Fate of registered clinical trials performed in Saudi Arabia

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The ClinicalTrials.gov was established by the United States National Institutes of Health in collaboration with the Food and Drug Administration (FDA) in 2000.[1] It offers the latest information on clinical randomized controlled trials (RCTs) for a wide range of diseases. One of the original goals of the site was to help patients find trials related to the treatment of their condition.[1] Subsequently however, the endorsement of its use had been to enhance the transparency of research, and to decrease the selective reporting of clinical trials.[2] The high rate of discontinuation and non-publication of RCTs is topical in the current literature, and has been identified as a common problem to research in general, and within clinical specialties.[1-5] Over the last 3 decades, researchers in the Kingdom of Saudi Arabia (KSA) had contributed significantly to the national and international literature. However, up-to-date there have been no reports that examined the magnitude, characteristics, and publication outcome of registered trials that were performed in KSA. The purpose of the study was to investigate the outcomes of KSA-related trials that were registered on ClinicalTrials.com with particular focus on the correlation between the extent of the contribution of the KSA investigators and the study design, completion, and publication rates.

This study was carried out at King Khalid National Guard Hospital (KKNGH), Jeddah, KSA. It was a review based on routinely available data with open access; hence, it did not require an ethical approval by KKNGH. An advanced search was carried out in the website ClinicalTrials.gov using the key word "Saudi Arabia". In view of the daily changes in the database, the search findings on a single day (19th April 2015) were documented and used for analysis. The inclusion criteria were phase 1 to phase 4 clinical trials that were performed completely or partly in KSA, and were registered on the website from January 2000 to December 2012. The latter date was chosen to allow adequate time for trial publication. We included all closed studies that had a status listed at the time of the search as "complete", "terminated" or "suspended". Open studies that had a status listed as "unknown", "recruiting" and "active not recruiting" were excluded. Using each study web page, the trial's responsible authority was identified. The selected studies were categorized into 3 groups according to the extent of contribution of KSA investigators: studies in which a KSA authority was responsible alone; studies in which a KSA authority was responsible jointly with others; and studies in which KSA researchers provided collaboration only, and were not amongst the responsible authorities. Using each trial web page, the following data was collected for every study: title, National Clinical Trial identification number (NCT-ID), status, sponsor, condition, intervention, design, phase, enrolment, start and completion dates, participating locations, recruitment, publication citation, publishing journal's impact factor (IF), duration from study completion and publication, and whether KSA investigators were included amongst the authors.

To determine whether a clinical trial had been published and to obtain the article's citation, we searched in the individual's study website and in PubMed using the study title and its NCT-ID. When a study had more than one listed publication, the relevant abstracts were reviewed, and the article reporting data that resembled the original study description closely was used. Furthermore, the correlations between the extent of contribution of KSA researchers and trials characteristics were assessed by comparing the 3 groups (responsible alone, responsible jointly with others, and collaboration only) using the following parameters: status (completed versus uncompleted), sponsor (industry versus others), condition (cancer versus others), intervention (drug versus others), phase (1-3 versus 4), randomization (yes versus no), blinding (yes versus no), recruitment (national versus international), publication (yes versus no), and KSA researchers inclusion in authorship (yes versus no). In addition, using the median value as a cut-off point we compared the 3 groups in relation to the sample size, participating locations, study duration, publishing journal's IF, and period from completion to publication. For statistical analysis a chi-squared test was calculated using the Social Science Statistics,[6] and significance was determined when $p<0.05$.

Our search identified 138 KSA-linked clinical trials. We excluded 57 open studies as their status at the time of the search was "unknown" in 19, "recruiting" in 19 and "active but not recruiting" in 19. Two more studies

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were excluded due to inadequate information and lack of KSA involvement. Of the 79 suitable studies, a KSA authority was responsible alone in 25 (31.6%), responsible jointly with others in 14 (17.7%), while provided collaboration only in 40 (50.6%). Seventy-two (91.1%) studies were completed while 7 (8.9%) were not completed (terminated 6 and suspended 1). The sponsors were industry in 52 (65.8%), universities in 16 (20.3%), and health care authorities in 11 (13.9%) studies. The top 5 sponsors and the number of studies they sponsored were: Pfizer 11 (13.9%); University of Dammam 10 (12.7%); Novartis 7 (8.9%); Hoffman La Roche 7 (8.9%); and Sanofi Pasteur 7 (8.9%). The top 5 conditions tested in the 79 clinical trials and the number of studies were: cancer 17 (21.5%); heart disease 9 (11.4%); neurological disease 8 (10.1%), diabetes and endocrine disease 7 (8.9%), and lung disease 7 (8.9%). The type of intervention and the number of studies were: drugs 63 (79.7%); biological 5 (6.3%); device 5 (6.3%); procedure 4 (5.1%), and others 2 (2.5%). Fifty-four (68.4%) studies were randomized and 34 (43%) were blinded. The phases of the various studies and their numbers were: phase 1 - 5 (6.3%); phase 2 - 9 (11.4%); phase 3 - 35 (44.3%), and phase 4 - 30 (38%). The sample size ranged from 3-8586 (median 287). The recruitment was national in 25 (31.6%) and international in 54 (68.4%) studies. The study duration ranged from 1-143 months (median 30). The number of participating locations for each study ranged from 1-544 (median 27). Forty (50.6%) studies were published in journals with an IF ranging from 0-54.4 (median 3.2). Only 14 (17.7%) articles had KSA investigators included amongst the authors. The timing of publication ranged from 26 months prior to study completion to 168 months after completion (median 18 months). Data comparing the 3 groups of KSA involvement in relation to a number of parameters are summarized in **Table 1**.

Randomized controlled trials are important in clinical practice as they provide a high level of evidence (LOE) research. We observed a paucity of RCT's performed in KSA in general (79 studies), and when a KSA body was responsible, in particular, 39 studies in 13 years. Blumle et al[2] reported that over a 3-year period, 807 clinical studies were approved by the Research Ethics Committee of the University of Freiburg, Germany. In recent years, the issue of uncompleted and unpublished trials has received considerable attention as it has a potential impact on patient care and safety.[1-4] Unpublished studies are a poor use of financial resources for funders, host establishments, and authorizing bodies. Additionally, there are non-financial and ethical costs, which include loss of knowledge through hidden data, as well as potential harm to study participants in the absence of the communal benefits that accompany the spreading of trial results.[3,5] Our analysis revealed that the RCT's performed in KSA had a relatively low discontinuation rate (8.9%). This may have been related to the relatively small number of included studies. Chapman et al[3] reported a 21% discontinuation rate in 395 surgical trials over a 2-year period, while Kasenda et al[4] reported a discontinuation rate of 24.9% for 1,017 RCTs over a 3-year period. The most common reasons for trial discontinuation are poor recruitment of participants, trial conduct problems, and withdrawal of management groups.[3,4] The publication rate of the KSA-liked trials reviewed here was 50.6%, which is low but within the range of 66-38.9% reported for trial publication in the literature.[1,3] The articles were published at a median of 18 months after study completion, which is relatively shorter than the duration stated by others.[1,3] Some articles were published fairly early, presumably as reportable data became available prior to the official completion date of a lengthy trial. Reasons for studies remaining unpublished include the possibility that the article had been rejected by the journal, or still under review. The trial may have been a pilot study with small numbers, and the results may have not been significant, or not what the authors expected. There may have been protocol deviation, slow enrolment, discourse within the study group, and difficulties getting long-term follow up. Furthermore, a higher rate of non-publication in studies funded by industry was reported by some authors,[1,5] but not others.[3]

Our assessment of the extent of contribution of KSA researchers to the trials was based on whether a KSA organization was posted as the responsible authority in the study website or not. The KSA researcher's involvement was undoubtedly strong when they were listed as the responsible authority alone. Conversely, the magnitude of their contribution to studies where they were jointly responsible or collaborators only could not be accurately defined. Nevertheless, we felt it was appropriate to report the results of the 3 groups independently as they could signify a range in the scale of KSA contribution to the trials (responsible alone being highest while collaboration alone being lowest). Our findings as shown in **Table 1** revealed that the rates of study completion and publication were not significantly influenced by the degree of KSA contribution to the trials. However, a number of other research characteristics were found to be significantly different. Studies with a higher level of KSA contribution (responsible alone)

Table 1 - Analysis of the 79 study characteristics according to the level of involvement of Kingdom of Saudi Arabia (KSA) researchers.

Study features	KSA responsible alone, n=25	KSA responsible jointly with others, n=14	KSA collaboration only, n=40	*P*-value
		n (%)		
Status				0.3062 (NS)
Complete, n=72	21 (29.0)	13 (18.0)	38 (53.0)	
Incomplete, n=7	4 (57.0)	1 (14.0)	2 (29.0)	
Sponsors				<0.0001 (Sig)
Industry, n=52	5 (10.0)	13 (25.0)	34 (65.0)	
Others, n=27	20 (74.0)	1 (4.0)	6 (22.0)	
Condition				0.3369 (NS)
Cancer, n=17	4 (24.0)	5 (29.0)	8 (47.0)	
Others, n=62	21 (34.0)	9 (14.0)	32 (52.0)	
Intervention				0.1486 (NS)
Drug, n=63	17 (27.0)	13 (21.0)	33 (52.0)	
Others, n=16	8 (50.0)	1 (6.0)	7 (44.0)	
Phase				0.0508 (NS)
Phase 1-3, n=49	20 (41.0)	6 (12.0)	23 (47.0)	
Phase 4, n=30	5 (17.0)	8 (27.0)	17 (56.0)	
Randomization				0.4812 (NS)
Yes, n=54	18 (33.0)	11 (20.0)	25 (47.0)	
No, n=25	7 (28.0)	3 (12.0)	15 (60.0)	
Blinding				0.0065 (Sig)
Yes, n=34	17 (50.0)	3 (9.0)	14 (41.0)	
No, n=45	8 (18.0)	11 (24.0)	26 (58.0)	
Sample size				<0.0001 (Sig)
≤287, n=40	22 (55.0)	7 (18.0)	11 (27.0)	
>287, n=39	3 (8.0)	7 (18.0)	29 (74.0)	
Study locations				<0.0001 (Sig)
≤27, n=42	25 (60.0)	6 (14.0)	11 (26.0)	
>27, n=37	0 (0.0)	8 (21.0)	29 (79.0)	
Study duration				0.0057 (Sig)
≤30 months, n=40	19 (48.0)	7 (17.0)	14 (35.0)	
>30 months, n=39	6 (15.0)	7 (18.0)	26 (67.0)	
Study recruitment				<0.001 (Sig)
National, n=25	25 (100.0)	0 (0.0)	0 (0.0)	
International, n=54	0 (0.0)	14 (26.0)	40 (74.0)	
Study publication				0.3401 (NS)
Yes, n=40	12 (30.0)	8 (20.0)	20 (50.0)	
No, n=39	13 (34.0)	6 (15.0)	20 (51.0)	
Publishing journal's impact factor				0.0220 (Sig)
≤3.2, n=20	10 (50.0)	3 (15.0)	7 (35.0)	
>3.2, n=20	2 (10.0)	5 (25.0)	13 (65.0)	
KSA in authorship				<0.00001 (Sig)
Yes, n=14	12 (86.0)	1 (7.0)	1 (7.0)	
No, n=26	0 (0.0)	7 (27.0)	19 (73.0)	
Duration from completion to publication				0.7047 (NS)
≤18 months, n=20	6 (30.0)	3 (15.0)	11 (55.0)	
>18 months, n=20	6 (30.0)	5 (25.0)	9 (45.0)	

NS - non-significant, Sig - significant

compared to the other 2 groups (responsible jointly and collaboration only) were associated with a significantly lower proportion of industrial sponsorships, smaller population sample size, fewer participating locations, shorter time duration, and lesser ability to recruit internationally. Studies with a lesser level of KSA contribution (collaboration only) were associated with a significantly higher publishing journal's IF, and a lower rate of inclusion of KSA researchers amongst the authors. Our results also verify that a number of other features were not significantly influenced by the degree of KSA contribution to the trials. These include: study condition; type of intervention; phase; randomization; and duration between study completion and article publication. We found the use of the NCT-ID in the search for publications in PubMed was not useful, as many of the registered trials do not cite this number in the publication. The NCT-ID should be included in publications to facilitate the location process.[1]

This study may have some limitations. The KSA trials not registered in ClinicalTrials.gov were not included. Some trials may have been missed because changes on the website may not be updated frequently enough. Some studies may have been overlooked, as they did not correspond with the search term. Some of the excluded articles may have been accepted but not published yet. Some publications may have been missed due to inconsistencies between the published results and the registered protocol posted at the initiation of the study. Furthermore, reasons for the non-completion of the 7 trials were not evaluated.

In conclusion, there should be an increased awareness of the availability and potential use of the web site ClinicalTrials.com in order to enhance its use by investigators and sponsors. This study demonstrated a paucity of registered clinical trials performed in KSA in general, and when a KSA authority was responsible in particular. The KSA-linked trials were associated with a relatively low rate of discontinuation (8.9%) and publication (50.6%). The latter, however was comparable with what is being reported in the current literature. The magnitude of the KSA contribution was significantly associated with a number of study characteristics relating to methodology, participation, recruitment, as well as the publishing the journal's IF. The non-inclusion of KSA researchers in the authorship of most of the studies reflects that they had a limited supportive role. The KSA researchers should be encouraged to take a more leading role in large multicenter international RCTs that provide a high LOE, and a major impact on their field.

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