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Risk Based Monitoring (RBM): A global study focusing on perception and merits among clinical investigational sites

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ABSTRACT

Background: Several approaches to clinical trial monitoring, including the Risk Based Monitoring (RBM) are aimed at the protection of the human subjects (safety), improved data quality, and ultimately, reducing the cost of drug development and operations. There exists minimal evidence globally about the perceptions and the level of confidence among the clinical staff on the merits of RBM. The present study assessed the perception among clinical research staff globally (developed and emerging countries) on the applicability and adaptability of RBM.

Methods: An electronic questionnaire survey consisting of twelve items was developed, validated, and then circulated globally via email to three thousand clinical research staff members at various investigational sites. This survey collected information on the use of RBM and factors that relate to clinical trial cost, data quality, subject safety, and the readiness to adopt RBM practices. The survey responses were summarized and analyzed by using the information e.g. responder's age, sex, clinical research role, global location, and experience in clinical research trials.

Results: Responses were received from ten countries, six emerging and four developed. Of the 3000 surveys sent to emerging (1,000) and developed (2,000) countries, a total response of 595 (261 vs 334) participants was received, respectively. The emerging versus developed group had 100 vs 137 participants with complete responses (CR); 34 vs 35 participants with partial responses (PR); and 127 vs 162 participants were disqualified with no exposure (NE) responses. About 67% of the overall responders were investigators, followed by 23%, 10% coordinator and other staff respectively. There was not significant difference in feedback between the researchers in developing versus emerging countries ($p = 0.20$) with regards to their perception of RBM reducing the overall cost of conducting a clinical research. Responders from emerging countries had a more favorable response than in the developed countries. Similarly, when asked if RBM will be more effective in addressing data quality ($p = 0.006$), patient safety ($p = 0.05$) and findings fraud/fabrication ($p = 0.01$), researchers from emerging countries indicated more confidence than researchers from developed countries. There was also a significant difference in the readiness to adopt RBM between responders of emerging versus developed markets ($p < 0.0001$).

Conclusion: This unique study performed across ten emerging and developed countries strongly supported the need for systematic global training, education, and implementation of RBM regulatory guidance, with an aim for better safety of subjects and improved quality of clinical trial data. Furthermore, studies with larger sample sizes are recommended to provide an evidence-based approach.

1. Introduction

Pharmaceutical industry is plagued by the complexities surrounding research and development. The drug developers seem to be constantly raging a war to fight against the changing landscape and the intrinsic and extrinsic factors that lead to an increased

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research and development cost. These factors consist of, but are not limited to, patent expirations, patent cliffs, generic competitors, drying pipelines, increasingly stringent and complex regulatory requirements, segmentation of patient populations, data quality issues and lack of blockbusters to name a few [1,2].

These challenges are paving ways to integrated solutions for the increase in cost and other inefficiencies in the drug development processes. One of the first efforts was made by the FDA in August 2013, by issuing a guidance called "*Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring* [3]." RBM is a quality driven initiative utilizing a flexible approach to monitoring [4]. This guidance and the implementation is thought to drive clinical research and monitoring costs down, while maximizing on the data quality and human research subject protection. Guidance on RBM practices and methodologies has since expanded globally with European Medical Agency's (EMA's) reflection paper on risk-based quality management to meet the requirements on ICH (International Conference of Harmonization) GCP section 5.1 and the recent addendum to ICH E6, with recommendation on international implementation of innovative approaches to quality risk management [5,6]. These recommendations and the global footprint of new Drug Applications (NDAs) has lead to much discussion regarding potential cost saving measures for drug developers and CROs [7,8]. However, there is no pragmatic data available on how this will benefit global clinical research investigators, their views on the merits of RBM, and applicability in different cultural and regulatory settings. At present, there is no robust data at a global level indicating that investigational sites are ready, trained, and aware to support the RBM practices. In addition, there is sparse evidence that indicates the clinical investigators globally have same level of confidence in the merits or their general perception about the applicability and adaptability of this approach.

This gap in understanding the benefit to clinical research sites and their readiness to adopt and implement RBM has the potential to delay the starting of meaningful clinical trials, and may lead to the conduct of less efficient trials. This survey research hypothesized that if the researchers/investigators from emerging and developed countries are surveyed for their perception regarding proposed merits of RBM, then there may be a significant difference in their understanding based on their age, gender, role, years of experience and location.

2. Material and method

An electronic, self-administered survey with a total of 12 items with twenty-seven multi-part questions, including forced choice and open-ended queries, was developed to collect feedback from clinical research staff globally. DrugDev, the world's largest consortium of global investigators, was enlisted to validate the questionnaire, to carry out the survey to maintain confidentiality of the data and ensuring privacy of the responder's identity. The country selection was random based on the DrugDev databank and research staff consortium. The population of interest was clinical research investigators, research coordinators and other staff across the globe with experience in conducting clinical trials and those who are/were aware of the RBM or utilized the methodology in one of their studies. The International Monetary Fund's List was used a reference to categorize the developed and emerging countries.

The flow diagram in Fig. 1 depicts the research methodology for survey creation and validation. The methodology utilized was cross sectional survey analysis. Survey measures used were both qualitative (open-ended questions) and quantitative (forced-choice questions) in nature. To validate the questionnaire, a pre-test of the survey was conducted with various subject matter experts (investigators, study coordinators and study monitors) from the clinical research industry who were actively working on studies utilizing RBM principles. Subject matter experts who validated the survey instrument were either affiliated with DrugDev or were research investigators or coordinators from outside of this organization. The respondent's decision to complete the survey was greatly affected by their interest in the topic but also by the appearance and clarity of the questionnaire. To handle this bias and to limit the impact on the overall outcome of success for the project, these subject matter experts were asked to review the questionnaire for the format, content, interview technique, appearance, clarity, relevancy, jargon, misrepresentation and bias, etc.

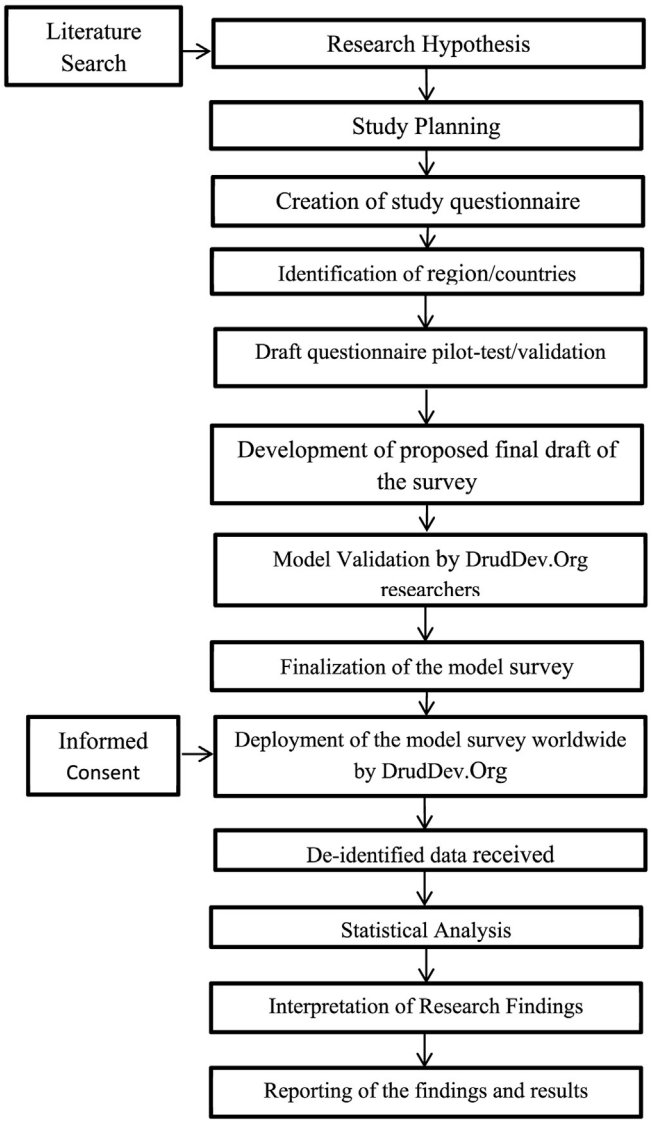

Fig. 1. Flow diagram of the survey methodology.

Applicable revisions were made to the questionnaire post this initial validation. A second validation was performed to attain feedback on the revised format and content. This attempt included a different set of industry experts, along with a few randomly selected individuals from the first round. The second round of validation came back with little to no change and aided in confirming the final model of the validated questionnaire. The questionnaire consisted of five general questions on demographics and experience, followed by questions to ascertain if the responders were aware of RBM. The responders were included in the analysis

based on their awareness and/or experience with RBM and those with lack of RBM experience were excluded from the report. The rest of the questions were based on five point linkert scale and focused on the merits of RBM as it relates to clinical trial cost, data quality, subject safety, readiness to adopt and support RBM, followed by two open ended questions on recommendation and additional thoughts. Responders had to be aware of RBM to adequately respond to the scope of monitoring practices utilizing RBM technique. Approximately three thousand randomly selected DrugDev members from their global investigator network were invited to participate in the survey. Data collection started from 28th July through 15th September 2014. De-identified data was then aggregated for the analysis.

A power analysis technique using PASS sample size calculator software was applied with the goal to have an estimated sample size of two thousand surveys sent to the developed countries and 1000 surveys sent to the emerging countries. An 8–15% survey response rate with alpha of 0.05 was estimated to provide adequate power to detect the difference between the two types of markets at 85–99%. Continuous variables were reported as means and standard deviations (SD) and categorical variables were reported as a percent (%). Fisher's exact test and two-sample *t*-test were conducted for comparing categorical and continuous variables respectively between the groups. It was considered statistically significant if the *P*-value was <0.05. Due to the exploratory nature of this analysis multiple comparison procedure was not accounted for. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

3. Results

Of the 3000 surveys sent globally, 595 surveys were collected with a total response rate of approximately 20% (sum of disqualified, partial and complete responses). Responders from developed countries accounted for approximately 11%. The details of the response rate in the two groups are summarized in Table 1. Of these, 595 surveys collected, which included surveys that had complete response (CR), partial response (PR) and surveys from those participants who were disqualified because of their lack of RBM experience (NE). The CR sample was defined as those that had completed the survey in its entirety. The PR sample represents those that answered some questions but not all. NE sample were those that did not have any exposure to RBM. Those that who did not completed the survey at all were characterized as no response (NR). The numbers of surveys with no response was computed by subtracting the number of disqualified, partial responses and complete responses from the total number of surveys sent.

One thousand surveys were sent to the researchers in the emerging countries (comprised of Argentina, Brazil, China, India, Russia and South Africa). Of these, 100 completed, 34 partially completed, and 127 surveys were received who did not have experience with RBM. Similarly, two thousand surveys were sent to researchers in developed countries (Australia, Germany, United States and United Kingdom). Of these, 137 completed, 35 partially completed and 162 surveys were received who did not have experience with RBM. The sum of the disqualified, partial and complete responses from both emerging and developed countries accounted for a total of 595. Of these 595 surveys, 289 were excluded from analysis as they answered “no” to the survey question “are you aware of Risk-Based Monitoring (RBM)?” Partial responders were also excluded from the analysis. With these above exclusions, survey results for 237 respondents comprised the basis of this report. The breakdown of responders in emerging and developed countries is provided in Fig. 2.

Demographic characteristics of the survey respondents are given in Table 2. The responders were asked to answer five demographics questions before answering on their experience with RBM. Demographic questions included their role in the study, gender, age, country of residence and experience as it relates to number of trials that they have worked on. The objectives of these questions were to evaluate the demographic trends between the emerging and developed countries and to analyze if the age, experience and work location had any impact on the opinion of the researchers when analyzed against their responses for RBM based questions.

Apart from demographics, the respondents were asked to answer 3 multipart questions to evaluate their experience and understanding with regards to how RBM practice relates to research cost and quality and their readiness to adopt RBM practices. In addition there were 2 open ended questions for general feedback on RBM.

Out of 237 responders, 100 were from emerging countries and 137 from developed countries. When looked at by role, the majority of the responders were clinical research investigators followed by study coordinators, and staff members. When responses were compared by sex; in the developed world; the number of male versus female responders were almost the same; however, in the emerging countries, there were more male responders than females, which could be attributed to higher number of male investigators. There were similar response rates by males in both regions; however, more females responded to the survey in the developed countries than emerging countries, which could be due to a high response rate by research coordinators/nurses. Age ranged between 30 to over 60 years, of which the majority of the responders were in their 50's. We observed that older the age group, the higher the number of responders.

Response rates by countries showed that, in the emerging region, the highest response rate was from India with 33% and China had the least response rate of 4%. Brazil, Russia and South America responded between 17 and 18%, and Argentina reported 11%. In the developed world, we noticed more variability in the response rate, with about 64% from the United States, 16, 13 and 7% by Germany,

Table 1
Response rate of the survey across the emerging and developed countries.

	Emerging countries n (%)	Developed countries n (%)	Total n (%)
Total surveys sent	1000	2000	3000
Complete responses (CR)	100 (10)	137 (6.9)	237 (7.9)
Partial responses (PR)[a]	34 (3.4)	35 (1.8)	69 (2.3)
Disqualified/No exposure (NE)	127 (13)	162 (8)	289 (9.6)
No response (NR)	739 (74)	1666 (83)	2405 (80.2)

[a] There were 80 partial respondents from emerging countries and 56 partial respondents from developed countries, 42 from emerging countries and 18 from developed countries clicked the survey but did not answer any questions. 33 and 35 of them answered demographic questions and the question “Are you aware of Risk Based Monitoring (RBM)?” but did not answer other further questions thus excluded from the analysis. 5 and 3 of them answered part of the questions and their responses were included in the analysis.

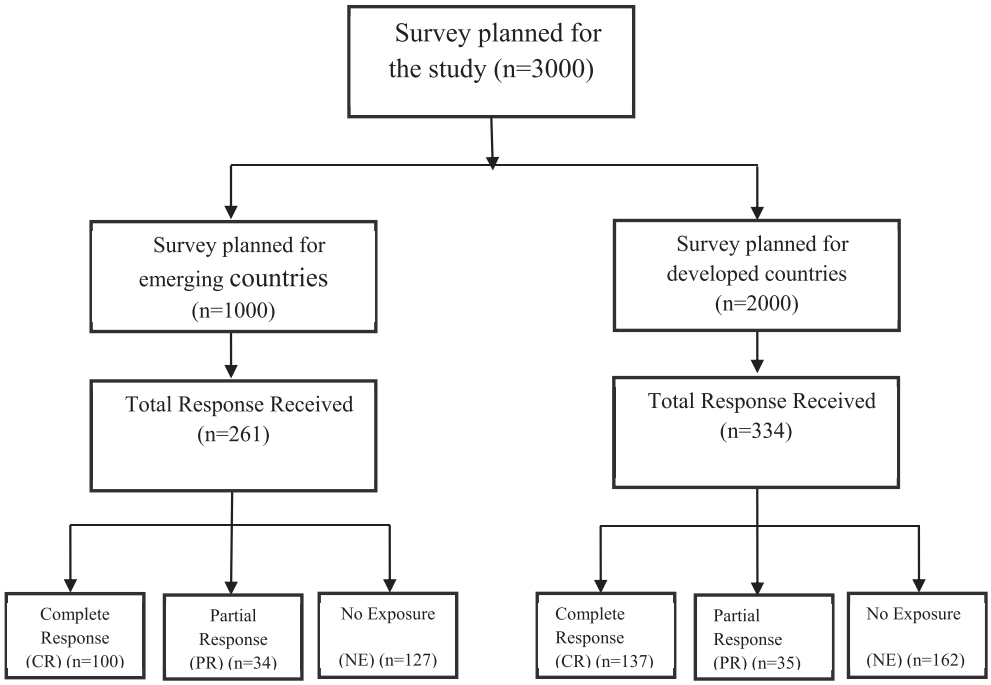

Fig. 2. Details of responses received for this survey.

Table 2
Demographics and Awareness of RBM among responders.

	Emerging countries n = 100 (%)	Developed countries n = 137 (%)	Total n = 237 (%)
Role			
Investigator	79 (79)	79 (58)	158 (67)
Coordinator/Research Nurse	16 (16)	39 (28)	55 (23)
Other Site Staff	5 (5)	19 (14)	24 (10)
Gender			
Female	37 (37)	72 (53)	109 (46)
Male	63 (63)	65 (47)	128 (54)
Age (years)			
<30	3 (3)	6 (4)	9 (4)
31–40	26 (26)	20 (15)	46 (20)
41–50	29 (29)	39 (28)	68 (29)
51–60	26 (26)	49 (36)	75 (32)
>60	16 (16)	23 (17)	39 (17)
Country			
Argentina	11 (11)	–	
Brazil	17 (17)	–	
China	4 (4)	–	
India	33 (33)	–	
Russia	17 (17)	–	
South Africa	18 (18)	–	
Australia	–	10 (7)	
Germany	–	22 (16)	
United Kingdom	–	18 (13)	
United States	–	87 (64)	
Number of Trials involved			
Less than 3	6 (6)	4 (3)	10 (4)
3 to 10	37 (37)	24 (18)	61 (26)
Greater than 10	57 (57)	109 (80)	166 (70)
RBM Awareness	100 (100)	137 (100)	237 (100)
I am/have been involved in a study using RBM	33 (33)	69 (50)	100 (43)
I am scheduled to be involved in a study using RBM	10 (10)	19 (13)	29 (11)
I have good knowledge of RBM and its practices	19 (19)	31 (22)	50 (21)
I have general awareness of RBM and its practice	55 (55)	63 (46)	118 (50)

United Kingdom and Australia respectively.

When assessed, based on involvement in number of trials in the last 5 years, in the developed world, about 80% of the responders had participated in more than 10 clinical research trials indicating significant exposure,, whereas 57% was noted in the emerging markets suggestive of lesser exposure. We observed a positive correlation of age and experience with the exposure to RBM and its core principles.

Participants aged between 40 and 60 years reported more exposure to clinical trials. When asked to rate their experience with RBM, 50% reported good knowledge of RBM, and also almost equal percentage of these responders were/are actively involved in a trial using RBM approach. We observed an interesting thing that, although there were 50% responders from developed countries, only 27% of these responded to having good knowledge of RBM concept indicating that a significant lack of relevant knowledge in the domain.

On the other hand, responders from emerging countries were only 33%; however 19% who were involved in clinical trial with RBM believed that they had good knowledge. These findings were indicative and implied that just being involved in a RBM trial does not necessarily mean one may have good understanding of the methodology. In addition, it also appeared that there was a varied understanding and interpretation of what constitutes a good understanding of RBM, and its applicability and adoptability. The developed world was more conservative in their response.

Feedback on RBM and research cost by the responder's country of residence and role is depicted in Table 3. We did not observed significant difference in feedback between the researchers in developing versus emerging countries ($p = 0.20$) in regards to their perception of RBM, and reducing the overall cost of conducting a clinical research. Responders from emerging countries more favorably responded than the responders in the developed countries. Similarly, when asked if RBM will be more effective in addressing data quality ($p = 0.006$), patient safety ($p = 0.05$) and findings fraud/fabrication ($p = 0.01$), researchers from emerging countries were significantly more confident than their counterpart. We also found a significant difference in perception on readiness to adopt RBM between responders of emerging versus developed markets ($p < 0.0001$).

When, the same questions were analyzed by role, investigators appeared to have much higher scores than research coordinators and other site staff, which could be due to their experience with RBM. The details are provided in Table 4. However, interestingly, their role did not have significant impact on their perception of RBM, as it relates to research cost, data quality and patient safety. When the data was analyzed by experience, we did not find any significant difference between responders in developed versus emerging regardless of their experience. This could be attributable to relatively small sample size in each category.

4. Discussion

To our best of our knowledge, the current analysis offers the only global characterization of RBM practices and perception of clinical research staff on its merits, since the launch of the FDA guidance in 2013. The drug development, especially clinical trials is a costly affair. The clinical trials monitoring, constitutes between 25% and 30% of the total trial cost [9]. Since RBM was launched there is a widely accepted perception among clinical research sponsors and CROs that RBM and its practices will help offset cost, improve data quality, minimize subject safety related findings, reduce data fraud and fabrication.

Given this perception, it is prudent to assess that current RBM methods are achieving the desired intent of reducing the overall research cost, protecting patients, and ensuring data integrity. This transformation will require global commitment and understanding. Although the literature on global perception of RBM in clinical trials is limited, our findings appear to derive some interesting deductions.

The results of our survey revealed that when data was assessed by location, significantly more researchers in the emerging countries believed in the proposed merits of RBM than researchers in the developed world (Table 3). Similar trends were seen for questions related to RBM as it relates to cost, data quality, patient safety, fraud detection etc. In all cases, researchers from emerging countries seemed to have more trust in RBM and its proposed merits then those in the developed world. The survey did shed some light on the readiness of the researchers to adopt RBM practices globally. Even though we observed that researchers globally state that they are ready to adopt and implement RBM practices at their respective research site, researchers in emerging countries were significantly more confident in their readiness than researchers in the developed world.

There was no significant difference between the two groups based on role and experience (Table 4). Thus these variables did not seem to have impact on their perception and understanding of RBM practices and implications on research cost, quality and patient safety. The reasons for the difference based on location are not clear. It will be interesting to study this further, to understand if these differences are associated with differences in culture, local and regional differences in managing clinical trials, or some other local intrinsic or extrinsic factors. Overall, the notable factor was that research staff in emerging countries had less experience than research staff in developed world, but had more trust in RBM and its merits. We hypothesized that this finding may be related to the fact that most of the early pilot work and feedback was from the developed world and they might have been more skeptical, as they have seen the hurdles with the current analytics and tools to support RBM. These analytics and tools will need further refinement and improvement to get desired outcomes [4,10]. Similarly, the developed world seemed more conservative in their response than

Table 3
Average scores for questions below by work location.

	Work location						*P*-value
	Emerging			Developed			
	n	Mean	SD	n	Mean	SD	
The Sum Score of RBM For Reducing **research related costs**	100	13.4	3.3	137	12.3	3.9	0.20
The Sum Score of RBM For **Human Subject Protection and Data Quality**	100	23.9	6.4	137	21.4	7.1	0.006
The Sum Score of Readiness To Adopt/Support RBM	100	25.7	4.4	137	22.6	5.2	<0.0001
RBM will **better support timely oversight** of data by the sponsors/CROs	100	3.6	0.9	134	3.3	1.2	0.01
Sum score of "RBM will be more effective in **detecting** data quality issues" and "RBM will be more effective in **addressing data quality** issues"	98	6.9	2.1	136	6.2	2.2	0.01
Sum score of "RBM will be more efficient in timely **detection** of patient **safety related** data" and "RBM will be more efficient in **addressing** patient safety related matter"	100	7.0	1.9	134	6.4	2.2	0.05
Sum score of "RBM will be more effective in **detecting fraud and fabrication** of data" and "RBM will be more effective in **addressing fraud and fabrication** of data"	98	6.6	2.1	131	5.8	2.2	0.01

Table 4
Average score response received for the questions specific to the role.

	Current role									*P*-value
	Coordinator/Research nurse			Investigator			Other site staff			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
The Sum Score Of RBM For Reducing **research related costs**	55	12.7	3.8	158	13.1	3.5	24	11.0	4.3	0.03
The Sum Score Of RBM For **Human Subject Protection and Data Quality**	55	21.2	6.6	158	23.1	6.7	24	20.7	8.3	0.08
The Sum Score Of Readiness To Adopt/Support RBM	55	23.3	6.0	158	24.2	4.6	24	23.3	6.0	0.48
RBM will **better support timely oversight** of data by the sponsors/CROs	55	3.2	1.1	156	3.5	1.0	23	3.2	1.3	0.09
Sum score of "RBM will be more effective in **detecting** data quality issues" and "RBM will be more effective in **addressing data quality** issues"	55	5.9	2.1	155	6.7	2.1	24	6.0	2.5	0.03
Sum score of "RBM will be more efficient in timely **detection** of patient **safety related** data" and "RBM will be more efficient in **addressing** patient safety related matter"	55	6.2	2.1	156	6.9	2.0	23	6.3	2.4	0.09
Sum score of "RBM will be more effective in **detecting fraud and fabrication** of data" and "RBM will be more effective in **addressing fraud and fabrication** of data"	53	6.0	2.2	152	6.3	2.1	24	5.4	2.4	0.16

their counterparts when asked about the knowledge on RBM. This is an example of an area where provision of additional training and experience could have a significant impact in making a more informed decision.

Our study was not free from limitations. First, the overall response rate to our survey was approximately 20%. The United States had the highest response rate, accounting for 64% of the overall responses from developed countries. Similarly, in the emerging countries, India had the highest response rate with 33%, and China with only 4%, even though a large number of clinical trials are conducted there. This variability may have resulted in not capturing some of the country-specific variances, and the responding sample may not have been representative of the industry at large. In addition, the low response rate and relatively small sample size could have led to a bias in comparisons between the two representative samples. One of the approaches to address these limitations would be to quantitatively define the cost benefit, data quality and patient safety achieved by a specific RBM practice at research sites that are utilizing RBM trials, and then measure the parameters against research sites that are not using RBM trials.

5. Conclusion

The present study could be among the first to collect evidence and address gaps in the understanding of RBM from a select group of researchers globally. The results from the current study inferred that investigators globally believed that RBM has the potential to drive the cost of drug development down while ensuring patient safety and data quality. However, there is variability in the perception of how RBM impacts drug development costs, data quality and patient safety which needs further exploration. There has been significant improvement in the types and utility of the RBM analytics since the inception of this study. It would be beneficial to understand if these technologies have resulted in the conduct of more cost-efficient clinical trials, with higher quality data and enhanced patient safety.

In nut shell, further studies involving larger populations and more evidence is recommended to extrapolate from other populations and to discover the transient nature of data quality impact based on RBM practices globally. This ethos of collaboration between public, private, government and researchers is critical to harmonizing RBM practices and international recommendations. Therefore, it is proposed that a global community of clinical trial fraternity with various roles and expertise is established to understand RBM requirements and drive local level pragmatic operational practices.

Declaration of conflicting interests

The Author(s) declare(s) that there is no conflict of interest.

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