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Ten years of clinical trial registration in a resource-limited setting: Experience of the Sri Lanka clinical trials registry

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Abstract

Aim: We describe our experience of the first 10 years at the Sri Lanka Clinical Trials Registry (SLCTR).

Methods: We analyzed all trial records of the SLCTR over the study period. We collected information regarding trial characteristics and completeness of data entry in the SLCTR data set.

Results: During the study period, 210 trials (63% of all applications) were registered with the SLCTR. The number of registered trials showed an increasing trend over the years. All trial registrations had complete entries for all the data fields studied. Only 17.6% of the trials were registered retrospectively. All the registered trials were interventional studies, and the majority (87.6%) were randomized controlled trials. A significant proportion of trials (28.6%) were on noncommunicable diseases, and 12.4% were on pregnancy and its outcomes. Several trials (9.5%) were international collaborative studies. A majority of the Principal Investigators (70.9%) were affiliated to a university. Most of the studies (41.9%) were self-funded by the investigators. Details of ethics review committee approval were available for 96.7% of registered trials. Over a third of the registered trials (37.1%) had completed recruitment at the time of analysis. A majority of the trials (72.8%) had updated trial data since registration.

Conclusions: There is a steady increase in the number of trials registered at the SLCTR. Complete entries for all the data fields were seen in all trial registrations. The SLCTR has made a positive contribution to the emergence of a healthy clinical research environment in Sri Lanka.

KEYWORDS

biomedical research, clinical trials, randomized controlled trials, registries, resource-limited setting, Sri Lanka

1 | INTRODUCTION

Several important initiatives taken over the last few years have contributed to the increasing acceptance of prospective trial registration as a step toward improving transparency in the conduct and reporting of clinical trials. The first major landmark on the road to prospective trial registration was the statement by the International Committee of Medical Journal Editors (ICMJE) in August 2004 that "all clinical trials involving human subjects should be prospectively registered before they will be considered for publication."[1] This stand was supported by the Mexico Statement on Health Research from the Ministerial Summit on Health Research in November 2004 that called upon "all major stakeholders, facilitated by WHO secretariat, to establish a platform linking a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials."[2] This call was converted into action by the World Health Assembly in May 2005 with the resolution WHA 58.34 that requested the Director General of the World Health Organization (WHO) "to pursue with interested partners the development of a voluntary platform to link clinical trials registers."[3] Following this, the International Clinical Trials Registry Platform (ICTRP) was established by the WHO in 2006, and its Registry Network and Search Portal were launched in May 2007.[4] In October 2008, the 59th World Medical Association General Assembly amended the Declaration of Helsinki with the revision that "Every

clinical trial must be registered in a publicly accessible database before recruitment of the first subject."[5]

Sri Lanka was one of the first countries to embrace the concept of clinical trial registration. The Sri Lanka Clinical Trials Registry (SLCTR) was established in November 2006, and the first trial was registered in February 2007. This was the first clinical trials registry in South Asia, and the first from a resource-limited country, to commence operations. The SLCTR was recognized as a Primary Registry of the Registry Network of the WHO-ICTRP in March 2008, being the fourth Primary Registry to join the Network. It remains as one of the few registries from a resource-limited setting. The establishment of the SLCTR and its early progress have been previously described.[6–9] The SLCTR completed 10 years in November 2016, and we report our experience over this period.

2 | METHODS

We analyzed all trial records of the SLCTR[10] from its inception (November 2006) to 31 October 2016. We excluded trial applications that were pending registration or were rejected. We analyzed entries in all the data fields in the WHO-ICTRP Trial Registration Data Set (TRDS),[4] and additional data regarding availability of a Universal Trial Number (UTN), timeliness of registration (prospective/retrospective), number of participating centers, countries of trial recruitment, state of ethics review approval, trial progress, and submission of trial updates and protocol changes. Data was entered into a custom designed spreadsheet and analyzed using MS Excel 2016. Our study was descriptive, and data has been summarized as numbers and percentages. Three study investigators (AdeA, MW, NS) extracted trial records, entered and cross-checked data, and analyzed the data.

3 | RESULTS

During the 10-year period under study, the SLCTR received 324 applications. Of these, 69 (21.2%) were rejected, and 21 (6.5%) were withdrawn by the applicant. Causes for rejection were application after trial commencement (i.e., for retrospective registration; $n = 39$), noninterventional studies ($n = 5$), incomplete applications ($n = 4$) and prolonged noncommunication by the applicant following submission ($n = 21$). There were 24 (7.4%) applications pending approval for registration. A total of 210 trials (64.8% of all applications) were registered with the SLCTR, and we describe their details.

The number of registered trials has gradually increased over the years (Figure 1). All the trials were interventional studies, and had complete entries for all 20 data fields in the ICTRP-TRDS and the additional SLCTR data fields. Less than a fifth (17.6%) of the registered trials was registered retrospectively. Of 172 trials registered in the SLCTR after the introduction of the Universal Trial Number (UTN) by the WHO in June 2009, 59 (34.3%) had obtained an UTN. There were 17 trials that had been registered with another clinical trial registry, of which 16 were multicountry studies. All registered trials had confirmed receipt of Ethics Review Committee approval, and 203 (96.7%) had submitted documentation of the approval status.

Of the 210 trials, 164 included both male and female participants, whereas 43 trials were conducted only in females and 3 only in males. A majority of the studies were in adults ($n = 188$), and 18 had child participants under the age of 12 years. Four studies did not have an age limitation. The most commonly studied health conditions were diabetes and other noncommunicable diseases (heart disease, hypertension, liver disease, metabolic diseases and cancer), which accounted for 60 (28.6%) of the registered trials. A total of 30 (14.3%) trials recruited women during pregnancy or in the early post-partum period, and 26 (12.4%) trials were directly related to pregnancy and its outcomes (Table 1). A majority of the interventions used ($n = 85$, 40.5%) were medicinal drugs, 41 (19.5%) were educational or behavioral changes, and 28 (13.3%) were herbal or plant products (Table 2).

Most of the registrations were randomized controlled trials ($n = 184$, 87.6%), and there were equal numbers ($n = 13$, 6.2%) of nonrandomized controlled trials and single arm studies. There were 60 (28.6%) double-blinded studies, 37 (17.6%) were single-blinded, and 113 (53.8%) did not conceal allocation. Standard treatment was the commonest type of control used ($n = 84$, 40%), 55 (26.2%) of the trials

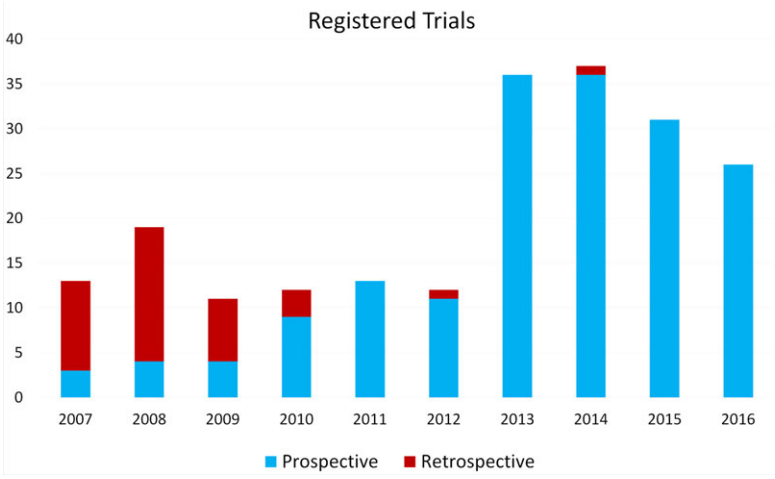

FIGURE 1 Number and timing of trials registered with the SLCTR

TABLE 1 Common diseases/health conditions studied

Disease/health condition	Number	Percentage
Diabetes (including gestational)	31	14.76
Pregnancy and its outcomes	26	12.40
Infections/infestations (including vaccines)	15	7.14
Mental health problems (including addictions)	14	6.67
Cardiac disease (including hypertension)	13	6.19
Musculoskeletal problems	12	5.71
Snakebite	8	3.81
Pain management	7	3.33
Cancer	6	2.86
Nonalcoholic liver disease	6	2.86
Poisoning	6	2.86
Metabolic diseases	4	1.9
Other disease/health conditions	62	29.5

TABLE 2 Characteristics of registered trials

	Number	Percentage
Intervention		
Medicinal drug	85	40.5%
Education/behavior change	41	19.5%
Procedure	30	14.3%
Herbal/plant product	28	13.3%
Nutritional supplement	15	7.1%
Drug vs. procedure	6	2.9%
Device	3	1.4%
Device vs. drug	1	0.5%
Drug/nutrition supplement	1	0.5%
Study design		
Randomized controlled trial	184	87.6%
Single arm study	13	6.2%
Nonrandomized controlled trial	13	6.2%
Masking		
Masking not used	113	53.8%
Double-blinded	60	28.6%
Single-blinded	37	17.6%
Control		
Standard treatment	84	40.0%
Active control	55	26.2%
Placebo	51	24.3%
Uncontrolled	13	6.2%
Dose comparison	7	3.3%
Purpose		
Treatment	127	60.5%
Prevention	29	13.8%
Supportive care	21	10.0%
Other	15	7.1%
Health services research	12	5.7%
Basic science	6	2.9%

used active controls and 51 (24.3%) used placebo. The purpose of most interventions (127, 60.5%) was treatment, 29 (13.8%) studies were on prevention of disease or complications, and 21 (10%) were on supportive care (Table 2).

A large majority of the registered trials ($n = 182$, 86.6%) were conducted only in Sri Lanka, and there were several international multicenter trials with Sri Lankan collaboration ($n = 20$, 9.5%). Most of the Responsible Registrants/Principal Investigators (149, 70.9%) were affiliated to a university either in Sri Lanka or in a foreign country, 40 (19%) were from a hospital setting, and 13 (6.2%) were affiliated with nonhospital institutions of the Ministry of Health, Sri Lanka. Only 3 (1.4%) Responsible Registrants were directly affiliated to the pharmaceuticals industry (Table 3). Most trials were self-funded by the investigators ($n = 88$, 41.9%), and 29 (13.8%) received pharmaceutical industry funding. Other trials were funded by grants from government and academic institutions (Table 3).

Over a third of the registered trials ($n = 78$, 37.1%) had completed recruitment at the time of analysis, and 25 (11.9%) had data regarding publications related to the trial record available at the SLCTR. Sixty-five trials (31%) were still recruiting, and 28.1% ($n = 59$) were pending recruitment of the first subject (Table 4). There were 153 trials (72.8%) with at least one trial update since registration. Nineteen trials (9%) had submitted protocol changes to the SLCTR.

TABLE 3 Affiliations of registrants and sources of funding

	Number	Percentage
Affiliation of responsible registrant/principal investigator		
University (Sri Lanka)	141	67.1%
Hospital (Sri Lanka)	40	19.0%
Ministry of Health (Sri Lanka)	13	6.2%
Foreign university	8	3.8%
Foreign healthcare institution	2	1.0%
Private healthcare institution (Sri Lanka)	3	1.4%
Pharmaceutical industry	3	1.4%
Source of funding		
Self-funded	88	41.9%
Academic research grant	41	19.5%
Pharmaceutical industry	29	13.8%
International research grant	27	12.9%
Government research organization	25	11.9%

TABLE 4 Status of registered trials

Recruitment status	Number	Percentage
Complete	78	37.1%
Recruiting	65	31.0%
Pending	59	28.1%
Terminated	5	2.4%
Suspended	2	1.0%
Other	1	0.4%

4 | DISCUSSION

We describe the experience of clinical trial registration at the SLCTR during its first 10 years. This is the first report of a clinical trial registry over such a long period. The steady increase in the number of trial registrations over the years is an encouraging trend. Several factors may have contributed to this, such as better awareness on the need for trial registration, improved visibility of the SLCTR and increasing acceptance of the SLCTR by the scientific community. This mirrors the global trend of progressive increase in trial registration reported previously.[11] Another healthy trend observed is the increasing number of trial applications from overseas researchers over the years. Although the SLCTR is a national registry, it welcomes trial applications from foreign applicants and international trial collaborations.

Analysis of all the trial records registered over a 10-year period is the main strength of our study. We have evaluated entries regarding all the data fields of the SLCTR data set, which includes the 20-item TRDS of the ICTRP, whereas previous studies have focused only on a few selected items of the TRDS.[12–16] The main limitation is the relatively low number of trial records in our study; the SLCTR contributes only a small proportion of trials registered at the ICTRP.[11] The lack of a robust trial industry in the country and of a regulatory framework for mandatory registration are likely to be the main reasons for this.

All the registered trials were interventional studies, as the SLCTR does not register observational studies. Registry policies on registration of observational studies vary within the ICTRP Registry Network; some of the Primary Registries accept observational studies for registration, others do not. The current version of the TRDS of the ICTRP is designed for interventional studies and is not ideally suited to record information from observational studies. The wide variability of observational study designs adds to this difficulty. A common data entry template for observational studies that can be used by all registries would clearly enhance the uniformity and quality of data collection.

The number of retrospective registrations at the SLCTR has declined over the years (Figure 1). Several trials were registered retrospectively by the SLCTR during an initial grace period, when the scientific community in the country was informed of the need for trial registration and requested to register trials in progress. Since 2011, there has been only one retrospective registration (where trial recruitment preceded the registration date due to an inadvertent delay by the SLCTR). The current policy of the SLCTR is to register only prospective trials. In spite of the drive for prospective registration, about half of the trials in the ICTRP Registry Network continue to be retrospectively registered.[13,16] Although enabling retrospective registration would ensure access to details of trials that may otherwise remain undisclosed, it may also allow researchers to register only positive ones after trial completion, thus undermining the twin principles of transparency and complete trial disclosure that underpin the drive for prospective trial registration.

These data provide important details regarding the current clinical trial scenario in Sri Lanka. Funding by the investigators was the main funding mechanism, industry sponsored trials were few, and affiliations of Principal Investigators to the pharmaceutical industry were uncommon (Table 3). These results point to an encouraging trend of investigator initiated academic trials. Many trials studied herbal or plant products, which is likely to reflect the continued acceptance of the alternative Ayurveda system of medicine in the country.

Previous studies have highlighted many inadequacies in reporting of the WHO-TRDS minimum data set;[13–17] these reports point to the difficulties faced by clinical trial registries across the world in maintaining quality of trial registration data. The SLCTR has evolved over the years in a constant endeavor to meet the stringent standards expected of an international clinical trials registry.[18] Quality improvement measures have included development and updating of standard operational procedures, a complete overhaul of the website with added security in 2012, scrutiny of all trial applications for inadvertent duplicate registration, maintenance of audit trails for all trial applications and internal audit. Flags are used in the website to indicate retrospective registration, protocol changes, outstanding progress reports, duplicate registration and trial completion. Links are provided to access results publications. The SLCTR insists on certain practices to ensure data quality. All trial applications, after initial scrutiny by the Administrative Assistant, are reviewed online by a technical expert committee (the SLCTR Committee). Trials are registered only if documentary evidence of ethics review committee approval is submitted, in order to ensure authenticity of the application. Contact information is verified by telephone and email communications before processing trial applications. If the Principal Investigator is a junior researcher, a senior collaborator is required to be named a Guarantor for the study. Regular email reminders are sent requesting progress reports, information regarding protocol changes, and details of results presentations and publications.

The SLCTR has continued to meet its key obligation of providing a national platform for clinical trial registration, while facing the many challenges posed by resource constraints inherent to a low-middle-income country. The difficulties in establishing and maintaining a clinical trials registry in resource-limited settings are well recognized.[9,12,19–21] The SLCTR was established without any external support or international funding, and the Ministry of Health remains its main financial provider. Expenses are kept to a minimum; the members of the SLCTR Committee work in an honorary capacity, and the main expenditures are for website maintenance and payment of salary for the Administrative Assistant. Costs are likely to escalate, and more staff will be needed to meet the increasing demands of ensuring data integrity.

Awareness on trial registration is a key element in the drive for complete trial registration at a national level. The SLCTR has regularly engaged in promoting awareness of prospective trial registration in the country. These activities include several lecture presentations at national and regional scientific meetings across the country, publication of journal articles,[6–9] regular updates in newsletters of professional organizations, and research presentations at national scientific meetings.

The SLCTR has been in constant dialogue with relevant stakeholders in Sri Lanka, and has consistently lobbied for the recognition of prospective trial registration as a matter of national health policy. From its inception, it has worked in close collaboration with the Ministry of Health. These efforts in advocacy have resulted in various policy measures that would lead to increasing compliance with trial registration in

the country. The guidelines for the conduct of clinical trials in Sri Lanka issued by the Ministry of Health states that "A clinical trial may be initiated in Sri Lanka only after registering the study in the Sri Lanka Clinical Trials Registry."[22] Only a limited number of ethics review committees accredited by the Ministry of Health are currently authorized to grant ethical approval for clinical trials in Sri Lanka, and they request all applicants to register with the SLCTR before commencement of a clinical trial. A draft Clinical Trials Act that would provide much needed regulatory legislation is awaiting cabinet approval, and this is expected to mandate that every clinical trial conducted in Sri Lanka is registered with the SLCTR.

5 | CONCLUSION

The Sri Lanka Clinical Trials Registry has completed 10 years of leading the march toward prospective trial registration in Sri Lanka. It has successfully faced the challenge of creating a sustainable mechanism for trial registration in a resource-limited setting. In addition to providing a national repository for clinical trial records, it has been in the forefront of the national endeavor to create a healthy environment for the conduct of safe and ethical clinical trials in the country. The 10-year landmark is only a milestone in a long journey ahead, and the SLCTR needs to prepare itself for the fresh challenges that will be posed by the changing landscape of clinical trials in Sri Lanka.

CONFLICT OF INTEREST

None.

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