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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Twenty plus years

Introduction

It has been 20+ years since initiation of systems to register trials as represented by launch of ClinicalTrials.gov (aka CT.gov) and ISRCTN in 2000 and several since with launch of the World Health Organization (WHO) International Clinical Trials Registration Platform (ICTRP).

The push for registration came in the 1980s and 90s from trialists concerned with large swaths of unpublished trials and publication bias. A presentation on behalf of a panel at a plenary session of the 8th annual meeting of the Society for Clinical Trials in Atlanta, Georgia (May 20, 1987) pushed for registration.[1]

The CT.gov was created as a result of the Food and Drug Administration Modernization Act of 1997.[2] The act required the U.S. Department of Health and Human Services (HHS), through the National Institutes of Health (NIH), to establish a registry of clinical trials of federally and privately funded trials conducted under investigational new drug applications.

Highlights in the history of registration (from https://clinicaltrials.gov/ct2/about-site/history) are listed below.

1997 U.S. Congress passes law requiring registration of trials
2000 CT.gov and ISRCTN registration sites launched
2004 WHO (Mexico City, November 2004) called for establishment of a network of clinical trials registers
2005 International Committee of Medical Journal Editors (ICMJE) require registration of trials as condition for publication [3] (*member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication.*)
2006 WHO establishes registration policy; launches ICTRP
2008 Declaration of Helsinki Revision promotes trial registration and results dissemination
2013 European Medicines Agency expands clinical trial database to include summary results

Registration sites

Table 1: Clinical trials registries

	Registry	Name	Custodian	Yr launched	Trials reg	As of
1	CT.gov	ClinicalTrials.gov	NIH Library of Medicine	2000	322,393	31 Oct 2022
2	ISRCTN*	ISRCTN	BMC; Springer Nature	2000	20,151	5 Nov 2022
3	ANZCTR	Australian New Zealand Clinical Trials Registry	WHO ICTRP	2005	29,299	2 Nov 2022
4	SLCTR	Sri Lanka Clinical Trials Registry	WHO ICTRP	2006	?	
5	ChiCTR	Chinese Clinical Trial Registry	WHO ICTRP	2007	37,264	2 Nov 2022
6	CTRI	Clinical Trials Registry India	WHO ICTRP	2007	?	
7	DRKS	German Clinical Trials Register	WHO ICTRP	2008	7,959	2 Nov 2022
8	IRCT	Iranian Registry of Clinical Trials	WHO ICTRP	2008	?	
9	PACTR	Pan African Clinical Trials Registry	WHO ICTRP	2009	?	
10	CRiS	Clinical Research Information Republic of Korea	WHO ICTRP	2010	5,749	2 Nov 2022
11	RPCEC	Cuban Public Registry of Clinical Trials	WHO ICTRP	2011	?	
12	EU-CTR	EU Clinical Trials Register	WHO ICTRP	2011	?	
13	ReBec	Brazilian Clinical Trials Registry	WHO ICTRP	2012	?	
14	TCTR	Thai Clinical Trials Registry	WHO ICTRP	2013	?	
15	REPEC	Peruvian Clinical Trials Registry	WHO ICTRP	2016	?	
16	jRCT	Japan Registry of Clinical Trials	WHO ICTRP	2018	2,574	3 Nov 2022
17	LBCTR	Lebanese Clinical Trials Registry	WHO ICTRP	2019	129	3 Nov 2022
18	NTR	Netherlands Trial Registry	WHO ICTRP	Closed	--	--
					425,518	

* Originally International Standard Randomised Controlled Trial Number; however, scope of registry widened to include other designs; now simply ISRCTN

Getting counts from ICTRP registration sites is problematic. Sites are not user friendly. Counts have to be requested. The question marks are due to “no reply” (some several) to e-mail requests.

Discussion

So where are we after twenty plus years of registration? Registration is voluntary so we have no way of knowing how many trials are not registered or how many are registered more than once on separate sites. Work by van Valkenhoef, Loane and Zarin give an estimate around 5% for duplicate registrations.[4]

There is evidence suggesting registrations are reaching steady state (Table 2). The number started in 2020 was just 20% of the number started in 2015.

Table 2: Five year changes in CT.gov registrations by year started

Year started	No. started	5 yr Change
2000	1,872	
2005	7,727	412.77%
2010	13,408	173.52%
2015	18,820	140.36%
2020	22,480	119.45%

But, regardless of growth of registration, evidence suggests that most published trials are not registered (Table 3). The NLM expanded indexing in MEDLINE to include CT.gov registration numbers in 2005; expanded to include registrations in ISRCTN in 2006, and expanded in 2014 to include most other registries represented in the ICTRP. Only 30% of all full length publications indexed to RzT were published.

Table 3: Full length MEDLINE publication type "randomized controlled trial" (RzT) by registration status

Year published	Indexed RzT	Registered in CT.gov or other WHO registries	Not registered	% not registered
2010	20,658	3,209	17,449	84.47%
2015	27,636	7,846	19,790	71.61%
2020	28,274	7,666	20,608	72.89%

In 2007 the FDA required (for trials under FDA control) investigators post summary tabular results (without comment) to registrations within one year of completion of trials with penalties up to $10,000 a day for every day late beyond the one year time period.

Only fractions of investigators post results. For 302,682 trials logged as completed on or after 1 Jan 2008, only 50,650 had results posted (as of 9 Nov 3022). Part of the problem is the time from completion (defined in the regulation by when the last person is seen) to posting is too short for capture of essential data and for editing.

Personally I am an agnostic regarding posting. It is hard to imagine how tabular postings without comment can be helpful. I might change my mind if someone can show me publications involving uses of posted results.

The primary reasons for registries are to help people find trials suitable to join and to aid researchers tracking the state and nature of trials. For the latter, one needs a fixed frozen dataset for analyses. At present the only dataset where that form of fixing is possible is with CT.gov; available via the CTTI-AACT (Clinical Trials Transformation Initiative-Aggregate Content of ClinicalTrials.gov). The CTTI-AACT was founded in 2007 by Judith Kramer, Robert Califf, and Rachel Sherman, Duke University, with funding from the FDA.

The logical fix would be to combine the registries into a single registry, were it not for nationalist pride. Even if merging is out of the question, the glossaries underlying registries should be standardized. That standardization is necessary is illustrated in Table 4 with start and end dates for CT.gov and selected registries. To standardize the stake holders would need to meet to agree on glossary changes.

Table 4: Glossary term variations for start and end date

	Registry glossary term	Definition
CT.gov	"Study start date"	The actual date on which the first participant was enrolled in a clinical study. The "estimated" study start date is the date that the researchers think will be the study start date.
	"Study completion date"	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events.
ISCRTN	"Overall trial start date"	A study starts when you begin planning the design of the study and developing the protocol. The overall start date should precede the ethics approval date and the recruitment start date.
	"Overall trial end date"	The end date of your study should be stated in your study protocol. In many cases, it is expected to be the last date that data is collected.
EudraCT	"Start date"	The 'start date' on the EU CTR refers to the date in which the study was authorised to proceed (latest date between the NCA approval and the Ethics Committee opinion dates). For trials marked as "outside of EU/EEA" (see question 94.), it is the date in which the study was uploaded in EudraCT by the third country data provider
	"Date of global end of trial"	This is the date on which the Clinical Trial is ended in all countries.
ANZCTR	"Date of first participant enrolment"	This is defined as the date of randomisation of the first participant for randomised trials. For non-randomised studies, it is defined as the date that the first participant commences treatment/intervention/ exposure. Anticipated date is mandatory if recruitment has not started. Actual date is mandatory once recruitment has started.
	"Date of last participant enrolment"	The anticipated date that recruitment into the study will cease. The actual date that the final participant was enrolled into the study. This is mandatory for studies which have completed recruitment.

Comments

Registries are for aiding people looking for trials to join and for researchers interested in tracking the state and nature of trials. Registries to be useful should be free and open to all. As it is now the only register where this is the case is for CT.gov.

Presently about 70% of all trials are registered on CT.gov. The other 30% are scattered across 17 registries comprising the ICTRP. Those registries are not amenable to analysis without systems for freezing data akin to that used for analyses of counts in CT.gov (Transformation Initiative-Aggregate Content of ClinicalTrials.gov (CTTI-AACT); developed by Judith Kramer, Robert Califf, and Rachel Sherman, Duke University, with funding from the FDA).

The ICMJE announcement specifies that registrations numbers should be the last entry in abstracts. Unfortunately, not even signatories to the 2004 announcement follow their own recommendation. Some journals, for example The Lancet and Ann Intern Med publish registration numbers in the middle of abstracts. Frustrating as that variation is for anyone reviewing abstracts for registration numbers, it is minor to when numbers are buried in bodies of manuscripts without mention anywhere in abstracts.

It would be useful if the ICMJE did periodic reviews of member journals to identify journals not complying with the posting recommendation, with reminders of the posting requirement.

The custodians of CT.gov regularly screen for publications from registered trials and, when found, post reference citations to associated registrations. This means users of CT.gov can access publications from information posted in registrations.

Also it would be useful to expand the search algorithm available via CT.gov by adding a search term “Study publication”. The addition would allow users to track publication records of registered trials over time, for example, by getting a count of trials with publications completed on or after 1 Jan 2015 compared to registrations of trials completed 1 Jan 2010 through 31 Dec 2014.

References

1. Report from the Panel on the Case for Registers of Clinical Trials at the Eighth Annual Meeting of the Society for Clinical Trials; writer Kay Dickersin; panelists Thomas C. Chalmers, R. John Simes, Kay Dickersin, Jean-Pierre Boissel, Curtis L, Meinert; **Controlled Clinical Trials** 976-81, 1988

2. 105th U.S. Congress (April 23, 1997). "H.R.1411: Food and Drug Administration Regulatory Modernization Act of 1997". U.S. House of Representative Bill Summary & Status. Library of Congress

3. Clinical trial registration: A statement from the International Committee of Medical Journal Editors (Catherine D DeAngelis, Jeffrey M Drazen, Frank A Frizelle, Charlotte Haug, John Hoey, Richard Horton, Sheldon Kotzin, Christine Laine, Ana Marusic, A John P M Overbeke, Torben V Schroeder, Hal C Sox, Martin B Van Der Weyden); **JAMA** 2004 Sep 15;292(11):1363-4.

4. Previously unidentified duplicate registrations of clinical trials: An exploratory analysis of registry data worldwide; Gert van Valkenhoef , Russell F Loane, Deborah A Zarin; **Syst Rev**; 2016 Jul 15;5(1):116.