

Research

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Volume 1 : Issue 1

Article Ref. #: 1000CTPOJ1101

Article History

Received: January 12th, 2017

Accepted: March 3rd, 2017

Published: March 3rd, 2017

Citation

Yukawa K, Fuji H, Sato H. Distribution and conduct of clinical trials involving music therapy: Registered clinical trials in the last 15 years. *Clin Trial Pract Open J*. 2017; 1(1): 1-9. doi: [10.17140/CTPOJ-1-101](https://doi.org/10.17140/CTPOJ-1-101)

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Distribution and Conduct of Clinical Trials Involving Music Therapy: Registered Clinical Trials in the Last 15 Years

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ABSTRACT

Objective: This study aimed to conduct an evaluation of music therapy clinical trials worldwide, to understand what trials have been conducted and to show the chronological changes. Additionally, we sought to clarify issues related to providing clinical trial registration information.

Methods: We searched the International Clinical Trials Registry Platform (ICTRP) database for “music therapy,” and identified the disease target for each article found.

Results: A total of 150 clinical trial studies were found in the ICTRP using the term “music therapy.” In these trials, music therapy was used for improvement of social functioning in schizophrenia and/or serious mental disorders, anxiety and depressive symptoms, and cancer symptoms. Twenty-five clinical trials were actively recruiting. Sixteen of the 25 trials were registered in the United States at ClinicalTrials.gov, of which 9 trials were conducted in the US. Seven trials were conducted in other countries such as Spain, Taiwan, and China.

Conclusion: A search for music therapy clinical trials retrieved 150 trials from the ICTRP, and the number of clinical trial registrations has increased yearly. Music therapy is widely used in patients with various diseases, including Alzheimer’s disease, anxiety, and arthritic pain and has the potential to improve certain disease outcomes, but there is not enough evidence to substantiate its efficacy. It is important to enlighten researchers and pharmaceutical companies on the proper management of the quality of such clinical trial information, as this is an important issue.

KEY WORDS: Music therapy; Clinical trial; Registration.

ABBREVIATIONS: ICTRP: International Clinical Trials Registry Platform; AMTA: American Music Therapy Association; JMTA: Japanese Music Therapy Association; IFPMA: International Federation of Pharmaceutical Manufacturers and Associations.

INTRODUCTION

Music therapy originated in the early 20th century in the United States and is practiced worldwide. The American Music Therapy Association (AMTA) was founded in 1998 in the US¹ and in Japan, the Japanese Music Therapy Association (JMTA) was established in 2001.² By combining the physiological, and social effects of hearing or playing music, music therapy can enable the recovery or improvement of mental and physical health. Music therapy can be divided into two types, namely, passive music therapy such as listening to music, and active music therapy such as performing to music, singing, or playing music.

In Japan, music therapy was administered by pioneering experts for a few decades following World War II. Music psychology was introduced into the curriculum of music colleges around 1955, and music therapy originated as a form of local volunteerism by music experts. In the 1990’s, there was an increase in the number of experts who were self-educated, had studied abroad, and had implemented music therapy at a local level.

Along with traditional Chinese medicine and acupuncture, music therapy is considered a complementary and alternative medicine strategy or as a familiar non-pharmacotherapy. A 2011 survey showed that music therapy was used by 3% of the Japanese population.³ Music therapy has also been recommended by the national center for complementary and integrative health for patients with Alzheimer's disease. Several studies have shown that music therapy helped relieve agitation and depression, and had a positive effect on patient's quality of life.⁴ Evidence for the benefits of music therapy is increasing, as music therapy has been found to improve quality of life for many patients with a range of diseases.

Numerous studies have demonstrated that music therapy cannot only provide minor benefits but also improve medical outcomes and the quality of life in a variety of conditions. Kamioka et al⁵ conducted a review on the efficacy of music therapy and evaluated the quality of systematic reviews (SRs) in the current literature. Music therapy has also been shown to improve outcomes during invasive procedures. For example, in controlled clinical trials of people undergoing colonoscopies and cardiac angiography, patients who listened to music in the operating room reported less discomfort during their procedures. Music therapy can also help restore lost speech. Music has been shown to help patients with stroke or those with traumatic brain injury who have damage to the areas of the brain responsible for speech. Moreover, music has also been shown to reduce anxiety and the side effects, such as nausea and vomiting, associated with chemotherapy and radiotherapy during cancer treatment.

In addition to these benefits, music therapy can also aid pain relief. Music therapy has been tested in patients with intense acute pain and those with chronic pain from arthritis; music therapy has been shown to relieve depression, and provides patients with a better sense of control over their pain when used as an adjunctive therapy. Moreover, music therapy improves patient quality of life,⁶ facilitates memory recall, reduces agitation, assists with communication, and improves physical coordination. The primary impairments of people with autism spectrum disorder include social interaction and communication difficulties. With music therapy, musical experiences and the relationships that develop through these experiences enable communication and expression, thereby helping address some of the core difficulties in patients with autism.⁷

The World Health Organization (WHO) has recognized the need for the establishment of a registration system for clinical trials as an important health-related policy issue.⁸ In July 2004, the International Committee of Medical Journal Editors (ICMJE), which includes other major medical journals, issued a statement that all medical journal editors should require that clinical trials be registered in a public trials registry.⁹ Furthermore, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) released the document, titled "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases".¹⁰ The WHO established

and released the International Clinical Trials Registry Platform (ICTRP) in August 2005 to promote the registration of clinical research information. The appendix details the inclusion of various national clinical trial registration systems in the ICTRP.

However, reporting of supportive evidence in the complementary and alternative medicine (CAM) field compared to conventional medicine is often insufficient. The purpose of the present study was to understand how music therapy clinical trials have been conducted internationally, and to investigate if the content of music therapy depends on the country in which it is conducted.

MATERIALS AND METHODS

On November 20, 2015, we performed a search using the ICTRP Search Portal,¹¹ which is managed by the WHO, to identify clinical trials containing "music therapy" in both the title of the trial and in the details of the intervention used. Identified trials were summarized on the basis of the country, phase, recruitment status, study type, conditions, and source-registry.

We recorded the number of registered clinical trials on all registers from 2001 to 2015. In addition, we performed a detailed analysis of the content of the trials currently in the recruitment phase. For countries in which 10 or more clinical trials were conducted, we analyzed the details of the intervention pertaining to subject age groups, illness type, and how the music therapy was conducted. All statistical analyses were performed using SPSS 18.0 J for Windows.

RESULTS

Characteristics of the Clinical Trials of Music Therapy

We included 150 clinical trials in our analysis; no trials were excluded. Their characteristics are summarized in Table 1.

Country

Four international clinical trials that were conducted in two or more countries were identified. The number of other clinical trials per country was as follows: The United States (39 trials); Iran (23 trials); Germany (12 trials); Australia (11 trials); China (10 trials); Brazil (7 trials); France (3 trials); Spain (3 trials); Taiwan (3 trials); the Netherlands (3 trials); the United Kingdom (3 trials); India (3 trials); South Korea (3 trials); Japan (2 trials); Sweden (2 trials); Canada (2 trials); Finland (2 trials); and Lebanon, New Zealand, Norway, Singapore, South America, Switzerland, Israel, and Hong Kong all had 1 trial.

Phase

Five trials were registered as being in Phase 1; 1 was in Phase 1-2; 6 were in Phase 2; 2 were in Phase 2-3; 6 were in Phase 3;

Table 1: Music Therapy Clinical Trial Characteristics (n=150).

		n	%
Country	International clinical trials	4	3.6
	United States	39	34.8
	Iran	23	20.5
	Germany	12	10.7
	Australia	11	9.8
	China	10	8.9
	Brazil	7	6.3
	France, Spain, Taiwan, Netherlands, the United Kingdom, South Korea, India	3	2.7
	Japan, Sweden, Canada, Finland	2	1.8
	Lebanon, New Zealand, Norway, Singapore, South America, Switzerland, Israel, Hong Kong	1	0.9
	Phase	Phase 1	5
Phase 1-2		1	0.7
Phase 2		6	4.2
Phase 2-3		2	1.4
Phase 3		6	4.2
Phase 4		2	1.4
Not applicable		122	84.7
Recruitment status	Not Recruiting	125	83.3
	Recruiting	25	16.7
Study type	Interventional	143	95.3
	Observational	7	4.7
Source-Register	ANZCTR (Australian New Zealand Clinical Trials Registry)	16	10.7
	ChiCTR (Chinese Clinical Trial Register)	8	5.3
	ClinicalTrials.gov	74	49.3
	CRIS (Clinical Research Information Service, Republic of Korea)	1	0.7
	CTRI (Clinical Trials Registry - India)	2	1.3
	German CTR (The German Clinical Trials Register)	6	4.0
	IRCT (Iranian Registry of Clinical Trials)	22	14.7
	ISRCTN (The International Standard Randomized Controlled Trial Number)	14	9.3
	JPRN (Japan Primary Registry Network)	2	1.3
	NTR (Netherlands Trial Register)	3	2.0
	PACTR (Pan African Clinical Trial Registry)	1	0.7
	ReBec (Registro Brasileiro de Ensaio Clinicos)	1	0.7

and 2 were in Phase 4. In 122 clinical trials, the phase was not identified.

Primary Sponsor

More than 80 trials were conducted by universities; in the remaining studies, the primary sponsor was not clear.

Study Type

There were 143 interventional trials and 7 observational trials.

The most frequent minimum age for inclusion in the trials was over 18 years.

Condition

Music therapy has been widely used in patients with various diseases, including Alzheimer’s disease, anxiety, arthritic pain, a variety of symptoms associated with cancer, such as depression or pain, chronic pain, dementia, or depression, mental and behavioral disorders, head injuries, Parkinson’s disease, pregnancy, schizophrenia, and stroke.

Source-Register

The number of trials per source-register (registration destination) was as follows: ANZCTR (Australian New Zealand Clinical Trials Registry), 16 trials; Chi CTR (Chinese Clinical Trial Register), 8 trials; ClinicalTrials.gov, 74 trials; CRIS (Clinical Research Information Service, Republic of Korea), 1 trial; CTRI (Clinical Trials Registry-India), 2 trials; German CTR (The German Clinical Trials Register), 6 trials; IRCT (Iranian Registry of Clinical Trials), 22 trials; ISRCTN (The International Standard Randomized Controlled Trial Number), 14 trials; JPRN (Japan Primary Registry Network), 2 trials; NTR (Netherlands Trial Register), 3 trials; PACTR (Pan African Clinical Trial Registry), 1 trial; and ReBec (Registro Brasileiro de Ensaio Clinicos), 1 trial. This information is summarized in Table 1.

Recruiting Status

Of the music therapy trials identified, 125 were not recruiting and 25 were recruiting (Table 1). Sixteen of those 25 trials were registered with the United States website ClinicalTrials.gov. Of those 16 registered trials, 9 were conducted in the United States, and 7 trials were conducted in other countries such as Spain, Taiwan, and China. In terms of target size, 7 trials were small-

scale, including 1 trial with less than 30 participants; 7 trials were medium-sized with one of them having 100 participants; and 11 trials were large-scale with more than 100 participants. Patient conditions often included anxiety. Seven trials were registered from 2008 to 2012.

Changes in the Number of Registered Trials

Figure 1 shows changes in the number of trials registered in the ICTRP. From 2001-2007, the number of trials increased from 0 to 5. In 2010, there were more than 10 trials, and in 2011, about 20 trials were registered. In 2014, there were 27 trials. Thus, there has been a steady increase in the number of trials registered to date.

Clinical Trials by Country

In the United States, clinical trials have investigated the use of music therapy as a treatment for a range of conditions such as cancer, pain, post-traumatic stress disorder, anxiety, stress, asthma, and burns (n=39). Danhauer and colleagues reported that patients undergoing bone marrow biopsies found music intervention to be beneficial and requested the use of music during future procedures.¹² Ripley and colleagues examined the

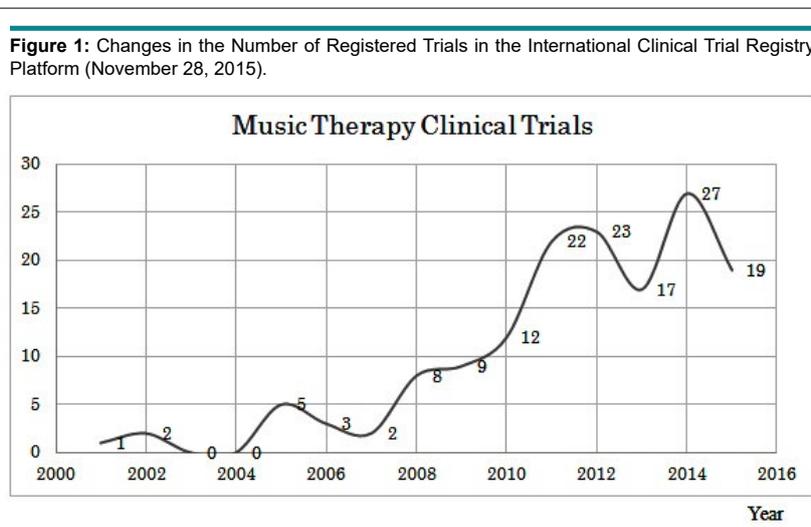


Table 2: Examples of Music Therapy-Related Clinical Trials by Country.

Country	Intervention
United States	Behavioral: Music Therapy
Iran	Music therapy group. The patients in this group participated in traditional group music therapy sessions, 5 sessions per week for 2 months in addition to routine treatment.
Germany	Music therapy for 15 min on 3 consecutive days
Australia	Music therapy. Weekly 45-min sessions for 16 weeks. This is a one-on-one session with a registered music therapist and the child participant's primary caregiver. Techniques used include making live music, such as singing, instrument playing, and movement to music.
China	Behavioral: peer support and yoga music therapy

efficacy of music intervention on vasodilator response, blood pressure, anxiety, and stress.¹³

A unique feature of the Iranian music therapy trials was the large number that used traditional music. Treatments, such as traditional music therapy sessions, were administered for pregnancy-related issues, childhood autism spectrum disorder, insomnia disorders, cardiovascular conditions, respiratory conditions, chronic kidney disease, pain, cancer, head trauma, schizophrenia, conduct disorder, obsessive-compulsive disorder, anxiety, and depression. For patients with obsessive-compulsive disorder, the treatment was effective in reducing obsessions, as well as comorbid anxiety and depression symptoms.¹⁴

In Germany, music therapy was used for treating lower and upper back pain, speech impediments, tinnitus, depression, anorexia, and obesity. For the treatment of pain, patients underwent a method known as intensive interdisciplinary pain treatment, combining cognitive behavioral therapy, physiotherapy, and music therapy. Patients undergoing such therapy listened to music 5-7 times a week for 20-30 min, underwent group treatment, and participated in stress management, relaxation, and diet therapy programs.¹⁵ Another form of doctor-directed music therapy that included live harp performances was found to reduce salivary cortisol and had beneficial effects on the physiological parameters of stable preterm infants in a neonatal intensive care unit (NICU).¹⁶ Music therapy was also used in the palliative care of cancer patients; in 55% of sessions, it was possible to deliver successful interventions.¹⁷

In Australia, music therapy was used to treat a range of psychiatric and developmental disorders including autism spectrum disorder, depression, mood disorders, and schizophrenia. Infant patients underwent active music therapy with a registered music therapist and their caregiver, during which they participated in live music-based activities such as singing, instrument playing, and movement to music. For psychiatric and developmental disorders, patients were encouraged to interact socially during group work using music.

In China, group therapy for adults was quite prominent. For conditions such as cancer, diabetes, cerebrovascular disorders, anxiety, depression, and schizophrenia, patients received a combination of therapies including music therapy, peer support, recreation, and yoga.¹⁸ Music therapy was also shown to reduce anxiety and create a more satisfying experience for women undergoing caesarean delivery.¹⁹

DISCUSSION

Registration Status of Music Therapy Clinical Trials

The efficacy of music therapy has been shown for many symptoms and diseases; it improves the quality of subjective sleep in insomnia patients²⁰ and psychological (e.g., anxiety) and physical symptoms in cancer patients. It significantly reduces anxiety during a colonoscopy (endoscopy of the cervix),²¹ and it

is effective in children with autism, specifically improving social interactions, verbal communication, the initiation of an action, and socio-emotional interactions. Moreover, music therapy improves non-verbal communication skills in therapy settings. It has also been shown to be effective in reducing psychological (e.g., anxiety) and physical symptoms in patients with coronary artery disease, especially after myocardial infarction.⁶ Music therapy also alleviates the general mental state of patients with schizophrenia by effectively reducing negative symptoms, depression, and anxiety.²²

Notably, the number of registrants for music therapy certification examinations has increased since the mandated registration of studies to the ICTRP in 2006. Furthermore, the annual number of registrations for the exam has exceeded 20 since Western Europe (EU), with an active music therapy community, joined the ICTRP in 2011.

Safety of Music Therapy

Music therapy is considered to be very safe and to have no negative effects, because it is a non-pharmaceutical therapy. This, however, may not always be true. Indeed, most clinical trials conducted on music therapy have found positive effects, but when patients do not follow the appropriate methods, such as the selected music, time, and number of sessions, among others, there may be adverse effects. Although some patients perceive music as positive and calming, others feel aroused when they listen to music.¹⁷ The CAMbrella project in Europe investigated the perspectives of CAM users and patients, in addition to their needs and attitudes.²³ The results of that investigation showed that the context of alternative therapies for individual patients is an important factor.²⁴ Therefore, an analysis of semi-structured interviews is needed to determine the effects of music therapy.

In regions where people use traditional music, or in developing countries, music therapy is generally not considered a valid therapy and medicines are used instead. It is possible that there is a culture of using familiar music without attributing a financial burden to it. For example, in Bali, Indonesia, there is a very famous music drama called “*kecak*” in which performers percussively chant “*cak*.” In audible high-frequency sounds can affect brain activity and this hypersonic effect has been studied in an electrophysiological investigation.²⁵ The relationship between the arts, such as music and dancing, and CAM are obvious, but this relationship also needs to be examined from a religious perspective, especially with regard to Iranian music and traditional music.

Issues with Registered Clinical Trials

We reviewed the details of the clinical trials in a recruitment phase and found two problems. Seven trials were registered from 2008 to 2012; however, these studies should have been completed on the basis of the retarget sample size and enrollment. In other words, after the researchers registered the trial, it is likely that no updates were made to the information in the clinical trial

registration. Based on the philosophy of promoting international knowledge in clinical trials, the information that is released to the public and professionals around the world must be kept up-to-date. Thus, managing the quality of such clinical trial data is an important issue.

Additionally, by registering at ClinicalTrials.gov, rather than in the country in which the trial is conducted, unless the country in question has no primary registry, other groups in that particular country may not have access to the relevant information. Music therapy is a non-pharmaceutical based treatment for the improvement of mental disorders, and it can have sedative effects. Music therapy is often used in complementary and conventional medicine. However, it is also used as an important therapy in studies of disease. If professionals and patients are not able to find the relevant clinical trials in their own country, the valuable knowledge pertaining to music therapy may not be broadly communicated.

The number of future clinical trials and professionals that will use this form of therapy depends on whether or not the training of music therapists becomes recognized with a national qualification. A more active approach is needed towards conducting clinical trials to a mass more evidence in support of music therapy and other complementary and alternative medicines.

Areas of Future Music Therapy Application

Unfortunately, we could not analyze the design of clinical trials related to music therapy, because of some missing registration information. However, we provide examples of pioneering clinical trials by phase.

In terms of phase 1 trials, the “*Effects of Music Therapy on Huntington’s Disease*” trial is a good example. Huntington’s disease is a progressive, neurodegenerative disease with autosomal dominant inheritance with motor disturbances, cognitive decline and behavioral and psychological symptoms. Because of communication problems, most patients are not able to express themselves sufficiently. Music therapy is a non-pharmacological intervention, alleviating communication problems, helping self-expression, and improving quality of life.

A pertinent example of a phase 2 trial is the “*Evaluating the Effects of Music Interventions on Hospitalized People With Dementia*” trial. As society ages, dementia is increasingly becoming a problem. For example, in Japan, with a super aging society, the government has estimated that the number of dementia patients throughout the country will exceed 7 million by 2025. Among elderly people aged 65 years or over, 1 out of every 5 will have dementia. Distress is one of the most common clinical manifestations associated with dementia. Although pharmacological intervention may be appropriate for managing distress, music therapy should be considered one of the non-pharmacological approaches to assist in alleviating distress for

dementia patients.

An example of a phase 3 trial is the “*Multimodal Music Therapy for Children With Anxiety Disorders*” trial. Although music therapy has previously been considered an effective intervention for children with mental health needs, its efficacy in clinical settings is unclear. In recent years, pediatric developmental disorders, such as dyslexia, attention-deficit hyperactivity disorder (ADHD), and attention-deficit disorder (ADD), have been gaining increased interest. Music therapy may be effective for treating these conditions, by improving children’s relationships and promoting communication.

Hopefully, such research efforts will increase so that clear evidence of the benefits of music therapy will be obtained.

LIMITATIONS

Since music therapy is currently conducted in highly varied ways, such as in clinical trials that combine music and rhythm exercises, it is not possible to define a specific and concise term for music therapy. In the future, it will be necessary to understand the specific details of the treatment regimens that include music therapy in combination with other treatments.

The inconsistent effects of music therapy have been noted; this inconsistency is attributed to differences in the number of sessions, content, and quality of the therapy. Thus, a more detailed analysis of the different types of therapeutic content is necessary. We also need to investigate whether “passive listening” or “individual therapy” can provide benefits for patients and improve their disease outcomes. In recent years, at least 50 randomized control trials of music therapy have been reported annually; thus, there is a need to review these trials and their content.

Furthermore, it is necessary to show that music therapy works for a variety of participants, including the elderly, children, and patients with specific disease such as those with dementia, Alzheimer’s disease, developmental disorders, autism, and mental illness, among others. A detailed analysis of these target groups will be needed in the future.

CONCLUSIONS

A search for music therapy clinical trials retrieved 150 trials from the ICTRP. These were conducted in 1 or more countries, including the United States (39 trials), Iran (23 trials), Germany (12 trials), and Australia (11 trials). The participants of these studies included adults from 18 to 51 years of age. Our review finds that music therapy has been widely used in patients with various diseases, including Alzheimer’s disease, anxiety, and arthritic pain. The number of clinical trial registrations has increased yearly. However, there is a need for future studies to take into consideration different participant groups. Moreover, the sharing of knowledge that is related to the management of

clinical trial quality between researchers and pharmaceutical companies is an internationally important issue.

ACKNOWLEDGMENTS

This research received the support of a 2015-2016 health labor science research grant (Practical Research on Medical Technology, Clinical Research Promoting Research project), titled "A study on diffusion and enlightenment of clinical trials and research for the nation and patients" (H27-Clinical research-general-001) from the Ministry of Health, Labor and Welfare, Japan.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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Appendix

Appendix: National Registries Included in the International Clinical Trials Registry Platform (ICTRP).	
2004	<ul style="list-style-type: none"> ● Mexico Statement on Health Research (http://www.who.int/rpc/summit/en/) ● The Ottawa Statement, International Committee of Medical Journal Editors. ● Clinical Trial Registration (ICMJE) ● Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases (International Federation of Pharmaceutical Manufacturers Associations, IFPMA)
2005	<ul style="list-style-type: none"> ● WHO/ International Clinical Trials Registry Platform (ICTRP) ● ClinicalTrials.gov ● Australian New Zealand Clinical Trials Registry (ANZCTR)
2006	<ul style="list-style-type: none"> ● ISRCTN.org
2007	<ul style="list-style-type: none"> ● Clinical Trials Registry-India (CTRI) ● Chinese Clinical Trial Register (ChiCTR) ● The Netherlands National Trial Register (NTR) ● The Clinical Trials Register (GermanCTR)
2008	<ul style="list-style-type: none"> ● Sri Lanka Clinical Trials Registry (SLCTR) ● Japan Primary Registry Network (JPRN)
2009	<ul style="list-style-type: none"> ● Cuban Public Registry of Clinical Trials (RPCEC) ● Iranian Registry of Clinical Trials (IRCT) ● Pan African Clinical Trial Registry (PACTR)
2010	<ul style="list-style-type: none"> ● Brazilian Clinical Trials Registry (ReBec) ● Clinical Research Information Service (CRIS)- Republic of Korea
2011	<ul style="list-style-type: none"> ● EU Clinical Trials Register (EU-CTR)
2013	<ul style="list-style-type: none"> ● Thai Clinical Trials Registry (TCTR)