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Magnitude and characteristics of clinical trials in the Kingdom of Saudi Arabia: A cross-sectional analysis

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A B S T R A C T

The clinical trial is an important type of research design in the spectrum of translational research. The extent to which clinical trials are conducted is a reflection of the level of advancement that exists within a healthcare system. This study aims at describing the clinical trial activity within the Kingdom of Saudi Arabia since 2000 through reviewing those trials that have been registered with clinicaltrials.gov in that time period. Since February 2000, 405 trials have been registered. These trials fall into one of 22 different ICD-10 codes, and with the top four being neoplasms (92), diseases of the circulatory system (57), endocrine, nutritional and metabolic diseases (46), and diseases of the respiratory system (25). About half (200) were classified as trials with both safety and efficacy endpoints. 52% were phase IV and 28% were phase III. About 64% were randomized, and with about equal numbers of those coming from industry (86) and university sponsors (85), and smaller numbers coming from hospitals (51) and other sponsors. A total of 24 phase III university- or hospital-sponsored trials have been registered during the 15-year time period. With a population approaching 30 million and very large annual healthcare expenses, it would appear that the level of clinical trial activity within the Kingdom during the past 15 years has been rather paltry. The emphasis has been on post-marketing phase IV trials. The academic setting (i.e. universities and hospitals) has seen a new trial registered every 11 months on average.

1. Introduction

The concept of registering clinical trials was first proposed by Professor Robert Simes in 1986 [1]. ClinicalTrials.gov is recognized as the oldest and largest database for the registration of clinical trials and is managed by the National Library of Medicine at the National Institutes of Health (NIH) in the USA [2]. It started receiving trials in September 1999, and first released its database to the public in February 2000. As of June 26, 2016 it contains 218,540 registered studies from 193 countries and free access is available for both US and non US residents [2,3].

According to the Declaration of Helsinki, every clinical trial must be registered before starting the recruitment of the first human volunteer [4]. The World Health Organization (WHO) also states “registration of all interventional trials is a scientific, ethical and moral responsibility” [5]. Registration of clinical trials increases transparency in dissemination of clinical research information. Dissemination of clinical trials findings is achieved through the publication of the trial's results in peer-reviewed scientific journals and the reporting in registries. Several earlier studies have shown that for many clinical trials the results were not reported on time after the completion of the trial [6]. After July 1, 2005, the International Committee of Medical Journal Editors (ICMJE) journals only accepted those trials for publication that were registered prior to the enrollment of the first subject [7]. Registration of clinical trials is imperative to avoid selective reporting and publication bias, as well [8].

This study aims at describing the clinical trial activity within the Kingdom of Saudi Arabia (KSA) since 2000 through reviewing those trials that have been registered with ClinicalTrials.gov in that time period. This is the first such study of its type for all registered trials conducted in the Kingdom.

2. Methods

2.1. Data source and study sample

This study is a descriptive cross-sectional study based on over 16 years of clinical trials record available in ClinicalTrials.gov since November 1999 to February 2016. We used the “studies map” and “advanced search” functions, and downloaded a dataset of 405 studies registered at ClinicalTrials.gov and for which Saudi Arabia is one of the participating countries. Clinical trials with terminated or suspended

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status identified during data entry were also included. The studied conditions were classified according to WHO International Statistical Classification of Diseases and Related Health Problems (ICD) 10th Version. The trials were summarized with respect to various characteristics provided by ClinicalTrials.gov on each of the trials.

2.2. Statistical analyses

Being a descriptive study and for which the unit of analysis is a clinical trial, the statistical analyses involved frequency tabulations and cross-tabulations. To support the tabulations counts were made of the clinical trials of various types, and these types were cross-classified with each other. The analyses did not involve any inference, but is exclusively descriptive.

2.3. Results

Since the inception of ClinicalTrials.gov, 405 trials from Saudi Arabia have been registered with the registry. These trials fall into one of 22 different ICD-10 codes, and with the top four being neoplasms (92), diseases of the circulatory system (57), endocrine, nutritional and metabolic diseases (46), and diseases of the respiratory system [25] [Table 1]. Among the 405 trials, about half (200) were classified as trials with both safety and efficacy endpoints, 185 (45.7%) enrolled more than 100 patients, 112 (31%) were double blind, fifty-two percent were phase IV trials and 28% were phase III, while 178 (44%) stated the industry as the primary sponsor (Table 1). Among the 185 university- or hospital-sponsored trials, the most common was a phase IV neoplasm trial [11] and next being a phase IV trial of diseases of the circulatory system [9]. A total of 24 phase III university- or hospital-sponsored trials have been registered during the 16-year time period. Fig. 1 shows that the trials registration rate was higher during 2011 and 2014. King Faisal Specialist Hospital and Research Centre (Fig. 2) and Bayer pharmaceutical (Fig. 3) funded the most trials in the Kingdom of Saudi Arabia.

2.4. Study results posted on ClinicalTrials.gov

The number of studies for which the results have been reported is only 51 (12.6%), and this is to be reconciled with the number of studies which are registered to be completed (n = 183). That is, less than one-third of all completed studies have had their results reported. From among those for which the results have been reported, the vast majority (45, i.e. 88.2%) were industry sponsored.

3. Discussion

The clinical trial is an important type of research design in the spectrum of translational research. The extent to which clinical trials are conducted is a reflection of the level of advancement that exists within a healthcare system – a single provider, an organization (e.g. a hospital), or a national healthcare system. ClinicalTrials.gov is an official platform for the registration of prospective clinical trials that provide information to the general public, health care professionals and researchers. ClinicalTrials.gov started its operation 17 years before, while Saudi Arabia launched a clinical trials registry i.e. Saudi Clinical Trials Registry (SCTR) in 2013 and since then it is mandatory to register trials on this registry [9]. The clinical trials department of the Saudi Food and Drug Administration (SFDA) was also contacted for the current status of clinical trials in the Kingdom. As per the SFDA list, the total number of trials registered were 66 and most of the important characteristics of these trials were not available in their list as proposed by the WHO for the registration of clinical trials in a registry [10]. It can be presumed that after several years of SCTR operations, it will provide valuable information for the general public and health care professionals like other registry portals available worldwide. Hence, the data

Table 1
Overall characteristics of clinical trials across the Kingdom of Saudi Arabia, Nov 1999–Feb 2016.

Characteristics	Clinical Trials – n (%)
Total No of Trials	**405**
Conditions studied	
Neoplasms	92 (22.7)
Diseases of the circulatory system	57 (14.1)
Endocrine, nutritional and metabolic diseases	46 (11.4)
Diseases of the respiratory system	25 (6.2)
Certain infectious and parasitic diseases	19 (4.7)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	18 (4.4)
Diseases of the digestive system	16 (4)
Mental and behavioural disorders	16 (4)
Diseases of the eye and adnexa	14 (3.5)
Diseases of the nervous system	14 (3.5)
Pregnancy, childbirth and the puerperium	11 (2.7)
Diseases of the musculoskeletal system and connective tissue	10 (2.5)
Factors influencing health status and contact with health services	9 (2.2)
Diseases of the genitourinary system	8 (2.0)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	8 (2.0)
Injury, poisoning and certain other consequences of external causes	7 (1.7)
Diseases of the skin and subcutaneous tissue	5 (1.2)
Certain conditions originating in the perinatal period	2 (0.5)
External causes of morbidity and mortality	2 (0.5)
Codes for special purposes	1 (0.2)
Congenital malformations, deformations and chromosomal abnormalities	1 (0.2)
Other	24 (5.9)
Endpoint classification	
Safety/Efficacy	200 (49.4)
Efficacy	103 (25.4)
Safety	20 (5.0)
Other	82 (20.2)
Study phase	
0	2 (0.6)
I	16 (4.6)
I/II	9 (2.6)
II	37 (10.7)
II/III	4 (1.2)
III	97 (28.1)
IV	180 (52.2)
Missing	60 (17.4)
No of study arms	
1	101 (28.3)
2	202 (56.6)
3	32 (9.0)
≥4	22 (6.2)
Missing	48 (13.4)
Intervention model	
Single group	123 (33.9)
Parallel	225 (62.0)
Crossover	12 (3.3)
Factorial	3 (0.8)
Missing	42 (0.1)
Masking	
Open label	215 (59.6)
Single blind	34 (9.4)
Double blind	112 (31.0)
Missing	44 (12.2)
Randomization status	
Randomized	252 (64.0)
Non-randomized	142 (36.0)
Missing	11 (2.8)
Enrolled participants	
< 100	125 (30.9)
100–1000	185 (45.7)
> 1000	89 (21.9)
Missing	6 (1.5)
Sponsor	
Industry	178 (44.0)

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Table 1 *(continued)*

Characteristics	Clinical Trials – n (%)
Hospital	88 (21.7)
University	97 (24.0)
Other	42 (10.4)
Study status	
Active/Ongoing	148 (36.5)
Terminated/Suspended/Withdrawn	74 (18.3)
Completed	183 (45.2)
Results reported	
Yes	51 (12.6)
No	354 (87.4)

was taken from ClinicalTrials.gov registry that provides a comprehensive list of more than 400 trials since 2000, containing characteristics that are essential for conducting a study.

This descriptive cross-sectional analysis of registered clinical trials conducted by industries and academic institutions such as universities and hospitals, demonstrated for the first time that the number of clinical trials are not sufficient in one of the largest country of Arabian Peninsula that has reached to nearly thirty million population [11]. Moreover, academic institutions in the Kingdom register merely one trial per year. Clinical trial activity in the KSA has also been affected by several challenges such as long ethical review process, difficulty in the recruitment of study subjects and inadequacy in financial recompense [11,12]. Several earlier studies also reported poor recruitment of study subjects as a major issue during clinical trials [13–16].

It is well documented in the earlier studies that reporting of results were more accurate on registries than publications themselves [17,18]. A study conducted in Denmark concluded that primary outcomes mentioned during the submission of study protocols to institutional review board were not consistent with the publication of these studies [19]. There is not much difference relatively in the ratio of completed and undone studies unlike reporting of results which is merely 12.6% of registered clinical trials i.e. n = 405. Results reporting feature was lately included in September 2008 by ClinicalTrials.gov and it might be a reason that results posting is observed low in this study, while some of the studies are still being conducted by investigators in Saudi Arabia [20]. Section 801 of the Food and Drug Administration Amendments Act (FDAAA) recommends to disseminate the research findings by ClinicalTrials.gov within 1 year upon completion of trial [21].

More than sixty percent of the studies were randomized trials that are also recognized as a gold standard for evaluating the efficacy and safety profile [22]. This study revealed that Saudi Arabia contributes merely 0.20% of global clinical trials which is still apparently higher than other countries in the region such as Lebanon (0.13%), United Arab Emirates (0.06%), Qatar (0.03%), Oman (0.01%), Jordan (0.05%), Yemen (0.001%) and Kuwait (0.03%) [23]. Sponsors' interest is mainly in conducting oncology trials that accords well with the global trial preferences. In the United States, recognized as a hub of clinical trials, half of the clinical trials are conducted on cancers and the participation of adults is merely 3% in these trials [24]. Sponsors have shown a great interest in Phase IV trials followed by Phase III in the Kingdom. Phase IV trials are usually conducted in a variety of designs as compared to earlier phase trials and recognized as an important phase of drug development due to its execution in a real world setting, and relatively provides a more authenticated efficacy and safety profile of a drug than the pre-marketing phases of the clinical trial [25]. According to the International Diabetes Federation, the prevalence of diabetes in Saudi Arabia is 17.6%. This study illustrates that clinical trials for diabetes mellitus patients are not adequate enough (26 trials only) for the Saudi population [26] faced with such a diabetes mellitus burden.

Saudi Arabia has the largest population base and is also recognized as the largest pharmaceutical market in the Gulf region. This study found that participation of academic institutions in clinical trials is higher than pharmaceutical industries that need to be addressed in order to overcome research interest gap between academic and pharmaceutical organizations [11]. According to Saudi Arabia's 2016 fiscal budget, there is a decline of 34% in health and social development budget as compare to 2015, which may adversely affect clinical trials activity of government academic institutions in the Kingdom, as well [27]. This study also reveals a sudden increase in the registration of clinical trials after the introduction of clinical trials regulation in 2009 by the KSA government while compliance to these regulations ensures the rights, safety, and wellbeing of study subjects. This study has several implications - there is a need to conduct more clinical trials and promote the awareness about reporting of results on clinical trial registries for evidence based clinical decision making and increased clinical trial transparency. Future research is also recommended to ascertain the dissemination of study findings by peer reviewed scientific journals.

4. Limitations of the study

This study is solely based upon the information as registered in ClinicalTrials.gov. There is the possibility that other trials not registered could exist. However, it is thought that the resource would include those trials of a higher quality and more rigorous.

5. Ethical approval

Not required.

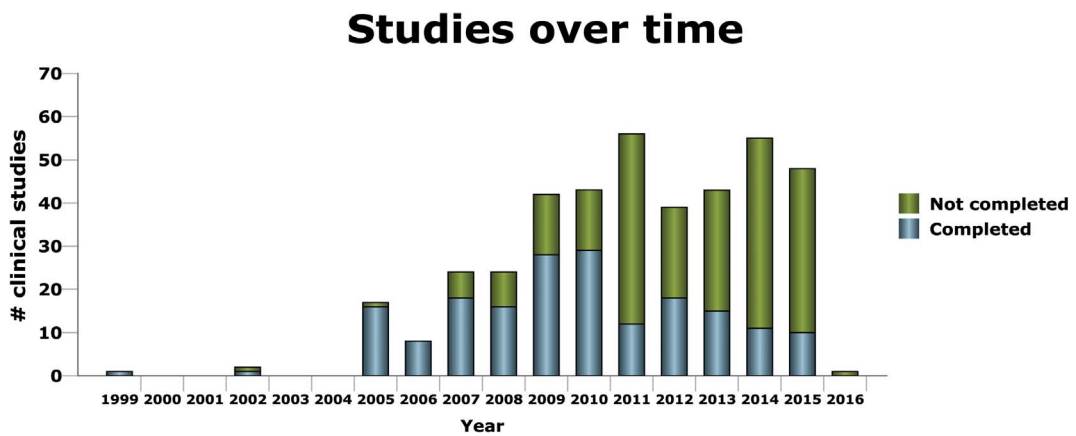

Fig. 1. Studies over time.

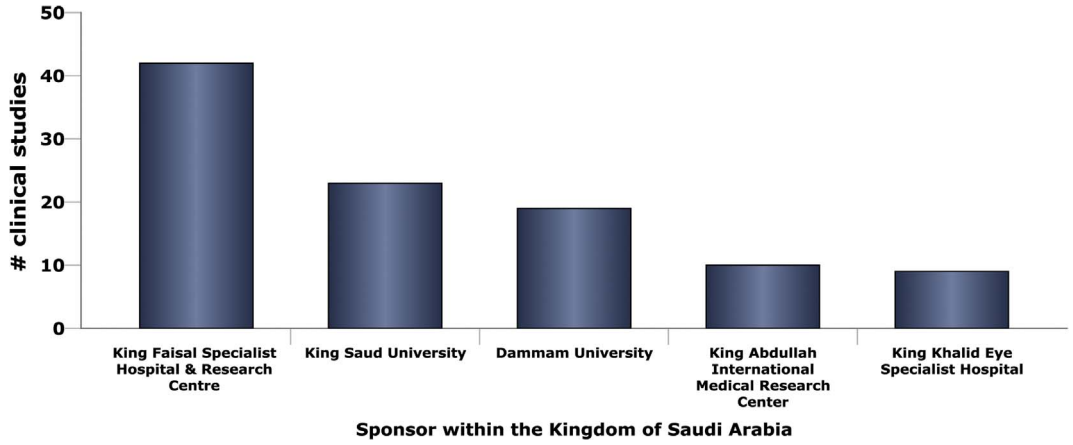

Fig. 2. Sponsor within the Kingdom of Saudi Arabia.

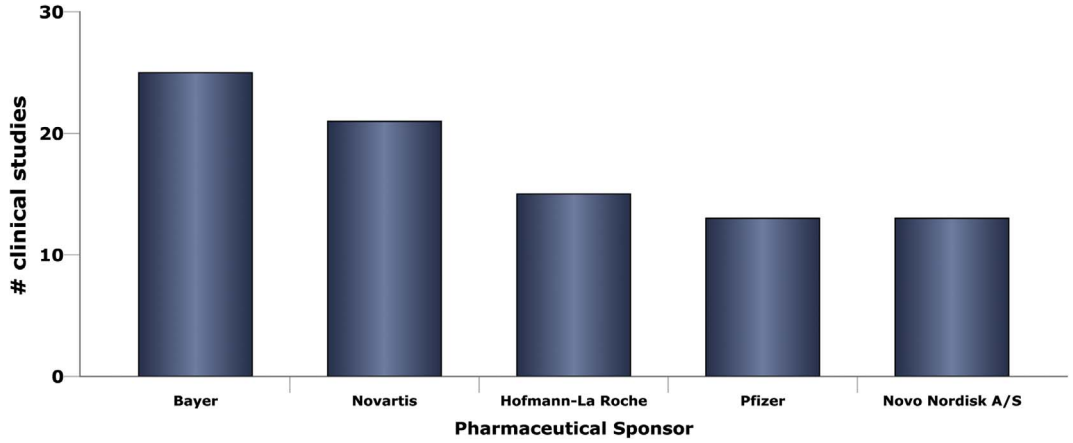

Fig. 3. Pharmaceutical sponsors.

6. Conclusion

With a population approaching 30 million and very large annual healthcare expenses, it would appear that the level of clinical trial activity within the Kingdom during the past 16 years has been rather paltry. The emphasis has been on post-marketing phase IV trials. The academic setting (i.e. universities and hospitals) has seen a new phase III trial registered every 8 months on average.

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