Sponsorship and Characteristics of Medical Device Clinical Trials Registered in Indian Trial Registry

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***Abstract*— The present day world has been experiencing rapid technological advancement on the one hand and an ever increasing number of diseases afflicting the human beings on the other. To deal with the later, medical devices are innovated and introduced in to the market (making use of the technological advancements), on a continuous basis across the world. However, introducing an innovated medical device to the market poses innumerable challenges and therefore, these have to be clinically trialed before its market launch to ensure safety and efficacy. India has emerged as one of the attractive and preferred countries by sponsors to execute clinical trials because of its various advantages. Sponsors play a crucial role for the successful conduction of clinical trials. Given the fact that Indian medical devices industry is growing at a faster pace, this paper attempts to understand and highlight the characteristics of medical devices that are registered in Indian trial registry. The present study has been carried out based on secondary data covering 108 medical device clinical trial registrations accessed from Clinical Trial Registry of India (CTRI) database pertaining to the period 2008-2014. These 108 medical device trials are analyzed based on the type of sponsorship.**

Keywords— Medical devices, Clinical trials, Sponsorship, India

I. INTRODUCTION

Medical device companies, (thanks to globalization) have spread their operations across the globe particularly in the realm of clinical trials [1]. Clinical trials are fundamental for enhancing knowledge among medical professionals as well as for improving the health care globally [2]. Of late, India has emerged as one of the preferred destinations to carry out clinical studies due to numerous advantages, primarily because of its diverse human gene pool and cost-competitiveness. Unlike pharmaceuticals, one of the major concerns in taking a medical device to market is the lack of guidelines for medical devices in India. Currently the medical devices are treated as drugs under India's Drugs & Cosmetic Act (1940) even though medical devices significantly differ from drugs in various aspects [3]. The Indian medical device regulation bill has been pending for approval for more than ten years now [4]. A special attention to medical devices in India, similar to other developed countries, would possibly accelerate faster growth in the Indian medical device sector.

Clinical research is hindered by various issues such as high cost, shortage of participants, slow trial results, lack of funding, regulatory barriers, incompatible databases etc., which impede in translating the basic science discoveries and inventions in to clinical studies [5]. The human resources involved in a clinical trial are the primary sponsor (PS), secondary sponsor (SS), principal investigator (PI, medical doctor), participants or patients, to name a few. Sponsor is the one who initiates a clinical trial and the sponsor could be from any entity such as industry or non-industry (Academic / Research Institutes / Hospitals / Government Organizations). These various entities of sponsors differ in the way they execute clinical trials i.e., with respect to the characteristics of clinical trials [6,7,8,9]. It might depend on various factors such as domain expertise, financial capability, patenting potential and so on. The different categories of sponsors might vary in terms of the number of participants, the type of device or disease addressed and locations they choose to carry out clinical trials [9,10,11,12,13,14]. This might depend on the sponsor's strategic decisions and the budget constraints to choose diverse population from varied geographic countries. The duration of the trial also may vary among the sponsor's categories. All of these together assists in achieving better clinical results which expedite the process of the device reaching the market. It has also been acknowledged that conducting trials in India will benefit sponsors to reduce cost up to 40% and time savings up to 70% for conducting phase 2 and phase 3 clinical trials [15]. Thus, conducting clinical trials in India provides numerous advantages to sponsors and Indian medical devices industry is also flourishing. Therefore, we attempt to determine the characteristics of medical device clinical trials that differ based on the type of sponsorship. Based on this we can draw managerial implications concerning the sponsors who wish to conduct clinical trials for medical devices in India.

II. REVIEW OF LITERATURE

A. Sponsorship: Industry / Non-industry

According to the ICH-GCP guidelines in Sections 1.53 and 1.54 the sponsor is defined as "*an individual, company, institution, or organization which takes the responsibility for the initiation, management, and/or financing of a clinical trial*" [16]. Based on the clinical trials data published in prestigious medical journals, it has been established that majority of the medical research have been funded by industry sponsors [17,18]. Also, patients stand to gain by themselves involving in industry-sponsored trials in getting access to new cutting edge technologies or devices or medications that are not yet in the market [19].

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Research studies on clinical trials categorized sponsors as industry (companies) and non-industry (universities/medical colleges, hospitals and government organizations) [2,7,8,12,20]. These studies revealed several differences between the industry and non-industry sponsors with respect to the characteristics of clinical trials which are discussed subsequently.

B. *Industry vs. Non-industry Sponsors: Characteristics of Clinical Trials*

There is ample number of research studies which used data from the US website namely, clinicaltrials.gov registry to analyze the characteristics of clinical trials based on sponsor categories [8,10,11,12,13,21]. Some of the trial characteristics include the type of intervention, disease of investigation, sample size (number of participants enrolled), age and gender of participants, number of study locations/sites, funding sources, number of sites and duration of the trial.

The primary concern for the sponsor is to achieve eligible participant enrolment to carry out clinical studies [19]. Additionally, industry sponsors are also responsible to fund the most influential clinical trial sites [17,18]. Empirical studies revealed that majority of the trials conducted by industry sponsors recruits more number of participants for carrying out clinical trials compared to other sponsor categories [11,13]. This finding has also been in accordance with the study related to pulmonary, critical care and sleep medicine clinical trials registered in USA clinical trial registry. This study revealed that industries in general sponsor trials involving a higher number of participants relative to trials sponsored by academic institutes or government organizations [8]. Another study analyzed the cancer clinical trials registered in 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 [7]. Also, country of origin of sponsor has some influence in participant recruitment. The study found that international funded sponsors were conducting clinical trials with more number of participants as compared to locally funded sponsors [13]. Yet another study from clinicaltrials.gov which focused on device trials related to spine surgery was retrieved and analysed. A logistic regression was performed on a total of 1,638 trials related to spine surgery. The results revealed that, industry-sponsor trials were more likely to perform multi-centre studies than non-industry sponsors (80% vs. 29%). Also, the number of participants was substantially more and the number of study sites/locations was approximately four times more when trials were industry-sponsored [21].

Clinical research studies were 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 trials. Among these trials, majority of the trials were related to medication followed by invasive trials [14]. Likewise, Alexander et al. [22] have categorized the trials based on the type of intervention such as device or drug or behavioral interventions. This study found that most of the trials in cardiology focused on assessing drugs followed by devices and other type of interventions.

Researchers have used clinical trial data and categorized trials based on the disease addressed by each trial. For example, recent studies have also assessed the characteristics of clinical trials investigating treatments related to concussion and brachytherapy procedures based on trials registered in clinicaltrials.gov database [23,24]. Using the data from clinicaltrials.gov as of June 2011, a total of 1,08,315 trials were comprehensively analyzed based on sponsorship categories i.e., whether the trial is industry-sponsored or government-sponsored. This study found systematic differences between the sponsor categories with respect to the type of study and medical intervention. Interestingly industry-sponsored trials focused primarily on drugs and devices; medical conditions especially related to cancer, cardiovascular and endocrine conditions. Whereas government-sponsored trials were related to mental health, viral infections and HIV [12]. Based on the clinical studies from clincialtrials.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 [11]. Moreover, cardiovascular trials are mostly carried out by industry sponsors compared to other sponsor categories [12].

The existing empirical studies primarily focused on assessing trials based on a particular disease or medical speciality area. Moving on to the various groups of sponsors, studies have classified sponsors in to different categories such as industry, government, medical college or research institutes (non-industry). However, studies in this domain hardly focused on medical devices data as a consolidated whole. Furthermore, all these studies investigated the characteristics of clinical trials from USA trial registry i.e., 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. We feel such an analysis is clearly warranted to understand the medical device sector in India which is important for economic, social and technological reasons. Therefore, it is essential to examine the characteristics of medical device clinical trials based on various sponsor categories. It is against this background that the research objective of this paper is formulated.

III. METHODOLOGY

A. *Data*

Data considered for this study, being predominantly secondary in nature, were obtained from Clinical Trials Registry of India (CTRI) database [25]. This database includes trials on drugs, medical devices, weight control equipment, cosmetics and personal care products (for ex: soaps, creams, shampoos, toothpaste etc.). CTRI provides information on the type of trial, primary sponsor (PS), secondary sponsor (SS), principal investigator (PI), target sample size, number of locations in which clinical trials are carried out, estimated duration of the trial and many other variables.

The sample selected for this study was based on intense keyword search such as medical device, device and equipment. Based on the results obtained from these keywords, further keywords such as stent, pacemaker, catheter and defibrillator were used. A total of 279 records were found using keyword search. After screening assessment, a few of them were excluded because they were not related to medical devices and some were duplicate studies. About 108 records were identified as medical device clinical trial registrations from the year 2008 to 2014 and hence formed the sample for the present study.

The Primary Sponsor (PS) of a clinical trial is considered responsible to ensure that the trial is properly registered and executed. Each clinical trial registration has a PS mentioned in the data field. The medical device trial registrations are classified by us based on whether the trial is registered by industry or non-industry sponsors. Industry sponsors are companies, whereas non-industry sponsors include medical college, research institute, hospital or a government organization. We found that 67% of the medical device trial registrations are by industry sponsors and within these, majority of them are MNCs as compared to non-industry sponsors.

B. Variable Description

The detailed definitions of each of the variables and their measurement scales are presented in Table I.

TABLE I. VARIABLE DEFINITION AND SCALE OF MEASUREMENT

Variable	Definition of variable	Scale of measurement	Reference
Invasiveness of device	Invasive: A device, which, in whole or in part, penetrates inside the body, either through a body orifice or through the surface of the body	Dummy (0,1)	[26]
	Non-invasive: A device which does not penetrate into the body		
Device category	The medical device can be either a stent or pacemaker or defibrillator	Dummy (0,1)	[14]
Disease focus	The focus of trials with different disease categories like cardiovascular or thermostability altering diseases or diabetes	Dummy (0,1)	[11,12,13,14,27,28,29]
Type of trial	It indicates whether the trial is an interventional trial, observational trial or in post marketing surveillance	Dummy (0,1)	[11,14,27,28,29,30]
Number of locations	The location where the clinical trial is carried out in order to test the device or treatment on participants	Numeric	[8,9,10,11,21,28,30]
Number of participants	The total number of participants (patients/subjects) recruited for a specific clinical trial to examine a new treatment	Numeric	[8,9,13,20,21,23,27,28,30]
Estimated duration of the trial	The expected time duration of trial, starting from enrolment of first patient to final submission of report	Numeric	[14,19,20,28,30]
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	Dummy (0,1)	[2,7,8,9,13]
Country of origin of PS	The primary sponsors can be from either India or a foreign country	Dummy (0,1)	[13]

C. Analytical Methods

The main objective of this study is to identify the characteristics of medical device trials that differ between industry and non-industry sponsors. Quantitative variables such as the number of locations in which the clinical trial is carried out, the number of participants enrolled for a clinical trial and the estimated duration of the trial, determine the sponsor's strategic decisions, expertise and the budget constraints. In order to investigate this, a two sample T-test has been used to examine the differences that exist between industry and non-industry sponsors with respect to the three quantitative variables.

Further to understand the determinants of industry and non-industry sponsors, a binary logistic regression analysis is performed. The logistic regression model is performed using IBM SPSS 20.0.0.0. In this model results, the Model Chi-square statistic, Pseudo-R-Squared values (Cox and Snell R2 and Nagelkerke R2), -2 Log Likelihood values, Hosmer-Lemeshow Goodness-of-Fit values, percentage of correctly classified pairs and Wald Chi-square values corresponding to each β coefficient are reported.

IV. RESULTS

First, the differences between industry and non-industry sponsors with respect to the selection of number of locations, recruitment of number of participants and the clinical trial duration is discussed. Following this, the determinants of industry and non-industry sponsors are examined using logistic regression model built in our study.

A. Industry vs. Non-industry sponsors: Locations, Participants and Trial duration

There exists a statistically significant difference between industry and non-industry sponsors in terms of the three quantitative variables which are presented in Table II. The result indicates that industry sponsors choose more number of locations (multiple sites), recruit higher number of participants and take a longer duration to execute clinical trials compared to non-industry sponsors. This finding is in agreement with literature as well. It is reported that the number of locations [10,21] and participants [11,13,21] selected for clinical trials by industry sponsors is always higher in number as compared to non-industry sponsors.

TABLE II. INDUSTRY VS. NON-INDUSTRY SPONSORS: T-TEST RESULTS FOR LOCATIONS, PARTICIPANTS AND TRIAL DURATION

Quantitative variables	Organization type of PS	Mean value	Computed T-value	P-value
No. of locations	Industry	4.63	5.037	0.000**
	Non-industry	2.64		
No. of participants	Industry	957.97	2.350	0.021*
	Non-industry	186.67		
Estimated duration of trial (in days)	Industry	1060.26	2.885	0.005**
	Non-industry	489.61		

***p<0.01; *p<0.05*

B. Determinants of Industry and Non-industry Sponsors

In this section, we present the analysis of binary logistic regression to identify the determinants of industry and non-industry sponsors. The dependent variable for logistic regression takes the value of 1 if the clinical trial has been registered by an industry sponsor. It takes the value of 0 if the trial is registered with a non-industry sponsor (Medical college / Research institute / Hospital / Government organization). The categorical predictor variables used in the logistic regression model and their corresponding scheme of coding are tabulated in Table III.

TABLE III. CODING OF CATEGORICAL PREDICTOR VARIABLES

Categorical variable	Variable level	Parameter coding
Invasiveness of device	Invasive	1
	Non-invasive	0
Device category	Stent	1
	Airway device	0
Disease category	Cardiovascular	1
	Others (Ex: Respiratory, diabetes)	0
Interventional trial	Yes	1
	No	0
Country of origin of Sponsor	India	1
	Foreign	0

The equation for binary logistic regression model for determinants of industry and non-industry sponsors is as follows:

$$\text{Logit (Industry sponsorship)} = \beta 0 + \beta 1 \text{ (Invasiveness of device)} + \beta 2 \text{ (Stent)} + \beta 3 \text{ (Airway device)} + \beta 4 \text{ (Cardiovascular disease)} + \beta 5 \text{ (Interventional trial)} + \beta 6 \text{ (Country of origin of Sponsor)} + \varepsilon \ldots\ldots (1)$$

In Equation 1, we verify whether there exists any statistically significant difference between industry and non-industry sponsors in terms of the characteristics of clinical trials such as device type, disease category, invasiveness of the device, type of trial (interventional / observational) and country of origin of the sponsor. The results of the binary logistic regression model are presented in Table IV. The model results are fairly robust. It may be observed that in this logistic regression model - F-statistic is significant and p-values corresponding to the Hosmer-Lemeshow goodness-of-fit statistic is high.

Four out of the six predictor variables differ significantly according to the type of sponsorship. Cardiovascular disease trials and country of origin of sponsor are the two variables that differed most significantly at 1% significance level. This suggest that if the clinical trial is related to a cardiovascular disease, then it is more likely to be registered by industry sponsors as opposed to non-industry sponsors. Similarly, if the trial is registered by India located sponsors then the probability of them being from an industry is high as compared to non-industry sponsors.

Predictor variables such as interventional trial and trial for airway devices exhibit negative relationship with industry sponsors. Interventional trial is found to be statistically significant at 5% significance level and the odds ratio is 0.129 with a beta value of -2.048. This would imply that the odds of sponsor executing interventional trials is 0.129 times lesser for industry sponsor as opposed to non-industry sponsor. Also, device category such as airway devices having an odds ratio of 0.25 and beta value of -1.385 would imply that the odds of industry sponsor choosing airway devices is reduced by 25%.

The classification that documents the validity of predicted probabilities showed that, the binary logistic regression model has correctly predicted the overall group membership at 85.2%. Also, the model has correctly predicted 77.8% of trials with non-industry sponsorship and 88.9% of trials with industry sponsorship.

Based on the results obtained in Table IV it can be inferred that there exist differences between industry and non-industry based sponsorships with respect to the characteristics of trials such as type of study (device/others like drugs), disease focus or medical condition [7,11,12,13]. Clinical trials related to airway type of devices are mostly preferred by non-industry sponsors. On the other hand, industry sponsors choose trials mostly related to cardiovascular diseases as compared to other disease categories [12]. Cardiovascular disease related trials involve huge risk because they include not only complex devices such as stent, pacemaker and defibrillator but also possibility of adverse reaction to patients is more. Therefore, the ability to handle such a trial needs expertise, funding and leadership potential of the sponsors. Having said this, non-industry sponsors such as research institutes or hospitals may lack sufficient funding and expertise in the medical device value chain to conduct trials for higher risk devices. This is corroborated by the results that we obtained. Another critical observation is that industry sponsors prefer observational trials. This suggests that most trials are being carried out to compare the effect of existing or imported devices on

participants. Thus, there is a dire requirement of innovation for developing new medical devices in India. This means that there is no "technology spill-over effect" in India as was observed by [31].

Table IV. LOGISTIC REGRESSION RESULTS FOR DETERMINANTS OF INDUSTRY SPONSORSHIP

Predictor variables	β	SE β	Wald's χ2	df	P-value	e β (odds ratio)
Constant	1.49	0.896	2.767	1	0.096	4.436
Interventional trial	-2.048	0.828	6.122*	1	0.013	0.129
Invasiveness of device	-0.784	0.85	0.851	1	0.356	0.457
Stent	0.149	1.072	0.019	1	0.889	1.161
Airway device	-1.385	0.781	3.144#	1	0.076	0.25
Cardiovascular disease	2.61	0.893	8.549**	1	0.003	13.599
Country of Sponsor	3.55	1.14	9.691**	1	0.002	34.819
Test		χ2		df	P-value	
Overall model evaluation test		66.50		6	0.000	
Hosmer and Lemeshow Goodness-of-fit test		2.278		7	0.943	
Model Summary						
Cox and Snell R^2		0.460				
Nagelkerke R^2		0.639				
-2 Log likelihood		70.982				
Classification Summary						
Observed frequency		Predicted frequency				
		Non-industry	Industry	Percentage correct		
Non-industry		28	8	77.8		
Industry		8	64	88.9		
Overall Percentage		85.2				

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

V. CONCLUSIONS AND LESSONS

In this study, we probed the characteristics of medical device clinical trials that differ significantly between industry and non-industry sponsors. The characteristics of medical device trials namely, the number of locations, participants enrolled, trial duration, type of trial (interventional / observational), invasiveness of the device, device type (Stent /Airway device / Others), disease category (Cardiovascular / Others) and country of sponsor (India / Foreign) were examined based on the type of sponsorship.

Our findings demystified that majority of the medical device clinical trial research in India is dominated by industry sponsors [17,18]. Also, foreign sponsors who are conducting clinical trials in India are from industry (MNCs). This may be because carrying out trials in India provides a lot of advantages to sponsors such as access to huge and diverse population, high global disease burden, reduced cost (almost half compared to developed countries), more skilled investigators, less regulatory barriers compared to the US FDA and so on [32,33,34]. All these advantages are the potential factors which benefited pharmaceutical or medical device companies [1,35,36] and are driving sponsors to shift their clinical trial activity to India and India has emerged as the "**clinical trial hub**". Thus, foreign companies are targeting Indian market to execute clinical trials and Indian population in turn will benefit through access to more advanced devices and therapies

The results emphasized that industry sponsors differ from non-industry sponsors with respect to the characteristics of clinical trials such as number of locations [9,10,21], participants [8,11,13], trial duration, type of trial [37,38], device type, disease category [11,14] and country of sponsor [13] which is in agreement with the literature as well.

It is interesting to notice that industry sponsors execute clinical trials in multiple locations with more number of participants and takes a longer duration as compared to non-industry sponsors. This is in line with the recent published literature which states that conducting trials in more locations and with higher number of participants yield better clinical trial output [39,40]. These findings imply that companies being financially strong and have proper expertise and leadership potential, could afford to test a device on a larger population (several thousands) which involves a huge amount of cost, resources and time. Our study also revealed that majority of the non-industry sponsors are located in India and are involved in conducting trials for devices related to respiratory diseases. On the other hand, foreign-located industry based sponsors are involved in trials for high-risk medical devices used in serious health concerns such as cardiovascular diseases. This implies that foreign industry based sponsors have the necessary expertise and experience required for conducting trials for complex devices. As it is known that India is a preferred destination for clinical trials, Indian based sponsors can make an effort to collaborate with the more experienced foreign industry based sponsors to financially and intellectually boost and support innovation of medical device technology in India which is currently under developed.

In summary, our study has substantiated what is generally observed in the literature. Clinical trials sponsored by industry involve more number of participants, execute trials in multiple locations and take a longer duration compared to trials involving non-industry sponsorship. This is because industries (particularly MNC's) deal with more complicated and risky diseases. Therefore, it is due to the very nature of diseases dealt by MNC's which warrants more participants, multiple locations and longer duration to ensure the safe application of

a medical device. Thus, clinical trials by industry sponsors gets clearly distinguished from that of trials by non-industry sponsors.

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