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Clinical trials in allied medical fields: A cross-sectional analysis of World Health Organization International Clinical Trial Registry Platform

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ABSTRACT

Background: Clinical trials are mandatory for evidence-based practice. Hardly, any data are available regarding the number of clinical trials and their methodological quality that are conducted in allied fields of medicine.

Objective: The present study was envisaged to assess methodological quality of trials in allied medical fields.

Materials and Methods: Registered clinical trials in World Health Organization International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/AdvSearch.aspx) in the following fields were extracted: Acupuncture; Ayurveda; biofeedback; complementary and alternate medicine; herbal; homeopathy; massage; naturopathy; Reiki; Siddha; Unani; and yoga. The eligible studies were assessed for the following key details: Type of sponsors; health condition in which the trial has been conducted; recruitment status; study design; if randomization was present, method of randomization and allocation concealment; single or multi-centric; retrospective or prospective registration; and publication status in case of completed studies.

Results: A total of 276 clinical trials were registered majority of which have been proposed to be conducted in the field of oncology and psychiatry. Most of the clinical trials were done in single centers (87.75%), and almost all the clinical trials were investigator-initiated with pharmaceutical company sponsored studies contributing to a maximum extent of 24.5%. A large majority of the study designs were interventional where almost 85% of the studies were randomized controlled trials. However, an appropriate method of randomization was mentioned only in 27.4%, and the rate of allocation concealment was found to be just 5.5%. Only 1–2% of the completed studies were published, and the average rate of retrospective registration was found to be 23.6% in various fields.

Conclusion: The number of clinical trials done in allied fields of medicine other than the allopathic system has lowered down, and furthermore focus is required regarding the methodological quality of these trials and more support from various organizations.

1. Introduction

Clinical trials generate high-quality evidence that may then get incorporated into national/international guidelines and meta-analysis, finally culminating in an evidence-based practice (EBP) [1]. For EBP, clinical trials have to be conducted with robust methodology and published to allow more transparency of the findings. In this era of shared decision-making, even patients should have access for such clinical trials, and this is the very purpose of creating clinical trials registry platform. There exist several regional clinical trial registries serving different regions of the world and the World Health Organization International Clinical Trial Registry Platform (WHO-ICTRP) initiated in 2006 serves as a portal of access to these registries [2].

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Studies of clinical trial registries in some of the portfolios in allopathic medicine revealed crucial findings [3,4] which include poor quality of publication of clinical trials in complementary and alternate systems of medicine [5] and dentistry [6] and also paucity of available data regarding the clinical trial methodology in these fields. In addition, there is no data on clinical trials conducted or published in other allied fields of medicine such as acupuncture, Ayurveda, homeopathy, massage, naturopathy, Reiki, Siddha, Unani, and yoga. Hence, the present study was envisaged with an objective to obtain a holistic view of methodological quality and trends of clinical trials done in all these fields.

2. Materials and methods

The study was conducted between September 2014 and January 2015. Following keywords were used for the search in WHO-ICTRP (http://apps.who.int/trialsearch/AdvSearch.aspx): Acupuncture; Ayurveda; biofeedback; complementary and alternate medicine (CAM); herbal; homeopathy; massage; naturopathy; Reiki; Siddha; Unani; and yoga. Individually, the above-mentioned keywords were used in the "Intervention" section without any limits in either the recruiting status or date of registration fields. Both authors independently retrieved the studies from the trial registry emerging from search results, and duplicate studies were removed from the final analysis.

Each of the registered studies was assessed for the following details: Source of primary registry (Clinical Trial Registry of India [CTRI], Chinese Clinical Trial Registry [ChiCTR], Korean Clinical Trial Registry [KCT], clinicaltrials.gov [CTG], German Clinical Trials Register [GermanCTR]; International Standards of Reporting Clinical Trials [ISRCTN], Netherland's Trial Register [NTR], European Clinical Trial Database [EudraCT], Brazilian Clinical Trial Registry [REBEC], Iranian Registry of Clinical Trials [IRCT], Hong Kong Clinical Trial Register, Australia and New Zealand Trial Register, Japan Clinical Trial Registry [UMIN-CTR]); type of sponsors (academic or commercial); health condition in which the trial has been conducted; year of registration; Institutional Ethics Committee (IEC) approval obtained or not; recruitment status (ongoing/completed); study design (observational/interventional [nonrandomized/randomized (open label, single blind, and double blind)]); if randomization was done, method of randomization (computer generated [CG], random number table [RNT]) and allocation concealment; phase of clinical trials (I, II, III, and IV); single or multicentric; type of study participants (patients/healthy volunteers); retrospective or prospective registration; and publication status in case of completed studies.

3. Results

3.1. Number of clinical trials

The search strategy revealed a total of 342 studies (acupuncture – 3; Ayurveda – 11; biofeedback – 27; CAM – 9; herbal – 53; homeopathy – 31; massage – 51; naturopathy – 15; Reiki – 9; Siddha – 7; Unani – 7; and yoga – 119). Of the studies retrieved under CAM ($n = 9$), one was proposed to evaluate Ayurveda, two studies retrieved under massage and one with naturopathy were proposed to evaluate acupuncture and after removing the duplicates and inappropriate studies, a total of 276 studies were included in the final analysis (acupuncture – 6; Ayurveda – 10; biofeedback – 25; CAM – 8; herbal – 53; homeopathy – 21; massage – 38; Reiki – 1; Siddha – 5; Unani – 2; and yoga – 107). A summary of various characteristics and methodological quality of various clinical trials is depicted in Table 1.

3.2. Characteristics of clinical trials

3.2.1. Acupuncture

A total of six studies were retrieved (3 – ChiCTR; CTG – 2 [one each in the United States (US) and United Kingdom (UK)] and one from KCT). All these studies were investigator-initiated (one each in the years 2005, 2008, 2010, and 2011 and two in 2012) and only four studies had mentioned that they had obtained IEC approval. Regarding the health condition in which the clinical trials are carried out in Acupuncture, one each was in ophthalmology (juvenile myopia), psychiatry (attention deficit hyperactivity disorder [ADHD]), cardiovascular system (chronic stable angina) and oncology (breast and head and neck cancer) and two were in the field of central nervous system disorders (cerebral palsy and spastic paralysis). All the studies were being done in a single center in patients, and only one study had been completed.

3.2.2. Ayurveda

There were a total of 10 studies (seven in CTG [US – 5; one each in Singapore and France], two in CTRI and one in GermanCTR) pertaining to this field. All these studies were from academia (three each in 2006 and 2007, two in 2012 and one each in 2009 and 2011). Regarding the health conditions where the studies are being carried out, seven were in the field of oncology (three in breast cancer, two in all types of cancer patients and one each in prostate cancer and chronic myeloid leukemia [CML]) and one each in mental retardation and lifestyle. Furthermore, 9 of the 10 studies are conducted in patients and one in healthy volunteers, seven are being carried out in a single center and three are multi-centric and only one was completed.

3.2.3. Biofeedback

A total of 24 studies were retrieved (15 – CTG [14 – US, 1 – Taiwan], 3 – GermanCTR, two each from ISRCTN [both from UK] and NTR, and 1 from ChiCTR) of which only 2/24 (8.3%) was from commercial sponsors. A total of five studies were conducted each in the field of psychiatry (one each in ADHD and alcohol de addiction, anxiety, cognitive behavioral therapy and psychotherapy) and urinary incontinence, three each in the disorders of central nervous system (two in cerebral palsy and one in migraine) and anal incontinence, two with lower limb disorders (one each with quadriceps inhibition and drop foot) and one each in insomnia, pelvic floor disorder, erectile dysfunction, cancer, diabetes mellitus, and neuropathic pain. Only 9/24 (37.5%) studies had mentioned about having obtained IEC approval, and a majority (23/24, 95.8%) were done in a single center. In addition, only one study was completed, and 23/24 (95.8%) studies were carried out in patients while only one in a healthy volunteer.

3.2.4. Complementary and alternate medicine

A total of eight clinical trials (6 – CTG [5 – US and 1 – Mexico], one each from CTRI and ISRCTN [Chile]) were registered. All the eight studies were from academia, and only three had mentioned about IEC approval. Half of the studies were being carried out in oncology (one each in CML, breast cancer, prostate cancer, and ovarian cancer), two in human immunodeficiency virus-infected patients and one each in ulcerative colitis and elderly population. Five out of eight studies were completed; two are ongoing, and one was terminated. All the studies were being carried out in a single center in patients.

3.2.5. Herbal

Fifty-three clinical trials (19 each from CTG and CTRI; 9 – ChiCTR; 3 – IRCT; 2 – UMIN–CTR and one from ISCRTN) have been registered of which 40 (75.5%) were from academics and 13 (24.5%)

Table 1
Summary of the analyses pertaining to registered clinical trials in allied medical fields from WHO-ICTRP (*n* [%]).

Types of studies (*n*)	Observational			Type of studies		Methodological quality		Retrospective registration
	Sponsored studies	Multi-centric	Completed	Interventional	Observational	Mention of method of randomization sequence	Mention of method of allocation concealment	
Acupuncture (6)	0	0	1 (16.7)	6 (100)		3 (50)	0	1 (16.7)
Ayurveda (10)	0	3 (30)	1 (10)	7 (70)		0	0	2 (20)
Biofeedback (24)	2 (8.3)	1 (4.2)	1 (4.2)	24 (100)		1 (4.8)	0	9 (37.5)
CAM (8)	0	0	5 (62.5)	1 (12.5)		0	0	5 (62.5)
Herbal (53)	13 (24.5)	13 (24.5)	3 (5.7)	49 (92.5)	4 (7.5)	10 (27.8)	4 (11.1)	23 (43.4)
Homeopathy (21)	0	2 (9.5)	0	20 (95.2)		6 (33.3)	1 (5.6)	3 (16.7)
Massage (38)	0	1 (2.6)	5 (13.2)	36 (94.7)	2 (5.3)	1 (2.8)	0	8 (21.1)
Yoga (107)	0	8 (7.5)	8 (7.5)	107 (100)		15 (18.3)	4 (4.9)	41 (38.3)
Others (5)	0	0	0	5 (100)		0	0	5 (100)

WHO-ICTRP: World Health Organization International Clinical Trial Registry Platform, CAM: Complementary and alternate medicine.

were sponsored by pharmaceutical companies. A total of 31 (58.5%) studies had reported of having obtained IEC approval, and only 3 (5.7%) had been completed and none of these has been published. In addition, 47 (88.7%) have reported patients as the study participants and the rest in healthy individuals, and only 13/53 (24.5%) were multi-centric and the remaining (40/53, 75.5%) were done in single centers. Majority, 13 (24.5%) were being done in the field of dermatology and others are as follows: 6 (11.3%) each in oncology and orthopedics; 5 (9.4%) – endocrinology; 4 (7.5%) – central nervous system disorders; 3 (5.7%) each in infections, psychiatry and respiratory tract; 2 (3.8%) each in patients with xerostomia and metabolic disorders and 1 (1.9%) each in ENT and burns. Three studies were completed, and none of them were published.

3.2.6. Homeopathy

A total of 21 studies (9 – CTG; 8 – CTRI; one each from EudraCT, ISCRTN, NTR and REBEC) have been registered in this field of which 10 (47.6%) had reported of having obtained IEC approval. Slightly less than a third of studies (6/21, 28.6%) were reported in the field of oncology, 4 (19.1%) each in respiratory and psychiatry, 2 (9.6%) each in orthopedics and diabetic foot and 1 (4.8%) each in dry eye syndrome, hormonal disorder and anesthesiology. All the studies were reported to be currently ongoing, done in patients, and only 2/21 (9.5%) were multi-centric. Six studies were completed, and none of them published.

3.2.7. Massage

Thirty-eight clinical studies (27 – CTG; 4 – IRTN; 3 – ISCRTN; 2 – REBEC and one each from ChiCTR and CTRI) have been registered in this field of which only one had mentioned of having obtained IEC approval and all were investigator-initiated. A total of 11/38 (28.9%) were done in the field of orthopedics; 6 (15.8%) each in oncology and central nervous system disorders, 5 (13.2%) in psychiatry, 3 (7.9%) in pediatric, 2 (5.3%) each in pregnant and fecal incontinence, 1 (2.6%) each in dentistry, burns and lymphedema patients. Only 1/38 (2.6%) was a multi-centric study, and 35/38 (92.1%) were done in patients and the remaining (3/38, 7.9%) in healthy individuals. Five out of 38 were completed, and only 2/5 (40%) were published.

3.2.8. Yoga

A total of 107 clinical studies (72 were from CTG, 20 – CTRI, 4 – NTR, 3 – UMIN–CTR, 2 each in ISCTRN and IRTN and one each in REBEC, ChiCTR, GermanCTR, and KCT) were registered in this field of which 25 reports of having obtained IEC approval. Slightly less than a third of these studies (32/107, 29.9%) were being conducted in the field of psychiatry, 17/107 (15.9%) in oncology, 10/107 (9.3%) in cardiovascular system, 11/107 (10.3%) in central nervous system disorders, 8/107 (7.5%) each in orthopedics and metabolic disorders, 5/107 in (4.7%) respiratory diseases, 3/107 (2.8%) in irritable bowel syndrome and one each in hormonal, genitourinary and ophthalmology. Only 8/107 (7.5%) were multicentric, and none of these had been published despite completion.

3.2.9. Others (Siddha, Unani, and Reiki)

A total of five clinical studies (two related to nephrology and one each in the field of orthopedics, metabolic and cardiovascular disorders) were retrieved pertaining to Siddha and two in the field of Unani (one each in orthopedics and dermatology). All these were registered in CTRI, investigator-initiated and had obtained IEC approval and done in single centers. Only one clinical trial was identified in Reiki registered in CTG that was ongoing in a single center for patients with pain and fatigue.

3.3. Methodological quality of clinical trials

3.3.1. Acupuncture

All the six studies in this field are interventional (two in Phase I and one in Phase II and others did not mention) of which five were randomized controlled clinical trials (RCT). Out of these, only three mentioned the method used for randomization (2 – CG and 1 – RNT) and all these studies did not mention anything about allocation concealment. Only one study has been completed and published, and one other was retrospectively registered.

3.3.2. Ayurveda

A total of 7 out of 10 studies in Ayurveda were interventional (RCT – 6 and nonRCT – 1; and one each were Phase II and III and rest did not mention the phase of clinical trial) and the remaining observational. None of these RCT mentioned the method of randomization as well as allocation concealment. Only one study was completed and published, and two were retrospectively registered.

3.3.3. Biofeedback

All the 24 studies were interventional (21 [87.5%] – RCT and 3 [12.5%] – nonRCT and none mentioned the phase of clinical trial). Of the 21 RCTs, only 1 (4.8%) mentioned the method of randomization (RNT), none about allocation concealment and only 5 (23.8%) were blinded trials (three are single, and two are double). Only one was completed and published, and 9/24 (37.5%) were retrospectively registered.

3.3.4. Complementary and alternate medicine

Out of the eight studies, only one was interventional (RCT with no mention on the method of randomization, allocation concealment, and open label). Five out of the total eight studies were

completed, but none of them have been published. Similarly, five studies were retrospectively registered.

3.3.5. Herbal

Forty-nine (92.5%) clinical studies were interventional and 4 (7.5%) were observational. Of the 49 interventional studies, 36 (73.5%) were RCTs and 13 (26.5%) were nonRCTs. Only 10/36 (27.8%) RCTs had mentioned a procedure for randomization (9 – CG and one reported coin toss/shuffling cards/dice throw). Also, only 4/36 (11.1%) RCTs had reported a procedure for allocation concealment (one each as SNOSE, precoded containers, pharmacy controlled, and an open list of random numbers). Similarly, the phase of clinical trials has been mentioned in 30/49 registered studies (11 – Phase 4; 7 – Phase 3; 6 – Phase 2; 3 – Phase 1 and one each had mentioned Phase 1/2, 2/3 and 3/4). A total of 26/49 (53.1%) reported the use of blinding technique (22 – double; 3 – single and 1 – triple) and the remaining (23/49, 46.9%) were open-label studies.

3.3.6. Homeopathy

A total of 20/21 (95.2%) studies were interventional (four each were Phase 2 and 3; two were Phase 1/2 and one had mentioned as Phase 2/3) of which 18/20 (90%) were RCTs. Only 6/18 (33.3%) had reported the procedure for randomization in which three had mentioned the use of CG while the remaining three had wrongly mentioned. Similarly, only 1/18 (5.6%) did mention the method of allocation concealment and 15/18 (83.3%) studies use one of the blinding techniques (14 – double; 1 – single) and the remaining were open label. Also, 3/18 (16.7%) studies did register their studies retrospectively.

3.3.7. Massage

Out of the total 38, 36 (94.7%) studies were interventional (2 – Phase 2; 1 each of Phase 4 and Phase 1/2 and 34 did not mention any phase of drug development) and 2 (5.3%) were observational. Thirty-three (91.7%) of 36 interventional studies were RCTs of which only 1 (2.8%) had mentioned RNT as a method of randomization and none about the allocation concealment. A total of 14/38 (36.8%) used blinding technique (seven, each was single and double-blinded) and 8/38 (21.1%) retrospectively registered their studies.

3.3.8. Yoga

All the studies ($n = 107$) were interventional (9 – Phase 2; 5 – Phase 1; 4 – Phase 1/2, 3 – Phase 2/3 and the rest did not mention the phase of study) of which 82/107 (76.6%) were RCTs. Of these 82 RCTs, only 15 (18.3%) mentioned a procedure for randomization (9 – CG; 4 – coin toss and 2 – RNT) and only 4 (4.9%) a method for concealing the allocation (two each SNOSE and central randomization). Nearly, half of the RCTs (42/82, 51.2%) were blinded (36 – single and 6 were double blinded). A total of 41/107 (38.3%) were retrospectively registered.

3.3.9. Others (Siddha, Unani, and Reiki)

Of the five clinical studies in Siddha, 4 (80%) were done in patients, all the studies were nonrandomized, registered retrospectively and only two had mentioned the development phase as Phase 2. Both clinical studies in Unani were randomized (1 – CTG and another had wrongly mentioned the method) and single blinded. Also, only one out of the total two studies did mention SNOSE as a method of allocation concealment. The single study in Reiki was a nonrandomized open-label study without having mentioned any phase of drug development and was prospectively registered.

4. Discussion

The present study was undertaken to understand the global trend of clinical trials that were being conducted in the allied medical fields that were registered in WHO-ICTRP. A total of 473 clinical studies have been registered majority being investigator-initiated, in single centers and only a small fraction of the completed studies were published. A large majority of the trials were conducted in patients suffering from cancer, psychiatric diseases, and central nervous system disorders except in the field of dentistry. Also, only a few studies have reported correct procedure for randomization and allocation concealment in case of RCTs, majority of the studies were open label and retrospectively registered.

EBP plays a pivotal role in the creation of healthcare policy and delivery of healthcare services [7]. For EBP to be effective, clinical trials/studies are mandatory in all the medical fields. We found that the total number of clinical trials done in fields other than the modern system of medicine is very less. We hypothesize the following factors to contribute for the same: Lack of trained researchers, poor support both from the government organizations and private pharmaceutical companies and absence of awareness of patients towards various concepts and importance of clinical trials. Furthermore, there can be more researches done in these areas due to the unawareness these trials might not be registered in any of the registries. Furthermore, the number of institutions dedicated to such allied medical fields is relatively less than the modern allopathic system of medicine. More programs in training the researchers involved in these allied medical fields and funding from various organizations both to support these researches and in promoting the development of new institutions in these fields are the need of the hour to improve the evidence generation. Also, more incentives should be given to the private pharmaceutical companies as there is a limited market in many foreign countries for these allied fields of medicine.

Not only the number of clinical studies but also their quality matter when it comes to acceptance of study results. Among various types of studies, RCTs stand at the top next to meta-analysis whose results are more credible, associated with lesser bias than observational and nonrandomized interventional studies [8]. In the present study, we found only few studies were RCTs irrespective of the field. To the best of our knowledge, this is the first study where a comprehensive assessment is done both for the number and quality of studies conducted in the allied medical fields. Furthermore, even those studies that have been designed as RCTs have not reported the method of randomization and allocation concealment in an appropriate way. The procedure of randomization involves generating the random sequence and not revealing the generated sequence until an eligible study participant reaches the study site which is the most important aspect. Randomization without concealing allocation will not serve the purpose of reducing confounding and selection bias [9]. Surprisingly, only 1.5% of the evaluated studies had reported the method of allocation concealment. The scenario has been similar in other fields of medicine as evident from a systematic review of 3159 trials conducted in Chinese traditional medicine, where only 4% had reported adequate randomization method [10]. Considering the importance of the same, Consolidated Standards of Reporting Trials, a widely known guideline for reporting randomized trials has laid down the method of randomization and allocation concealment as one of the essential 25 reporting items [11]. Also, another widely used scale for assessing the quality of RCTs, Jadad scale, considers both these essential elements [12]. Unlike allocation concealment, use of blinding technique to reduce the ascertainment bias is not essential for all RCTs. When present, blinding increases the credibility of the

study especially when the outcome measures are subjective, of course, may compromise the external validity in some cases [13]. Reports have documented an exaggeration of the treatment effect to an extent of 17% in case of open-label design than those using the blinding strategy [14]. Only a small fraction of the evaluated studies in the present study used one of the blinding techniques while a large majority was of open-label design. More focus is required in improving the methodological quality of studies conducted in these fields.

We also found that only a few of the completed clinical trials are published eventually. Only the published data forms a source for EBP. Studies that had assessed the publication fraction of registered clinical trials in the registry reported a publishing rate of only 46–70% [15,16]. It is unethical not to publish the results of a completed study irrespective of the nature of findings, and this constitutes a scientific misconduct. There exists a need for increasing the awareness for making the data available both for the scientific community and public.

The study is limited in the fact that we restricted to elicit the characteristics of the trials from the WHO-ICTRP without actually trying to contact any of the investigators and there can be modifications in any/many of the trials before/during the conduct of clinical trials.

5. Conclusion

The number of clinical trials done in allied fields of medicine other than allopathic system are low down, and furthermore focus is required regarding the methodological quality of these trials and more support from various organizations.

Source of support

Nil.

Conflicts of interest

None declared.

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