

## Review Article

# Determinants of performance measures of clinical trials: a study of Indian medical devices industry

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## ABSTRACT

Developing new medical devices require extensive clinical investigations to enter the market successfully. In recent years, India has emerged as one of the attractive and most preferred countries to carry out clinical trials, primarily due to diverse human gene pool and cost-competitiveness. However, unlike other healthcare products such as therapeutic drugs, there is a lack of regulations over usage of medical devices. Moreover, prior systematic empirical analysis that examine the medical device based clinical trials is also not well established. This study attempted to ascertain the determinants of participant recruitment, selection of locations and time taken to conduct medical device clinical trials. Medical devices that are clinically tested in India in the period of 2008 to 2014 were obtained from CTRI website. 108 out of 279 records were identified as medical device clinical trial registrations. Collected data was analyzed to know the device type, disease category, sponsors involved, participant enrolment, locations and the duration of the device trial. In this study, the category of sponsorship, device type and disease category were found to have significant influence with respect to the selection of number of participants, locations and the time taken to execute medical device clinical trials.

**Keywords:** Clinical trials, Sponsorship, Participant recruitment, Locations, Duration, India

## INTRODUCTION

India has become one of the attractive and preferred countries to execute clinical trials because of its various advantages such as cost savings, huge population base, largest pool of patients with many diseases; high quality of research professionals and investigators and state-of-the-art infrastructure.<sup>1-3</sup> While the clinical trial activity in the USA and other developed countries exhibited a decreasing trend, global share of clinical trials happening in India grew from 0.9% in 2008 to 5% in 2013.<sup>4</sup> Despite the fact that Indian medical devices industry is tremendously growing at a faster pace and India has emerged as one of the preferred clinical trial destinations by sponsors, yet it is not free of challenges. The first and foremost challenge is to achieve a sufficient number of

trial participants to test the device performance which facilitates in translating clinical research in to medical practice.<sup>5</sup> Clinical trials are conducted in a variety of locations and the selection of these trial sites depend on the sponsors strategies and constraints.<sup>6</sup> Another crucial challenge in the clinical trial activity is the duration of the trial and is one of the vital factors that should be considered by the sponsors while selecting a clinical trial site.<sup>7</sup> As the clinical trials are carried out to examine the performance of the device on humans, appropriate study population is required to perform this activity effectively. The study population may spread across diverse geographical locations and there are no clear guidelines on choosing the number of participants from various locations for a clinical trial. The duration of the trial may have a bearing on the time taken for a medical device to

reach the market and therefore understanding the factors causing the variation in clinical trial durations is important. Conducting trials with more number of participants and in multiple locations yield better results, but it calls for a huge amount of resources and infrastructure which may not be feasible in all the cases.<sup>8</sup> However, there are some factors such as sponsor related, device related and disease related factors that influence the execution of clinical trials. This paper attempts to empirically understand the factors that influence the recruitment of number of participants, selection of number of locations and time taken to carry out medical device clinical trials which is important for economic, social and technological reasons.

## LITERATURE REVIEW

To begin with, we discuss some of the challenges such as enrolment of number of participants, selection of number of locations and the time taken to execute clinical trials. Further, factors such as sponsor related, device related, disease and/or speciality area related factors that influence participant recruitment, selection of locations and time taken to perform clinical trials is described in this section.

### *Participant recruitment during clinical trial stage*

Public participation for clinical trials is one of the central challenges facing the clinical research enterprise which assists in translating clinical studies in to medical practice.<sup>5</sup> One of the “key determinants” for the successful completion of a clinical trial is the recruitment and retention of adequate number of participants/sample size.<sup>9</sup> If this is not achieved properly, it will have negative implications such as prolonged trial duration, cost and sometimes termination of clinical trial. Research studies point out that recruiting participants for clinical trials has always been the greatest problem which has a huge impact on the cost and time taken for the development of a medical device.<sup>10,11</sup> It has been concluded that low participant enrolment rates may affect the generalizability and validity of the clinical trial findings.<sup>12-14</sup>

### *Selecting the locations/sites for clinical trials*

A clinical trial site is an “epicentre” for medical research because of the core process of clinical research takes place there.<sup>15</sup> The trial site involves many challenges such as the availability of several well-trained investigators and sub-investigators, research nurses, study coordinators, data managers as well as other medical specialists such as pathologists, radiologists, etc.<sup>16,17</sup> Carrying out clinical trials in multiple locations or otherwise named as multi-centre trials were typically regarded as the “gold standard” for evaluating medical treatments. However, this might not be feasible in all the cases. It has also been ascertained that some of the clinical trial locations have been terminated due to low

participant enrolment.<sup>18</sup> Implementing clinical trial globally or otherwise known as international clinical trials (conducting trials in multiple countries) pose many advantages to sponsors economically in terms of cost and also in getting access to potentially eligible patients which leads to generalizability of the results, early study completion and efficient trial output. Hence, one of the primary challenges for clinical trials conducting in multiple countries is to meet the participant recruitment goals in a specified time frame. As stated by Karlberg and Speers, clinical trial industry needs to identify approximately 50,000 new study sites annually for carrying out clinical trials.<sup>19</sup> One of the major challenges faced by multi-centre trials is the efficiency to recruit participants at individual trial locations. Further, the review of literature related to key outcomes of absorptive capacity i.e., degree of intra-cluster and extra-cluster linkages is brought out in the subsequent sections.

### *Clinical trial duration*

One of the crucial aspects sponsors should consider while selecting a study site is the duration of the study protocol.<sup>7</sup> Defining the duration of the clinical trial study is very difficult and is one of the challenges facing the clinical trial industry.<sup>20</sup> Clinical trial duration incorporates various aspects such as design and finalization of the protocol, regulatory and ethics committee approvals and is dependent on the number of participants. The duration of the study varies considerably for each type of interventions being investigated.<sup>21</sup>

The above research studies clearly revealed that participant enrolment, selection of number of locations and trial duration are some of the challenges which need to be addressed for successful clinical trial execution. However, there are some factors that are related to these three challenges which are discussed subsequently.

### *Factors influencing clinical trial execution*

There are various factors such as sponsor related, device related, disease and/or speciality area related and type of trial related factors that influence participant recruitment, selection of locations and time taken to conduct clinical trials.

#### *Sponsor related factors*

Literature has categorized sponsor as industry (companies) and non-industry (universities/medical colleges, hospitals and government organizations). According to a study by Dainty and Karlsson, the primary concern for the sponsor is to achieve eligible participant enrolment to carry out clinical studies.<sup>21</sup> This research also highlighted that involving in industry-sponsored trials offers numerous benefits in getting access to new cutting-edge technologies or devices or medications that are not yet in the market.

Using the dataset from [clinicaltrials.gov](http://clinicaltrials.gov) website as of September 2010, based on 96,346 trials and dataset from International Clinical Trials Registry as of March 2014, analysis revealed that majority of trials conducted by industry sponsors recruits more number of participants for carrying out clinical trials compared to other sponsor categories.<sup>22,23</sup> This finding has also been in accordance with the study by Todd et al. related to pulmonary, critical care and sleep medicine clinical trials registered in USA clinical trial registry. Based on the results from this study it has been found that the trials involving higher number of participants were more likely to be funded by industry sponsors as compared to the number of participants involved in trials funded by other sponsor categories.<sup>24</sup> Dear et al analyzed the cancer clinical trials registered in [clinicaltrials.gov](http://clinicaltrials.gov) database and the logistic regression analysis revealed that industry sponsors recruit patients with more advanced disease (in this case cancer) as compared to non-industry sponsors.<sup>25</sup>

#### *Device related factors*

Medical devices can be invasive or non-invasive according to the guidelines given by Global Harmonization Task Force (GHTF) on medical device classification.<sup>26</sup> Using the data on cardiovascular clinical trials, trials are divided in to four categories such as medication, invasive devices (pacemakers, implantable cardioverter defibrillators, and ventricular assist devices), diagnostic testing/imaging and non-invasive devices (continuous positive airway device and other lifestyle interventions) based on the intervention being examined in each of the trial. Among these trials, majority of the trials were related to medication followed by invasive trials.<sup>27</sup>

#### *Disease or speciality area related factors*

Researchers have used clinical trial data and segregated the interventional trials based on various speciality areas like oncology, cardiovascular, mental health and disease states like coronary artery disease, arrhythmias, heart failure.<sup>27</sup> Several studies have also assessed the characteristics of clinical trials investigating treatments related to concussion and brachytherapy procedures based on trials registered in [clinicaltrials.gov](http://clinicaltrials.gov) database.<sup>28,29</sup> Based on the clinical studies from [clinicaltrials.gov](http://clinicaltrials.gov) database as of September 2010, the results revealed that cardiovascular trials accounted for the largest proportion of trials assessing medical devices (20.2%) compared to oncology and mental health. In cardiovascular trials, the participant enrolment for clinical trials is nearly twice as large (average 100) compared to other disease related trials. Cardiovascular and mental health trials were more oriented towards later phase research (phase 3 and phase 4).<sup>22</sup> Important barriers to participation in cardiovascular trials are longer duration and intensive trial testing.<sup>14,18</sup>

#### *Gaps in literature*

Most of the literature emphasize on the influence of sponsor related and disease related factors on the characteristics of trials such as participant enrolment and location of trial sites. However, the factors related to the duration of the trial have been evaluated only to a limited extent. Furthermore, studies focusing on the influence of the type of device on locations, participants and trial duration has not been addressed so far to the best of our knowledge. Additionally, there are a lack of empirical studies using clinical trial data to identify factors relevant for the selection of number of locations, participants and the time taken to execute clinical trials in India specifically for medical devices. Furthermore, all these studies investigated the characteristics of clinical trials from USA trial registry i.e., [www.clinicaltrials.gov](http://www.clinicaltrials.gov). However, to the best of our knowledge, there has not been any systematic empirical analysis that examined the medical device based clinical trials registered in Indian trial registry [www.ctri.nic.in](http://www.ctri.nic.in). It is against this background that we formulate our research objective.

### **OBJECTIVE, SCOPE, SAMPLE, CONCEPTUAL MODEL AND METHODOLOGY**

#### *Objective*

To ascertain the determinants of recruitment of number of participants, selection of number of locations and time taken to carry out medical device clinical trials

#### *Scope*

This study is confined only to clinical trial registrations of medical devices registered with Clinical Trials registry of India (CTRI). The medical device trial registrations may comprise both new medical device registration trials and trails comparing a device to an already existing medical device product. The study does not focus on the clinical trial registrations for pharmaceutical products registered with CTRI.

Clinical trials, being considered the means of assuring safety and efficacy of the medical devices on human subjects, the scope of this study does not include the mode or method of execution of clinical trials. However, details of clinical trials which can shed lights on perceived involvement of managerial decisions like allocation of resources, in terms of human resource and time consumption are considered under the scope of this study. Having said that, details of clinical trials like number of participants enrolled for a clinical trial, number of locations where clinical trials have been executed, total duration of clinical trials, are considered a surrogate of effective performance outcomes of clinical trials, and are included within the scope of this study.

### Sample and data collection

Data considered for this study, being secondary in nature, were obtained from Clinical Trials Registry of India (CTRI) database.<sup>30</sup> CTRI is a free and online public record system for registration of clinical trials in India (www.ctri.nic.in). The sample selected for medical device clinical trials in India was identified through an intense keyword search. Total number of records found using keyword search was 279. Out of these 279 records, some of the records were excluded after screening assessment

because a few of them were not related to medical devices and others have multiple entries (duplication of same record) and hence omitted from the study. About 108 records were identified as medical device clinical trial registrations from the year 2008 to 2014 and the rest of them was drugs.

### Variables

The variables used in this study are tabulated in Table 1.

**Table 1: Definition of variables.**

Variable Name	Variable definition
<b>Sponsor related</b>	Organization type of PS The primary sponsors can be from Industry or Non-industry. Industry sponsors are companies, whereas non-industry sponsors include medical college, research institute, hospital or a government organization. <sup>18,23-25</sup>
	Country of origin of PS The primary sponsors can be from either India or a foreign country. <sup>23</sup>
<b>Device related</b>	Invasiveness of device Invasive device: A device, which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body Non-invasive device: A device which does not penetrate the body. <sup>26</sup>
	Device category The medical device can be either a stent or pacemaker or defibrillator.
<b>Disease / speciality area related</b>	Disease focus The focus of trials with different disease categories like cardiovascular or thermostability altering diseases or diabetes. <sup>22,23,27</sup>
	Speciality area of focus The focus of trials with specialty subject areas like cardiology, neonatology, and respiratory medicine and so on. <sup>22,23</sup>
<b>Trial administrative related</b>	Number of locations The location where the clinical trial is carried out to test the new device or treatment on participants. <sup>18,19,22, 24, 32, 33</sup>
	Number of participants The total number of participants (patients/subjects) recruited for a specific clinical trial to examine a new treatment. <sup>18,22-24,32</sup>
	Estimated duration of trial The expected time duration of trial, starting from enrolment of first patient to final submission of report. <sup>21,27,33</sup>
	Type of trial It indicates whether the trial is an interventional trial, observational trial. <sup>22,27,33</sup>
Phase of trial It indicates the trial in a particular phase (Phase 1, 2, 3, 4). <sup>18,27,33</sup>	

### Conceptual model

In this section, we propose a conceptual model to understand the determinants of selection of number of participants, locations and the time taken to execute medical device clinical trials.

Studies discussed in the literature demonstrate that recruiting adequate number of participants, and selecting more number of locations have always been the greatest challenges which has an enormous impact on the cost and time taken for the product reach the market.<sup>11,18,31</sup> It has been found that participant enrolment, selection of locations and trial duration are some of the challenges faced during the clinical trial execution process. Hence,

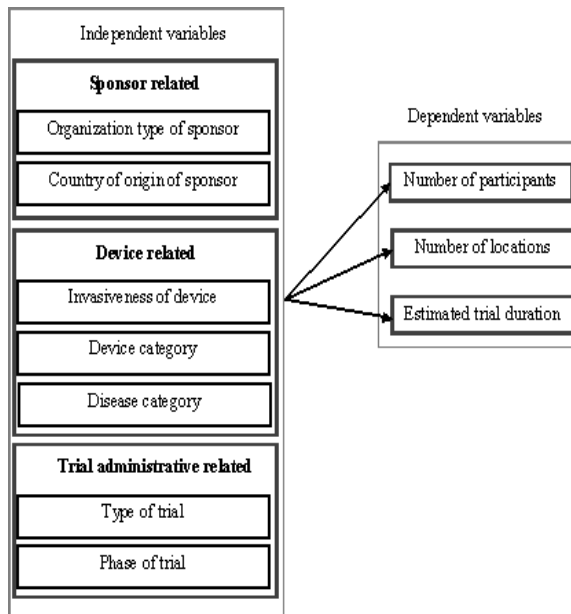
these three variables are considered the dependent variables for this study.

The conceptual model for the selection of number of participants, locations and trial duration is depicted in Figure 1.

### Method of analysis

A conceptual model has been developed to identify the effect of sponsor related, device related, disease or speciality area related and trial administrative related variables on the selection of number of participants, locations and trial duration for conducting medical device clinical trials. To empirically test the proposed conceptual model, a Stepwise Backward Elimination Multiple

(SBEM) Regression analysis is done on the three dependent variables to identify the significant predictor variables. Since the present study is exploratory in nature, it is apt to use SBEM regression analysis to effectively identify the significant predictors.<sup>32</sup> The models were built using IBM SPSS 20.0.0.0. In all the three model results, the Adjusted R<sup>2</sup>, t-values for each coefficient, F-Statistic from ANOVA and the Variance Inflation Factor (VIF) are reported.



**Figure 1: Conceptual model for participants, locations and trial duration.**

## DISCUSSION

In this section, a SBEM regression analysis is performed to identify whether there exists any statistically significant influence of sponsor related, device related, disease or speciality area related and trial administrative related variables on the outcome variables i.e., number of locations, participants and trial duration required for conducting medical device clinical trials.

### **SBEM regression models: participants, locations and trial duration**

The data on the number of participants, locations and trial duration is skewed. Therefore, the logarithmic transformed value is considered for further analysis. The categorical independent variables namely organization types of sponsor, country of origin of sponsor, invasiveness of device, interventional trial, phase of trial, device category and disease category are coded as shown in Table 2.

The regression model for the log transformed (number of locations, number of participants and trial duration) as the dependent variable is described below:

### *Log (Number of participants)*

$$= \beta_0 + \beta_1(\text{Organization type of PS}) + \beta_2(\text{Country of origin of PS}) + \beta_3(\text{Invasiveness of device}) + \beta_4(\text{Stent}) + \beta_5(\text{Airway device}) + \beta_6(\text{Cardiovascular disease}) + \beta_7(\text{Interventional}) + \beta_8(\text{Phase 4}) + \varepsilon \dots \dots (\text{Model 1})$$

### *Log (Number of locations)*

$$= \beta_0 + \beta_1(\text{Organization type of PS}) + \beta_2(\text{Country of origin of PS}) + \beta_3(\text{Invasiveness of device}) + \beta_4(\text{Stent}) + \beta_5(\text{Airway device}) + \beta_6(\text{Cardiovascular disease}) + \beta_7(\text{Interventional}) + \beta_8(\text{Phase 4}) + \varepsilon \dots \dots (\text{Model 2})$$

### *Log (Estimated trial duration)*

$$= \beta_0 + \beta_1(\text{Organization type of PS}) + \beta_2(\text{Country of origin of PS}) + \beta_3(\text{Invasiveness of device}) + \beta_4(\text{Stent}) + \beta_5(\text{Airway device}) + \beta_6(\text{Cardiovascular disease}) + \beta_7(\text{Interventional}) + \beta_8(\text{Phase 4}) + \varepsilon \dots \dots (\text{Model 3})$$

The results of the SBEM regression analysis for the three dependent variables are tabulated in Table 3. Predictor variables such as organization type of sponsor (company / non-company), invasive device type and cardiovascular disease related trials showed a significant positive influence with respect to the three dependent variables (number of participants, number of locations and trial duration).

From Table 3 it is observed that companies have a significant positive influence at 5% and 1% significance level in all the three models. This indicates that sponsors from companies choose more number of locations (multiple sites), recruit higher number of participants and take a longer duration to execute medical device clinical trials in comparison to research institutes or medical colleges or hospitals. This finding is in agreement with literature as well. It is reported that the number of locations and participants selected for clinical trials by industry sponsors is always higher in number as compared to non-industry sponsors.<sup>19,22,23,33</sup> This could be because sponsors from companies are financially stable and may have more expertise in executing clinical trials as compared to other sponsor categories.

Device type such as invasive also have a statistically significant positive influence with respect to the three dependent variables. This specifies that invasive medical devices involve more number of participants, tested in multiple locations and take a longer duration for clinical testing compared to non-invasive device type. This could be because the risk and complexity involved in invasive devices is higher compared to non-invasive device type.

Device category such as stent showed a significant positive influence at 5% significance level in terms of the

number of locations. This indicates that stent requires relatively more number of locations to perform clinical trials as compared to other device categories. On the other hand, airway devices showed a significant negative

influence (1%) with respect to the trial duration. This suggests that airway devices take relatively less duration for clinical trials as compared to cardiac related devices such as stent, pacemaker etc.

**Table 2: Coding of categorical predictor variables used in model 1, 2 and 3.**

Categorical variable	Variable level	Frequency of observations (N)	Parameter coding
Organization type of sponsor	Company	72	1
	Medical college/hospital	36	0
Country of origin of sponsor	India	72	1
	Foreign	36	0
Invasiveness of device	Invasive	60	1
	Non-invasive	48	0
Interventional trial	Yes	79	1
	No	29	0
Phase of trial	Phase 4	33	1
	Others (Phase 1, 2 and 3)	75	0
Device category	Stent	20	1
	Airway device	24	0
Disease category	Cardiovascular	49	1
	Others (Ex: Respiratory, diabetes)	59	0

**Table 3: SBEM regression model results- participants, locations and trial duration.**

Predictor variables	Model 1: Log (number of participants)			Model 2: Log (number of locations)			Model 3: Log (estimated trial duration)		
	Beta	P value	VIF	Beta	P value	VIF	Beta	P value	VIF
<b>Predictor variables</b>									
Constant		0.000			0.000			0.000	
Organization type of sponsor	0.312	0.043*	1.919	0.177	0.058#	1.328	-0.185	0.101#	1.640
Country of origin of sponsor	-0.155	0.259	1.334	0.076#	0.324	1.290	-0.070	0.469	1.327
Invasiveness of device	0.346	0.023*	1.785	0.362	0.027*	1.736	0.378	0.001**	1.212
Stent	-0.122	0.454	1.278	0.191	0.039*	1.103	-0.074	0.518	1.278
Airway device	0.058	0.732	1.600	-0.003	0.975	1.600	-0.323	0.008**	1.163
Cardiovascular disease	0.419	0.009**	1.985	0.429	0.00**	1.364	0.163	0.105#	1.946
Interventional	0.244	0.071#	1.123	0.016	0.832	1.119	-0.108	0.252	1.110
Phase 4	0.175	0.107#	1.090	0.032	0.654	1.084	0.153	0.090#	1.056
<b>Model statistics</b>									
Number of observations	108			108			108		
Multiple R <sup>2</sup>	0.325			0.441			0.400		
Adjusted R <sup>2</sup>	0.270			0.396			0.352		
Standard error of estimate	0.579			0.326			0.408		
F statistics	5.958 with p value=0.000			9.758 with p value=0.000			8.258 with p value=0.000		

\*\*p<0.01; \*p<0.05; #p<0.1.

Interventional trial and phase of trial have a significant positive influence with respect to the number of participants and trial duration. However, there is no significant difference has been observed with respect to the selection of number of locations. This indicates that

interventional trials involve more number of participants for clinical studies as compared to observational trials. Also, later phase trials (phase 3/phase 4) take a longer duration for clinical testing as compared to early phase studies (phase 1/phase 2).

It is further interesting to see that cardiovascular disease trials also have a significant positive influence at 1% significance level in all the three models. This reveals that trials that are related to cardiovascular disease involve more number of participants and are tested in multiple locations and usually take longer duration as compared to respiratory or other disease related trials. Our findings are well-supported by the recent literature in this domain as well. It has been established that the number of locations and participants selected for cardiovascular disease trials are much higher in number as compared to other disease categories.<sup>22,27,34</sup> Moreover, since cardiovascular trials took a longer duration as it was perceived to be one of the important barriers for clinical trials.<sup>14,18,34</sup>

## CONCLUSION

To summarize, this study explored the determinants of selection of number of participants, locations and trial duration for carrying out medical device clinical trials that are registered in Indian trial registry i.e., CTRI. These three outcome variables are an indicative of performance of clinical trials. Based on the empirical findings of the proposed conceptual model, it is established that category of sponsorship (company / non-company: research institute, medical college, hospital), device type (invasive / non-invasive) and disease category (cardiovascular /others) have a statistically significant positive influence on all the three outcome variables.

It was corroborated from the findings that the sponsors from companies choose relatively higher number of locations (multiple sites), recruit a higher number of participants and take a relatively longer duration to execute clinical trials in comparison to other sponsor categories.<sup>19,22,23,33</sup> In contrast to non-invasive medical devices, invasive devices, especially those which deal with cardiovascular diseases require higher number of locations, participants and take a longer duration for clinical trials. Based on these empirical findings it can be construed that carrying out clinical trials with higher number of participants and in multiple locations help to generalize the findings considering diverse set of population and hence enhance the efficacy of the medical device. All these aspects facilitate the sponsors to penetrate the market at a quick pace and consequently this drives the economic performance of these sponsors.

This paper has made a key contribution to the literature. It has ascertained the determinants of recruitment of number of participants, selection of number of locations and time taken to carry out medical device clinical trials in the context of an emerging economy like India.

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