DATA
BASICS

A PUBLICATION SUPPORTED BY AND FOR THE MEMBERS OF
THE SOCIETY FOR CLINICAL DATA MANAGEMENT, INC

SCDM
Society for Clinical Data Management
DATA DRIVEN

To advance excellence
in the management
of clinical data

This Issue

Letter
From the Chair

Demetris Zambas

Dear SCDM member and friends,

One of the great aspects of being involved in an organization like SCDM is the opportunity to be part of something larger and more significant for our professional community than just our personal contributions. In the context of strengthening and supporting a discipline that is critical to the development of new therapies and medical devices, the relevance and importance of our organization becomes even more significant. Our mission is quite simple. It is to be *The World's Leading Advocate for the Discipline of Clinical Data Management.* Many individuals have contributed to this vision through the creation and dissemination of information through our training programs and publications.

Eighteen years ago the Board of Trustees formed the GCDMP© committee "to determine standards for good clinical data management practices." Two years later the first version of our GCDMPs© was published and instantly became the global standard of reference for Clinical Data Management practice. Since then, it has been a major factor in many of our educational offerings and the CCDM™ program. The GCDMP's© are widely referenced by regulators around the world in publications as well as domain specific guidance documents. Personally, I have routinely found myself using the GCDMP's© as a reference when having to deal with both daily operations as well as challenges which arise all too often in our line of work.

To assure that our GCDMP's© remain relevant, we have had a standing GCDMP© committee focused on maintaining and adding content. With the acceleration of changes across this domain driven by the infusion of digital technologies SCDM has initiated a major update to the GCDMP's© and in conjunction the relevant updates to training content and curriculum. We must assure we continue to offer relevant and current guidance rather than retrospectively describing and addressing issues that the discipline and our industry are faced with.

In an effort to assure that this body of information is available to the public and more specifically, Clinical Data Management professionals, the Board of Trustees took part in a historically significant vote recently. It is my pleasure to announce to our community that the Board has unanimously agreed to publicly publish our GCDMP's©. The primary primary driver behind this decision is to assure that we are indeed making our vision a reality not only for the membership of SCDM but for the practice of Data Management around the world. We hope that through this action we are not only supporting the CDM discipline but more importantly, enabling data managers to further advance the ability for Clinical Research organizations to deliver therapies for the world's unmet medical needs. ■

Happy reading!
Best regards,

Demetris Zambas
2016 Chair, SCDM
Board of Trustees

Letter From the Editors

Dear Readers,

"I like my data like I like my house: clean and locked!"

With that quote, we'd like to welcome you to the Fall issue of Data Basics.

In this issue, you will discover quick and easy recipes to help you deliver a clean database to the "Biostatistician's table". This issue covers topics ranging from using analytics for database build to leveraging reporting tools that help improve data quality prior to database lock.

The article "A Sponsor's Role: 21 CFR, Part 11" provides a winning recipe for creating and maintaining high-quality, regulatory-compliant electronic data capture systems.

To foster successful relationships between Clinical Data Management and Clinical Operations teams, flip to the article "Clinical and Data Management: A Time to Heal". In this article, the author proposes the secret ingredients of collaboration, understanding and mutual respect.

A good housekeeping rule is to use an analytical dashboard for building better case report forms as discussed in the article entitled "Using Analytics to Gain Efficiencies in Database Builds".
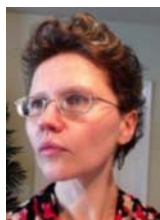
Claudine Moore   Margarita Strand

Take a few moments to read the article "Clinical Trial Data Reporting Methodologies – Historical and Current Perspective of Reporting Tools that Support Data Cleaning, Tracking, Reporting and Forecasting at Gilead Sciences, Inc.". The authors share a kitchen table story about the positive impact of change in clinical trial data reporting methodologies.

And finally, be adventurous and try something new for dinner. The chefs recommend reading the article "Wearable devices – Future of healthcare; steps towards a better life", which discusses how to handle data from wearable devices with therapeutic and diagnostic capabilities.

We hope you will find an abundance of appetizing, thought-provoking ideas in this issue that will help ignite your creative spark.

Enjoy! ◼

Best Regards,

Claudine Moore and Margarita Strand
Data Basics Co-Editors

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SAVE THE DATE

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A Sponsor's Role: 21 CFR, Part 11

By Derek Petersen

Introduction

The digitization of clinical trial systems has undoubtedly ushered in a new era for clinical trial operations as a whole. The ability to leverage what seems to be an exponentially increasing amount of computing power comes with enormous possibilities, both in terms of optimizations and hazards. As such, the United States Federal Government has rightfully designated certain safeguards meant to tame the scope of dangers that dwell within this electronic landscape.

21 CFR, Part 11: A Brief Overview

Part 11 of Title 21 of the Code of Federal Regulations (21 CFR, Part 11) outlines the criteria by which electronic records, electronic signatures and handwritten signatures executed to electronic records shall be deemed "trustworthy, reliable and generally equivalent to paper records and handwritten signatures executed on paper."[1]

In broad strokes, the procedures and controls that must be implemented in order to obtain compliance with these regulations include:

1. A robust set of checks and validation processes to ensure the system performs accurately, reliably and consistently toward its intended behavior

2. The generation and protection of records to ensure the data are readily available for inspection

3. Controls around system access and signature execution, including clearly defined consequences for the falsification of data, to ensure only qualified and authorized individuals are able to impact the data

4. An audit trail to document the initial generation of and subsequent changes to the data

These principles must be applied to all electronic records submitted to the agency, as well as all electronic records that are maintained in support of a submission.

A Shared Responsibility

In order to optimize the management of its development pipeline, a sponsor will often leverage the resources and expertise of one or more contract research organizations (CROs) to partake in the development, configuration and/or maintenance of the electronic systems selected to accomplish certain trial activities. The form of these systems can vary, including basic electronic data capture (EDC) to more advanced interactive web or voice response systems (IxRS), electronic diary systems (eDiaries), clinical data management systems (CDMS), clinical trial management systems (CTMS) and electronic trial master file (eTMF) systems. Within this sponsor/CRO operational model, the CRO may even assume many of the primary administrative, technical and/or logistical responsibilities of employing the system(s). Depending upon the exact nature of the sponsor/CRO relationship, a Transfer of Obligation(s) should be established to formally declare, in a written agreement, the precise character of the expectations and responsibilities held by each party toward the conduct

of 21 CFR, Parts 312, 314 or 814 – activities conducted for Investigational New Drug Applications, Applications for Food and Drug Administration Approval to Market a New Drug or the Premarket Approval of Medical Devices, respectively.[2] It is important to note, however, that such a transfer would not ultimately preclude a sponsor's obligation to perform steps of due diligence to ensure the quality and integrity of trial data.[3]

Furthermore, a sponsor's role in the fulfillment of 21 CFR, Part 11 compliance cannot be diminished because conformity to the regulation does not result from a singularly executed activity or off-the-shelf product or feature offered by a CRO. Conformity results from a series of coordinated steps between a CRO and sponsor, all of which combine to result in the balanced development, testing and implementation of an electronic system that has been equipped and validated to achieve its intended performance. Most electronic systems, for example, are built to include features within the application that help to enable compliance. Audit trails and system-access controls (e.g., username/password assignments and expirations) are common examples of such functionality; however, the mere presence of these features does not itself translate directly into compliance. Compliance is achieved through the diligent and proper validation and utilization of these system functions over time, thus resulting in a system that is performing as intended.

Validation

It could be argued that the most important element of compliance is the process employed to validate the system. This process is the backbone of assurance that all other procedures and controls for the system will execute as planned when utilized properly. As mentioned before, each party within a sponsor/CRO model bears responsibility toward achieving and maintaining a 21 CFR, Part 11 compliant state for a system. Even in the most skewed of scenarios where CROs and/or third-party vendors are responsible for operating and maintaining a system with minimal involvement from the sponsor during the trial conduct phase, the sponsor should still provide adequate oversight during the system's development in order to ensure the system's design and construction are poised to attain the intended performance.

A sponsor could fulfill this duty in various ways, the most basic of which may involve the retrospective review of the CRO's validation documentation (e.g., system specifications and testing scripts) compiled during the CRO's internal validation exercises. This type of assessment is particularly critical regarding the review of system processes or functionality that cannot be easily accessed by someone other than the system developer (e.g., the inspection of metadata tables in the database that can only be accessed by a system administrator). That said, some system functions are more easily encountered by routine users (e.g., edit checks) and therefore rest more squarely in the realm of processes that can be directly governed under the sponsor's oversight.

If time and resources allow, a sponsor may want to review the CRO's validation plan prior to the CRO's commencement of internal testing, in

order to ensure the testing exercises and thereby the outcomes of testing (e.g., results from all testing cycles), will be produced as expected. This type of hands-on approach by the sponsor – before and after the CRO's testing stage – may not always be feasible, though the sponsor's review of the final products of testing would be considered a minimum of best practice. At any point during the process, if the sponsor identifies gaps within the CRO's validation plan or has specific questions regarding the outcome(s) of certain test cases, these should be communicated and subsequently explored by the CRO.

Beyond the review of a CRO's internal testing process(es), a sponsor will most often perform user acceptance testing (UAT). Rarely will a sponsor conduct UAT for all elements of a system. The breadth and depth of such a task would be immense for modern day applications and would almost certainly not be a valuable use of sponsor resources given the context of testing that should have already been performed by the CRO. Alternatively, a more resource-efficient approach is the performance of a risk assessment to identify a sub-sample of critical fields and functions that should be targeted for the sponsor's review within the system. Notably, alignment between the Clinical Data Management and Biostatistics teams during this assessment and selection process will serve as a powerful step to preemptively mitigate potential impediments that could hinder the subsequent stages of analysis.

Another significant consideration related to the UAT process is the definition of test data. In most instances, the sponsor should create distinct test data (e.g., ordinal values, drop-down options, etc.) and/or test scenarios (e.g., pathways of a subject through the system) that were not included within the CRO's validation plan. This robust approach to the creation of test parameters will maximize the probability of discovering system malfunctions. However, depending on the depth and scope of the CRO's validation plan, this may not always be the most efficient approach. In some cases, a sponsor may decide to utilize the same parameters formulated within the CRO's validation plan. This approach may serve as a verification of the CRO's internal validation processes and thus the elements of the system tested by the CRO. When utilizing this strategy, the sponsor should devote sufficient effort to the review of the CRO's validation plan to ensure the necessary set of testing criteria are included for inspection. If the sponsor fully endorses the specific aims of the CRO's plan, this approach can save time and money, given that new, distinct testing conditions would not be reformulated. Opportunities to discover system malfunctions, however, may be missed if the breadth of the established test parameters is not fully commensurate with the specific level of risk that must be controlled for within the validation process for the given system. In this way, a sponsor must always make balanced and educated decisions when determining the character and degree to which oversight should be performed.

Conclusion

21 CFR, Part 11 provides direction to enable the valid and reliable implementation of electronic records and electronic signatures within the contemporary landscape of digital applications developed to accomplish a vast range of trial activities. When a sponsor and CRO work together to develop and/or utilize these systems, compliance is attained through partnership and persistence in order to ensure that a given system is designed and implemented to achieve its intended performance throughout the trial's lifecycle.

For additional information regarding system design and development, see the chapter for Design and Development of Data Collection Instruments within the *Good Clinical Data Management Practices* (GCDMP©) manual, published by the Society for Clinical Data Management.

References

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3. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, (1996). Guideline for Good Clinical Practice E6. *Part 5.2.1.*

Author Biography

Derek is a Senior Clinical Data Analyst for Shire Plc. He has worked within clinical research for over nine years and received his certification in Clinical Data Management (CCDM) in 2012. Derek also serves on the Data Basics Editorial Board for the Society for Clinical Data Management. Prior to data management, he worked in program management for Sanford Health, a large healthcare system in the United States. His areas of interest include risk-based quality assurance, data quality metrics and data harmonization.

Clinical and Data Management: A Time to Heal

By Stacy Surensky

"A productive discussion should be less about finger-pointing and more about collaborating to improve outcomes and maximize the effectiveness of healthcare dollars."

- Ron Cohen, M.D. President and CER, Acorda Therapeutics, Inc.[1]
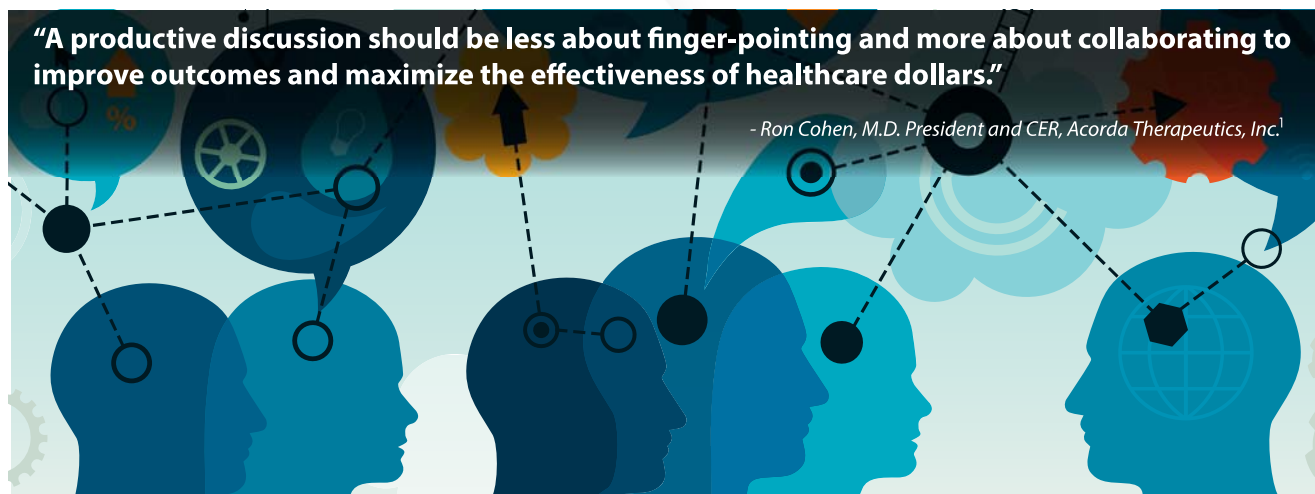
A Long History of Heightened Tension

People new to clinical development may be puzzled by the strained relationship that sometimes exists between Clinical Operations (Clinical) and Data Management (DM). The truth is, those people are not alone. While industry veterans are more accustomed to the tension, they generally are as unsure of its origins and what continues to drive it as someone who has just begun working in the field. There seems to indicate that there is a strong desire to see this relationship improve, but that, as of yet, little progress has been made.

People in our industry understand that although it might be easy to dismiss the often-elevated stress level between Clinical and DM as "the nature of the beast," doing so denies sponsors and Contract Research Organizations (CROs) alike the benefit of a more cohesive effort toward completing their trials. It also denies Clinical and DM the opportunity for a healthier, more productive, and more enjoyable relationship. Consequently, it is imperative that these two groups examine their interactions and look for ways to improve them in the era of patient-centricity and heated debates around drug affordability and policy-making.

Why Healthy Relationships Matter Now

Clinical development is a high-stakes endeavor. Providing complete, concise, and clean data on time and within budget is critical for sponsors and CROs alike. But a healthy relationship between Clinical and DM has implications beyond just the trial at hand. Teams that experience positive interactions built on trust and respect tend to have greater job satisfaction. And greater job satisfaction leads to greater retention and better intra-team chemistry long-term, which is critical to producing excellent results.

Making a conscious effort to develop a more positive alliance between Clinical and DM does much more than simply make the work environment more pleasant. I strongly believe that it directly affects the data integrity, the quality of clinical trials, the achievement of sponsor's business objectives, and the value of the products made available to the patients.

Understanding the Backstory as a Way to Move Forward

One mistake that is frequently made in the effort to improve the Clinical/DM relationship is to focus only on interactions and how to make them better. What is often lacking is an understanding of what is beneath the surface of those interactions. What drives Clinical to behave the way they do? Why does DM react to pressure or criticism a certain way? Answering those types of questions is a good first step toward a resolution.

The search for answers should start with a look at the background of the typical person in each role. Clinical folks often have a master's degree in biology, business administration, or nursing. Some are PharmDs. The rigorous coursework required to attain that type of degree tends to leave Clinical with a strong sense of confidence about their knowledge, skills, and ability to grasp the complexities of a clinical trial.

Folks in DM may come from a nursing, psychology, or an information technology background. Although I encountered a Data Manager with Ph.D. in Chemistry once, often they have a bachelor's degree in some field unrelated to data management. They are frequently "self-made" experts who have learned their trade on the job from colleagues and from their own trial and error, and working their way to Certified Clinical Data Manager (CCDM) certification. Data Management has a firm belief that this type of "trial by fire" has given them a deep, unvarnished awareness of what truly matters in data collection.

As for the work pressures that affect their roles, each experiences high expectations for the quality of their contribution. Clinical is a very visible position and one that tends to feel accountable for the outcome of cross-functional activities and for mistakes or miscalculations made by anyone involved in the trial. They often experience the need to develop and display their mastery of all aspects of a study.

Core DM tasks involve an extended amount of time in front of a computer, however, Data Managers are increasingly expected to be expert

communicators who can serve as a bridge between the front end (i.e., protocol design) and the ultimate outcome (i.e., statistical analysis) of a trial. They have the experience and business acumen to understand the importance of collecting the right amount of the right data, but may not have the practice, the clout, or the expertise to deliver their opinions in a constructive and compelling manner.

Figure 1[2]

MindTools Top Values Exercise

Use the following list of common personal values to choose the 10 top values of what is important to you.

Accountability	Excellence	Perfection
Accuracy	Excitement	Piety
Achievement	Expertise	Positivity
Adventurousness	Exploration	Practicality
Altruism	Expressiveness	Preparedness
Ambition	Fairness	Professionalism
Assertiveness	Faith	Prudence
Balance	Family-orientedness	Quality-orientation
Being the best	Fidelity	Reliability
Belonging	Fitness	Resourcefulness
Boldness	Fluency	Restraint
Calmness	Focus	Results-oriented
Carefulness	Freedom	Rigor
Challenge	Fun	Security
Cheerfulness	Generosity	Self-actualization
Clear-mindedness	Goodness	Self-control
Commitment	Grace	Selflessness
Community	Growth	Self-reliance
Compassion	Happiness	Sensitivity
Competitiveness	Hard Work	Serenity
Consistency	Health	Service
Contentment	Helping Society	Shrewdness
Contin. Improvement	Holiness	Simplicity
Contribution	Honesty	Soundness
Control	Honor	Speed
Cooperation	Humility	Spontaneity
Correctness	Independence	Stability
Courtesy	Ingenuity	Strategic
Creativity	Inner Harmony	Strength
Curiosity	Inquisitiveness	Structure
Decisiveness	Insightfulness	Success
Democraticness	Intelligence	Support
Dependability	Intellectual Status	Teamwork
Determination	Intuition	Temperance
Devoutness	Joy	Thankfulness
Diligence	Justice	Thoroughness
Discipline	Leadership	Thoughtfulness
Discretion	Legacy	Timeliness
Diversity	Love	Tolerance
Dynamism	Loyalty	Traditionalism
Economy	Making a Difference	Trustworthiness
Effectiveness	Mastery	Truth-seeking
Efficency	Merit	Understanding
Elegance	Obedience	Uniqueness
Empathy	Openness	Unity
Enjoyment	Order	Usefulness
Enthusiasm	Originality	Vision
Equality	Patriotism	Vitality

And so, as with any relationship, Clinical and DM come to the table with "baggage." What we need to do is find an effective way to convince both groups to check their bags at the conference room door.

Of Alignment and Language

For all its seeming complexity, there are those who wonder if the problem with the Clinical/DM relationship is as much one of communication as anything. I feel that the two groups are more in alignment than they believe, and that significant improvement in relations can be achieved simply by each side working to deepen their understanding of the other's lexicon and communication style.

After all, Clinical and DM are working toward the same goals. Everyone finds it rewarding when a trial succeeds – both emotionally, i.e., helping the patients, and in terms of the impact on their growth and ultimately their career. So, perhaps an increased effort toward understanding what the "other side" sees as the most effective way to achieve the shared objective can help the two groups find a more mutually beneficial middle ground.

An Experiment in Perspective

As a Certified Professional Coach and clinical development professional with more than 20-years of experience, I thought I should test this hypothesis. I conducted an experiment in comparing the values that drive the behavior of Clinical and DM. With me providing input as a DM leader and with a colleague sharing her perspective as a clinical operations leader, we each selected our Top 10 Values from a list of values compiled by a career guidance organization called MindTools.

Figure 2[3]

Top 10 Values

Clinical Operations Leader	Data Management Leader
Accountability	Accuracy / Quality Orientation
Accuracy	Clear-mindedness
Challenge	Elegance
Compassion	Expertise
Efficiency	Insightfulness
Excellence	Making a difference
Intelligence	Practicality
Strategic	Resourcefulness
Teamwork	Strategic
Timeliness	Teamwork

* Highlights represent top 3 values.

We then highlighted the three values from that short list that we felt were most important. The results from this exercise revealed both expected similarities and distinct differences in our approach:

While this type of comparison won't necessarily result in immediate behavioral change, in my case it did open my eyes to the differences in our perspectives. My colleague's top three values are accountability, excellence, and timeliness. This makes sense, as she is being held responsible for outcomes by the sponsor and therefore needs her team to be accountable as well. And what the sponsor is looking for is an excellent result delivered on time, so she has adopted that focus as well.

One of my top values is accuracy. Because being accurate can take longer, there is a possible conflict with her timeliness value. At some level you already know your values and have a good guess as to the other person's drivers. But seeing them on paper brings them to the forefront. As a result, this exercise caused me to think about how I can better communicate with Clinical by framing communications in a way that resonates with them. It also helped tune my listening so I can better hear what my colleague needs from my team of data managers as we work together to give our sponsors the best possible product.

I would strongly encourage Clinical and DM teams to go through this type of process. It probably won't change your relationship immediately, but an awareness of the results — and perhaps revisiting them periodically — will, I believe, begin to bring down barriers over time.

An Informal Observation about Personality Types

I believe that good listening, informal observations, and acknowledging what we hear and see can help bridge the gap between Clinical and DM. My organization, PROMETRIKA, recently conducted a round table[4] with Clinical and DM to talk about the best way to facilitate reporting and identification of data trends. The two groups were invited in equal numbers. Of the Data Management invitees who accepted the invitation, only 33% actually attended. On the Clinical side, 100% of invitees who said they would attend ultimately participated in the session.

These numbers make me speculate that while DM has strong opinions about how trials are run and wants to express those opinions, they may be less likely to speak their mind in an open forum setting. Many from Clinical in attendance said afterward that they wished DM was better represented.

What are the effects on DM and the Clinical/DM relationship of missing out on opportunities to be heard? What are the assumptions that cause us to skip meetings where our opinions matter? Is it that DM team members tend to be more introverted or that we simply don't feel we have enough substance to contribute? It may be that it's time for us to ask ourselves some tough questions. And the same maladaptive assumptions and behaviors exist on the Clinical side and should be questioned. Why can't we, Clinical, trust DM to do its job? What is driving our need for control? Are we failing to encourage, and listen to, feedback?

A Prescription for Healing

Moving Clinical and DM toward a more positive, aligned relationship starts with increasing our ability to understand what another person is experiencing emotionally — raising what Michael Beldoch, and later <u>Daniel Goleman</u> coined as our "emotional intelligence" or EQ, as distinct from our IQ. But it can't stop there. People in these two very different but critically important roles have to take action, and I would encourage those on the DM side to begin the process and be courageous enough to go first.

There are Three Key Steps that can Lead to Immediate Improvement:

Create Dialog

To promote constructive conversation, it is important to adopt an "asking" as opposed to a "telling" communication style, as the former has been shown in studies to improve collaboration and foster creativity. Team members should ask open-ended questions, especially those that start with "what," "where," and "how." Questions beginning with "why" tend to put the listener into a defensive posture.

People should also seek to validate each other's emotional connection on the issues. You don't have to agree with the content, but showing empathy goes a long way. This can be done with statements like, "Of course you feel strongly that this field should stay on the form since it was so challenging to reconcile the data on the prior project."

Demonstrate Credibility and Earn Respect

Team members could come to meetings — both formal and informal — ready to share relevant experiences and best practices as a way to demonstrate their credibility and earn respect in advance of addressing the inevitable sticky issues that arise.

Another aspect of this step is for Clinical and DM to speak their mind confidently, but as objectively as possible. State the specific data collection needs clearly, describe the reason you are requesting this change. What are the benefits of following your recommendation? What is the impact of going with an alternative? And, team members should make a concerted effort to listen carefully to what the other person is saying and reply using some of the same words and phrases. So often people are busy preparing their response in their head before the speaker even finishes a statement.

Be a Facilitator

People in both groups frequently believe they are speaking (and must speak) for everyone on their team or even everyone in the room. A more valuable approach, and one that will help a group achieve consensus more quickly, is to encourage everyone at the table to share their thoughts in a free-flowing exchange of ideas. Don't be attached to a specific outcome. Bring diverse perspective together. Be an integrative thinker. Be a gentle and confident master facilitator.

Great Results from Diversity of Opinions

Clinical trials are more efficient, more effective, and frankly, more enjoyable when Clinical and DM work in harmony. However, it is important to remember that a successful team isn't one that is always in agreement. What is important is that both groups feel that their opinions are valued and respected, and that they are very comfortable sharing them.

The Clinical/DM relationship won't be repaired overnight. But every milepost on the path to healing is a notable achievement. In the end, a strong, healthy relationship is achievable and worth striving for.

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3. Figure 2. PROMETRIKA Clinical Operations and Data Management selected values. *Boston, July 2016.*

4. PROMETRIKA Roundtable Event. How can pre-trial planning of tools between Clinical Operations and Data Management teams be improved to yield a more efficient and effective clinical trial process? *Boston, MA, June 2016*

Author Biography

Ms. Stacy Surensky, *Director CDM has over 20 years of experience in the biopharmaceutical industry. Her technical expertise includes Data Management, Database Programming, and SAS® programming. She spearheaded the strategic global expansion of data management teams and led cross-functional teams in the successful completion of clinical studies in preparation for regulatory submissions.*

Prior to joining PROMETRIKA, Ms. Surensky was Senior Director, Data Management at Vertex Pharmaceuticals, and held various leadership positions at Averion, PAREXEL, and ImmunoGen.

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Clinical Trial Data Reporting Methodologies – Historical and Current Perspective of Reporting Tools that Support Data Cleaning, Tracking, Reporting and Forecasting at Gilead Sciences, Inc.

By Maria Fernanda Valverde da Silva, Jared Smith, Valerie Reaves, Manasi Ghosh, Robert Complita, and Ligia Kilinski Cevasco

Summary

Clinical data reports are an important tool for data review. Independent of the complexity and extent of a clinical trial, data metrics are used in cross-functional teams to analyze multiple aspects of the trial, such as the conduct, results and efficacy of a study. The Clinical Data Management (CDM) team at Gilead achieved a significant improvement with the tools provided to our study management teams (SMT) to address their data management needs. However, there is a demand for increased functionality, delivery method and format of the reports. While basic SMT needs are being met, the lack of standardization is noticeable not only across the different Therapeutic Areas (TAs) within the company, but also across different studies within the same TA.

Gilead has been working with the flexibility to define report parameters around subject status, data sweep time points and data-cut dates, in addition to other popular reports. All that led to a production of complex reports from their components. Now we have reached a point where there is a demand for simplicity, standardization and additional metrics, such as Investigator signature status, time to completion for data entry or Source Data Verification (SDV), projections and protocol deviations. By analyzing the current practices and tools within each team, we determined that we need to explore new options and approaches to better satisfy the needs of our team, which can be achieved through:

1) Analyzing the current practices and tools within each TA/team and synthesizing the best solution from their components

2) Exploring the limits of our current tools and practices to assess how they can be adapted and

3) Collaborating with other study team members to make fully informed decisions.

Nevertheless, there are some challenges, considering various approaches and needs between TAs, additionally the relevant data source changes over the course of a study (e.g. enrollment vs. conduct). Furthermore, the platforms we currently have limit our ability to provide a report that is interactive with the ability to integrate data from various data sources. For instance, the integration of Interactive Voice/Web Recognition Systems (IXRS) and Electronic Data Capture (EDC) in real time, which is a challenge based on consistent specifications from various TAs. The focus of this article is to provide a historical review, to discuss the current state of Gilead CRF data collection metrics and forecasting tools, and to identify unmet needs in the current product through a survey with CDM and Clinical Operation (ClinOps) members. The article also outlines the company's future direction, including initiatives and goals to create a set of reporting tools that are standard and meet the needs of all TAs.

Introduction

Clinical trial management requires efficient assessment of the clinical data for factors that lead to the timely delivery of complete, consistent and accurate data for analysis. Data reports are tools that a Study Management Team (SMT) utilizes to assess the state of clinical data collected during a study and to help inform decision-making during the course of a trial. Reporting tools, whether designed to provide overarching trends within a study population or to report data of granular detail for a single subject, can support the role and benefit all members of the SMT if designed to provide high-value information accurately and in a timely and accessible manner.

Currently study data reports at Gilead are created using multiple methods and platforms, are distributed via email lists or are saved to a network directory accessible to team members.

The following methods are used to create Case Report Form (CRF) reports:

- manually by a Clinical Data Manager (CDM),

- SAS-programmed reports by Clinical Programmers (CP) utilizing data from transferred datasets, and

- Medidata Business Objects XI (BOXI) reports by EDC programmers.

Although these data reports largely meet the needs of the SMT, they could be further improved in terms of content and distribution methods. Most reports are generated and distributed by the Clinical Data Manager, EDC Programmer or Biometrics Clinical Programmer on a study-by-study basis.

The lack of a standardized suite of reports results in several issues, such as:

1) Increased ad-hoc requests from the SMT,

2) Difficulty in comparative analysis across different studies,

3) Inconsistent expectations from the SMT (based on past experience with non-standard reports) and

4) Resource redundancy.

A need for standardized study report activities and metrics has been determined to solve this issue. While there are no regulatory instructions related to metrics, there are guidance documents that discuss the importance and can help with standardization of Metrics, i.e., the Good Clinical Data Management Practices (GCDMP) from the Society of Clinical Data Management[1].

The challenge lies in developing one-size-fits-all-report detailed enough to provide value, but encompassing and flexible enough to meet the needs of all members of the SMT.

Historical Review of Gilead CRF reporting tools and Data Review

Prior to 2011, studies at Gilead were conducted and reviewed using multiple EDC platforms due to changes in preferred EDC vendors and inheritance of studies on other EDC platforms by way of corporate acquisitions. These include, but are not limited to:

- DATATRAK
- Medidata Rave
- Oracle (formerly PhaseForward) InForm
- Oracle Clinical & Remote Data Capture (OC/RDC)
- OmniComm TrialMaster
- Gilead custom SAS reports (legacy studies)
- XClinical MARVIN

Table 1: EDC vendors used for each category of reports.

METHOD OF PRODUCTION			
	EDC reporting tool	SAS programmed	Manually produced
Projected Visits	Medidata Rave	Medidata Rave Oracle InForm	Oracle Clinical
CRF Tracking	Medidata Rave XClinical MARVIN	Oracle InForm	
Outstanding Query	Medidata Rave Oracle Clinical Oracle InForm XClinical MARVIN		
Lab Listings		Medidata Rave Oracle InForm	
Subject Tracker	Medidata Rave XClinical MARVIN	Medidata Rave Oracle InForm	Oracle Clinical
Data Cleaning Progress Report	Oracle InForm XClinical MARVIN		DATATRAK Medidata Rave Oracle Clinical Oracle InForm Gilead custom SAS reports
Data Cut Tracker			Medidata Rave, Oracle InForm, Oracle Clinical
Outstanding SDV	Medidata Rave Oracle InForm XClinical MARVIN	Oracle Clinical	Oracle Clinical
Subject Enrollment Tracking	Medidata Rave Oracle InForm XClinical MARVIN		
Query Detail	Medidata Rave Oracle Clinical Oracle InForm XClinical MARVIN		

The available metric reports were generally of limited scope (e.g., SAS-programmed expected visit date projections and overdue data-entry reports). Outstanding data query reports were available to the SMT through the EDC platform's reporting module. These reports were saved to a specified location on a network directory and distributed via e-mail on a scheduled or ad-hoc basis to SMT members. Data-cleaning trackers are created manually by the CDM team and distributed on an ad-hoc basis. Table 1 shows which methods of platforms were used on each type of most common reports used during the course of a study.

With no guidance, the standard for producing data reports was for the study lead Clinical Data Management Associate (CDMA) to adopt existing metrics from concurrent studies within the TA. This approach to developing reports, combined with the use of multiple EDC systems, created an environment in which the available experience and technical expertise of the study team members shaped the final product delivered for each study. The result, though meeting the immediate needs of the SMT, left undesirable high level issues of resource management and clinical trial management within Gilead by:

- Creating one-off specification and programming efforts not transferrable to other therapeutic areas within Gilead.
- Producing an inconsistent product between TAs that subsequently creates advantages or disadvantages for the SMT relative to other studies or therapeutic areas within Gilead.
- Developing technical expertise, but not sharing across data management TAs, does not promote the creation of robust clinical data metrics that benefit all members of the SMT and all therapeutic areas.
- Using multiple EDC platforms creates an environment of specialized knowledge within the clinical team members of the SMT that is not transferable to other therapeutic areas within Gilead.

Current Gilead CRF Reports and Data Review

In 2011, Gilead chose Medidata Rave as the sole EDC system for all therapeutic areas. This was a step closer to standardization as Rave allows the production of data reports primarily through BOXI reports, Rave 360 reports and the Rave Reporter module.

Currently, data review for sources outside of Medidata Rave are handled by SAS reports and edit checks or are manually produced using a combination of Rave Reporter and MS Excel.

Table 2 provides a complete list and description of the programs and/or platforms used for report generation and data review at Gilead.

Table 2: List of the programs and/or platforms and its description used for report generation and data review at Gilead.

PLATFORM	DESCRIPTION
Medidata Rave	
Business Objects XI (BOXI)	Users can create their own reports and have an ability to save the specs in their individual account or for public use (among users with the URL, study, and Reporter Module access). These reports can be set-up to run automatically on a scheduled basis and either saved within BOXI or emailed as an attachment. Any variable that is available on the CRF captured in Rave can be pulled for the report.
JReview	Similar to BOXI, users can create their own reports. However, these reports are only for individual use. Report configurations can be saved and run at a later date. Any variable available on the CRF captured in Rave can be pulled for the report.
Medidata Reporter Module	Medidata provides a few pre-programmed reports that are available to any user with access to the report module. These reports cannot be modified in Rave. A user can download the report and modify it in MS Excel.
Rave 360 Reports	Pre-programmed reports that are modifiable by the user. Reports can be viewed from a macro level. Data can be drilled down to the micro (subject) level.
SAS	
SAS Programmed	Statistical Programmers (SP) program reports using SAS based on specifications provided by the CDM team. The reports can be automatically run on a scheduled basis or manually. While these are some of the most comprehensive and validated reports, they are also the most costly at this time.
JMP	Clinical Data Managers use JMP to create metrics from SAS datasets. Specifications can be saved and reports can be run manually at a later date.
MS Excel	
Vendor Reports in MS Excel	Majority of external vendors contracted to handle portions of the clinical data (i.e., labs, central ECGs, radiological data, IXRS) provide metrics to Gilead CDM and clinical operations. When applicable, these reports are used for data cleaning and specified in the Data Quality Review Plan (DQRP).
Manually produced MS Excel	MS Excel tracking spreadsheets are created by importing of data from any available report and then manually modifying the fields. These reports are distributed to the study team or are used a data cleaning tool by the CDM team.

With a variety of programs available to generate reports, it is difficult to reach uniformity. If there is no identified standard, it is difficult to assess the overall status of different studies. Having no common way of reporting data within the same TA based on study team requirements makes it difficult for a CDMA to adopt the approach another CDMA has previously taken for a similar study. This results in different ways of presenting the data in a study data report. Table 3 outlines how specific metric reports are generated for each therapeutic area within Gilead.

Table 3: Metric reports generated for each therapeutic area. CV (Cardiovascular), HBV/ HCV (Hepatitis B/C virus), HIV (Human Immunodeficiency Virus), ONC (Oncology), PH I (Phase I studies), RESP (Respiratory).

CURRENT METHOD OF METRIC GENERATION						
Report	Therapeutic Area and Method of Report Production					
	CV	HBV/ HCV	HIV	ONC	PH I	RESP
Projected Visits	BOXI	BOXI	BOXI	BOXI		
CRF Tracking	BOXI	BOXI	BOXI	BOXI		
Outstanding Query	BOXI, Rave 360	BOXI, Rave 360	BOXI, Rave 360	BOXI, Rave 360	BOXI, Rave 360	BOXI, Rave 360
Lab Listings	SAS	SAS	SAS	SAS		
Investigator Response Assessment	NA	NA	NA			
Subject Tracker	BOXI MS Excel	BOXI, Manual MS Excel, Rave 360	Manual MS Excel	SAS		
Data Cleaning Progress Report	Rave 360	Rave 360	Rave 360	Rave 360	Rave 360	Rave 360
Data Cut Tracker	Manual MS Excel	Manual MS Excel	Manual MS Excel	SAS		
Outstanding SDV	Rave Reporter	BOXI, Rave 360	BOXI			
Reconciliation of e-Learning vs. UAW	Manual MS Excel	NA	SAS			
Subject Enrollment Tracking	Rave 360	BOXI, Rave 360	BOXI	Rave 360	Rave 360	Rave 360
Special Character Issues	SAS	SAS	SAS			
Query Detail	Rave Reporter	BOXI, Rave 360, Rave Reporter	Rave Reporter	Rave Reporter	Rave Reporter	Rave Reporter

Based on the data in Table 3, several conclusions have been made about the current state of metric generation:

1. Most reports are being generated through Rave. With no established standard for metric reporting across therapeutic areas, CDMAs are utilizing many different reporting functions within Rave to provide data review, cleaning, and reporting.

2. In some cases where the functionality of one report type is too limited or not flexible enough, multiple Rave-based reports are used.

3. Time point based metric and data cleaning reports and data from outside vendors are primarily produced using SAS programmed or manually generated MS Excel reports.

4. Some methods are standard and familiar across all TAs, while others are TA and/or data manager specific.

This variety of reporting tool leads to questions about efficiency of the metric reports:

- What type of data is required?
- Who will benefit from the data?
- How will the data be used?
- Are we being productive?
- Does the return on investment substantiate the need for the report?

Survey to Evaluate Current CRF Data Reports

In order to meet the project goal of determining unmet SMT needs, a survey was created to determine the current satisfaction and expectations of the study teams in different TAs. The survey was distributed to members of Clinical Operations and Clinical Data Management across TAs, both employees of Gilead and outside contractors. Thirty-six responses were received in the following breakdown by TA:

Table 4: Survey responders' breakdown by TA.

THERAPEUTIC AREA	NUMBER OR RESPONDENTS
Infectious Disease (HIV, HCV, HBV)	21 (58%)
Respiratory, Inflammation and Oncology (RIO)	9 (25%)
Cardiovascular	5 (14%)
Phase 1	1 (3%)

A summary of a subset of the survey results is presented below with a focus on core areas as identified by the initiative team.

1. Report Category Most Preferred

Five types of reports were presented in the survey:

Table 5: Types of reports presented in the metrics survey.

TYPE OF REPORTS	EXAMPLES
Real-time EDC study reports:	Data status, page status, query status, enrollment status
IXRS enrollment reports:	Subject level, site level, stratification factors
RIO reports:	Test completion status, test results trending, safety profiles
Projections:	Upcoming projected visits, missing data, eCRFs SDV, PI signoff
Program/TA level reports:	Historical, site key performance indicators (KPIs), such as the query response turnaround time, time between patient visit and eCRF data entry and patient enrollment.

According to the survey, real-time EDC study reports are the preferred overall type of metric supplied in the different TAs, as demonstrated in **Figure 1**.

Figure 1: Preferred type of study reports used at Gilead Sciences in different therapeutic areas. N= number of responses.
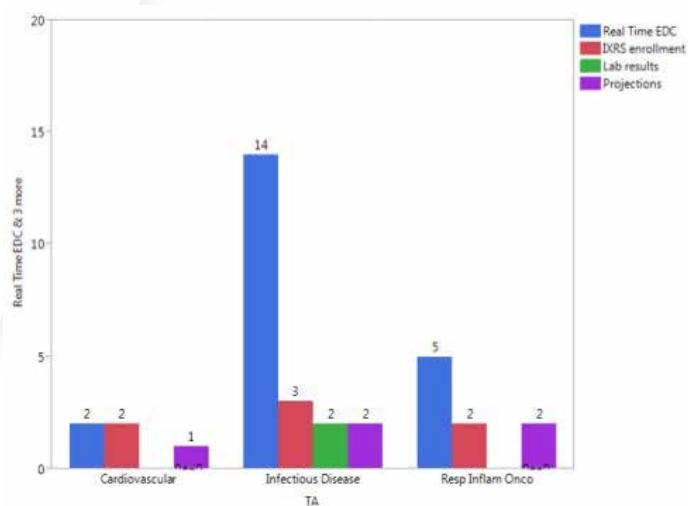
2. Most Valuable Report for SMT:

The participants were asked to rank the most valuable metric currently provided. Two types of study reports stood out (as indicated in **Figure 2**): eCRF tracking and forecasting and Subject status tracking:

3. Valuable Report for SMT Not Currently Provided

In addition to the ranked-choice questions, a request was made to the responders to provide input on missing reports and future reporting tools. Respondents requested the following standardized data reports in order of preference:
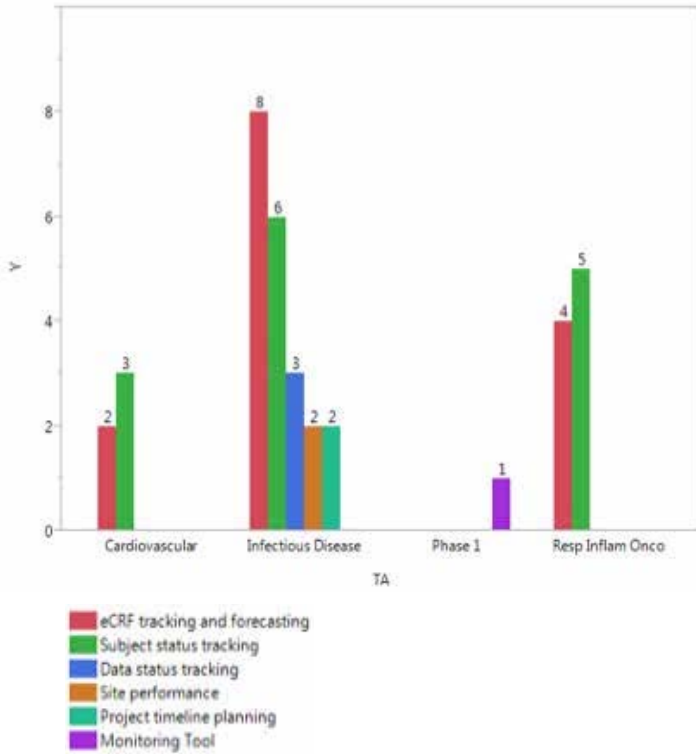
1. Metrics and data from other core laboratories

2. Pharmacokinetic/Pharmacodynamics (PK/PD) sample collection reports

3. Protocol Deviations and protocol amendments

4. Sample reconciliation trackers (e.g., EDC vs. central lab).

Figure 2: preferred targets for data reports by different therapeutic area. N= number of responses.

4. Preferred Delivery Method

The participants were asked to rank the best way to establish the study reports and how they should be presented. According to **Figure 3**, a plurality of respondents chose a single comprehensive report with multiple tabs.
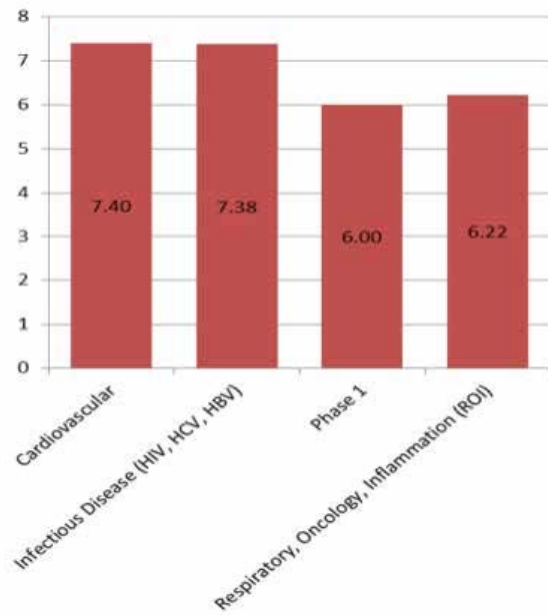
Figure 3: overall preferences of the study reports
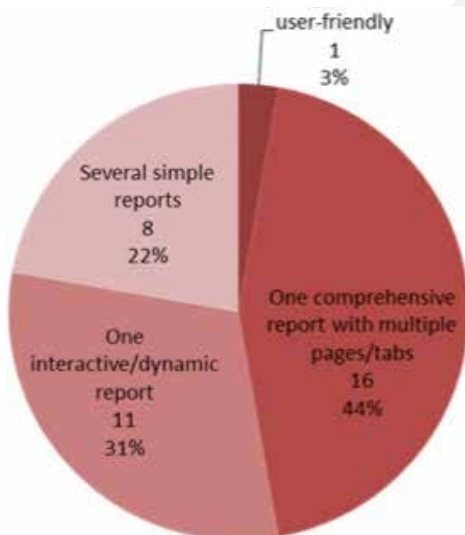
5. General Satisfaction with Current Data Reporting Tools/Reports

Finally, respondents were asked to rate their overall satisfaction with current data reporting tools and reports on a scale of 1 to 10. Overall the SMT is moderately satisfied with the current reports (**Figure 4**):

Figure 4

6. Requested Improvements to Data Reports

The survey requested participants provide input on improvements to the current metric reporting. Below is a summary of that input:

Time-point based reports – the request for reports built around time-points was a common request.

- Quick snapshot of data status
- The BOXI reports… concentrating on the individual data sweep
- The routine BOXI report… milestone trackers
- Filterable spreadsheet that updates daily with new data entered into EDC and SDV'd pages…
- Data sweep reports, missing data, SDV needed, Investigator sign offs needed, etc.
- …identify the data that is pre data-cut and not have someone from CDM spend hours manually checking…
- …data that should be entered (given projections from Baseline visit)

Real-time or daily reports – the need for real-time or daily data metrics reporting was also frequently requested.

- Quick real time snapshot of data status
- Real time, covering all essential study variables and outputs
- Must be updated in real-time…

Survey Conclusions

From the questionnaire we learned that the SMT is moderately satisfied with the current metric reporting.

SMT feedback:

- The basic needs of the SMT are being met with the focus on EDC reports – CRF status and subject tracking
- BOXI is a popular format
- Email delivery is the preference
- One report with multiple tabs is preferred

There is also a demand for increased functionality:

- Flexibility to define report parameters around subject status, data sweep time-points, and data cut dates
- Interactive, real time reporting
- Integration of all data sources, particularly IXRS and EDC
- Additional reports such as Principal Investigator (PI) signature status, time to completion for data entry or SDV, projections, protocol deviations
- Simplify and standardize

Overall Evaluation of Current Data Reports

Overall, the expectations of the SMT are being met, but opportunities still exist to produce data reports that are standardized across all TAs and to provide data reports that are more sophisticated.

Opportunities for improvement include, but not limited to:

- Standardized subject tracker or other data report that can be used for data-cut analyses. Each TA currently builds their own trackers either through manual MS Excel files or through SAS programming.
- The Clinical Operations group needs a tool(s) that can help them communicate clear expectations to CROs, CRAs and external vendors. Specifically, a planning and forecasting tool(s) is needed that can monitor visits, close out visits, and study milestones.
- The Clinical Operations group has a need for user-friendly reports that can be quickly run by members of the clinical team and are readily available at the first patient first visit (FPFV). Examples of reports that would benefit Clinical Operations across all TAs include:

  1. Reports that can drill down to country/region-level metrics,

  2. Data-cut specific reports that can provide an update on the specific set of subjects or the time-point when the data cut was applied and

  3. Investigator Signature Report

- A lack of standard data reports makes it difficult to create a model for assigning resources in clinical operations and programming across TAs.
- Real-time missing CRF pages and protocol deviation reports are needed.

- Other useful reports: Quality of Life (QoL) tracking and vendor-related reports.

To meet the opportunities that have been identified above and to improve the data reports being provided to the SMT, the data source must first be standardized. To standardize the data collection in the EDC for most CRFs across TAs, the Global Library (GLIB) was created in 2012. Associated tools have been developed to take advantage of the standardized data source and to allow for standardized tools for Data Validation specifications (DVS), Data Transfer Specifications (DTS), and data quality reporting, as described in the Data Quality Review Plan (DQRP). The continued leverage of Clinical Data Interchange Standards Consortium (CDISC) standardized data meets many of Gilead-identified goals and justifies the cost and effort associated with producing the more sophisticated reports that have greater drill-down filter options that the SMT requested.

Figure 5 illustrates how a standardized data reporting tool is built upon our current data sources. This model allows for the discussion and improvement of data reporting without the limitations of TA-specific differences in data collection. Although there are many data-reporting platforms in the model below, they are being used in a standardized fashion. Moving forward, the focus of data reporting tools initiative can be increasingly directed toward refinement and improvement, rather than creation and maintenance.

Figure 5: Representation of current data reporting at GSI: In 2012, GSI implemented a Global Library (GLIB) of standardized core EDC elements (e.g., folders, eCRFs, fields, etc.) consistent across all TAs. Standardized forms and data collection fields in the GLIB should be leveraged to create standardized reports across studies.

Standardization of Data Reporting

Standardization is the clear response to a number of challenges faced by the life sciences industry. Data needs to be exchanged in a quick, structured and uniform manner. There is higher pressure to get products

to market leads with an increased amount of data handling in a shorter period of time. As consequence, there is increasing pressure on the Biometrics department to deliver. Implementation of a standardized, streamlined tool where data from different systems are organized, stored and made available to the entire company is the solution.

Metrics are typically used to monitor productivity and ensure the process is operating as intended and resources are properly allocated. Prevention of processing errors is possible by identifying and eliminating the underlying causes via monitoring study metrics.

Mapping the study-specific data into a standard reporting structure creates a data tool that produces consistent outputs and helps increase familiarity among study teams.

In addition to the variety of metrics within clinical data management at Gilead, it is important to clearly define and built a tool to satisfy the high data quality metrics.

Future Direction

The large number of EDC studies in Medidata Rave makes it difficult to identify areas that can be improved in study startup or study execution activities without a top-down summary view that allows management to see the big picture. For example, by developing a number of simple metrics that apply equally well to a single study or an aggregated group of studies, we can measure and visually display performance at the department level, TA, indication, and/or individual study.

Furthermore, the rich set of historical information that has been tracked in the Medidata Rave Sequel (SQL) database allows us to program these reports so that they can pull data from many years of metrics at any time, such as:

- Site performance metrics (e.g., average days to enter visits into the EDC database, average days to respond to queries, average number of AEs/SAEs per site)
- Study-build metrics (e.g., percentage of edit checks that fire queries or adherence to standardized study build timelines).

However, moving forward, each study team should be able to leverage standardized reporting tools both within and across TAs/programs to meet study-level reporting needs with an expected effectiveness (both standardized and automated).

Conclusion

For clinical study data, metric reports are important tools for data monitoring and data cleaning. While the core needs of the SMT are being met by existing data reporting tools, gaps in reporting have been identified along with a noticeable lack of standardization across Clinical Data Management (CDM) teams in different therapeutic areas (TAs). Due to ever-increasing study volume, there is a demand for increased reporting functionality, higher efficiency of delivery methods and report formatting that is tailored to the needs of the end-user. Multiple external study data sources contribute to the complexity electronic case report form (eCRF)

captured in the electronic data capture (EDC) system, Interactive Voice/Web Recognition Systems (IXRS); central laboratory data, among others. The reporting platforms we currently have limit the ability to provide reports that pull data from all data sources.

Providing inaccurate or incomplete study data reports pose a risk to the study milestones, which in turn have a cascading effect on other studies and related tasks that the CDMA works on. The process inefficiencies have logistical impact causing CDMAs to perform time-consuming manual review. Lack of standards makes it difficult for the CDM management team to allocate resources based on time. Better utilization of resources is an important benefit of standardization considering the fact that standard processes are validated providing a better estimate of an average time to complete the task.

The implementation of the GLIB allows for the discussion and enhancement of data reporting without the limitations of TA-specific differences in data collection.

References

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2. *The following are Gilead Sciences internal documents and are not available to the public:*

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   2) SAS Data Validation Specifications (sDVS) Template
   3) sDVS Manual
   4) BOXI Data Validation Specifications (bDVS) Template
   5) bDVS Manual
   6) Electronic Survey - Metrics Reporting of Clinical Trial Data

Author Biography

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# Wearable devices – Future of healthcare; steps towards better life

By Namrata Belekar

Over the last two decades, the healthcare industry is persistently exploring means to achieve better treatment strategies, newer equipment for quicker, efficient surgeries and progress towards patient engagement programs for better compliance to long-term regimes. Besides the medical fraternity, government and research organizations, technology developers, manufacturers, insurance providers, distributors and retailers; patient groups have also made attempts to address the typical fear of surgeries and inconvenience caused to patients and their relatives/ caregivers.

For quick access to real-world data and benefit to the larger population, IT companies are continually developing robust database software, eDiaries, ePatient Reported Outcomes (ePROs) and various devices.[1] These are designed based on the consumers' mode of accessing the technology.

The devices are broadly divided into four categories:

1. **Fitness and wellness** – These measure the speed, calories burnt, sleep time, stride rate, etc. Global players are Nike, Adidas, Fitbit.

2. **Healthcare and medical** – Headsets that measure brainwaves, clothes with sensing devices. Global players are Medtronic, Cardionet.

3. **Industrial and military** – Remote operation for business purposes

4. **Infotainment**
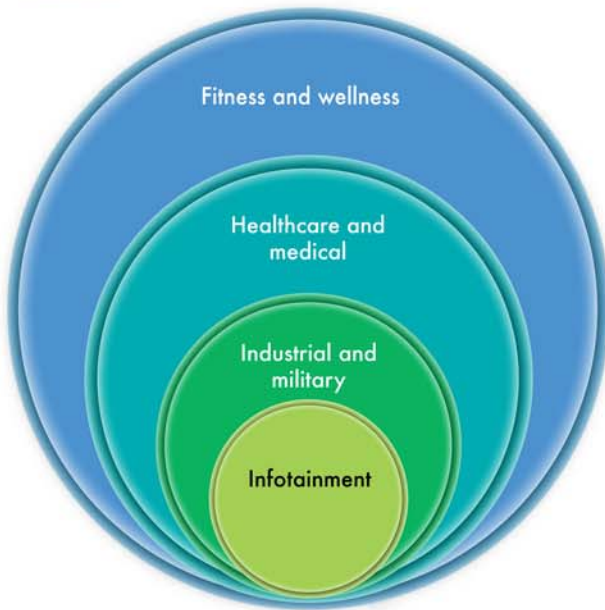
These devices can be further classified as 'wearable' and 'non-wearable' devices.

Wearable devices are mobile devices worn on a user's body or are attached to their clothing. These devices are supported by either Android, iOS or Windows. Physicians have found chronic disease management possible in diabetes, obesity, heart diseases, etc. through such devices. The devices are therefore changing the treatment approaches for patients.

Fitbit, GetActive, Goqii, Pebble are few commercial smartwatch type devices which have a mobile coaching and fitness tracking service which count footsteps. Fin ring worn on the thumb (developed by RHLVision Technologies) is a Bluetooth enabled device when connected to mobile, car stereo or laptop allows gesture control commands, which enables the user to have separate commands (max. 10) for each finger joint when the Fin functionality is customized to that user.

Google glass (developed by Google), is an optical head-mounted ubiquitous computer (like eyeglasses), where the user can communicate using internet via visual, gesture and voice commands. However, this device has been banned due to its privacy-violating capabilities.

Few wearable devices with therapeutic or diagnostic use fall under the regulation of 'medical devices'. These assist in remotely receiving, monitoring and analyzing complete data, eradicating delays and transcription errors.

The Food and Drug Administration (FDA) guidance recommends that manufacturers should follow human factors and usability engineering guidance during the development of new medical devices, focusing specifically on user's safety, device interface, which includes displays, controls, packaging, product labels, and instructions for use, precision and accuracy[3]. A well-designed user interface can facilitate correct user actions and prevent or discourage actions that could result in harm (use errors). Such interfaces should be designed based on the use-related problems collected from customer complaint files, sales staff, journals, professional meetings, newsletters, relevant internet sites, etc. and on past experiences with similar devices.

Manufacturers conduct a 'risk analysis' that includes risks associated with device use and the measures implemented to reduce those risks. As per the Association for the Advancement of Medical Instrumentation (AAMI), risks are defined as a combination of the probability of occurrence of harm and the severity of the potential harm.[4] Due to possible risks posed to multiple stakeholders, 'risk management' becomes a vital concept pertinent to devices.

Medical device studies, usually conducted for claims data, are often single center, parallel-group designs to closely monitor the disease cure over weeks. Some commercially used devices and their related study data are presented here:

1. **FreeStyle Libre Flash Glucose Monitoring System**[5]: It is indicated for measuring interstitial fluid glucose levels in patients (age ≥4 years) with diabetes mellitus. A thin (5 mm long) sterile fibre is inserted on the back of the upper arm skin for 14 days. It automatically captures glucose readings through day and night. The sensor fibre is water resistant and need not be removed during bathing/ swimming. In a study conducted by Abbott Diabetes Care, 93.4% of patients surveyed (n=30) replied as 'strongly agree' or 'agree' for a question that while wearing the sensor, they did not feel any discomfort under their skin. (29 patients completed the study; 1 patient was prematurely terminated from the study after 3 days due to skin irritations in the area where the sensor touched the skin). With every painless 1 second scan, the device provides a current

glucose reading, trend analysis and glucose history. This device is an advance over conventional glucose testing with lancets, test strips and blood.

2. **24-hour Ambulatory Blood Pressure Monitoring (ABPM)**[2]: It uses a small digital Blood Pressure (BP) machine that is attached to a belt around the waist and is connected to a cuff around the individual's upper arm. It is small enough for an individual to resume normal routine activities and even sleep with it on. A clinical study was conducted to compare the office based random-zero (RZ) BP readings using sphygmomanometers vs. ABPM readings in Dietary Approaches to Stop Hypertension (DASH) patients and to gauge the patient's perception on wearing the ABPM device. Of the total 321 adult patients, 54% were men and the mean age for both men and women patients was 45 years. The findings are summarized below:

- Out of the total readings from both devices, more than 90% possible waking and sleeping readings were obtained from ABPM, thus showing better patient compliance.
- Between the readings, none of the estimated treatment effects differed between ABPM and RZ-BP or between waking and 24-h ABPM, showing consistency between devices.
- Interference in daily routine work activities showed the following results:(~45%- not at all, ~45% -somewhat, 5–10%- a lot)

Although between 15 and 20% of participants reported that the monitor interfered with their sleep 'a lot', 96% of participants reported that, except for showers, they wore their monitor for the full 24-h period, which is consistent with the completeness of the study data.

3. **Pulse Oximeter**[6]: It is a sensor device attached to the patient's index finger (or sometimes earlobe) for easy, painless measure of peripheral oxygen saturation (SpO2).

4. **D`OXYVA** (deoxyhemoglobin vasodilator)[7]: It is a pressurized, single-use cartridge containing supersaturated carbon dioxide [CO_2], which sprays a highly concentrated vapor of water and CO_2 gas solution onto the skin surface in a painless, non-invasive manner at ambient temperature and pressure to increase skin perfusion (skin microcirculation). It is attached to the skin, about 1 cm from the wound bed or on left thumb for 5 minutes, minimum twice daily, over a period of few weeks at home. This device significantly improves the tissue microcirculation with cellular oxygenation for wound healing, thus resulting in improvement in pain, quality of life, sleep and mood.

These devices are widely used not only in day-to-day treatment, but also in various clinical studies involving hypertension, diabetes or diabetic foot ulcer, sleep patterns, etc., where continuous need of patient intervention is needed. Thus, these devices help in accurate, timely readings, preventing frequent visits to sites. To launch such devices, a clinical evaluation[8, 9, 10] reports should be prepared by every manufacturer as per the European Commission's guidelines on medical devices.

This report includes the actual clinical data, analysis and conclusions about device safety and performance. Analysts collect huge data from various search engines, process it using software like Hadoop and clean it into meaningful data. However, hospitals and pharmaceutical companies do not disclose such data, affecting its accurate market analysis as well as risk analysis.

RISK ANALYSIS[3]: This is used to identify and analyze the tasks that, if performed incorrectly or not performed at all, could cause serious harm. All risks associated with the warnings, cautions and contraindications in the labelling should be included in the risk assessment. Various risk analysis approaches, such as Failure Modes Effects Analysis (FMEA) and Fault Tree Analysis (FTA) are used. In FMEA, the team brainstorms the possible scenarios that could lead to use error. While in FTA, a diverse team begins by deducing and considering "faults" (use-related hazards) associated with device use and explores how they might lead to failure modes. The results are then used to inform plans for simulated-use testing, which can confirm and augment the findings of the analytical risk analysis processes.

The FDA has characterized the data collected from health professionals as 'incomplete, inaccurate, untimely, unverified or biased'. Such collected clinical data needs evidence of quality of life (QoL) which depicts the user's feelings such as self-care, pain, discomfort, anxiety, depression, etc. while using the device. Examples of QoL questionnaires are EuroQol five dimensions questionnaire (EQ-5D-5L), Visual Analog Scale (VAS) pain index, etc. which are widely used for these purposes. Regulatory bodies face challenges to track the use of such devices, their safety, quality, precision and accuracy that confirms the data reliability across different medical/ physical conditions and connectivity to servers and factors affecting data integrity.

Few challenges that influence adoption of wearable devices are as follows:

1. **Appearance:** Patients give more weight to the effect on appearance rather than the device's utility or functional need. Components or accessories that are applied or connected to the patient play a major role.

2. **Connectivity:** Cloud based technology enables easy synchronization with servers. Components that the user uses to connect, configure, handle to control device operation, such as user graphic interface, Wi-Fi connectivity, device navigation, quality, aesthetics and the issues encountered, result in user's long-term acceptance.

3. **Data security:** In addition to personal data security (Health Insurance Portability and Accountability Act (HIPAA) of 1996), complete product information outlining the purpose of the device, who can access the data, use of multiple encryption methods to protect data privacy and data transmission with audit trail should be considered to safeguard clinical data.

4. **Pricing:** The cost incurred for traditional methods vis-à-vis the cost of the device; influence the buyer's decision for its adoption. Limited battery life, including cost of replacing a battery, repairing, etc. cannot be overlooked.

5. **Changing consumer behaviour:** With the overlapping use of smart phones, wearable devices and various other gadgets, user preferences keep changing. Unpredicted possibilities such as stopping, interruption of device during travelling or network issues may occur. Hence, continuous use, enhancements, advertisements and training for devices become a major factor in their adaptability. Based on a survey in 2014, 22% of the population showed a positive response vs. 78% remained neutral[1].

6. **Untrained hospital staff and illiterate population:** Government hospitals are understaffed and ill-equipped to undertake specialized treatment. Hence the majority of population, especially those who live in rural areas, are unaware of such devices and spend more in traveling cost rather than for the treatment cost. Also, all devices and training material documents are in English, which is a barrier for illiterate people or those not familiar with English.

On April 30, 2014, Amazon.com launched a separate section for buying wearable devices. Google, Microsoft, Apple are making huge investments in this area. Estimates of Apr 2015 predict that sales of such devices may reach up to $53 billion, with 25-35 % annual growth in next 3 years.

With the growing use of devices in larger populations, they empower the user with ambulatory care and self-diagnostic capabilities. Use of mobile medical devices enables medical teams to access the integrated data in real-time. Thus, with acceptance of technology, the use of wearable devices is a step towards a better life that possesses the potential to transform the future of healthcare.

Key words: Challenges, HIPAA, medical device, safety, technology

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Author Biography

Namrata Belekar, Assistant Manager, Clinical Data Management at SIRO Clinpharm, has over 11 years of experience in CDM. She holds a degree in Pharmacy from Mumbai University, India and was CCDM certified, in 2011. Currently, she is responsible for leading the full scope as well as standalone CDM trials in data management at SIRO. She has experience in handling trials for various therapeutic areas including oncology, diabetes, neurosciences and ophthalmology to name a few. Namrata is an active member in quality standards development. She works in data technology initiatives to build robust dashboards through visual analytics and contributes in to business proposals as well.

Using Analytics to Gain Efficiencies in Database Builds

By Jennifer Bush

Efficiencies in database build have long been looked at based on utilization of standards, global libraries and templates to facilitate the design and build of the electronic case report forms (eCRFs). With the advances in analytics, a data driven approach should be considered to utilize the data from past studies to improve the eCRF design.

Analytics has been present in the pharmaceutical industry for many years, spanning multiple aspects of trial development, from manufacturing and research and development (R&D) through portfolio planning and clinical trial operations. Today for clinical trial operations management, most companies have moved from transactional based reporting to some level of analytics. Many of the analytical dashboards currently utilized evolved from the transactional reports or listings into reports displayed in an analytics application, with some companies making the larger leap to true analytics – dashboards with real-time or near real-time data feeds that are visual, based on actions and no longer based on previous Excel capabilities from historic reporting tools.

Now that there are sufficient options to provide operational analytics functionality for clinical operations, what would happen if these analytics were taken even further? From a data management and study design perspective, what if we addressed the concerns we hear from investigator sites routinely about eCRFs – they collect too much data, are too complicated and have too many queries? Research has shown that only 2.4% of the critical data entered in a case report form is every queried1 as a result of a monitoring performing SDV, and monitors and investigator site staff alike spend many hours responding to queries generated from the Electronic Data Capture (EDC) system.

How can analytics be utilized to develop a better eCRF? Three use cases below offer insights into analytics beyond looking at the average time for sites to enter data, the sites with the most discrepancies and which sites take the longest to close a query. While these are all important measures and provide valuable insights, having analytics also offers an opportunity to look for improvements in the design of eCRFs for data collection.

Use Analytics to Identify the Most and Least Commonly Queried Data Elements:

In reviewing data from an analytics application across a number of studies, a drug program or even a therapeutic area, it is relatively easy to determine what data is queried the most or the least. Using that data provides a chance to understand data elements that are queried the most and potentially an opportunity to re-evaluate the design of those elements on a CRF. The first step needs to be an understanding of why those elements are the most queried. This may be due to the way the question is worded, it may need to be clearer, or provide different opportunities for data entry – possibly simplified into multiple data entry fields to capture complex questions or include branching logic to allow an easier flow to provide the data. Perhaps it is queried the most because it is collected differently in the source documentation or Electronic Health Records (EMR/EHR) systems and the differences result in transcription errors. It could be due to the eCRF lacking the specific units of measure used

by the sites, requiring study coordinators to convert the result so it can be entered in the eCRF field, it could be due to a different type of data required in the CRF, for example a list of values that does not contain values captured in the source records. Once the reasons for the queries are determined, through review of the CRF design, and potentially even discussion with investigator sites, a redesign of the CRF questions/fields could save time and reduce queries significantly for future studies.

Furthermore, using the analytics data to determine the data fields that are the least queried on a CRF can provide valuable insights as well. Again the first step is to determine why those fields are the least queried. Is it because they are straightforward questions that are simple to answer – perhaps a blood pressure reading for example, or perhaps it is part of a data element that is not possible to change – such as an electronic patient reported outcome (ePRO) response directly from the patient, or an electrocardiogram (ECG) reading directly from a device? In this case there may be no change needed to the CRF. However, other reasons could be cause for further evaluation:

- Is the data not frequently queried because it is not part of a monitoring review plan?
- Is it never part of a critical element in a risk based monitoring study design?
- Is the data a variable not used in analysis?

Identifying some of the potential reasons why the data are seldom queried, beyond simplistic question writing and capture on the CRF, can trigger an evaluation of the CRF field:

- If the data is never used for analysis and is not a critical variable, is it worth the investment to develop, program and test the edit check and clean the data on that variable?
- Does the query need to exist?
- Does the data element even need to exist?

Historically, eCRFs have captured many data elements that are never utilized for analysis – either for that particular protocol, or for exploratory analysis later, which is a common reason given for inclusion of data fields on eCRFs. Using analytics may provide an objective way to evaluate data fields collected today versus what may be needed in future studies, reducing both CRF and query design time and investigative site staff data entry time.

Predict the Most Commonly Queried Data Elements Based on Past Study Data:

The pharmaceutical industry as a whole is moving in the direction of predictive analytics. In the clinical operations space, these predictive analytics are most commonly used for enrollment and drop-out predictions and adverse event planning, to name a few examples. However predictive analytics capabilities can be expanded beyond clinical operations needs and can be utilized in many other areas, including CRF design.

Using Analytics to Gain Efficiencies in Database Builds

Looking at historical data for a particular drug program or therapeutic area, if you can reasonably predict at the start of the database build the CRF fields that are most likely to be queried, how can you use that to your advantage?:

- Can you provide better guidance in CRF completion guidelines, site newsletters and information to the CRAs during study team training to reduce these queries?
- Can the questions/fields be modified and improved to produce fewer queries?
- Do the amount of edit checks need to be reduced?
- Are the queries leading to modifications of data for critical study end-points?

Are there opportunities to remove edit checks from CRFs?

In a similar vein to reviewing data elements with the fewest number of edit checks, another opportunity is to review data elements in which edit checks are written but the edit is never utilized. A first review of analytics data could determine:

- Are there queries that have never "fired" on a particular CRF field?
- Is the edit check on a critical variable or non-critical variable?
- If the edit check is on a non-critical variable and has never fired, is the edit check required to be continually programmed and tested with each new database build?

These are just three use cases in which analytics could help design a more efficient eCRF, potentially reduce edit checks and reduce queries. With the volume of data we have available in analytics applications, looking beyond operational dashboards and focusing on providing operational efficiencies based on historical data reviews and predictive analytics offers new capabilities to improve not only eCRF design and build, but many areas in the clinical trial process where data is collected, reviewed or analyzed.

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Author Biography

Jennifer *is a life sciences professional with over 17 years of industry experience in both business and IT environments. Jennifer has worked in large pharma, large CRO and IT, working in both business and IT departments managing data transformation and loading, EDC implementation and managing development of clinical trial management systems. Jennifer now works as a Life Sciences Product Strategist at Oracle focusing on clinical trial management and monitoring offerings and holistic risk based monitoring.*

Ask SASsy

By Kelly Olano

Dear SASsy,

What is an easy way to remove the formats from all the variables in a SAS data set?

Unformatted in Union City

Dear Unformatted,

When formats are permanently associated with SAS data sets, it is difficult to open them in DATA steps/procedures or view them in SAS Explorer. Especially if you don't have the associated format catalog! In that case it is necessary to first invoke the NOFMTERR option to avoid the error but still keep the formats, or FMTSEARCH option for identifying the location of the format catalog. Removing the formats permanently may be an option if the formats are not needed and you don't want the headache of using the options. Removing formats permanently is simple using the DATASETS Procedure. Here is an example:

```
LIBNAME sasdata "c:\folder";

PROC DATASETS LIBRARY=sasdata NOLIST;
     MODIFY somedata;
     FORMAT _all_;
RUN;
```

The LIBRARY= option specifies the libref where the SAS data set somedata resides. The NOLIST option suppresses the printing of the directory. Removing it will create a listing of all of the SAS data sets in the directory. The MODIFY statement identifies the SAS data set that will have the formats removed. It is possible to have multiple MODIFY statements in one DATASETS procedure. The FORMAT statement with _all_ strips the formats off of all of the variables in the SAS data set. To remove formats only from a subset of variables in the data set, just specify them in the FORMAT statement, as seen below.

```
LIBNAME sasdata "c:\folder";

PROC DATASETS LIBRARY=sasdata NOLIST;
MODIFY somedata;
FORMAT var1 var3 var5;
RUN;
```

Happy Programming!

If you have a question for SASsy that you would like to see in a future edition of Data Basics, please email kelly.olano@cchmc.org. Thanks!

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