Knowledge, Perceptions and Practices of Risk-Based Monitoring Among Clinical Practitioners in the United States

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Declaration Page

I declare that this thesis that I now submit for assessment on the program of study leading to the degree Master of Science in Pharmacy Administration and Policy Regulation has not been submitted for the purpose of a degree at this or any other higher education institution. It is entirely my own work and has not been taken from the work of others save to the extent that such work has been cited and acknowledged within the text of this work.

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Abstract

This study investigated the current knowledge, perceptions, and practices of Risk-Based Monitoring (RBM) using written and verbal responses to an ethics review board approved questionnaire. Responses were collected from individuals involved in the practice, oversight, and implementation of clinical trial monitoring in the USA. RBM was viewed as a positive force with a bright future. However the results suggested that a renewed focus on change management strategies is needed to ensure RBM practices penetrate all levels of clinical trial management. The site sponsor/site operational relationship was identified as a key RBM component. Shortcomings in this relationship were identified as significant operational barriers to effective RBM practice. Respondents indicated that current RBM training efforts were lacking. Because RBM is new and its practices deviate significantly from the past total monitoring efforts, both industry and the clinic need to work harder to ensure that everyone involved in clinical trial monitoring understands these differences. Fortunately, overcoming the identified barriers will not require massive changes to current RBM practice. By refocusing efforts on the sponsor/CRO and investigative sites to attain RBM governance, develop quality control plans, institute an optimal RBM platform, and improve training, the true promise of RBM is within reach. Each of these are critical pieces to an effective RBM implementation methodology and correcting initial stumbles in their implementation can assure the RBM future is as promised.

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Table 1. Abbreviations

CM	Centralized Monitoring
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Clinical Research Organization
CTTI	Clinical Trials Transformation Initiative
DRP	Data Review Plan
EDC	Electronic Data Capture
EMA	European Medicines Agency
US-FDA	United States Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Council for Harmonization
IT	Information Technology
iQMP	Integrated Quality Management Plan
KRI	Key Risk Indicators
OSM	On-site Monitoring
QbD	Quality by Design
PhRMA	Pharmaceutical Research and Manufacturers of America
R&D	Research and Development
RMV	Remote Monitoring Visit
SDR	Source Data Review
SDV	Source Data Verification
SMP	Site Monitoring Plan
TCBI	TransCelerate BioPharma Inc.
RBM	Risk-Based Monitoring
RMP	Risk Management Plan

Chapter One: Introduction

1.1 Introduction

This chapter introduces the background and significance of the research question that this study will address with the aim of developing a clear picture of the overall goals and content of this study. In order to truly understand a problem, one must develop a clear understanding of its scope, significance, and background. Let us begin.

1.2 Problem Background

Biopharmaceutical companies are constantly striving to help patients to live healthier lives through developing new medicines and conducting robust and meaningful clinical trials with the hope that through careful management of patients and acquisition of data the drug may be proven safe and effective. The clinical trial process is mired in complexity, with ever-evolving regulatory standards and burdensome administrative costs (Bois, 2016; Shukla, 2016). A large part of these regulations and costs are related to trial management and execution (Alsumidaie/Henderson, 2016). In an effort to improve efficiencies, reduce errors and ensure an expeditious time to market, integrated monitoring approaches are being considered and implemented across the pharmaceutical industry (Wilson, 2014). The current principal focus to these efforts is the identification and implementation of risk management methodologies at a much earlier phase of trial execution than had previously been considered (Knepper, 2015; Alsumidaie/Henderson, 2016). Rather than relying upon the data acquired in a trial to identify risks and design strategies to avert them, regulatory agencies are requiring that industry work harder to use pre-trial data and our vastly increased understanding of biological modes of action and human systems to identify likely risks during the study design phase and thus ensure risk mitigation practices are implemented effectively and proactively during study conduct (ICH, 2016; FDA, 2013; Brosteanu, 2017;).

Moving away from conventional drug development practices towards a more risk-based philosophy in conjunction with harnessing advances in technology is not only greatly supported by regulators but is a golden opportunity that the pharmaceutical industry should seize and further explore (ICH, 2016; FDA, 2013; Alsumaidaie/Henderson, 2016). A couple of key questions one might ask at this stage are: What is the industry doing to adhere to this new regulatory mandate? Is the industry being innovative with risk-based approaches to monitoring?

Risk-based monitoring (RBM) is defined by the International Committee on Harmonization (ICH) as "An adaptive approach to clinical trial monitoring by performing on-site, remote and centralized activities to reduce risks in areas that have the most potential to impact subject safety and data quality" (ICH, 2016). A risk-based approach to monitoring is a reimagined proactive approach to clinical trial implementation and study oversight. It utilizes data and site level information to determine where to focus monitoring efforts in order to maximize patient safety and data quality. It also ensures that the right technology is implemented in monitoring so that a real-time analysis of trending information across the clinical trial sites can be implemented. It is only under these conditions that risk based monitoring can truly function to identify and avert potential crises of human health (Sullivan, 2015; Shukla, 2016). The idea of data driven monitoring is a combination of data trending, utilization of key risk indicators, remote surveillance, centralized activities and targeted on-site visits: each of these efforts are supposed to focus resources on risks factors that have the most influence on safety, data integrity and quality (TCBI, 2013; Wilson, 2014; Shukla, 2016).

RBM is the practice of using relevant clinical data to guide the "monitoring activities" that are carried out at any given site contemporaneously, as an alternative to fixed-interval monitoring schedules (TCBI, 2013). Risk-based monitoring is part of a clinical trial quality

management system and its methodology is built on the concept called “Quality by Design” (QbD) (Korieth, 2017). The pharmaceutical QbD is a systemic approach to improve product development and at the heart of it is building in quality (Yu, 2014). RBM is a central component of QbD risk-assessment and trial management (FDA, 2007; TCBI, 2013). In fact, RBM has become a requirement of the ICH E6 (R2) guidance addendum and thus organizational processes, systems, and stakeholders will need to be changed to ensure RBM is truly as efficient as it can be in adopting modern technologies in clinical trial execution. (Heering, 2016; Young, 2017).

The ICH E6 (R2) guidance is relatively new, having been issued in November 2016 and few trials have been executed from start to finish under its guidance. Currently, there is no consensus on the best strategy for implementation of the RBM strategy mainly because of the general and aspirational nature of the ICH E6 (R2) guidance. Consequently, the practitioners may not fully understand how to apply the ICH E6 (R2) guidelines to specific clinical trials. . No single strategy will work for every trial and the whole point is to think deeply about the problem at hand, thus universal solutions simply do not exist and everyone must find their way (Shukla, 2016). This is of course a new wrinkle to trial management, RBM trials may look quite different from one another in a way prior trial management simply did not accommodate. This is of course not ideal, when stakeholders as large as a modern pharma or the FDA must change course, it’s not as simple as wishing it so. RBM is new and there is variance amongst different industry functional roles in the application and understanding of the ICH E6 (R2) guidelines. Herein I explore the root of this variance in understanding of RBM, attempt to determine the extent of disparity in the implementation of RBM and attempted to develop sound recommendations for furthering practical RBM implementation.

1.3 Research Question, Aim and Specific Objectives

Clinical trial execution is expensive, slow, and full of risk. One of the major objectives of regulatory and industry partners across the globe is to harmonize and streamline this process. Risk based monitoring is a key component of this effort, in fact the FDA now mandates that an RBM approach be taken to trial monitoring. The aim of this study is to assess the progress that the pharmaceutical industry and their clinical site partners have made in the implementation and execution of RBM. The specific objectives are two fold, to assess the practice of RBM, and to understand the perception of RBM among clinical trial practitioners in the United States of America. Through an assessment of the current practice of RBM, an understanding of the progress made in changing course from traditional monitoring to RBM can be made. In seeking to gain an understanding of the perception of RBM it is possible to gain a better understanding of its strengths and weakness from those who know best, the individuals responsible for trial management and patient safety.

Chapter Two: Literature Review

2.1 Introduction

A review of the literature is a critical aspect of each study and plays a part in establishing a clear background understanding of a problem and its potential solution. This chapter presents the findings that have been developed from other reports and theories revolving around risk-based monitoring with the aim of demonstrating the problems and the potential solutions that have been proposed by other researchers. This information is critical in devising a research methodology that is suited for the problem and plays a vital role in developing a credible theoretical and practical basis for recommendations that will be developed in addressing the problem.

2.2 Risk-Based Monitoring

RBM is a focus on preventing or mitigating important and likely sources of error in the conduct, collection and reporting of critical data and processes necessary for human subject protection and trial integrity (FDA, 2013). RBM involves identifying critical data and processes, then performing a risk assessment to identify and understand the risks that could affect the collection of critical data or the performance of critical processes. Monitoring plans and data review plans are often developed focusing on the important and likely risks to critical data and processes (Hurley, 2016; Alsumidaie/Henderson, 2016; Wilson, 2014). This re-imagined approach to monitoring promises to reduce the time-consuming and costly practice of onsite 100% source data verification (SDV), while refocusing efforts on improving data quality (TCBI,2013; Shukla, 2016; Buyse,2013; Sullivan,2015). To realize the impetus and the evolution of risk-based monitoring it is worthy to mention what monitoring is, how monitoring is conducted and reference existing initiatives that are gaining traction in the industry.

2.2.1 What is Monitoring?

According to ICH-GCP, monitoring is the act of overseeing the conduct of a clinical trial; that is, assuring the trial is conducted according to protocol, good clinical practice (GCP), standard operating procedures (SOPs) and regulatory requirements (ICH,2016; FDA,2013). Monitoring is a quality measure put in place to ensure the integrity of the trial data, and the rights, and the well-being of study participants are protected (ICH, 2016). Monitoring is an ongoing process conducted before, during and after the trial. Monitoring is an FDA/EMA-mandated process whereby the integrity of the clinical trial process is validated. The validation process has historically been personnel-intensive, estimated to be approximately 1/3 of any prospective clinical trial operating budget (Shukla, 2016; Lindbald, 2013). According to the Pharmaceutical Research and Manufacturers of America (PhRMA) US biopharmaceutical companies in 2017 spent over $70 billion (in U.S. dollars) on research and development (R&D), meaning upwards of $20 billion is spent each year on monitoring (Nawrat, 2018). Due to the size, complexity and number of clinical trials today, regular intervals of 100% onsite monitoring is proving to be an ineffective, expensive and inefficient process resulting in a push to not only reduce clinical trial costs but find innovative ideas to modernize monitoring (TCBI, 2013; Sheetz, 2014).

2.2.2 How is Monitoring Conducted?

The sponsor determines the appropriate extent and nature of monitoring, based upon considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. Once patients have signed a consent form and enrolled into a study, it is the responsibility of the sponsor to ensure the trial is adequately managed, from ensuring clinical sites adhere to the approved protocol (regulatory agencies play a role in protocol approval) and to ensure that data is collected and documented in accordance to regulatory

compliance (ICH, 2016; TCBI, 2013). Therefore, the sponsor appoints a person with appropriate training and scientific and/or clinical knowledge to monitor a clinical trial. The site monitor often known as a Clinical Research Associate (CRA) functions as a member of the trial team and acts as a link between the sites, study team and the sponsor. Typically, the monitor conducts regular visits to the site according to an agreed-upon site monitoring plan (Khare, 2016).

2.2.3 Traditional Monitoring Approach versus RBM

It is important to make a distinction between Source Data Review (SDR) and Source Data Verification (SDV). Source Data Review is a holistic approach that allows for the evaluation of investigator involvement, protocol compliance and other critical processes during trial execution. Most potential issues can be identified remotely and discussed immediately to identify the root cause, resolve and prevent future occurrences before a monitor even gets to the next scheduled visit (TCBI, 2013; King, 2015).

In the traditional study data management approach, monitoring focuses on SDV and SDR in person by a clinical research associate (CRA). Importantly, traditional monitoring practices require an audit of all study data points while on site (at the investigative site/location), regardless of the type of study, safety risks and the experience of the site staff. The monitor goes to the site, reviews all source data for missing information, ensures every data point has been transcribed correctly, assesses the protocol and study medication compliance and accountability, as well as investigator oversight (Hurley,2016; Khare,2016). Basically, all sites, events and data are treated equally and everything is monitored regardless of importance.

The industry is moving away from the traditional “one size fits all” mentality of the 100% Source Data Verification (SDV) model to a RBM model which is trial-specific and based upon key risks being identified proactively and using those identifications to focus

monitoring efforts and the analysis of data trends in real-time to areas of significant concern (Shukla, 2016; Von-Niederhausern, 2017; Manasco, 2016). Source Data Review and Source Data Verification are performed on the most-critical data points identified by the study team (Ghone, 2015). To better demonstrate how the traditional approach differs from risk-based monitoring approaches refer to Table 2 for the basic highlights.

Table 2. Traditional vs RBM Approaches

Traditional	Risk-Based
Visits driven by: • Pre-determined monitoring visit schedule • Independent of workload and quality Monitors activity includes: • 100% SDV (even on low value areas) • All sites and events treated equally • Effort focused on quality control and subject safety (Brosteanu,2017; King,2015; Von-Niederhausern,2017)	Adaptive visits driven by: • Quality • Safety signals and data trends • Regulatory compliance (adopt ICH E6 R2) • Informatics solutions; Use of centrally and statistically data driven surveillance approach Monitors activity focused on key areas: • SDR/SDV on critical data and processes (only a sample of patients and source data is monitored) • Subject safety and data integrity • Site engagement: Focus on sites with greatest need based on risk. • RBM is a combination of targeted onsite, remote and central monitoring. (Brosteanu,2017; Diani,2017; Ghone,2015; PerkinElmer,2017; TCBI,2013)

2.2.4 Risk-Based Monitoring Initiative

It's universally recognized that clinical trial sites have varying levels of experience and quality, but traditional monitoring approaches are not designed to manage these potential differences (Manasco, 2016; Knepper, 2015). The Risk-Based Monitoring initiative was established by TransCelerate BioPharma Inc. (TCBI) in an effort to drive efficient and effective solutions into the Research and Development industry (TCBI, 2013; TCBI, 2015). TransCelerate BioPharma Inc. was launched in 2012 as a non-profit organization to improve the health of people around the world by simplifying and enhancing the research and

development of innovative new therapies (Alsumidaie/Henderson, 2016; TCBI, 2013; TCBI, 2015).

TransCelerate has unique attributes in leadership participation from the world's leading biopharmaceutical organizations; robust partnerships with industry organizations such as the Association of Clinical Research Organization (ACRO); Coalition for Accelerating Standards and Therapies (CFAST); Clinical Trials Transformation Initiative (CTTI) and Society for Clinical Research Sites (SCRS); as well as collaboration and insight from global regulatory authorities, the European Medicines Agency (EMA); the US Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) . This vast partnership enables them to create value for the industry (Alsumidaie/Henderson, 2016; Korieth, 2017; TCBI, 2013; TCBI-website; Underwood, 2016).

Using TransCelerate's Risk-Based Monitoring quality risk management framework has key benefits such as the following (TCBI, 2013):

- RBM can be adopted during any phase of a clinical trial and by any size organization
- RBM can be deployed and scaled mutually as necessary
- Source data review (SDR) is a fundamental practice

RBM is an adaptive approach to monitoring that focuses on key study risks and critical data identified by the study team. RBM is a "fit for purpose" approach, and RBM practices are an umbrella over multiple roles in the study and must be performed on-site (clinic) and remotely (sponsor) (Wilson, 2014). This requires identifying a robust clinical trial quality management system that incorporates available RBM technology that can aggregate data to identify potential key study risks, expose issues and provide analytical data trends (Sheetz, 2014; Brosteanu, 2017; Limaye, 2018). Largely, for the above reasons about nineteen TransCelerate Member Companies (TCBI, 2015) across the industry have chosen to implement RBM's proactive and adaptive approaches to clinical trial management by

directing monitoring focus on the areas of risks identified by the study teams, and which have the most potential to impact patient safety and data quality (TCBI, 2013; ICH, 2016; Underwood, 2016; Hurley, 2016; Ghone, 2015).

The Food and Drug Administration (FDA) has specified interest in receiving data to confirm that RBM methodology is effective. Some TransCelerate Member Companies (such as but not limited to Pfizer, Merck and Eli Lilly) have voluntarily piloted programs to test the efficacy of RBM practices (Alsumidaie, 2016; TCBI, 2014). In a follow-up, TransCelerate arranged for the submission, review and feedback from these RBM pilots. TransCelerate also piloted a program to research quantitative performance metrics in order for current and future Member Companies to understand how RBM is working. A publication sharing the experience of TransCelerate Biopharma's approach to RBM defined eight specific factors that can be used to assess the success of RBM and central monitoring, they are listed below (TCBI,2014; Wilson,2014).

- Quality: Average number of major/critical audit findings per audited site
- Quality: Percentage per site of unreported, confirmed severe adverse events (SAEs) compared to total SAEs
- Quality: Significant protocol deviations rate per treated subject/total number of deviations/total number of subjects for the protocol
- Cycle-time: Median number of days from patient visit to eCRF data entry
- Cycle-time: Median number of days from query open to close
- Cycle-time: Median number of days from significant/major issue open to close
- Efficiency: Average monitoring (all types) cost per site
- Efficiency: Average interval between On-site monitoring visits per site

The TransCelerate consortium defined three aspects of monitoring that are core to RBM implementation (Ghone, 2015; TCBI 2013; TCBI, 2015). Central, Off-site (Remote), and On-site Monitoring, their definitions are below:

- On-site Monitoring: On-site monitor visits occur on a flexible schedule based on remote and centralized monitoring analysis with reduced SDV and increased SDR. Before the visit the monitor reviews only the key variables pre-identified to be monitored at the site and ensure appropriate issue resolution, review that protocol procedures are properly performed. SDV the data in the CRFs relates to the source documents. SDR the critical study documents in the site binders are correct and accurate. Establish appropriate PI oversight and management of trial subjects (Brosteanu, 2017; FDA, 2013; ICH, 2016; Khare, 2016).
- Off-site (Remote) Monitoring: Certain activities that were previously done onsite are done remotely. Remote visits can supplement the scheduled onsite monitoring visits to resolve issues and improve site relations between or instead of onsite visits. Communication is two-way (FDA, 2013; ICH, 2016; Goldfarb, 2017).
- Central Monitoring: Statistical monitoring system/platform of trial data to identify sites that are outliers which will drive the remote and onsite visit frequency. The central monitoring system ensures that key risk indicators (KRIs) are defined and set up in the system to support the study, processing and reviewing study data in the system for signals and then clinical data scientists and central monitors (CM) alerting action management for follow-up for issues resolution (FDA,2013; ICH,2016; Wilson,2014).

The implementation of RBM is in its early days with relatively few studies comparing RBM methods to traditional monitoring, however the early results are promising (Bakobaki, 2012; Von-Niederhausern, 2017; Brosteanu, 2017; Diani, 2017; Olsen, 2016).

2.3 Evolving Regulatory Guidelines

The following timeline exemplifies that regulatory agencies have been leading the movement on monitoring processes as far back as 1988 when the FDA guidance for

Monitoring of Clinical Investigations (which retired in 2010) was initiated. The ICH E6 was released in 1995 and revision (R1) surfaced in 1996 providing flexibility in how trials were monitored. In 1998 the FDA Guidance (21CFR 312- FDA requirements for Clinical Trial Quality broadly describes sponsor responsibilities for clinical trials) provided standards for minimal on-site monitoring and in 2007 introduced risk-based approach concepts in clinical research. Clinical Trials Transformation Initiative (CTTI) in 2009 focused on clinical trial monitoring efficiency and effectiveness (Brosteanu, 2017; Underwood, 2016). Between 2008 and 2011 fifteen FDA sponsor-investigator warning letters were issued, citations were for "inadequate monitoring" (O'Reilly, 2013). In 2011, the FDA issued modifications to the monitoring process, in an effort to encourage the biopharmaceutical industry to adopt faster and less costly practices, by changing their practices and adopting RBM. A quality risk management approach was recommended by the FDA and Risk-Based Monitoring (RBM) came out of the guidance. The European Medicines Agency (EMA) Draft Reflections Paper and FDA Draft Guidance on RBM were both issued in 2011 (FDA, 2011; EMA, 2011).

In reaction or response the formation of TransCelerate-BioPharma Inc. occurred in 2012 and was supported by the FDA in 2013 in the review of pilot RBM plans as previously mentioned. The FDA final "Guidance for Industry: Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring" was issued in 2013 and the ICH E6 Revision(s) was developed in Nov. 2016 which became mandatory in 2017. The Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), 5.18.3 dated November 2016 states "Sponsors should develop a systematic, prioritized, risk-based approach to monitoring clinical trials" (ICH, 2016).

Back in time when the original ICH E6 (R1) was created, clinical trials were heavily paper-based. In the past twenty years technological advancements in the pharmaceutical research space has allowed for greater assortment of risk-based methodologies and practices

to be carried out (EMA,2013; Hurley,2016; Shukla, 2016). The ICH E6 (R2) addendum chiefly addresses these advancements in new technology and in turn the enhanced capabilities to incorporate risk management processes to increase clinical trial efficiencies.

2.4 Discussion

Simply stated, stakeholders benefit from RBM. RBM benefits investigative sites by preventing a mass generation of queries and circumventing queries being issued months or years after the initial data entry (Bois, 2016). Site personnel can redirect their focus on core job responsibilities and improving inspection-readiness tasks as a result of spending less time addressing and chasing query resolution (Manasco, 2016). Regulators can benefit from RBM by enabling different groups to work close together. Sponsor companies can reap the benefits of RBM by improving allocation of resources, protection of subject safety, upholding data integrity and adherence to GCP compliance. RBM aids patients in clinical trials by implementing streamlined processes and focusing attention to data that is critical thereby increasing patient safety (Bakobaki, 2012; Manasco, 2016; Sheetz, 2014).

Without a doubt, RBM is certainly a work in progress and is gaining traction. Industry has for a long time sought approaches through which they can ensure that clinical trial execution is more streamlined, given advancements in technological capabilities (Bois, 2016; Alsumidaie/Henderson, 2016). Out of necessity TCBI developed a standard approach to the implementation of RBM that can be adopted for any type, phase and stage of a trial. It is believed that RBM methodology improves efficiency by changing the focus to central or off-site monitoring activities that are intended to identify potential risks and issues and to identify them sooner than relying totally on on-site monitoring visits (Diani,2017; Underwood,2016). The TCBI member companies (20+ leading Bio-Pharmaceutical companies) have been piloting the RBM methodology on various types of trials. Lessons learned from these pilots are meant to inform and evolve the RBM methodology. Leveraging

TCBI recommendations and keeping regulatory guidelines in scope by promoting consistent practices are crucial for reliable outcomes (Brosteanu, 2016; Gough, 2016).

Although, RBM approaches have been formally introduced by the key TCBI members (mostly very large pharma on the industry side), many of the investigative sites and personnel at the execution level, have misconceptions about how RBM works and their role in effective implementation (Alsumidaie, 2016; Bois, 2016; Khare, 2016; Manasco, 2016).

This raises questions about the approach of the industry to ensuring that the requirements of ICH E6 R (2) recommendations are well understood and practical implementation practices are addressed (Bois, 2016; Khare,2016; Limaye,2018). One of the factors that has widely been researched on and is cited as the key stumbling block to effective use of RBM is robust education and availability of training materials (King, 2015; Manasco, 2016). In addition to falling short on basic education to various stakeholders, the RBM regulatory guidelines are written in a manner that can be challenging to understand as well as to implement (Korieth, 2017). RBM methodology may be misunderstood by Clinical Research Organizations (CRO) and site representatives (Wolfs, 2018). Misinterpretations of the intent of RBM purposes and practices have led to questions at the site level regarding RBMs ability to reduce data errors and thus a certain hesitance to execute RBM (Bois,2016; Goldfarb,2017; Manasco,2016), however, literature shows that RBM methods do improve clinical trial efficiencies (Buyse,2013).

Research findings point to the fact that RBM is indeed the wave of the future (Diani, 2017; Lindblad, 2014). To reap the benefits and meet regulatory expectations, industry must seek best-practices to address barriers to implementation.

Chapter Three: Research Methodology

3.1 Introduction

It is important that the research project be guided by well-defined research objectives and has a sound methodology to ensure integrity of the results. This chapter presents the methodology used herein.

3.2 Research Problem

As outlined in the prior chapter, an awareness of the problem of risk based management (RBM) implementation and compliance to regulatory guidance does indeed exist (Artyomenko, 2015; Bois, 2016). Researchers have been active in dissecting the RBM related guideline from different perspectives in an attempt to understand its implementation. This study seeks to build on prior existing findings by focusing its attention on the pharmaceutical industry. The study investigated how RBM is viewed and implemented by those who are tasked with clinical trial execution, data collection and data management.

3.3 Research Questions

Creating the right types of research questions is a key step that will aid in addressing the research problem. For this project, the research questions are as follows: What is the current knowledge, perceptions, practices, barriers, and benefits of Risk-Based Monitoring (RBM) as reported by practitioners within the pharmaceutical industry in the United States of America? What are the factors that affect the levels of understanding of RBM?

3.4 Research Methodology

The basic research methodology employed was a combination of quantitative and qualitative survey using a questionnaire. Responses were de-convolved into interpretable

findings using both qualitative and quantitative interpretations of the survey data to analyze the state of RBM within the pharmaceutical industry in the United States of America.

As this research seeks to explore the knowledge, attitude and practices (KAP) of practitioners in the pharmaceutical industry an approach similar to a previously reported KAP study was used (Green, 2001). This approach requires the use of primary data that has been retrieved from a defined population. The quantitative design that was adopted aimed at ensuring flexibility in addressing the research questions and making sure all critical ideas/issues were addressed as a thorough understanding of the problem is developed. The input of randomly selected individuals was sought and their perceptions and opinions related to RBM were recorded and captured on a data spreadsheet. Although, the questionnaires did not contain personal data such as name, date of birth, geographic location etc. it did ask for gender and role title. Thus the information recorded on the data spreadsheet was de-identified (each participant was assigned a random number) following the basic rules for protecting personal information.

3.4.1 Study Sample

Survey participants were self-selected based upon their response to an email inviting participation in the study. Inclusion criteria were: current employment in industry, a job responsibility in clinical trial execution and management. Survey invitations were sent to contacts developed over decades of work in pharmaceutical industry and by asking contacted individuals to forward the invitation to others in their field.

3.4.2 Study Site

The study was conducted by remote administration of a survey. There was no physical location tied to this study.

3.4.3 Questionnaire Design

Questionnaire design is central to this study. The following are some of the factors that were considered in questionnaire design:

- Readability: It must be readable to attain the goal of being understood and interpreted equally by all respondents. To ensure readability, questions were reviewed by a field expert, refined to be succinct, and framed in easy to understand English (the native language of respondents).
- Language complexity: The complexity of language used in any questionnaire is critical to ensure that responses are to the actual question being asked, and not based upon on unclear or vaguely framed question. Although clinical trial execution is complex and RBM is a deep and multifaceted area, the questionnaire was kept as simple as possible. All respondents have at minimum a college degree B.A./B.S. and all respondents are employed in clinical trial management, thus the use of technical terms in the survey was deemed appropriate and not a factor that would bias response in this population.
- Design: The design of the questionnaire, especially its internal structure and ordering of the questions, plays an important role in defining the levels of readability that can be attained. A simple layering and numbering of questions was used throughout, simplicity of format is a key design parameter to ensure clarity.

The use of questionnaires in this study instead of other primary research approaches to data collection was mainly driven by the ability to maintain confidentiality and ease of completion. Survey respondents are all busy with full time jobs, spread across the country (United States of America). As such, in-person or other interview techniques were deemed impossible. Accuracy is an integral value of the research, the survey incorporates a certain level of redundancy, asking the same question in different ways with the belief that if

consistent threads or themes were to emerge in the data that perhaps this could guide the discussion and highlight important areas.

3.4.4 Choice of Questions

Questions were layered in a manner that centered on obtaining key information pertaining to participant demographics (related to trial management experience), their knowledge of RBM, their perception of RBM, and their thoughts on best RBM practices (current observations and future recommendations).

3.5 Validity and Reliability

As defined by Professional Testing, Inc., "validity is arguably the most important criteria for the quality of a test". Tests with high validity can be said to accurately measure what they are designed to assess. For a survey such as this, content validity can be used to assess general relevance to the subject matter that the survey is intended to measure (PTI, 2006). Content validity was assessed by expert review of the survey tool and questions were revised, if necessary, prior to seeking ethics clearance.

Reliability is another metric used to assess the quality of a test. Reliability refers to the consistency of response elicited by the test, if an individual takes a test or survey multiple times. It measures conservation or consistency in the response of the respondents. A perhaps better description of reliability is to use the word "repeatability" (PTI, 2006). Test with poor reliability may generate vastly different scores or responses when asked to measure the same thing twice. Interpretation of the results of test with poor reproducibility/repeatability is difficult if not impossible as the outcome can be thought of as a random event. It is important to recognize that repeatability may be influenced by word choice, phrasing, order and complexity of the question. It must be measured using subjects from the same population the test or survey is intended to assess. Content validity must be appropriate in order to measure repeatability (Bolarinwa, 2018). For example, if

the general public were to take a board certification exam in dermatology the results might look rather random (i.e. poor reliability) however, the same test among medical doctors with 4 years residency and relevant experience may result in better repeatability or reliability. The repeatability/reliability of the survey for this study was assessed using the volunteers from the appropriate subject population prior to seeking ethics clearance.

3.6 UWC Ethics Committee Clearance

Ethics approval from the Office of the Director: Research and Innovation Division of the University of Western Cape was a requirement to carry out this study. Approval was granted on 08Jun2018 after review of the survey questions, study design, and de-identification procedures.

3.6.1 Consent

Per the UWC ethics committee obtaining consent was a requirement for this research study. Informed consent documents (ICD) were provided to each study participant prior to data collection. Each individual was provided the ability to withdraw the consent at any time. The purpose and intent of the study was described (see appendix 1. ICD) and individuals had to affirmatively consent and provide their signature and date prior to the collection and use of their feedback and data. See Appendix 1for consent form sample.

3.7 Analysis

Responses to questions with multiple choice answers were analyzed using quantitative methods including charts, numerical calculations and basic statistical calculations. Responses to questions eliciting a written response were analyzed using a narrative analysis in order to determine the overall respondents theme and relevance to the research questions. The flexibility presented by this approach is important in giving the research both qualitative and quantitative dimensions while ensuring the research

questions are accurately addressed. Narrative analysis as used in the study is guided by the research objectives and questions and is dependent on the level of objectivity attained by the researcher. Presentation of the findings will be by themes.

3.8 Primary Data

The primary data and survey responses for this study are held in storage. Survey responses were transcribed to an electronic document and analyses conducted from there.

Chapter Four: Results and Discussion

4.1 Introduction

This chapter presents study findings, the survey questionnaire was administered to individuals for whom their daily work is the design, implementation, monitoring, oversight and data review of a modern clinical trial. Through analyses of their response to survey questions, a synopsis of the current knowledge, perceptions and practices of RBM amongst clinical trial practitioners in the United State, is provided.

4.2 Results and Analyses

4.2.1 Pre-Test Validity, Validation of Survey Prior to Administration

Prior to administering the questionnaire to subjects, the content validity of the survey was reviewed by an expert in the field (20+ years in clinical research with roles from site physician to VP positions at major pharma). The expert review was favorable, indicating the questions were topical and understandable. Slight modifications were made to one question that was identified as potentially confusing. Subsequent to this review, the questionnaire was administered to a small group of subjects, twice. Each individual was asked to complete the quantitative portion of the questionnaire and their responses recorded as response #1. The questionnaire was then re-administered (about a week later) and their response recorded as response #2. For this pre-test validation, a sample size of three was utilized. This testing was done to determine if there were any problems with a portion of the questionnaire that would lead to poor reproducibility/repeatability of response.

In order to evaluate correlation in response for this pretest survey, the potential responses to each question on the survey were assigned a numerical value (including sub-questions). For instance, if a particular question had 5 potential responses listed, the first

possible response was assigned a value of 1, and the last (in a list of 5 possible) was assigned 5. Thus, questions for which the respondent provided identical answers on the first and second testing will have the same numerical score and be plotted as overlapping symbols.

The results of the pre-test repeatability assessment are shown in Figure 1 for each of the three respondents. The graphs demonstrate that the responses recorded for the first and second administration of the questionnaire were highly correlated (mostly identical). No systemic problems were identified with the survey. In fact, among the 138 recorded responses (3 respondents, 23 score responses, 2 administrations) only a single answer changed (respondent 1, question 8- see Figure 1). The change was noted as insignificant, differing in degree only, e.g. selecting "strongly agree" vs. "agree".

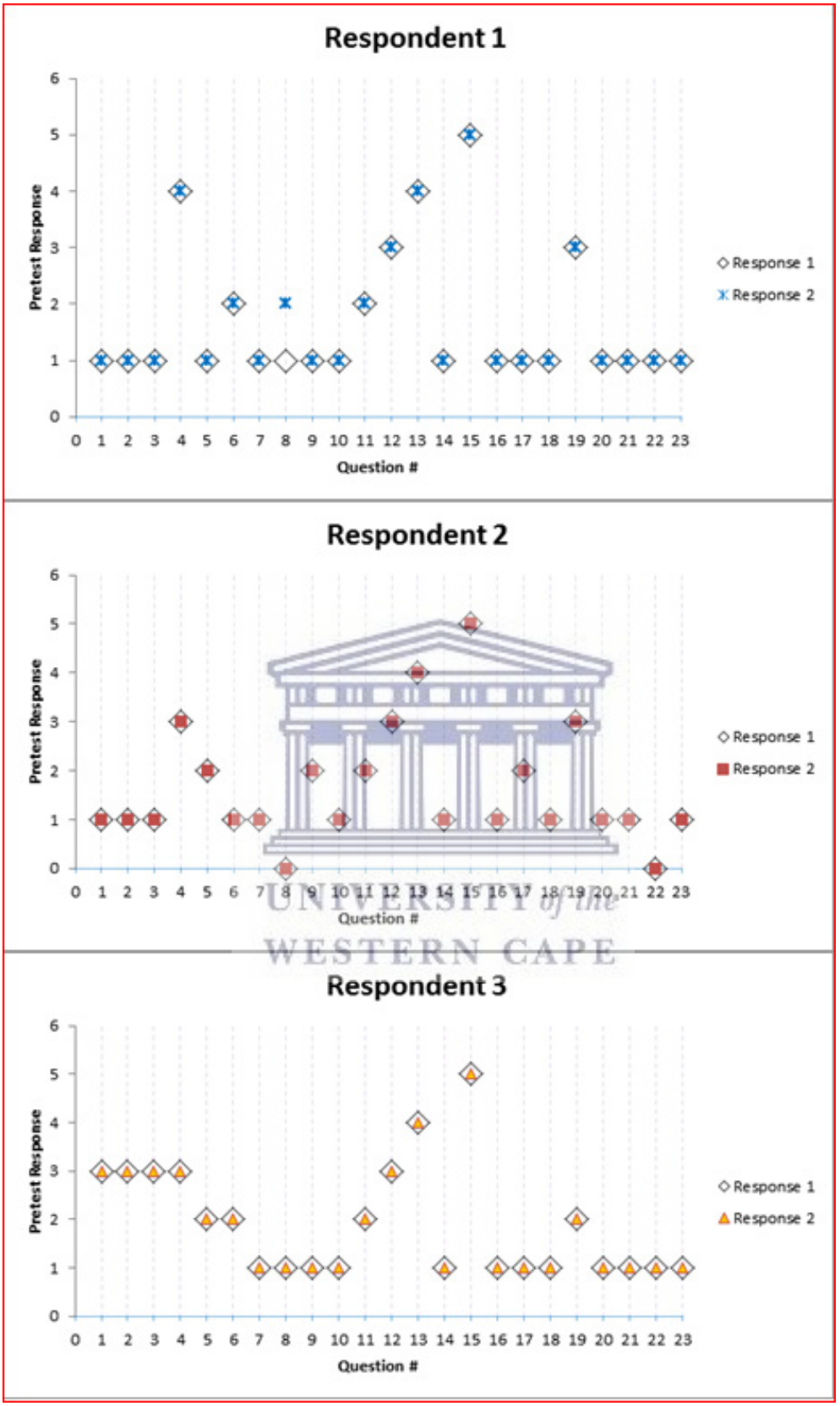

Figure 1. Pre-Survey Test Response for Repeatability.

4.2.2 Limitations

Prior to beginning subject recruitment and administration of the survey an investigation into the sample size required to reach significance was undertaken. Ideally the survey would be administered to a sufficiently large number of participants such that the results could be stated to represent the state of clinical trial management in the USA. In this case, statistical treatments could be implemented for quantitative results, providing a confidence interval to each such response. For the sample size calculation it was assumed that 25,000 individuals represent the population of individuals participating in clinical trial management in the USA. In order to reach a 95% confidence interval for the results one would require minimally 378 respondents (see Figure 2). It was determined that within the budget and time constraints of the project (zero budget; 2 months available for survey administration) 378 respondents were an impossible goal.

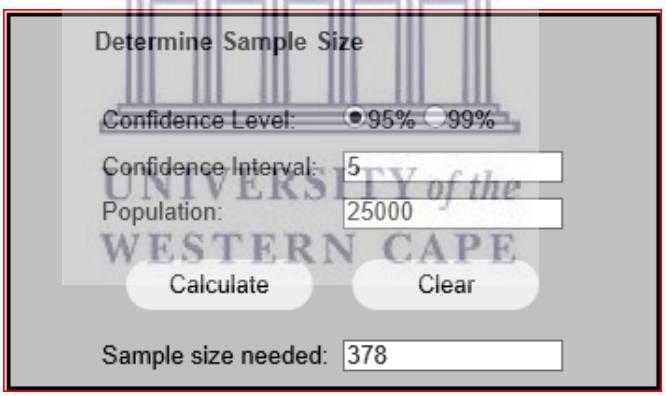

Figure 2. Calculated sample size required to obtain a 95% confidence interval for the results based upon a population of 50,000 individuals. https://www.surveysystem.com/sscalc.htm

The following study limitations were identified:

- Subject Enrollment:
  - Small sample size and uneven sample size distribution of respondents that completed the questionnaire.
  - Unequal practitioner role distribution (majority of respondents were from the sponsor perspective).

- Enrollment timeframe:
    - Ethics committee approval was granted 08June2018 and collection of informed consent documents commenced 12June2018 through 11September2018.
    - As the timing of the study fell during the summer months the recruitment timeline competed with vacations and US holiday's which directly impacted respondent availability and thus challenged study enrollment.
- Questionnaire non-compliance:
    - Follow-up conversations were difficult to arrange which contributed to unclear and ambiguous responses and inability to further assess the completion and accuracy of questions.
- RBM is a moving target:
    - Due to the ever-evolving regulatory environment changing guidelines and further advancements in technology, the RBM of today will invariably look different tomorrow, this study presents a snap-shot in time.

Please note that all findings/results will be presented at face value and statistical relevance assessed qualitatively as a within study comparison, as noted, the statistical power of this study is limited by enrollment and this should be considered in interpretation and extension of the findings presented.

4.2.3 Study Enrollment

Twenty-eight questionnaires were dispatched. Twenty-two informed consents were signed and dated and questionnaires were completed. Twenty-two questionnaires were completed with six spoilt questionnaires (Figure 3).

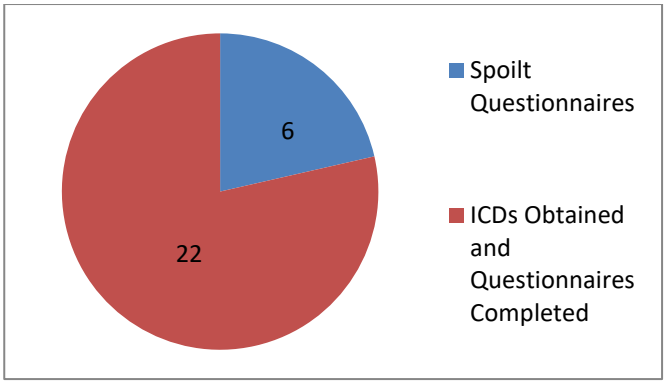

Figure 3. Study Enrollment, Questionnaires and Informed Consent Documents. Number of valid questionnaires for this study vs. Spoilt questionnaires (data not included, incomplete or missing informed consent).

Based upon the study enrollment and the presumed population of clinical trial practitioners in the USA, a calculation was made to determine the margin of error associated with the study responses. The results of that calculation are shown in Figure 4, and demonstrate that the study has a ± 21% margin of error associated with any response. This margin of error is driven by sampling size, not population. In other calculations (not shown) the total population was varied from 5,000-50,000, given 22 respondents the same margin of error was calculated.

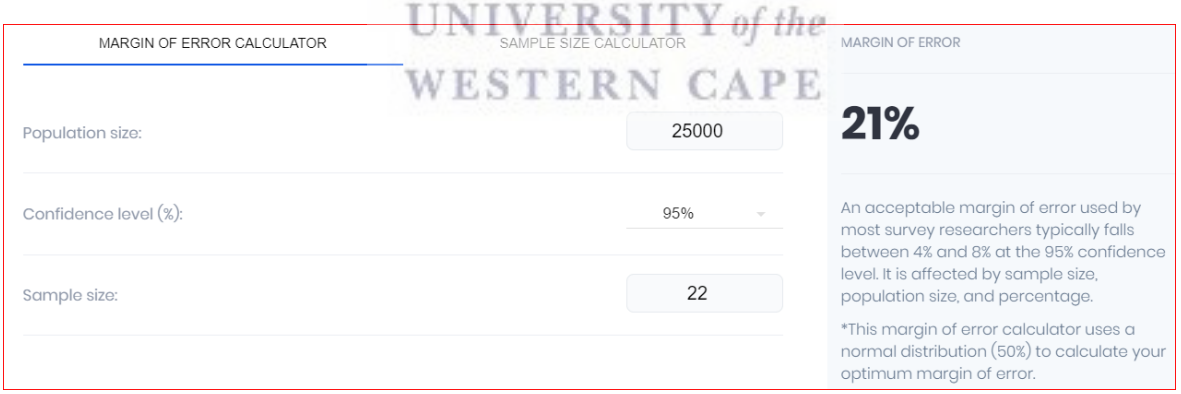

Figure 4. Calculation of the margin of error associated with the study responses https://www.pollfish.com/lp/margin-of-error-calculator/

Because of the sample size limitation, the conclusions of this study must be phrased as a qualitative sampling of the opinion of the current knowledge, perceptions and practices of RBM amongst clinical trial practitioners in the United State states.

4.2.4 Demographic Information

The demographics of the questionnaire respondents composed of 70% female and 30% male (Figure 5).

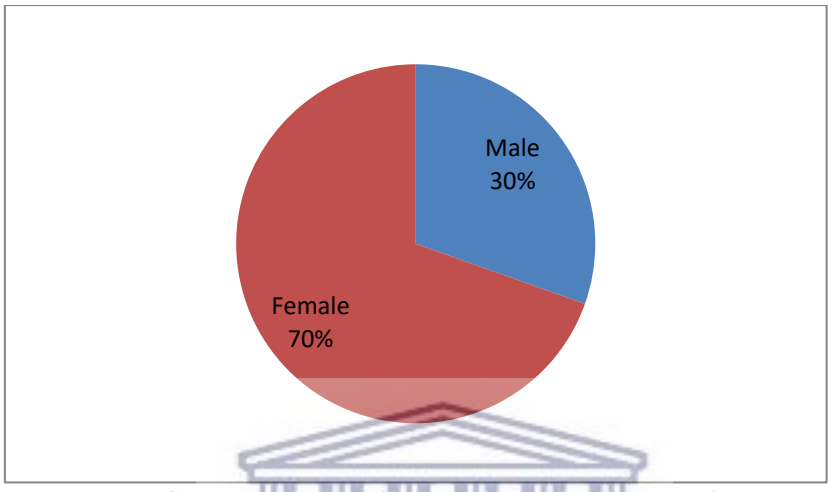

Figure 5. Respondent Gender. Number of Female vs. Male respondent's that completed a questionnaire.

Fifteen respondents worked for a pharmaceutical company (sponsor); five for a clinical research organization (CRO) and three at investigative sites. As noted in Figure 6 although a variety of roles across the industry provided input, there was a preponderance of sponsor related roles notably clinical site leads that completed the questionnaire.

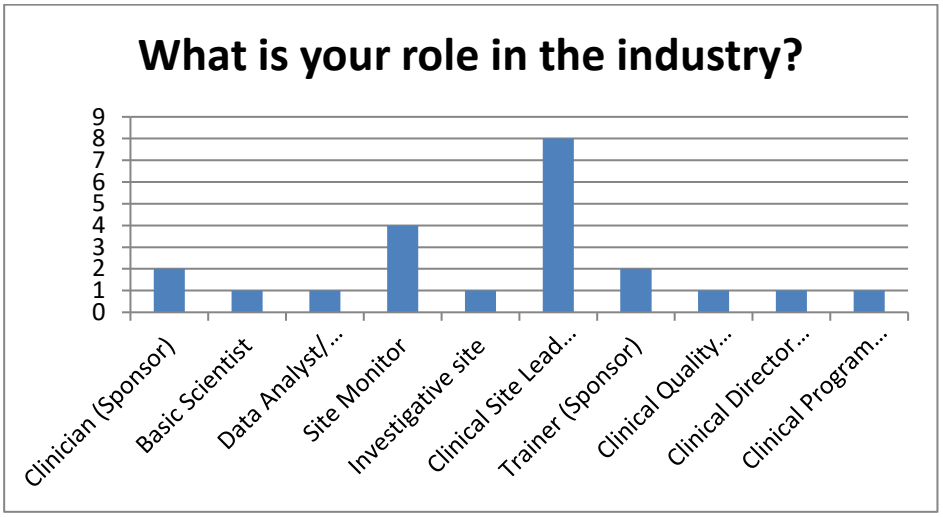

Figure 6. Respondent's Role in the Industry.

4.2.5 Knowledge of RBM

In an effort to assess the respondent's level of knowledge of RBM they were asked to define the goals and key concepts of RBM succinctly, their responses are summarized in Table 3 and indicate that most respondents have a basic concepts understanding of RBM. In reviewing them you will find the term "risk" in nearly all responses- a key component of RBM is in fact, risk management.

Table 3. Respondents Knowledge of RBM

RBM is a shift in the focus of data reviews and analyses performed centrally versus onsite.
Assessing the risk of a study and overseeing monitoring and compliance based upon the identified risk
Monitoring which is done both remotely as well as on-site where parameters targeted during each type of review have been identified according to the level of source data.
Using specifically defined criteria to identify risks and risk thresholds that determine monitoring activities and frequency.
RBM is an approach to site oversight that clearly defines key risks for that study, and then uses centralized monitoring to identify potential risks so that they can be addressed quickly and appropriately.
RBM is a type of centralized monitoring where the sponsor/CRO is able to identify specific critical data points that can be programmed to be monitored centrally rather than on-site
A targeted approach to onsite monitoring which is aligned with different risk targets (high/low/medium). More time can be focused on the higher risk categories.
RBM is the process of monitoring a clinical program by use of identification of key data points and risks that ultimately impact quality and or safety.
Removing 100% SDV and moving toward an approach to review data based on risk or at high risk sites.
Prospectively identified plan-program and/or protocol specific- to monitor most important aspects of trial. To ensure patient safety and data quality.
Identify and mitigate risk related to patient safety, data integrity and GCP.
RBM looks for trends, signal, data inconsistency and fraud
Real-time safety review is critical. Safety review is a priority it is not all about cost. Identifying patterns, trends and the need to get head of this or data review/query resolution can have a domino effect.
It is an adaptive approach to monitoring leveraging data and site level information to determine how, when and where to monitor, focusing on risk that make the most impact on data and patient safety. It is not a one size fits all approach to monitoring.
RBM key concepts are of two purposes which are: Controlling the data quality and Ensuring the safety of patients.
RBM is about cost reduction and focused data review.
Target monitoring for sites with a lot of subjects, queries and missing data.
Identify possible risks and developing a plan of action for both sides to mitigate the risks
An attempt to monitor the safety of the study and participants and usually involves a safety monitoring plan.
An approach to monitoring that directs monitoring focus to patient safety and data quality.
Focus on main data points, Mitigate areas of risk, Cost effective for sponsors
Enhance human subject protection and quality of the clinical study data by focusing on the most relevant and important data, key study conduct and reporting.

As another means of assessing the respondent's general familiarity with and understanding of RBM, they were asked to provide approximately three words that came to mind when they thought about RBM. Their responses were tallied together to generate a word cloud representation of RBM key descriptor's (Figure 7). In this representation, the size of the word indicates its prevalence in the combined response; words common to many respondents are thus presented in larger typeface (Figure 7).

Figure 7. Word cloud representation of responses to question 2.A. Generated from study data responses using Worditout.com

The predominant terms were, "Efficient", "Quality", and "Safety", and were mentioned in 5, 4 and 3 respondents questionnaire's respectively.

Respondents were asked to self-assess their awareness of the current ICH E6 (R2) guidelines using the following rankings, none, low, medium or high. Interestingly, although the prior knowledge assessment had indicated a broad general awareness of RBM, there was wide variability in respondent's awareness of the ICH E6 (R2) guidelines (Figure 8).

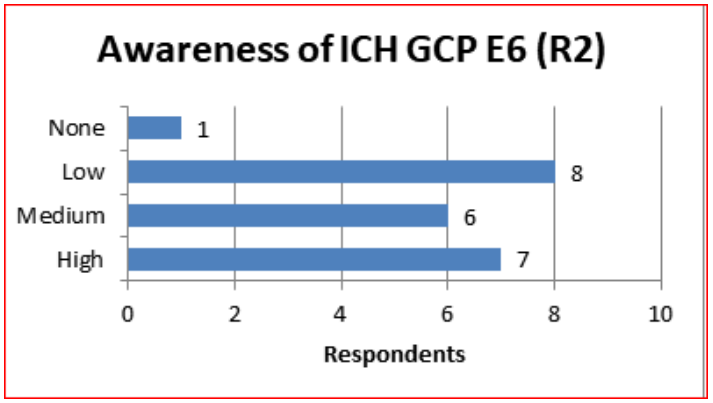

Figure 8. Respondent's Current Level of Awareness of ICH E6 R2 Addendum

Many respondents indicated either no or low familiarity 9/22 (41%) while only 7/22 (32%) indicated a high level of familiarity with this industry standard guidance. In breaking this data down along lines of affiliation we found that individuals employed by a sponsor or CRO were predominantly aware of the guidelines (~66% scored as high or medium) whereas 100% of site personnel were relatively unaware of the guidance, reporting either low or no awareness. As mentioned in the pretest section, the statistical power of this study is low due to enrollment limitations and thus we cannot state with confidence the generality of these findings.

Henceforth, this document will present and discuss all additional study findings without further reiteration of this limitation.

Taking the question of ICH E6 (R2) guidelines a bit farther, respondents were asked if they had a clear understanding of these regulatory guidelines (as opposed to awareness). Forty six percent (8 sponsor; 4 CRO; 2 site) of the respondent's stated they did not have a clear understanding or were unsure, while 54% (10 sponsor; 2 CRO) stated they had a clear understanding (Figure 9).

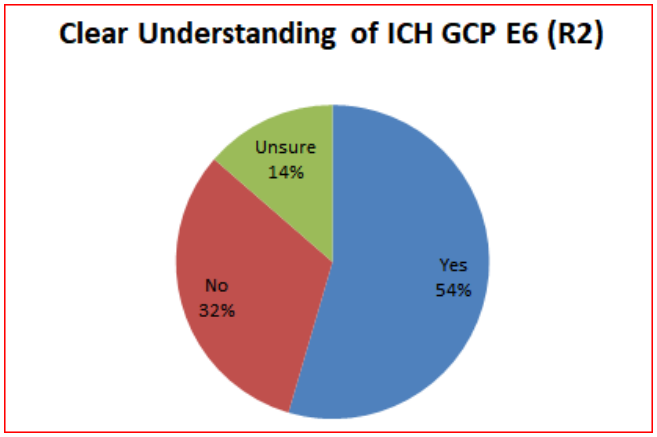

Figure 9. Respondents understanding of ICH GCP E6 (R2)

These results contrast with the prior question on awareness, only 1 respondent had indicated no awareness of the guidelines (4.5%). As part of this question, respondents were asked to explain their answer. Many stated that although they were aware of the ICH E6 (R2) regulatory guidelines, the guidelines were not applicable to their current work and thus their understanding was superficial. Clearly RBM is not a component of all clinical trial management and execution in the USA.

When asked if their company/institution had implemented policies and processes to adhere to the E6 (R2) guidelines 73% (13 sponsor; 3 CRO) stated Yes; 4% (1 site) stated No; 14% (3 sponsor) stated they were Unsure and 9% (1 CRO; 1 site) stated it was not yet applicable (Figure 10).

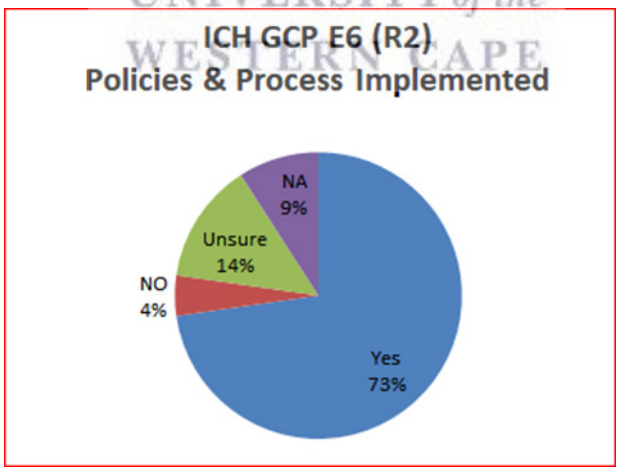

Figure 10. Has your company implemented policies and processes to adhere to the guidance's?

Respondents were asked to briefly summarize (to their knowledge) the most effective plans and the policies and processes that have been implemented at their institution regarding the ICH E6 R2 guidance. Table 4 indicates the types of implementations deemed effective by study respondents.

Table 4. Policies and Processes Implemented; Summary of Effective Plans

Addition of in-house central monitors was created to perform data reviews. Study teams determine the actions needed based upon input.
Committees have been put into place to evaluate the feasibility of RBM for new protocols. Trainings are given for everyone to understand this new kind of monitoring approach.
The most effective plans have study teams involved early to ensure proper planning up front. Also, control plans need to have periodic review to determine any necessary changes. All of this must be well documented.
Cross-functional input from key stakeholders who understand the overall goal of RBM and work collaboratively to ensure RBM is designed properly, along with proper oversight, conduct and timely addressing of all identified issues.
Promote a change management strategy to increase awareness of regulatory guidelines. Build trust in the RBM approach. Engage the executive leadership team to ensure proper resources.
Early introduction to RBM is a key factor for understanding & embedding the intent of RBM.
Clarify RBM myths and help roles understand that RBM is not just focused on cost-savings.
Utilize a centralized RBM platform that aggregate key risk indicators. Use signals and analytic systems and tools.
Systematic, prioritized risk-based approach using onsite, remote and centralized activities that are based on study design.
Develop processes to oversee quality, investigator oversight and risk management has been implemented.
Establish RBM orientation training (self-study and instructor led option for live questions).
Remote/centralized monitoring supplements on-site visits for some studies. Studies being started mostly have remote monitoring.
Having in-house CRAs was part of answer to RBM but their success limited by inexperience, lack of role definition, and lack of communication with existing organizational structure. Operational structure /CRO status limits adoption of RBM as CROs must do work as requested by sponsors.

The responses to this question can be summarized as falling into two major themes; 1) Effective RBM implementation requires buy-in and education on what RBM is and what it is NOT at all levels, 2) Implementing a central monitoring platform strategy is key. These answers mesh nicely with the concepts and intent of RBM introduced previously, central monitoring refers to the real time trending and oversight of clinical site data, this is typically a focused effort directed at data that will inform the study team of performance in areas identified as high risk and is a fundamental component of RBM (King, 2015; Limaye, 2018). These responses seem to indicate that RBM implementation is beginning but not yet complete in the USA.

As the prior data points indicate, knowledge of RBM is spotty and shallow for many involved in clinical trial management and execution. There are several ways that

the knowledge of RBM could be limited, unclear regulatory guidelines, lack of awareness, lack of education and lack of effective training. Respondents were asked to indicate their level of agreement to a number of statements using a Likert scale. The definition of a Likert scale is a 5 or 7-point scale that offers a range of answers from one extreme attitude to another, for instance 1-Strongly agree; 2-Agree; 3-Unsure; 4-Disagree; 5-Strongly Disagree. Using a Likert scale can be a reliable method to measure opinions, perceptions and behaviors with a greater degree of nuance than a simple yes or no question. Respondents were asked to base their answers (coded using the 5 point Likert scale indicated) on how much impact they feel the below categories have in limiting RBM knowledge in their day-to-day work and experience (Figure 11).

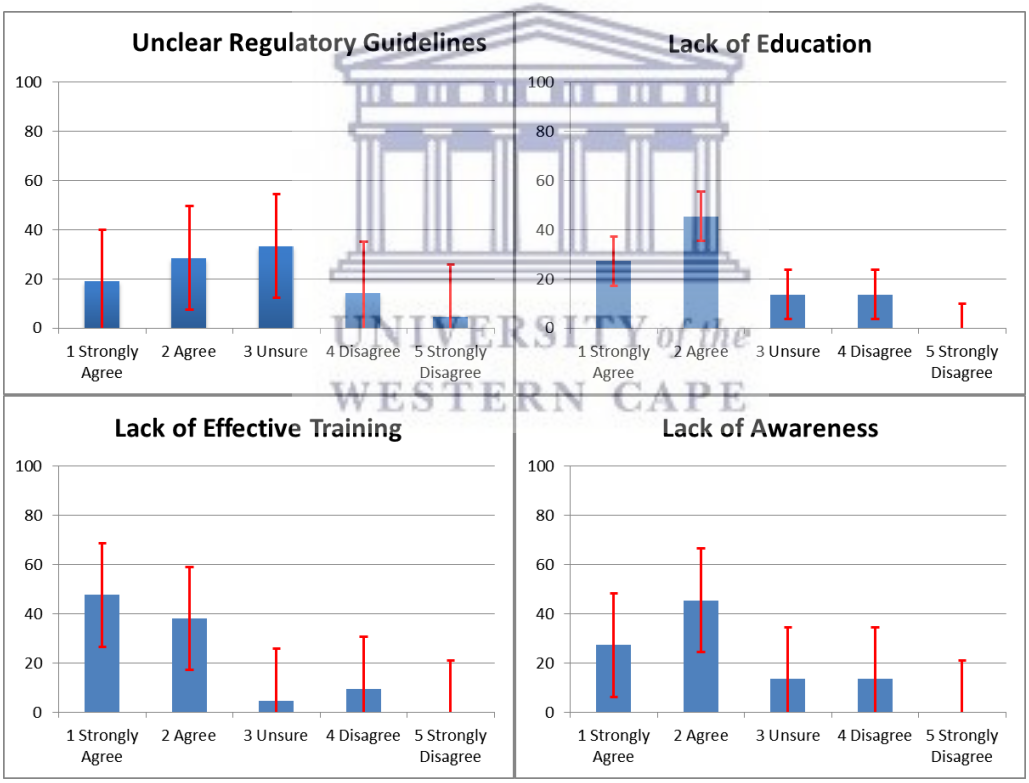

Figure 11. Ways that Knowledge of RBM could be limited.

The responses to these questions indicate that the lack of effective training is the most significant barrier to RBM knowledge in the field with 48% of the respondents indicating strong agreement with the statement that "Lack of Effective Training" was a contributing to a lack of RBM knowledge; "Lack of Education", and "Lack of Awareness"

were ranked most important 27% of the time while "Unclear Regulatory Guidelines" were indicated as the most important barrier by only 19% of respondents.

Respondents were then asked to recommend strategies to mitigate the barriers they had identified; their responses are shown below in Table 5. The study respondents again were remarkably consistent, in 7 out of the 13 responses the word "training" was used, another theme was that there exists a hidden "cultural barrier" in transitioning to RBM from traditional monitoring. Numerous individuals' responses indicated a general feeling that RBM is new, unproven, and thus suspect, with one individual stating, "It will be important to do studies and share objective data that" RBM "has improved safety, data and efficiencies". Although the literature is full of studies demonstrating RBM effectiveness or its non-inferiority to traditional monitoring practices (Brosteanu, 2017; Diani, 2017; Ghone, 2015; Hurley, 2016; Wilson, 2014), it is clear that on the fields of the RBM battle, not everyone is yet convinced.

Table 5. Possible Recommendations for mitigating RBM knowledge limitations

Study team members do not understand monitoring or the reason RBM is being required. I have heard from TCB members and other sponsors that implementation of RBM takes years of change management,
Although RBM is subtle to my role, general training should be provided as well as specific training that is applicable to each role.
The meaning of RBM is not consistent with everyone and every organization. Thus studies have been implemented using RBM before all parties were comfortable with the concept. More-in-depth training and evaluation should be performed before starting studies this way.
Mitigations need to be realistic and achievable. When they are identified then they should be included in study plans and or protocol to ensure follow through. These mitigations often get lost and teams go into "fire-fighting" mode instead of looking holistically and systematically.
Senior management agrees is critical aspect of drug development. Then ensures proper awareness, training, follow up and continuous feedback and process improvement is in place. Ideally, one key person is the internal expert who organizes and puts processes in place. And…all of above is done at each vendors and site level with the key personnel who interact with patients (investigators, coordinators, data managers etc.)
Need clear and concise RBM training industry wide
Promote a change management strategy to increase awareness of reg. guidelines. Build trust in the RBM approach.
CRAs fear of letting go of 100% SDV despite data that shows otherwise. They are afraid they may miss something and will be responsible for errors. Change the mindset of the whole SDV process of matching vs critical thinking. Checking things that are validation checks vs. identifying trends, learning new way of SDR that is comprehensive and think about what is

critical to safety, quality and study specific KRIs/endpoints. Teams tend to default to traditional approaches. People are not understanding the data behind the concept and defaulting to 100% SDV. As RBM evolves it will be important to do studies and share objective data that has improved safety, data and efficiencies.
I think a more hands on approach are needed for RBM implementation. For our company it was rolled out in a couple of slide decks with no real data behind it and no way to "play" in the tools or platforms. I find people are more comfortable when allowed to use and understand the tools prior to implementation.
Having a uniform approach in the pharma industry on implementation of RBM
More training on E6 guidelines. Need more hand holding and introduction on team calls.
Provide "cliff notes" version; more guidance on literature available; repeat training options; scenario based training & live training with groups. RBM is too piece meal and I'm not sure who is doing what and the various systems involved.
Provide comprehensive process and training. Provide investigative sites other options and not just RBM. Describe how sites will benefit from a RBM

These sentiments in fact represent a significant and previously recognized barrier to RBM implementation. Effective "change management" has been previously suggested as a key pillar of effective RBM implementation success. Change management was identified as major tool to overcome institutional memory and fear of RBM in a recent paper (Korieth, 2017; Limaye, 2018; Sheetz, 2014).

Numerous respondents echo these findings, mentioning change management or effective management as a significant tool to overcome barriers to RBM implementation. Once again, these findings reinforce the idea that RBM has been spoken of in global terms but implementation on a practical level is lagging in the US pharma. On the basis of the responses so far, one could speculate that it is not RBM practices that are the barrier, it's the simple fact that in order to implement RBM, it must replace traditional monitoring practices, and the act of change is the barrier (McGurk, 2014).

4.2.6 Perceptions of RBM

Using a Likert scale respondents were asked to indicate their current perceptions of RBM. The majority of respondents (17/22, 77%) indicated a "very" or "somewhat" positive perception of RBM, whereas only ~12% of respondents had a "somewhat" or "very" negative perception of RBM (Figure 12). Taken in the context of the prior responses

the data seem to indicate that although not everyone understands RBM, the vast majority think it is a positive force in clinical trial management.

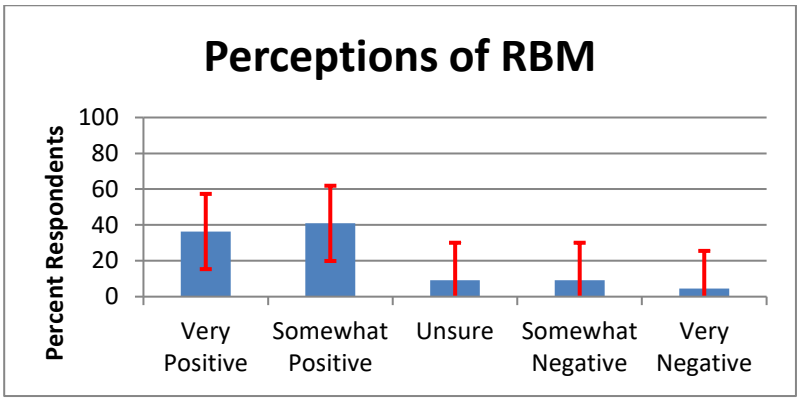

Figure 12. Respondents Perceptions of RBM.

Respondents were then asked to "please explain why you feel this way." Their responses to this question are shown below (Table 6).

Table 6. Explanation of Respondents Perceptions

Monitoring needs multiple options and to be more flexible. Over the past decade the quality of on-site monitoring has greatly declined. I am optimistic that RBM will help to focus monitors attention on what is critical to the outcome of the trial and lessen administrative burden.
In the end it's about looking at the data and outliers. You don't need to travel and conduct on-site visits to notice transcription errors.
I have seen and heard the frustration from sites who are asked to scan pages, send information to CRO without the responsibilities of RBM being explained to them. They are not compensated for this additional time, thus when visits are conducted at the site, they are frustrated and no longer have the time for us as the budget was already used.
RB approach allows teams to plan and utilize resources more effectively where the most need is.
I feel very positive about RBM. I have monitored using RBM and been involved with RBM related activities since 2008.
Once study teams are well educated and there are adequate resources RBM will help bring additional quality into the monitoring process without increasing time or cost
I do not have much experience. My one experience caused a key inclusion criterion to be overlooked, and the study was reverted to 100 % SDV as a result.
I feel this way because RBM is a more streamlined and in my opinion effective approach to monitoring. As a PM, I also see the benefit of resource and budget used more appropriately.
It was never efficient to monitor 100% of the data, especially when not all data is used to move a trial onto the next phase. Using a RBM approach, monitors can now focus their time onsite to review key data, i.e. primary and secondary endpoints, safety issues, etc., which has a high impact on having quality data the trial can use to submit to move the trial to the next phase or to be approved.
Note: if designed and implemented properly – overall goals can be achieved. Must have "buy in" from everyone involved in all aspects of trial. Not implemented enough. Need more team strategy and team accountability.
RBM will increase trial quality by focusing on high value data points
RBM approach will appropriately monitor the data as you progress thru the study.
The paradigm for ensuring data quality has changed. The more we identify patterns and data that impacts quality RBM is better than traditional ways. Getting in front of risk to quality and free up

CRs to do things that cannot be seen remotely is more efficient use of onsite time.
I think RBM is beneficial and understand the pros for using it. It allows teams to focus on the real data, CRAs to see the bigger picture and not just be box checkers.
I say somewhat positive because RBM has not been implemented by most companies.
Regardless of training slide-decks there is a lack of awareness on implementation plans/practices. The specifics are not clear and the actual putting the "theory" into action is an uncertain space.
I have no direct experience and have no idea if RBM actually works. However, what I have read thus far I have concerns.
Change is always difficult at first but I can see the long term goal with this method
I have helped build data workflows for RBM of trials data
I think the sites and monitors are nervous about RBM, because errors could be reoccurring because a monitor does not visit the site.
I lack direct RBM experience
I am very optimistic about the potential for more effective execution of studies by incorporating RBM, but I don't see the industry embracing RBM practices- not uniformly or willingly.

Respondents were then asked to identify "What is the root of deficiency in understanding the RBM approach?" Their responses are displayed in Table 7 below. The respondents returned to the common refrain that change management is needed to manage this transition. Numerous individuals suggested that the approach and goals of RBM are understood but that their implementation collides with reality and prior practice, leading to uncomfortable feelings all around. Practitioners are begging for someone to step in and level the playing field by laying out clear concise goals and practices for RBM implementation from the top down, from the highest levels of study management to the first year study monitor at a new clinic. Everyone must understand what RBM is and how it works so they can be prepared to respond to RBM based data queries effectively and efficiently while still having time to run the trial. Reading between the lines, one might almost imagine that RBM has effectively been implemented on top of traditional monitoring practices rather than in place of them. RBM was never supposed to run concurrently with total monitoring.

Table 7. Perception as to the Root Deficiency in Understanding RBM Approach.

Quality built in the beginning and creating risk plan is well understood. However, the central monitoring process, data reviews, monitoring actions driven by data reviews need more training for the roles which will be impacted.
Unclear understanding of the GCP guidelines. Unclear understanding of how the Sponsor wants to implement said guidelines. Inefficient programming of data feeds; ability to review the data remotely.

Each sponsor, each CRO defines RBM differently but one common point is that the impact on the site time has not been taken into consideration.
Lack of experience, lack of time to gain knowledge, and for some people, not understanding the benefit well enough or the fear of change.
Need exposure to the RBM process.
People think it is about reducing source data verification and that may be an outcome but that is not why it should be implemented. People to need to understand how central monitoring works. One huge obstacle to that is having the available software and resources to run it. Teams need to be able to use Quality by design techniques to identify critical processes and data points that will increase data quality. This is a culture shift for the industry and sponsors/CRO need to implement RBM will solid training in a step wise approach.
I think it is complex and sometimes difficult to understand what needs to be reviewed. I don't have an understanding of the operational aspects of RBM.
It is difficult to have a shift or change of any kind rolled out to the team, but in our industry, better quality of a study always used to equal more monitoring. It is a challenge to shift this train of thought.
There are deficiencies in understanding the RBM model for each functional group.
Communication and compliance, and identified accountability of importance, and then ensuring everyone understands, are trained and continual feedback and processes in place.
Unclear implementation of RBM across sponsors and studies.
Lack of trust in RBM approaches. If SDV is not 100% the data may be dirty.
Lack of awareness & training
A hasty roll out, not having enough examples or experience to back it up. Not letting the people using the system become familiar with it.
In my opinion the RBM challenges are: The central importance is the need to protect the well-being of study participants and maintain the integrity and validity of study results per GCP. In order to achieve this GCP states that all clinical trial should be actively monitored or reviewed which includes 100% SDV. This approach limits the benefit of cost control and also increases the length of time it takes for data to be reviewed.
Lack of early communication. Clear communication early on to the end users. End users need to know what they need to do. The manners in which implementation expectations are communicated to the Monitors are insufficient- need to be determined and effectively share with the team as a whole. Change is difficult and Industry is slow to implement new processes due to comfort in traditional ways.
Lack of training, experience and knowledge. I do not completely understand all the details about RBM and have yet to really see how it works.
Fear of change if you do something one-way for years and years it's hard to adopt a whole new method
The approach is well understood. The problem is efficient digitation of data collected during trials or extraction from clinical notes (thinking pragmatic trials within large integrated healthcare network)
I believe I understand the RBM methods, but unsure how to actually implement in my current work.
Additional burden to sites.
RBM is a shift from the usual on-site monitoring. Changing the established norm is difficult. Delay in fully incorporating a RBM approach. There may be initial costs when changing to a RBM system. The priority of most sponsors is the race to approval and changing the way work is done does not seem as high a priority. ICH E6 in 2016 and FDA Guidance in 2013 were silent on specifics of RBM and it is not universally implemented.

When asked if training platforms could improve RBM perceptions, 20/22 respondents agreed, responding “yes”, with a single “no” and one “unsure” response

recorded. Despite the varying opinions as to the root deficiency in the knowledge of RBM, essentially everyone feels that developing effective training platforms will improve the perceptions of RBM (Figure 13). The study data repeatedly reinforce the idea that RBM implementation is facing a significant training and understanding barrier in the USA. Individuals largely feel that RBM is positive or could/should be, but many are left unsure how they can help and what to do about it.

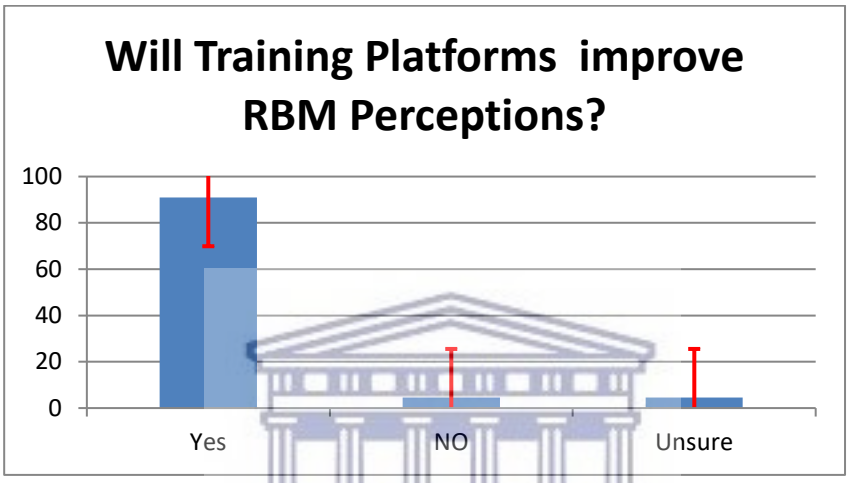

Figure 13. Improve RBM Perceptions with Training Platform.

Respondents whom had indicated that training platforms would improve RBM perceptions were asked to choose and rank types of trainings that would be helpful; Simulations, Coaching/Mentoring, Lectures, Group discussions/Tutorials or Role Specific. Respondents strongly agreed that role specific training (37%), group discussions/tutorials (36%), and simulations (23%) were effective training types. 36% were unsure about coaching/mentoring. Interestingly, the vast majority of respondents (73%) felt lectures were not an effective training approach. Given that the respondents in this survey had thus far demonstrated adequate to exceptional understanding of RBM in theory, and yet kept pointing to implementation challenges, it makes sense that efforts would be better spent on practical trainings, not intellectual enrichment.

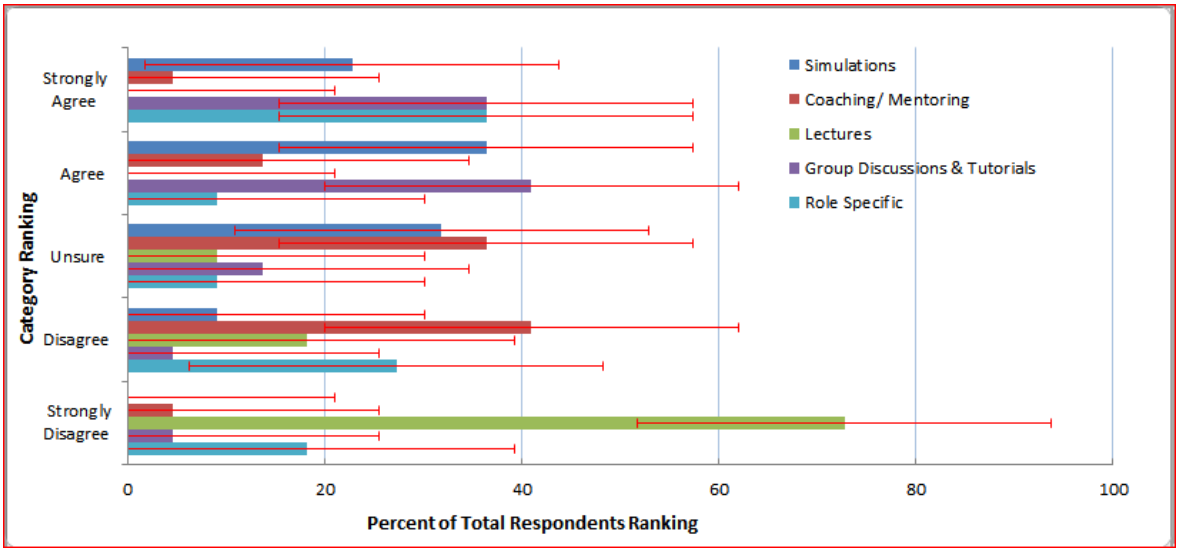

Figure 14. Types of Trainings that would Improve RBM Perceptions.

One respondent from a CRO stated that training of all types would be useful but effective training platforms will involve resources (personnel, time and cost) and are not likely to happen without more regulatory expectations and mandates.

4.2.7 RBM Practices

Respondents were asked to indicate their level of agreement with the following statement, "The RBM approach when properly designed and conducted is superior to traditional monitoring practices." They were given a Likert scale of responses to choose from and the data is shown in Figure 15:

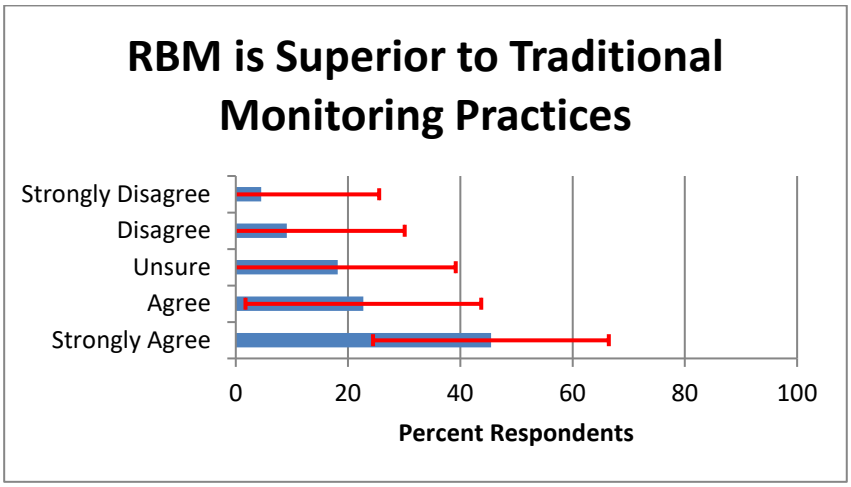

Figure 15. RBM Approach when Properly designed & Conducted is Superior to Traditional Monitoring

68% (over 2/3) of respondents agreed or strongly agreed that RBM was superior to traditional monitoring practices with only 14% disagreeing or strongly disagreeing with the statement (note 18% were unsure). Respondents were then asked to explain why they selected the response they did, their response is shown in Table 8.

Respondents who had selected "agree" or "strongly agree" were clearly strong advocates of RBM and their detailed responses read like an RBM advertisement or manual. Those who chose "disagree" or "strongly disagree" had a number of complaints; however none of them were related to RBM's performance. Instead their complaints were either laments to the loss of interpersonal interactions as a consequence of RBM's reduced site visits, or expressed concerns over the lack of complete data monitoring RBM entails.

Interestingly, a recent publication analyzing implementation of RBM in an academic setting contains quotations from study monitors that nearly exactly match these-suggestions that monitors are uncomfortable with the long gaps between visits when RBM has been implemented (Von-Niederhausern, 2017). Although the majority of respondents agreed that RBM is superior to traditional monitoring it is clear, both in this study, and the wider literature that clinical trial practitioners are uncertain about the benefits of RBM.

Table 8. Reasons Why Respondents felt RBM was Superior to Traditional Monitoring.

Strongly Agree	The previous model of 100% source document review has been shown to be a low value model. RBM should allow faster mitigation of site data and refocus while reducing the amount of onsite monitoring visits.
Strongly Agree	For the protocol and CRFs to be developed by teams which will take into consideration the needs of clinical data entry, data analysis, data review and source data. Training will then be created both for all parties, sponsors, CRO and the sites in order to ensure that all data points are listed before the first subject is enrolled.
Strongly Disagree	For the protocols and CRFs to be developed by teams which will take into consideration the needs of clinical, data entry, data analysis, data review and source data. Training will then be created both for all parties, sponsor, CRO and the sites in order to ensure that all data points are listed before the first subject is enrolled. A companywide understanding of the model and how it will be implemented across all studies. A clear understanding of how RBM impacts an individual's job.
Agree	It's difficult to define 'traditional' as there have been changes to monitoring practices in the past as well. When industry moved to 100% SDV requirements, this made a difficult burden on study teams. The RBM approach allows teams to put the effort where it's needed and to leverage real experience from the trial in order to determine the best monitoring activities (including frequency).

Strongly Agree	With RBM there is more focus on source data review, site staff study execution, site records.
Unsure	RBM sounds great in theory, but I will need to see it be productive to believe it will be a superior approach
Unsure	My RBM experience is very limited.
Strongly Agree	The approach is superior by narrowing in on key data points and risks specific to a study that ultimately impact quality and or safety and use resource and budget appropriately.
Strongly Agree	Again – IF designed and implemented appropriately
Agree	low value data points are replaced with high value ones increasing efficiency
Strongly Agree	The FDA agency is on board so Industry doesn't have a choice! If the FDA carries out an inspection on a study starting in 2017 and a company is using a traditional monitoring model as opposed to an RBM approach the FDA will most surely address this. The traditional model is mired in longer filings and delays which translates into higher development cost of market
Strongly Agree	Immediate benefits were seen in safety signals. Site data-clinical listings- reviewed by clinician prior to on-site SDV. Definitive cost-savings is not yet clear.
Strongly Agree	With RBM centralized monitoring is introduced and extensive data is reviewed. This helps determine if sites should receive more extensive quality review or intervention.
Unsure	RBM has potential but nothing concrete to reflect upon. I doubt efficiency because I have not seen any proof of outcomes. I feel F2F interactions are important and site performance may suffer with less visits. Data is not everything!
Disagree	In my opinion RBM has yet to be proven effective. My gut tells me that it's risky and I don't have enough knowledge to determine if RBM approach is better than traditional.
Agree	Having done the 100% verification the other way, I fear that much data will be incorrect but could simplify processes overall.
Agree	There has been a large push to digitize data vs historical paper-based processes and chart-review. In addition, there is a huge push to standardize data models, centralize monitoring and produce standardized dashboards with rules to warn of critical incidence and relative risks.
Disagree	RBM removes a personable working relationship between the site and monitor. I also believe that it is time consuming for the monitor and that time is not considered as part of the CRAs allocation.
Unsure	Lack of RBM experience and exposure
Strongly Agree	RBM should be part of a total quality management system. The system should build in quality by design and risk management with goals of continual improvement in study conduct. Protocol and CRF design, training and site selection must also be examined. Sponsors need to spend more time planning and incorporate risk management (identification/evaluation/communication/review/reporting). Centralized systems should lead to more targeted on-site monitoring. Centralized monitoring can more quickly identify issues at all sites so issues are resolved faster and recurrence mitigated.

The questionnaire then took a different tack and began to explore the practice of RBM, turning away from a perception based assessment and seeking to define some metrics of the current state of RBM in clinical trial practice. Respondents were asked if

their institution/company practices RBM, if they had been trained in RBM, and when RBM practices had been implemented at their institution/company. Their responses are shown below (Figure 16):

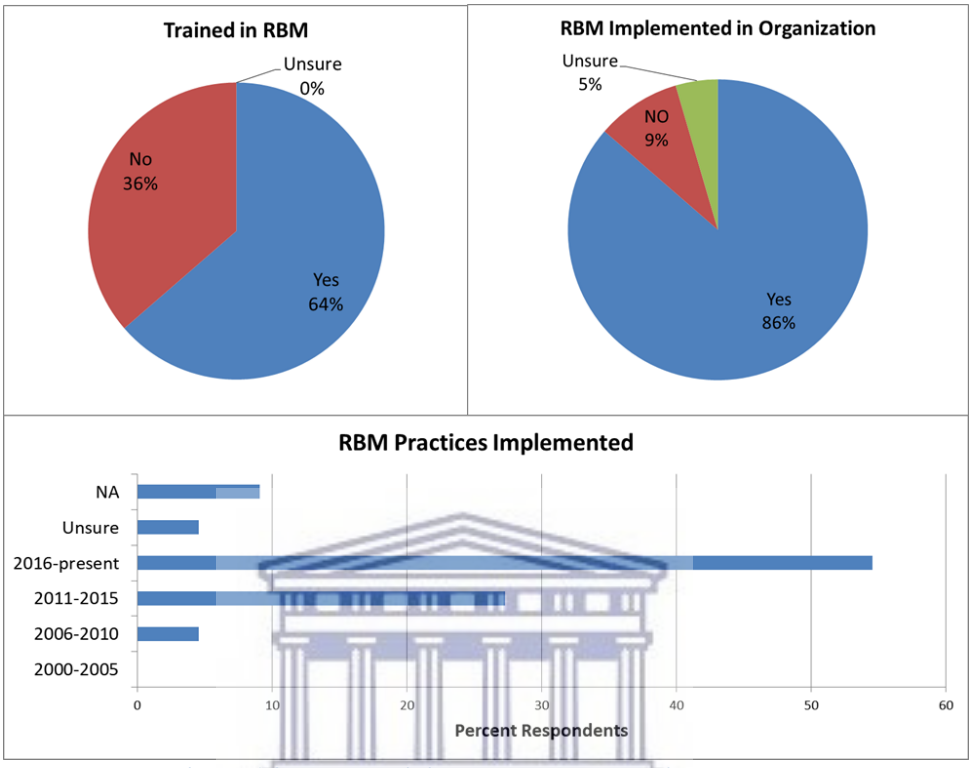

Figure 16. RBM Training and Implementation.

Although 85% of respondents indicate that RBM had been implemented in their organization, only 64% indicated that they had been trained in RBM. When asked to state when RBM had been implemented, most selected 2016-present (55%) with a few indicating RBM began as early as 2006-2010 time frame. The apparent disconnect between training (64%) and implementation (85%) is a consequence of the fact that RBM is not yet a part of all trials, and has only recently been implemented. Thus, individuals working at a company running a RBM trial may not have been exposed to RBM. Individuals were asked to identify the stage of RBM implementation at their institution/company and their exposure to RBM practices, their responses are shown below in Figure 17.

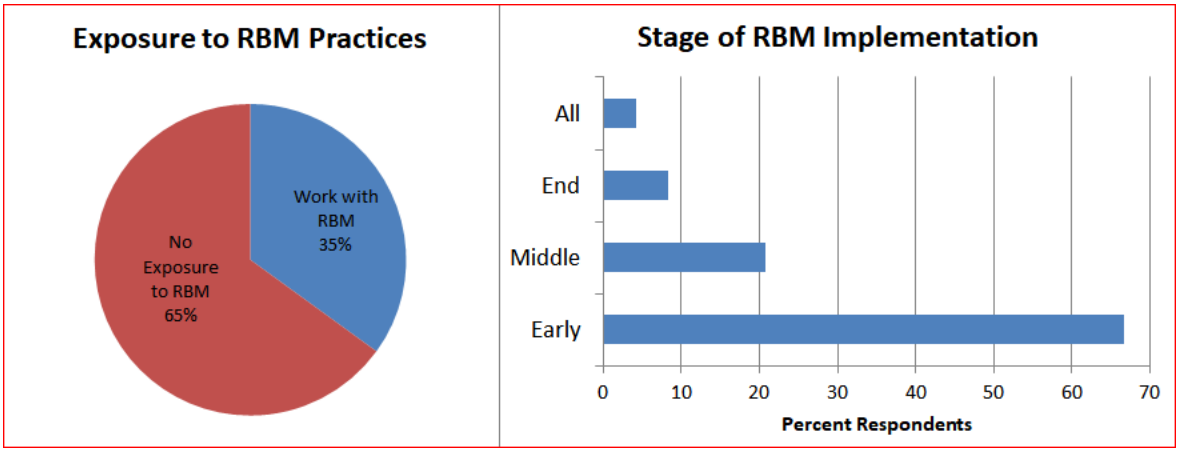

Figure 17. Exposure to and Stage of RBM Implementation

Again their responses are illuminating, serving to show that although RBM has been and continues to be an industry and regulatory buzz word its real world practice is in its infancy. The majority of respondents indicated they do not work with RBM, while those that had any RBM experience whatsoever indicated it was in early stage of the RBM implementation/adoption process. One respondent stated their study is in the feasibility stage and this is their first exposure to risk-based monitoring approach. When asked what they think is the focus of RBM the most frequent word phrases used in their answers are shown in Figure 18:

Figure 18. Most frequent word phrases (count) found in response to question "What is the focus of RBM?" (Figure made using https://tagcrowd.com/)

Respondents were asked "what key factors may influence the implementation of the RBM approach?" and their responses are shown in Table 9, and suggest RBM requires a radical shift of thinking for everyone. Respondents also indicated that RBM requires communication during the planning phases throughout the organizations as roles and relationships between roles change when RBM is in place. Taking a risk-based approach in writing the study protocol and CRF, designing and implementing training and using a risk assessment to inform site selection is a new concept. Importantly, each of these crucial

tasks begins months to years before a single patient is enrolled in a trial, and months to years before the CRA or CRO knows anything about the trial- risk assessment and management must be engrained from the start for this to work. Because RBM is new, its current implementation is one that comes late to this process with few current studies designed top to bottom as RBM studies. Thus, much of the critique directed at RBM in the response to this survey reflect the fact that tacking RBM onto the middle or to the end of a trial is difficult; not impossible, but difficult! Sponsors need to spend more time planning during the white-boarding process and incorporate risk management in areas of risk identification, evaluation, communication, reviews and issue reporting and then translate these into effective RBM based study protocols.

Table 9. Opinion on What Key Factors Influence RBM Practices.

Implementing RBM in select trials spanning multiple therapeutic areas with various countries and populations to gain knowledge and lessons learned before full roll-out has been very beneficial.
Role-specific training and change management actions are needed to support teams with implementing RBM.
Do not have any positive examples of RBM at this time. We need to take a step back & review RBM planning. Take a closer look at protocols and impact on sites. As RBM impacts the sites just as much as the sponsor. Need sites buy-in to help sponsors conduct studies using RBM and compensate sites for the time they allocate to remote, central monitoring and on-site visits. CRAs' time must also be allocated for work remotely done and on-site visits.
The two critical pieces are having the right tools that can identify trends. Training study teams to know what risks to look for. Educating study teams properly, support from experienced RBM subject matter experts, and implementing a robust RBM platform that harness central monitoring, analytic review of trends and handling risk mitigations.
Following the prescribed process. Do not revert back to traditional monitoring habits/processes.
Do not work with RBM yet. Would need orientation training.
Meeting regularly and reviewing the data regularly that gave us confidence. Sharing lessons-learned.
Practice. The more you use the systems, the more comfortable you will be in trusting them. RBM is here to stay but many are not comfortable because they are new to the RBM concepts.
Proper awareness, training, focus on RBM's importance. Identify the "owners/champion's" who utilize RBM across functional teams to help design, implement, and continuously improve RBM tasks.
Sponsor must be willing to buy-in on RBM to resource/implement RBM and roll-out effectively.
Big barrier is the lack of systems and lack of technology. Some small Biotech's don't have an EDC system or resources to set up their own system. Companies struggle in selecting the right model/CRO/Vendor. If sponsors are not well informed they don't know how to manage. On the flip side if a company sets up their own systems it may not be efficient. The perception of where the real risk lies is displaced. There is a lack of trust in the FDAs guidance of RB approach. What if a study gets inspected and the FDA states the data is not good enough?

Building the infrastructure for internal central review is important. Address technology barriers. Buy-in is essential and one of the biggest barriers. Getting the sites buy-in on how timely data review works effects RBM outcomes. Early RBM effectiveness is impacted by the sites performance and data entry.
Educating the key players on the rationale, how it benefits the study and data. Having hands on demonstrations so people can see how the system works.
Lack of uniform understanding of the principles and approach, emphasis of RBM needs to be focused on identifying risks earlier before the start of the trial and not only on centralized monitoring.
More than one way to raising knowledge. Use multiple ways to communicate and repeat guidelines. There is not enough referencing of specific guidelines. There is opportunity for innovation.
Resistance to change is a major limitation to RBM approaches. Some people are not comfortable with skipping over non-critical data points.
Ability of organizations to have the technical ability and time to implement or to outsource (data privacy and security concerns).
The high amount of protocol deviations that occurs reduces confidence in RBM methods.
Motivation for implementation requires regulatory mandates. CROs work for the sponsors and must adhere to their mandate to implement RBM.

When asked "Do you feel the RBM practices implement in your organization have been beneficial?" the response was split nearly evenly between "unsure", "no", and "yes", hardly an enthusiastic endorsement (note that error bars overlap, see Figure 19).

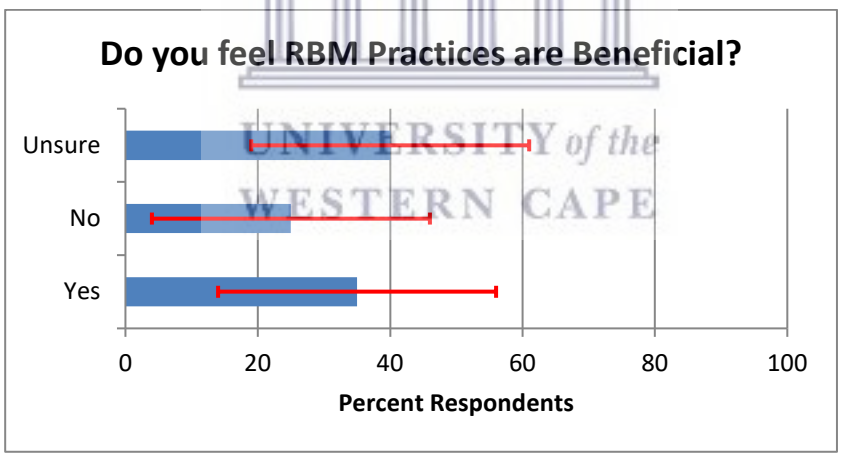

Figure 19. Are RBM Practices Beneficial?

The major conclusion thus far from this study is that the lack of effective training is impacting RBM implementation and practice. In fact, when asked, "Will training platforms improve RBM perceptions" (see Figure 13 above), 91% of respondents selected YES. Within the 21% error margin of this survey that represents a statistically significant finding. Perhaps the responses to the question "Do you feel RBM practices are beneficial (see Figure 19) would look a bit different with more training and RBM knowledge.

When asked to explain why they felt that RBM practices were or were not beneficial (Figure 19) respondents provided the following explanations (Table 10). As might be expected, given that the vast majority of respondents indicated RBM practices were early or not yet adopted, most indicated that their response to the question was tied to their lack of experience, see italic (emphasis added) response in Table 10.

Table 10. Respondent's Explanation for their choice when asked "Do you feel RBM practices implemented in your organization have been beneficial?"

While we are in the *early stages of RBM*, we have taken a *step-wise approach to implementation* to gain knowledge and *apply lessons learned before full roll-out company-wide*.
It has brought frustrations to the sites, the CRAs, and the RCSLs and thus has made our working relationships tenses and as more on-site visits were needed, the acceleration of data-analysis and the cost-saving aspects were not reached.
Has increased company understanding of RBM and the recent E6 guidance. Improved interest and drive to take advantage of what RBM can offer.
Hard to determine. In my organization it has been implemented but *it is still very new* and the benefits are yet to be seen.
Not sure too early to tell. I don't know what exactly is being implemented that impacts me directly
Difficult to tell. I think this puts more of the CRA focus on reviewing the right data that impacts clinical trials. They are also able to review more subjects at visits, which increases the chances of finding trends while onsite.
I am not entirely sure and benefits are difficult to determine.
This is based on colleague's opinions *as my studies have not switched to RBM*.
Still too early to tell, but I agree with the RBM concept.
It is too soon to tell as it was just rolled out to the majority of our group. The training has not been great or useful.
Hard to tell at this point- *too early to tell*.
Too early to tell. Unknown- data not available
Have not seen any concrete data. *So far my company has done very little in regards to RBM* training. I feel investigative sites are too dependent on the monitors to guide, direct, and train them. Even if I have an RBM study I would still look at 100% SDV and not just for the critical data points identified by the study team.
I've seen the centralized RBM group on some of my studies and only got the items pertaining to my sites, so I don't get to witness big picture parts and results
We extract information from clinical notes (either trial notes or normal care for pragmatic trials and put them in a dashboard to easily identify problem in enrollment, retention and adverse effects.
Our company began centralized monitoring and it has yielded benefits for studies. We also established a new role (in-house- CRA) to reduce CRA workload. Not much communication, or not enough, about the new in house CRAs so that limited the effectiveness of the role. It also impacted the CRA/monitor role but this was not acknowledged, and the in-house CRA role differed by study causing confusion and conflict. Centralized monitoring was not used system wide- only for new studies- this decreased the perception of its importance.

It would seem that the predominantly un-enthusiastic response to RBM practice illustrated in Figure 19 reflects a lack of experience with RBM, not a negative bias or

negative experience. This suggests that the perceptions of RBM are being formed today; it will be interesting to see what the picture looks like in a decade from now

Hopefully, the future will show that RBM has been effectively implemented by harnessing cross-functional disciplines and finding a way for them to work together and achieve improvements in study conduct while regularly assessing if risks are managed (Landray, 2012). RBM should include more centralized monitoring activities because having data available electronically opens up many opportunities for improvement that were not available with paper-based data (Young, 2017). Taking advantage of the advances in innovations and technology can begin to change the need for on-site visits. Ideally, use of centralized monitoring efforts will focus on data and processes that are critical. Only when less effort is spent on low value tasks will the return on the RBM investment increase (Sullivan, 2015; Buyse, 2013).

Regulatory statements are very clear that a risk-based approach should be used but concrete mandates for RBM are lacking. The data collected herein demonstrate that there is an awareness and knowledge of RBM as a concept, and that there is a significant potential for positive change and a strong movement is in place driving practice towards an RBM approach. However, the data also demonstrate that there exists a lag in operational RBM directives at multiple levels in the process, and this is a strong impediment to RBM adoption. Many people are unsure what their role is and how to play the RBM game (Wolfs, 2018).

Both the ICH E6 (R2) and FDA Guidance are silent on RBM specifics, this silence was probably intentional and does allow sponsors greater flexibility and interpretation, (Limaye, 2018). As noted by respondents, RBM may be happening on some studies but without clear standards, policies and training resources it is difficult for them to assess or see the benefits of RBM. Another theme emerging from this study is that

ignorance of the RBM challenges and benefits may limit its gains. Making uninformed assumptions as to the reasons and purpose in developing and utilizing RBM approaches and methodology were rooted as the main cause of the lack of understanding.

4.2.8 Common RBM Misconceptions

Because the implementation of RBM is still in a very early phase (Figure 17) there are relatively few people with concrete, experiential observations of RBM. Consequently numerous misconceptions about how RBM works were identified during this study; see Table 6, Table 8, and Table 9 for additional examples. Some of the common misconceptions and the RBM fact are detailed in Table 11. Other recent studies and articles have identified similar disconnects between RBM truth and operational misconceptions:

Table 11. Myths vs. Truth

RBM Misconceptions Expressed by Respondents	RBM Facts
RBM does not apply to all studies.	All studies should follow a risk-based approach to monitoring with ICH E6 R2. Different monitoring methods and management tools may be needed depending on studies/programs. (ICH, 2016; EMA, 2013; TCBI, 2013).
There will be more risks by monitoring fewer patients.	There will be less focus on data transcription compliance. The monitor will still verify quality of SDV and SDR and focus on source documents identified as critical. (Alsumidaie/Henderson, 2016; Ghone, 2015).
RBM only benefits the sponsor not to study teams and sites.	The study team and sites benefit from focused support where it is needed. The purpose of RBM is to be adaptive to where risk is anticipated or detected. RBM plays a key role in quality control. (Brosteanu, 2017; Von-Niederhausern, 2017; Bois, 2016).
RBM means less site engagement and relationship building.	RBM may actually increase contact with sites as central monitoring/remote visits augment onsite and targeted visits. Monitoring plans and continuous data-driven assessments of site risk will focus the time of the site monitor on the value added activities. This will enhance the quality of the site relationships and study outcomes. (Wilson, 2014;Manasco, 2016; Niederhausern, 2017; PerkinsElmer, 2017; Diani, 2017)

4.3 Recommendations

Lastly, this study asked respondents to highlight systems that lead to efficient implementation of RBM and then to make suggestions to improve RBM in the future. Their responses are shown in Table 12:

Table 12. RBM highlights and suggestions to improve future implementation.

Examples most helpful in the efficient implementation of RBM systems.	What could be done to further improve implementation of RBM systems?
The next phase of clinical trials should be utilization of direct source from devices or subject-rated scales via electronic capture and RBM should evolve with these advances.	Looping in internal Regulatory and Quality Assurance team members is a key to the success of RBM. When regulations are updated the RBM model should be flexible to allow for changes to be adapted.
RBM needs to focus on the study end points and patient safety. In theory this can be done via the various data feeds if the study was set up correctly at the start.	Regular listing reviews to review the data/AEs/Safety/end points. If any abnormalities/outliers were found, then a focus on those issues would be done onsite during regular monitoring visits.
Reduced cost/travel/time, less burn out for monitoring team. More real time review of data. Very little findings onsite related to transcription errors resulting in significant changes to end points.	The regulatory bodies will not modify their guidelines. But the sponsors can implement them while keeping in mind the feasibility and the logistics required for RBM with the sites, the CRAs and the clinical teams.
We may find that industry best practices should be defined and shared so that we can all keep pace with what's appropriate and grow into successful use of RBM industry wide.	Even if RBM isn't used, having the early and regulatory reviewed identification of risks trends is valuable.
Dedicated trained cross functional team	Training, processes, integration into team
Change management strategy. Increase visibility of TransCelerate within the organization. Champion exposure of TCBI within a company. Have an internal group that can provide SMEs to sit on project teams to act as a resource conduit/guide to get a study familiar with implementing RBM. Trainings-RBM SME: sit on study team meetings, develop slide-decks; provide reference to free web-ex's, get on an RBM listings & receive email notifications to keep current and exposure to what other companies are doing.	Continual focus on all aspects of improvement. Share information across the monitoring/compliance team on a regular basis so that all are aware of trends, sites with outlying data. Ensure understanding of RBM guidelines; how the sponsor wants to implement the practice and a better understanding of how other sponsor's implement the practice.
Better Training. Industry is much regimented. We need to be willing to let go of yesterday's best practices to embrace tomorrow's next practices. Traditional monitoring has reached its expiration date and it's time to move into the 21st century.	standardized , practical training Sites need more awareness
Hands on demonstrations.	A huge barrier is when systems don't communicate. A CTMS is a package or system that aggregates all operational data for a study. It is a place where data analytics and identification of data trends can be run. Thus, having a robust CTMS where data can be pulled from operational and clinical databases to look at study data on a holistic level is critical. Robust systems and tools: CTMS is a must! SMEs, iQRMPs, KRIs, SMPs, Adequate trainings for monitors and Sites.
My company is still implementing RBM, difficult to see/know results.	Socialize RBM at all levels. At a high level there is buy-up but we had to get buy-up at every level of the

	organization and make RBM .relevant to their role.
More referencing to guidelines. Communication- If monitors are unaware of implementation practices they can derail attempts at change management. Monitors can unintentionally communicate to sites opposing intent if they do not have buy in to the intent of RBM. Don't lose track of referencing specific guidelines/requirements to gain buy in. Collaboration is a huge piece especially when you have multiple partners/vendors.	How does this impact the sites? Need a F2F-live introduction/orientation of RBM processes. Maybe at the start of the study during the IM. Need to convince the monitors and site staff of the benefits and show some real examples of RBM successes. It is not always about the cost-savings. Constant interaction with the sites is what makes a study successful. Limited direct F2F contact raises concerns for me. Sites rely on their monitors on more than just the data. Relationships may be compromised with less frequent visits. Even though RBM is the wave of the future I am old-fashioned and think that the sites and the study will suffer from lack of attention, recruitment and sites interest will dwindle.
Noticing trends that I couldn't see at the detailed levels	Site training & understanding is not happening.
Access to electronic systems to such as centralized lab, ECGs, and IRB vendors.	Electronic sources for the sites to use that could be monitored on line.
For centralized monitoring there was a wealth of training and information when it began.	I have not had much exposure to RBM approach and so far I have not been trained by the sponsor- little has been discussed on what the site needs to understand about the RBM purpose etc.
	Companies should enthusiastically endorse and implement changes. Communication of changes and opportunity for discussion should be provided.

Chapter Five: Suggestions for the Future

5.1 Introduction:

Based upon the responses gathered it is clear that most clinical trial practitioners have a basic understanding of the concepts and goals of the RBM approach. However, the findings also demonstrate that the practice of RBM is currently hindered by a lack of cross functional collaboration, clearly defined roles and responsibilities, and a lack of operational training. Despite these early stumbles the perception of RBM is generally positive or optimistic, however due to the aforementioned lack of training and clearly defined roles, there are numerous potentially troublesome misconceptions about RBM. The future of RBM is bright but in order to attain that it is clear that much work remains to be done.

This study has identified a number of strengths and weakness in the current strategy to implement RBM. Based upon these findings I identified a few practical steps that could be taken to smooth the transition to RBM. These are summarized below, by topic.

5.2 Improving RBM Implementation

5.2.1 Attain Governance

Attaining commitment from executive level decision making was cited by more than one respondent as a critical factor in ensuring that risk-based decisions are relevant to meeting regulatory compliance. Availability of executive leadership support is a necessary driver towards incorporating RBM practices, as implementation is affected if there is a lack in executive leadership support to ensure enough resources, tools, training are available.

5.2.2 Develop Quality Control Plans

It was stressed by respondents that irrespective of study phase, development of an Integrated Quality Management Plan (iQMP) is an important step (Khare, 2016; TCBI, 2013). RBM must be viewed as an integrated end to end approach, starting with risk assessment and defining critical data. Respondents also suggested that utilizing an effective quality management system (QMS) to embed quality control plans that clearly define the risk assessment expectations such as study monitoring plans (SMP) and data review plans (DRP) will strengthen RBM implementation. The QMS should build upon a quality by design (QbD) and risk management foundation with goals of continual improvement in study conduct (Brosteanu, 2017; FDA, 2007; Knepper, 2015). The SMP should define the minimum expectations for on-site monitoring and the DRP defines the central and remote monitoring strategies (Buyse, 2016; Khare, 2016; Ghone, 2015).

Having quality control plans in place is highly beneficial in helping to define the monitoring approach including the amount of SDV and SDR strategy (Journot, 2011). In conjunction to developing quality control plans (e.g. iQMP, SMP, DRP etc.) RBM shifts the focus away from dependence of on-site monitors to review data points and places emphasis on centralized and/or remote monitoring activities and study management (Hurley, 2016; Khare, 2016).

5.2.3 Institute an Optimal RBM Platform

Respondents indicated that it would be optimal to include RBM discussions and planning very early in the development of the project, e.g. during the study design phase, protocol writing and CRF design. During the white-boarding process of a study the team needs to discuss RBM processes and technologies in order to minimize redundancy and minimize missing crucial implementation steps. In order to carry this out there needs to be engagement and understanding by the investigators, site staff as monitoring (onsite, remote

and central) will be adapted based on findings and trends at the site (Khare, 2016; King, 2015).

5.2.4 Improve Training

Lack of robust training was cited as being a key impediment RBM (Figure 11, Figure 13, and Figure 14). Embedding risk-based activities, reducing complexity, while developing a deeper understanding of RBM is a struggle for the industry. Individuals that are poorly trained lack a clear direction and purpose leading to confusion and negative perceptions, this in turn pose a threat to implementing any change.

Respondents were of the view that difficulty in developing a clear picture as to the intent of RBM includes basic information being camouflaged by an overwhelming amount of facts and figures. When information is presented in a manner that is highly scientific or technical, the average stakeholder may not develop meaning out of the content. It became apparent that RBM training must extend beyond the borders of the CRO or sponsor and include investigators and site staff, they are not currently involved enough in the RBM process.

Respondents offered potential training solutions to make RBM practices less intimidating to study teams and to help teams slowly develop a picture of the risk-based situations involved in their organization. The below training suggestions may help ensure stakeholders are comfortable with the goals and implications of a risk-based approach:

- Make trainings short and less technical
- Develop a company specific website dedicated to RBM implementation
- Host RBM orientation/introduction classes and open-forums/office hours to address questions and answers,
- Provide references and tools
- Create a core change management team dedicated to training those new to RBM.

- A panel of RBM subject matter experts to act as resources and ensure clear consistent delivery of complex strategies and technical systems in order for study team members to develop a clear picture on the operational aspects of RBM.

5.2.4.1 Collaboration and Communication

As a part of training, collaboration and communication plays a critical role in defining the key elements that should be of focus to ensure universal awareness and understanding of the risks and benefits of the RBM process. Sponsors need to effectively communicate RBM expectations, goals, decision making and the types of RBM methods and systems they are planning to use.

Chapter Six: Final Analysis and Conclusions

6.1 Final Analysis

The outcomes of this study are in line with findings that have been developed by other researchers (Knepper, 2015; Limaye, 2018; PerkinElmer, 2017; Sullivan, 2015). This study has shed light on drug development practitioner's RBM engagement, a crucial aspect to implementation. The findings from this study show that a lack of consistent clear cut RBM implementation among practitioners has led to wavering perceptions about RBM and a tendency for practitioners to default to past practices (such as 100% SDV) rather than implementing RBM best practices. The difficulty in breaking away from the past is hindering successful implementation of RBM in the present. It is also evident that in addition to the existing knowledge gaps, available advanced technology systems to aid in identifying and interpreting critical data are far from being utilized in a meaningful way (Hurley, 2016; Wilson, 2014). If the industry is to see a widespread uptake in centralized and remote monitoring the following barriers were identified and recommendations to overcome them are provided.

Table 13. Barriers to effective RBM implementation and strategies to overcome them.

Barrier	Recommendation
• Unclear regulatory guidelines • Willingness to act; no interest • Inefficient technology; software risks • Don't have the time and resources • Don't have appropriate funding for technology. • RBM activities and steps not well defined • Difficult for users to identify relevant portions applicable to their role-specific RBM activities • Inconsistent risk categorizations • Impact of RBM are not clearly demonstrated • Controls are not transparent or easily discernable • RBM is not a priority- too busy getting routine things done.	• Provide ICH E6 background (Heering, 2016). • Provide process clarity and guidance throughout the lifecycle of the study • Role specific training to address specific purpose and activity (Wolfs, 2018). • Consistent and clear risk assessments • Controls and mitigation to clearly demonstrate by documenting unmitigated and mitigated risks (TCBI,2014) • Define levels of risk associated with the level of SDV & SDR (Ghone, 2015). • Categorize risks appropriately in the IQMP, KRI, and develop control plans study monitoring and data review decision making (Khare, 2016).

The key remit for the industry is to proactively get ahead of emerging risks and identify, manage and adapt to changes to the mandated regulations pertaining to risk-based monitoring. While much progress has been made with the RBM initiatives and availability of TransCelerate resources, it will most likely be several more years for this approach to be truly considered "business as usual" for many biopharmaceutical companies (TCBI, 2015). RBM is not a one and done process but a progressive undertaking with continual implementation and evaluation. Awareness on the impediments and areas that are problematic have been alluded to by existing researches and further acknowledged by the respondents in this study.

6.2 Conclusions

The survey conducted as part of this study attempted to generate a clear picture of RBM knowledge and perceptions amongst practitioners in the US. Regulatory agency staffs were not included as survey respondents as they guide but do not implement RBM practices. Implementation is the responsibility of industry and clinical site staff. Because RBM is new,

this study seeks to identify if RBM awareness has penetrated through all levels of trial management staff and then to identify training gaps on the side of the pharmaceutical industry that can be addressed to ensure RBM understanding and practice are linked. My findings suggest a particular focus should be placed on information availability, training and education to ensure implementation of RBM approaches are in line with the evolving regulatory guidelines. Finally, this study seeks to gain the insights and opinions from various industry stakeholders to determine to what extent practitioners feel RBM practices have impacted the efficiency of clinical trial execution and management.

Clinical trial execution is tasked with ensuring that the study protocol is written in a manner that is in line with existing regulatory guidelines and then seeing through its execution. A major component to clinical trial execution is information management and dispersion, if you cannot ensure that study team members and other industry roles are aware of the principle rationale of the ICH E6 (R2) guidelines and the role of RBM in implementing them, RBM is only a sentence in the protocol and will never become part of the execution of the trail (Heering, 2016). Information is part and parcel to understanding RBM's intent and implementation of its practices.

One of the major conclusions of my study is that industry must do a better job identifying and using effective training platforms to ensure study team members all have the understanding required to make appropriate, objective, and fast decisions surrounding RBM implementation (Alsumidaie/Henderson, 2016). In essence, by seeking to determine if the RBM concepts are understood by the various industry roles involved in the drug development process and gage the level of their awareness of existing regulatory requirements, this project strives to ascertain if misperceptions and lack of knowledge limits implementation of RBM practices.

Practitioner insights gained from this study suggest that changes to strategy formulations within the clinical trial management and execution space are needed in order to ensure RBM approaches are widely understood, adopted and applied consistently in accordance with regulatory agencies and ICH E6 (R2) guidelines.

RBM is happening, not just in the US but globally (Korieth, 2017). Following a risk-based approach is not a suggestion- it is a requirement of the FDA (ICH E6 (R2)). Invariably change to existing practices comes with varying degrees of uncertainty and even resistance (Artyomenko, 2015; Korieth, 2017; McGurk, 2014). Planning for the future with a risk-based approach to monitoring can be impactful and set organizations up for success yet a crucial outcome from this project highlighted RBM perceptions within functional groups for existing studies varied from the negative naysayers to positive promoters spreading RBM accolades.

Lack of awareness and understanding of regulatory guidance, insufficient training structures, over-reliance on sponsors to train internal (study-teams, data-analyst, statisticians etc.) and external stakeholders (clinical-research-organizations, out-sourced vendors and investigative sites), poor early study engagement, limited allocation of time and resources, lack of advanced technology have come up as impediments to ensuring consistent adoption and embracing of RBM practices. This is certainly a distressing condition and places R&D in a precarious position considering the role played during drug development research and healthcare research in the long-lead time to get buy-in from various stakeholders.

However, all is not lost, for the challenges appear to be a result of issues that can be dealt with by keeping too restrictive thinking at bay and open mindsets willing to explore innovative risk-based approaches. The barriers to RBM mainly circle around awareness and training methodology and finding the right technology currently being used. With leadership

endorsement the willingness to act can be changed to ensure that information about RBM is not only obtained but effective practices utilized in conjunction with innovative technology.

To date several TransCelerate Member Companies have implemented a Risk-Based approach to clinical trial monitoring and adoption of risk-assessment is steadily growing (Korieth, 2017; TCBI, 2015). The years to come will be defining years for biopharmaceutical companies as they forge a path to implement effective Risk-Based Monitoring practices. Companies should be encouraged to invest in a pro-industry cultural attitude of sharing best practices which not only helps their own interests but also aid other companies to incorporate RBM processes.

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Appendix 1

Title of Research: Knowledge, Perceptions and Practices of Risk-Based Monitoring (RBM) among clinical trial practitioners in the United States.

Consent to Participate in a Research Survey

You are being invited to voluntarily participate in a research survey about your drug development experiences related to your knowledge, perceptions and practices of Risk-Based Monitoring (RBM).

The survey will be conducted as a questionnaire and a semi-structured interview and you will be asked questions about your general role in the drug development industry and questions about regulatory guidance and trial management techniques.

Your participation is entirely voluntary and you may choose to participate or not, or to stop the questionnaire/interview at any time with no consequence. You will not be compensated for your time.

The survey administrator will ask you for your gender. No other personnel information will be collected nor will you be asked to divulge proprietary information. Please note all responses will be reported only in an aggregated form and never associated with any individual or company.

In-depth questions and interviews with open-ended questions allows researchers to understand individual perceptions, experiences, suggestions to better understand and recognize outcomes that may not surface from highly structured questionnaires. Therefore, this research survey/interview aims to collect information to answer specific questions associated with RBM.

The information you share will be kept as confidential as possible. It is not likely your information will be given to others without your permission. Your information will be used and disclosed only for the purpose of this mini-research project to analyze the survey data and possibly combine your information with information from other sources not directly related to this survey.

If you choose to participate, the survey will require approximately 15-20 minutes of your time. By signing this consent you are agreeing to the following statements:

- I have read this form and the research survey has been explained to me.
- I have been given the chance to ask questions, and my questions have been answered.
- I agree to be in the research survey as described above.
- I am not giving up any legal rights by signing this form.

_____
Print Name

_____
Signature and Date

Appendix 2

Title of Research: Knowledge, Perceptions and Practices of Risk-Based Monitoring (RBM) among clinical trial practitioners in the United States.

Questionnaire

Demographic information:

1. Gender Male ☐Female ☐
   What is your role in the industry?
   - Clinician (Sponsor) ☐
   - Basic Scientist ☐
   - Data Analyst/Statistician ☐
   - Monitor ☐
   - Investigative Site ☐
   - Other (_____) ☐

Knowledge of RBM:

2. [A] Please define the goals and key concepts of RBM succinctly.

   [B] Please provide three words that come to mind when you think about RBM.

3. [A] What is your current level of awareness of the ICH GCP E6 (R2) addendum?

☐High
☐Medium
☐Low
☐None

[B] Do you have a clear understanding of E6 (R2) regulatory guidelines?

☐Yes
☐No
☐Unsure

[C] If applicable has your company implemented policies and processes to adhere to guidance?

☐Yes
☐No
☐Unsure
☐NA

[D] If policies and processes have been implemented briefly summarize the most effective plans.

[E] There are several ways that the knowledge of RBM could be limited. I have listed 4 of them below. Please indicate your level of agreement with each item using the following scale:

(1-Strongly agree; 2-Agree; 3-Unsure; 4-Disagree; 5-Strongly Disagree)

Please base your answer on how much impact you feel they have in limiting RBM knowledge in your day-to-day work and experience.

i.	Unclear regulatory guidelines	Choose an item.
ii.	Lack of awareness	Choose an item.
iii.	Lack of education	Choose an item.
iv.	Lack of effective training	Choose an item.
v.	Other (.....)	

[F] Describe possible recommendations for mitigating each of the issue outlined above.

Perception of RBM:

4. [A] What are your perceptions about the impact of RBM on effective execution of clinical trials?

☐Very Positive
☐Somewhat Positive

☐Unsure
☐Somewhat Negative
☐Very Negative

[B] Please explain why you feel this way.

5. [A] In your opinion what is the root of deficiency in understanding the RBM approach? (In other words what are the impediments (limitations/challenges) which act as obstacles in understanding RBM methods?)

6. [A] Will developing training platforms improve the perceptions of RBM?
☐Yes
☐No
☐Unsure

[B] If yes, which of the following types of trainings may be helpful? (Choose all that are applicable and rank them in order of importance, only those that are applicable)

- Simulation (Simulators are used to imitate real work experiences.) ☐
- Coaching/Mentoring. ☐
- Lectures. ☐
- Group Discussions & Tutorials. ☐
- Role Specific Training ☐

7. [A] Please indicate your level of agreement with the following statement (based upon your current understanding of RBM) regardless of your implementation or practice:

i. The RBM approach when properly designed and conducted is superior to traditional monitoring practices.
☐Strongly Agree
☐Agree
☐Unsure
☐Disagree
☐Strongly Disagree

[B] Please explain the reasons for your choice above.

RBM Practices:

8. [A] Have you been trained in RBM?

☐Yes

☐ No

[B] In your opinion,

(i) What is the focus of RBM?

(ii) What key factors may influence the implementation RBM approach?

9. Please indicate if your organization implements RBM approaches.
   ☐Yes
   ☐ No
10. If yes, when did your organization implement RBM practices?
   ☐2000-2005
   ☐2006-2010
   ☐2011-2015
   ☐2016-present

11. If you answered yes to question #9, please indicate if any of the following RBM practices have been implemented?
   ☐Remote Monitoring
   ☐Centralized Monitoring
   ☐On-site
   ☐Other (_____)

12. If you answered YES to question #9, what stage of RBM implementation have you experienced?
   ☐Early
   ☐Middle
   ☐End
   ☐All

13. If you answered NO to #9, is there a plan in place to implement RBM?
   ☐Yes
   ☐No

14. [A] Do you feel the RBM practices implemented in your organization have been beneficial?
   ☐Yes
   ☐No

[B] Please give a brief explanation to the response given above.

15. [A] Give examples of things that were most helpful in the efficient implementation of RBM systems in your organization.

[B] Based upon your response above, what could be done to further improve the efficient implementation of RBM systems?

16. Please provide suggestions/further insights or commentary in regards to the future of RBM.

Thank you for taking time to participate in this study!