulted in complex multi-centre, multi-regional clinical trials becoming the standard for evaluating medical therapies prior to regulatory approval or as post-registration commitments. In turn, the legal, operational, training, and quality processes have also become more complex due to the increase in the number of sites, site staff, data variables, labs, etc.

The need to improve productivity in drug development has been recognized since the 1990s, but has only recently become a core issue in the development of new therapies. Between 1994 and 2003 the funding for all biomedical research in the United States has more than doubled: from \$37.1 billion in 1994 to \$94.3 billion in 2003. Funding for phase I-IV clinical trials by the pharmaceutical industry and National Institutes of Health has increased from 37% to 64% of their biomedical research expenditures<sup>1</sup>.

During the same period, however, the Food and Drug Administration rate of approval for new drug therapies dropped from 35.5 to 23.3 molecules per year<sup>2</sup>. DeMasi estimated the cost of drug development had increased to \$802 million in 2000. Dickson and Gagnon in 2004<sup>3</sup>, and McGee in 2006<sup>4</sup>, observed that the increase in therapy development time from 7.9 years in the 1960s to 12.8 years in the 1990s was associated with factors including:

- increased regulatory requirements,
- increase in trial length,
- the need for more study subjects in clinical trials,
- an increasing difficulty of recruiting subjects (and an increase in the number of trial sites to get subjects), and
- an increase in the average number of procedures performed on subjects.

Electronic data capture ('EDC') is considered one of the key productivity tools to address the industry's productivity issue. Survey results at the DIA 3<sup>rd</sup> Annual Clinical Forum showed that EDC use in trials had increased to 58%, up from 13% in 2001. The promise of EDC systems to remedy some of these issues associated with more complex trials continues to be evasive. Promises of reduced queries and higher data quality are challenged by trial sites, where processes and technology are not supporting each other, resulting in greater workload and costs at the trial sites<sup>5</sup> and at the sponsor.

Three trends are clear from these studies and historical review:

1. Trials are becoming increasingly complex,
2. The additional complexity is resulting in increasing trial length and cost, and
3. Data collection continues to be a central issue in clinical trial efficiency.

Clinical trial organization and data collection efficiency affects the trial stakeholders in different ways. For the director of clinical trials it affects the overall length of the trial, the additional effort required to verify that the results are valid, and the usability of the data by downstream end user. For the investor in the biotechnology sector, clinical trial inefficiency is a pervasive, systematic hindrance around the investment portfolios performance where high costs consume scarce capital and reduces metrics.

In twenty-five years of clinical trials data management and statistical analysis several operational issues have been identified which affects the progress of trial completion. Addressing these core issues has a direct impact on the time and direct cost drivers for clinical trials and supports the scientific integrity of the trial. Repeating these efficiencies over the many clinical trials in a drug development program, improving the return on investment to stakeholders, will become a key

metric for biotech management performance in the future, and may make or break the future of the biotech where effective management is considered a key predictor of suitability by investors.

This paper takes a closer look at what impedes clinical trial performance and some of the solutions available to assist in improving the efficiency of clinical trials and the return on investment ('ROI') to investors. Streamlining clinical trials through focused trial objectives and consistent data collection and statistical methodologies will accelerate clinical development timetables and lead to faster time to market. Repeating the procedures across multiple clinical trials in a drug development program will have positive effects on ROI.

**Improving trial /study planning**

The foundation stone of clinical trials are the protocols that describe the objective(s), design, methodology, statistical considerations, and organization of the clinical trial. In addition, the protocol describes operational details such as: selection criteria for trial subjects; the schedule of tests, procedures, medications, dosages; duration of the study; and the safety and efficacy parameters. In essence, the protocol is the blueprint of the study.

Protocols undergo many levels of review within a study, and require regulatory approval before the study can commence as a whole and usually for each site to participate in the study. In addition, the protocol has a direct impact on the work performed by contract research organizations (‘CROs’) engaged in aspects of the study.

**Regulatory and Site Protocol Approval Process**

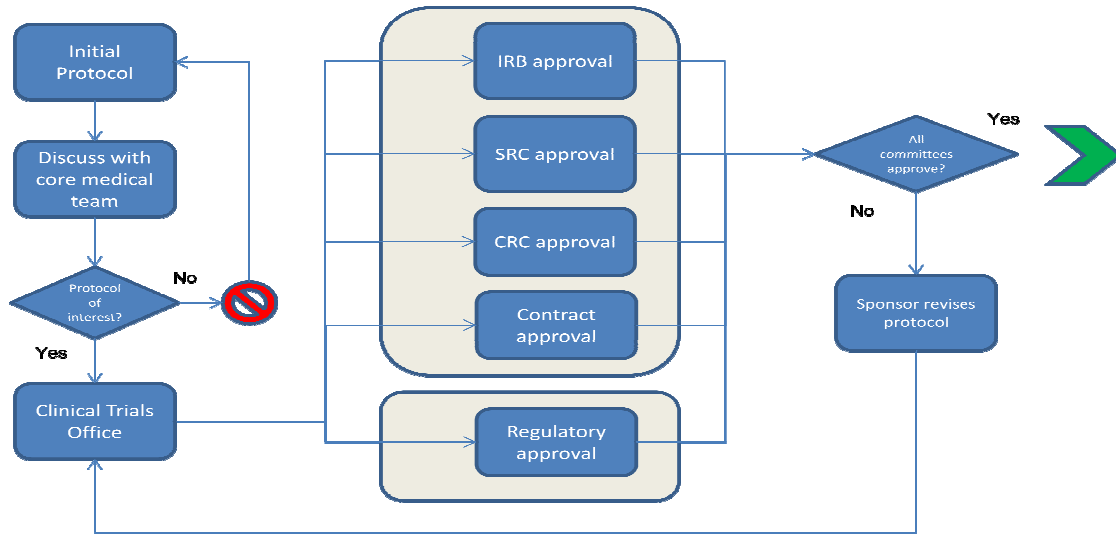


Figure 1: The regulatory and site protocol approval process. The approval process is dependent on parallel paths of approval, with a second parallel path for each site within the trial. Each site can independently stop the approval process for amendments to the protocol.

It is not atypical for a protocol to undergo two to four revisions relatively late in the study planning process. [Figure 1] Whereas some of these revisions are minor clarifications or administrative changes, some revisions are deemed substantial by the regulatory authorities. Substantial revisions will trigger a new round of reviews by regulatory and ethics committees where a reasonable response time is required and may potentially triggering further reviews, questions, or a ‘clinical hold’. In addition, it is likely that any revision which is deemed substantial will also result in some form of change order with the internal departments or CROs associated with the trial, adding further delays.

As an example, one of the primary areas where revisions occur is the study subject inclusion/exclusion criteria to improve subject recruitment. Difficulties in recruiting subjects have resulted in many trials being terminated early, with significant issues in the analysis of the data due to statistical power estimations, or the trials being extended to manage the issue. The stakeholder effects for delays include additional months of trial overhead costs without additional deliverables due to slow recruitment and protocol amendment review, delays to new rounds of investment capital, disruptions of contracted deliverables between the biotech and the biotech’s pharma partners and/or existing investors. Ethically, subjects who might have received the treatment may have been excluded unnecessarily.

In many respects writing a protocol is similar to legal submission in a court of law. As such, the question becomes ‘if you were preparing for a legal proceeding, would you wait until the last moment prior to submission to consult the subject matter expert (also known as a lawyer) to provide input on your submissions?’

Subject matter experts and CROs aggregate protocol development and clinical trials planning knowledge from hundreds of studies, including key considerations on writing protocols which when acted upon can result in the minimum number of revisions. For an early stage biotech company, the early integration of this knowledge can prevent months of delays associated with revisions, additional reviews, and operational issues such as slow recruitment due to restrictive inclusion criteria. If even one round of reviews can be avoided, the benefit to the trial is approximately 35 to 90 days and the associated unplanned costs.

### *Intelligent Trial Design and Efficient Technology Decreases Costs Associated with Analyzing Data Processing data in a timely manner.*

The key purpose behind any clinical trial is to collect data needed to evaluate the trial's primary end points. Study design often includes additional information that is collected for secondary or tertiary endpoints. Inefficient study design includes unnecessarily expanding primary endpoints to capture extraneous data. This often results increased data collection and analysis costs, reduced data integrity, and can confound the analysis.

The golden rule of information generation is that the value of the information must exceed the cost of generating/collecting that information. This rule provides a guide to clinical development teams as to the value of each data point prior to collection.

Data variables may be classified generally into three tiers:

1. Core data which is required to support safety and primary endpoints for the study;
2. Non-core data which is highly useful to support secondary or tertiary endpoints;
3. Non-core data for exploratory use.

Tier 1 (Required for the study) data variables are critical data to collect. This data has been mapped by the subject matter experts designing the study as essential to achieving one or more study endpoints. Generally, these data points would include baseline data, data measuring independent and dependent effects, and data supporting suspected data safety and efficacy effects. The inclusion of these data points is unquestioned. The failure to collect sufficient tier 1 data will often result in inconclusive results to support one or more endpoints. It may result in further trials or data mining in the subject files to collect the missing data and/or submission rejection by the regulatory authorities. These extend the data collection and analysis period of the trial, adding additional months of unplanned costs.

The definition of tier 1 data also defines the process for determining whether any of the data in tiers 2 and 3 ought to be collected as part of the study. For tier 1 a set of inclusion criteria was developed and mapped to previously identified study critical endpoints. By extension, a subject matter expert can also define a set of inclusion criteria for tiers 2 and 3 to help identify which datasets map to secondary endpoints or indirectly to primary study endpoints, and provide the reasonable value to the study. Secondary objectives such as quality of life data may be important for a trial, where some findings in this secondary objective would clearly affect the market potential of the drug and thus the benefit to stakeholders.

Typically the process for including secondary data is informal. The application of a methodical approach to defining which data points should be included and how those data points will be best collected and integrated has a profound effect on clinical trial efficiency. It allows the rationalization of the study to include only data of reasonable value compared to the study objectives and difficulty of collecting the data. It also becomes part of the risk management of the study as each data point included (and many of those excluded) has been fully analyzed to justify their purpose in the study.

### *Effective real-time data collection*

In concept the process of collecting data in a clinical trial is relatively simple. Study procedures are performed, and clinical data is collected and recorded for analysis. Performing this data collection electronically greatly improves efficiency, and provides critical data in real-time. The cost savings are significant.

Each step in the data collection process [Figure 2] is dependent on the previous step. Data points entered into the system with undetected errors result in considerable work being performed on those data points and related data points in the query process when the CRA verify the data to the source records (source data validation ('SDV') procedures) and at each subsequent stage of the data management process. This increases the phase 2 and 3 use of costly data verification and management procedures in the trial. It also reduces the available data for interim analysis and the data quality overall.

A key assumption is that a raw data point which has been inputted into an EDC system is of less value than one which has undergone SDV as the additional certainty of it being without data entry or other error has an intrinsic value. Similarly, a complete subject visit binder (the complete set of CRFs for a subject for one trial visit) has greater intrinsic value than an incomplete binder as the completeness and cross referencing for inconsistencies of all associated data points during quality control and SDV further decreases errors, and its availability for inclusion in interim analysis and drug safety monitoring board ('DSMB') reviews allows researchers to support conclusions with greater certainty.

The other key assumption is that as any data point moves through the process, the incremental cost of additional work increases significantly. Simply, research associates ('CRAs') (stage 2) cost more than data entry staff and coordinators (stage 1), and clinical data managers ('CDM') (stage 3) more than CRAs.

If we use these two assumptions in the concept of the increasing value of the data, we can identify drivers which will guide us to how to improve the efficiency of data collection. Some of the objectives of making a trial more effective would need to impact one of the following three metrics:

1. More data from the trial is available at each stage of the process. More conclusive early analysis is possible to permit additional guidance in the trial.
2. The data from the trial is more accurate at each stage of the process. More data points have been confirmed to be correct and the risk of expensive error correction work has been reduced; or
3. The cost of trial steps have been reduced with comparable data quality and study time constraints.

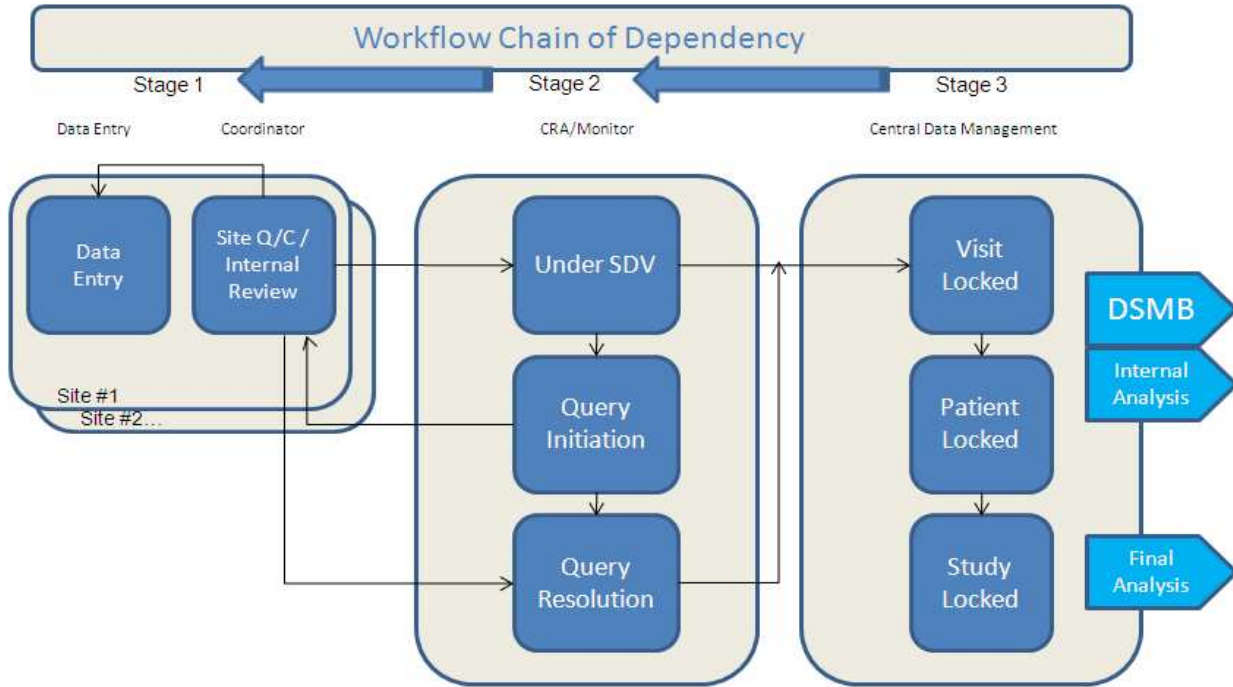


Figure 2: Clinical trial data collection and verification process. Stages 2 and 3 are dependent on the initial accuracy of stage 1. As the data moves from step to step in this process additional work is performed on each data point. The value of the data and the additional labour costs both increase.

Where data collection becomes complex is the number of skilled, and very busy, people who need to become involved in the process. Data collection and reporting must compete for time in the busy schedules of the primary investigators, doctors, nurses, laboratory technicians, data entry, study coordinators, CRAs, central data management, DSMBs, etc, required for a single site study. To find sufficient subjects for the study, it is common to need to involve more than one site, adding a further layer of complexity associated with using multiple sites staff using local methods of performing similar tasks, interpretations of the protocol, etc.

In such a complex environment, two types of significant process variability exist in the execution of the data collection process. The first is the variable timing of subject recruitment and will not be addressed in this paper. The second is the data collection processes where site training and operating habits result in controllable variability in data entry timing accuracy and completeness, which contributes to inefficiency in the data collection process.

The objective of trying to remove inefficiency from data collection starts with two targets: remove unnecessary variability from the data collection process; and make the solution a natural and palatable extension of the standard process. The second objective exists simply because if you build a better mouse trap but it is too frustrating to use, it will not be adopted by the targeted users.

Sufficient data to benchmark significant efficiencies through forward planning and rationalization of trials has been collected over a large sample of studies. Early identification of data issues results in the remedying of data errors by data entry and site coordinators prior to expensive additional work being performed on the data at later phases of the data collection process. The benefits include fewer data points going through the query process which takes both time and effort, and increases costs.

### *The earlier you find an error the cheaper it is to fix it.*

Concepts of process planning, developed in other industries, appeared in 1960s. One of the core elements of production planning is to avoid developing ‘fixes’ for productivity issues, but to instead focus on addressing the fundamental problems that hobbled productivity.<sup>6</sup> The most common fix which appears in clinical trials is the data cleaning exercise, where at various points in the trial (but most commonly at the end of the trial) the data set is audited and errors and missing data points resolved. One extreme case describes a two year study where a further year was spent cleaning the data to make it useable. In this example, a fix [data cleaning] was attempting to recover from incomplete and inaccurate data input [the fundamental problem]. The core of the problem stems from the need to what is in essence is a reprocessing of the data: retrieve the subject files from storage a second time, map which subject file belongs to which set of records in the EDC system, and to input and correct any inconsistencies the additional data creates with original data. The entire subject data file then needs to undergo SDV and CDM processes for a second time.

Field experience with defining and implementing data management service level standards (‘SLS’) for trial sites to facilitate the timely input of data at regular intervals, site quality control requirements, and to permit SDV to occur only on completed eCRF forms and visits has demonstrated that poorly defined SLSs and a positive correlation to the number of queries generated, the speed of query resolution, the number of days to database lock, and to the final data quality. In environments with strong SLSs and controlled data management processes, a 10% increase in usable end data can be observed with resulting shorter database lock and statistical analysis periods, and reduced costs.

### *Terminating when you have effectively demonstrated that the study will not achieve its objectives*

The analysis of a study is basic statistics. As the data is collected and analysed, the ability to determine the outcome becomes increasingly clear. Even when insufficient data has been collected to make a submission, interim/futility analysis can determine the probability of achieving any particular endpoint. Interim analysis provides the basis for many decisions. With more data, and higher quality data, the risks involved in futility analysis are decreased.

Statistically it is quite simple to determine from interim data how difficult it will be to for the trial to demonstrate an objective. The very real risk in interim and futility analysis is that incomplete or inaccurate data which has not been effectively cleaned will result in an incorrect decision which would lead to the termination of a study on a drug which is actually efficacious.

Ending a study which is unlikely to support the drug development program is an exercise in stopping good money being thrown after bad money. It is a step that should be taken with diligence and caution. Proper consideration may lead to trial amendments rather than termination.

### *The potential to improve productivity*

The effects of lost productivity in a single clinical trial can be measured in months of overhead and increased variable costs associated with the end deliverable of useable data and analysis. Over the course of a drug development program these productivity losses can be repeated many times, with a significant impact on the timeliness of the drug launch and the cost to complete the program. Competitive considerations such as first to market become critical to the success of the program.

Through the use of subject matter experts and data end users early in protocol development, establishing service level standards with sites, and performing interim and futility analysis at key points in the trial, it has been demonstrated that the potential productivity benefits of well managed clinical trials can be realized in the following areas:

1. Number of queries: 88% reduction in queries.
2. Accuracy: percent of analyzable/valid data fields/points as intended by the protocol: increase from 87% to 96%.
3. Reduced direct labour costs for coordinators, monitors and database managers: reduced by 34%.
4. Trial data lock for interim and final analysis: reduced by 90 days.

The data collection and cleaning process and time requirements can be significantly improved without incurring significant costs and can produce significant improvements in efficiency with a direct bottom line effect. While some of these concepts are new to the clinical trial process, the conceptual proof of their merit has been established in other data processing industries with measurable efficiency and cost benefits.

For the biotech company, the improvements in performance can mean the difference between further rounds of funding and the winding down of the company. The ability to demonstrate trends in improving cost and time management across multiple clinical trials and programs, with direct impacts on investor ROI, is one of the keys to differentiating one biotech from another during investment decisions.

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