June 11, 2012

Members,
Standing Committee on Social Affairs, Science and Technology

At the conclusion of our respective hearings before the Standing Committee on Social Affairs, Science and Technology in May 2012, you invited each of us to provide additional information and best practices regarding transparency and accountability in the clinical trials process and regulatory system. Further research and reflection on whether Canada should create its own clinical trials registry and what level of oversight should be provided to ensure compliance have led us to the following recommendations.

In our view, Canada should not create its own registry, however, clinical trials registration should be legally required, and a government regulatory agency (not a federal research funding agency, or any other agency that reports to a federal research funding agency) should be empowered to strictly enforce compliance with that requirement.

Attached is a ~~one~~ two page summary of our recommendations designed to ensure meaningful transparency and accountability in clinical trials and an Appendix that provides a comparative review of select documents.

Sincerely

Françoise Baylis, PhD, FRSC, FCAHS
Professor and Canada Research Chair in Bioethics and Philosophy
Dalhousie University

Matthew Herder, BSc, LLB, LLM, JSM
Assistant Professor, Faculties of Medicine and Law
Dalhousie University

Trudo Lemmens
Associate Professor
Scholl Chair in Health Law and Policy
Faculty of Law
University of Toronto

Recommendation 1: It should be mandatory for ALL clinical trials (including Phase 1 trials as well as observational studies) that are conducted in Canada or that are conducted abroad by Canadians whether in the role of principal-investigator or co-investigator to be included in a clinical trial registry.

> There is an abundant literature in support of the argument that it is important from a public health perspective to register all trials, and not only phase 2 and 3.[1]

Recommendation 2: Canada should not create an independent clinical trials registry, but should require Canadian principal and co-investigators to register in an existing registry(ies).

> Creating a Canadian registry would be labour-intensive, time-consuming, and costly.

Recommendation 3: There should be a limited number of registries in which Canadian principal and co-investigators can register trials.

> One of the benefits of a registering clinical trials is having access to "a complete view of research." This accessibility can be hindered if there is an excessive number of registries in which data might be stored. This explains the need to limit the number of eligible registries. The regulatory agency responsible for oversight of registration and results disclosure should identify the limited number of eligible registries based on criteria for content, quality and validity, accessibility, unique identification, technical capacity and administration.

Recommendation 4: Canada should create a mandatory results reporting requirement in connection with the trial registration obligation.

> Results reporting is the logical continuum of the clinical trial registration requirement. Both are essential to obtain meaningful transparency.[2] The U.S. FDAAA requires both trial registration and results reporting.[3] Research ethics guidelines such as the the Helsinki Declaration[4] and the Tri-Council Policy Statement[5] also require both.

Recommendation 5: The mandatory registration and results reporting requirement should be entrenched in law and clear penalties for non-compliance should be outlined in the legislation.

> Studies indicate that in the absence of strict penalties, a substantial number of studies are not registered.[6] The U.S. FDAAA imposes penalties of up to $ 10,000 per violation per day.[7]

Recommendation 6: A government agency should be empowered to monitor compliance with the clinical trials registration requirement and results reporting requirement and enforce penalties in the event of non-compliance.

Recommendation 7: Canada should do more than simply catch up with other jurisdictions. Canada should reclaim its leadership role.

> In October 2004 the Canadian Institutes of Health Research hosted a meeting to foster international consensus on trial registration. This resulted in the development of what is known internationally as the first "Ottawa Statement." Two further statements were developed on the basis of this first statement. Part 1 highglights key principles for registration of clinical trials,[8]

Part 2 addresses the implementation of these principles, and Part 3 addresses results reporting.[9] Canada should aim to be at the forefront of the current initiative.

Consistent with expert opinions and policy proposals in place in the United States and Europe, Canada should move beyond clinical trial registration and mandatory results reporting to require access to full protocol and raw data.[10] Only in this way can the health and welfare of Canadians be sufficiently protected.

See Appendix A for a brief comparative review of select policies on clinical trials registration.

APPENDIX A

The following tables clearly illustrate the weaknesses of the current situation in Canada (TCPS2), and show the incremental benefits of other approaches, two of which are Canadian (CIHR Policy and Ottawa Statement). This data can be used to inform and implement the above recommendations.

Guiding Principles for trial registration and results disclosure

PRINCIPLE	JUSTIFICATION
Transparency and accessibility	*Registering of trials is essential to make sure all results are publicly available (to avoid the selective reporting of trial results)*
Integrity and accountability	*Registering of trials is essential to make sure that ethical obligations to participants are met (e.g., avoid unnecessary duplication and increased burden on participants; identify gaps in research)*
Advancement of science and innovation	*Registering of trials will facilitate the effective and timely development of evidence-based medicine*

Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, CIHR, NSERC, and SSHRC, December 2010 http://www.pre.ethics.gc.ca/pdf/eng/tcps2/TCPS_2_FINAL_Web.pdf

STRENGTHS	WEAKNESSES
Clinical trial registration [Art 11.3] • Register all clinical trials in a recognized and easily web-accessible public registry • Registry must be compliant with WHO or ICMJE criteria as of Nov. 2010 • Provide REB with the name of registry and the identification number	• The standard of "recognized and easily web-accessible" is too low. E.g., every univeristy could have its own registry and comply with this standard • Potential for multiple registrations • No central repository of registration information as information is reported to local REB
Reporting (disclosure) of trial results [Art. 11.12] • REBS are to ensure that researchers publish or otherwise disseminate clinical trials data	• The standard "otherwise disseminate" is too low. E.g., a letter to all research participants and nothing else might satisfy this standard. • The reporting requirement makes no mention of including relevant data in a registry; falsely assumes that an REB does this kind of work; no provisions for public reporting as in the superceeded CIHR policy. **No requirements re:** • Public disclosure of trial information during trial • Data retention
Monitoring and adherence • Adherence to TCPS 2 required as a condition of funding	**Only applies to CIHR, NSERC and SSHRC funded researchers and institutions**

• The 'Panel on Responsible Conduct of Research' may review allegations of breach of an Agency policy in accordance with 'Tri-Agency Framework: Responsible Conduct of Research'	• 'Tri-Agency Framework: Responsible Conduct of Research' makes no mention of clinical trial registration. • There has never been a serious sanction for alleged or confirmed allegation of breach of Agency policy

CIHR "Policy on registration and results disclosure of controlled and uncontrolled trials funded by CIHR" *Google's cache of http://www.cihr-irsc.gc.ca/e/42831.html on March 17, 2011*

Strengths	Weaknesses
Prospective registration of trials • Register all CIHR funded trials in a WHO/ICMJE endorsed registry • Registration must include, at least, the WHO Trial Registration Data Set • Preferably register the trial in only one WHO primary registry or registry acceptable to ICMJE • Provide CIHR with the name of registry and the identification number	**Only applies to CIHR grantees**
Public disclosure of trial information during trial • Information in registry to be updated annually • Report major protocol changes to CIHR and the registry • Report early stopping or termination of a trial to CIHR and the registry	**Only applies to CIHR grantees**
Public reporting (disclosure) of trial results • Submit final report to CIHR • Publish trial results in an open access journal or archive in open access repository (include adverse events or harms in publication) • Submit trial results to publicly accessible databank (include reporting of adverse events or harms)	**Only applies to CIHR grantees**
Data retention • Consistent with Health Canada requirement, retain original micro-level and metadata for 25 years	**Only applies to CIHR grantees**
Monitoring and adherence • The 'Panel on Responsible Conduct of Research' may review allegations of breach of an Agency policy in accordance with 'Tri-Agency Framework:	**Only applies to CIHR, NSERC and SSHRC grantees** • 'Tri-Agency Framework: Responsible Conduct of Research' makes no mention of clinical trial

Responsible Conduct of Research'	registration. • There has never been a serious sanction for alleged or confirmed allegation of breach of Agency policy

The Ottawa Statement, Part One: Principles for international registration of protocol information and results from human trials of health-related interventions
http://ottawagroup.ohri.ca/statement.html

STRENGTHS	WEAKNESSES
Prospective registration of Trials • Protocol information and results from all trials – regardless of topic, design, outcomes, or market status of interventions examined – should be registered and publicly available	**Statement of principle only; non-binding**
Elements of registration • Obtaining an internationally unique identification number, • Registering the original protocol approved by the IRB/IEC along with subsequent amendments • Registering the trial results	**Statement of principle only; non-binding**
Assignment of Unique ID • Every trial should have a Unique ID from a single international source. To facilitate efficient searching, multiple national or regional registers should be linked.	**Statement of principle only; non-binding**
Oversight role for REB • Responsible to ensure: (i) trial has a unique ID; (ii) relevant documents registered prior to enrolment; (iii) amendments reported and registered; (iv) unique ID appears on consent forms; and (v) encouraging publication of trial results	**Statement of principle only; non-binding**
Policing and sanctions • Trial registration should be a legal requirement, with enforcement of meaningful sanctions against those found to be in violation	**NA**

Food and Drug Administration Amendments Act (FDAAA) 2007, Section 801

STRENGTHS	WEAKNESSES

Prospective registration of trials • Protocol information for phase 2 – 4 interventional studies of drugs, biologics, or devices regardless of sponsor type (e.g. industry, government, or academic)	**Omits important studies from registration** - The World Health Organisation and International Committee on Medical Journal Editors both recommend registration of all interventional studies in human beings regardless of intervention type. - Also excludes observational studies.
Elements of registration[11] • Organization's unique protocol identification number • Secondary identifiers (e.g. from other registries) • Brief protocol title • Study type (interventional, observational, expanded access) • Whether FDA regulated intervention • Whether Section 801 trial • Investigational New Drug or Investigational Device Exemption information • Sponsor / Responsible Party information • Study Description (Brief description only) • Status (date protocol last verified, overall recruitment status, and study start date) • Study design (primary techniques used in protocol, primary purpose (e.g. treatment, prevention), study phase, intervention model, number of arms, primary and secondary outcomes, enrolment) • Eligibility criteria (gender, age limits, accepts health volunteers) • Protocol location, contact, and investigator information	
	Oversight role for REB not clearly defined in the FDAAA 2007
Public disclosure of "basic results", which consists of[12]	**Under-inclusive and potential for significant delay in disclosure**

• "Participant flow: Progress of research participants through each stage of a trial according to group, including the number of participants who dropped out of the clinical trial • Baseline characteristics: Demographic and baseline data for the entire trial population and for each group) • Outcome measures and statistical analyses: Aggregate results for each primary and secondary outcome measure according to group; statistical analyses as appropriate) • Adverse events: List of all serious adverse events; list of other (not including serious) adverse events in each group that exceed a frequency threshold of 5% within any group; both lists include adverse events, whether anticipated or unanticipated, and grouped by organ system • Key dates and contact information • Description of agreements, if any, between the sponsor and the principal investigator that would restrict dissemination of results by the principal investigator"	• Only products that are approved by the FDA are required to disclose results. • There is potential for significant delay: generally results must be made available within 12 months of trial completion or within 30 days of FDA approval **Does not require "full clinical reports"**
Policing and sanctions • Clear penalties are in place for non-compliance with the requirements of the FDAAA	**Some evidence suggests that the requirements are not being strongly enforced[13]**

REFERENCES

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[1] See e.g. Gøtzsche P, Why we need easy access to all data from all clinical trials and how to accomplish it, *Trials* (2011), 12:249 ("Easy Access"); Doshi P, Jefferson T & Del Mar C, The Imperative to Share Clinical Study Reports: Recommendations from the Tamiflu Experience, *PLoS Medicine* (2012), 9(4): e1001201 ("Imperative"); Dickersin K & Rennie D, Registering Clinical Trials, 290 *JAMA* 516 (2003) ("Registering Clinical Trials"); Rennie D, Trial Registration. A Great Idea Switches from Ignored to Irresistible, 292 *JAMA* 1359 (2004) at 1359 ("Trial Registration").

[2] Krleža-Jerić K et al, Prospective Registration and Results Disclosure of Clinical Trials in the Americas: A Roadmap Towards Transparency, 30(1) *Panam J Pub Health* 87 (2011) at 93; Lemmens T & Telfer C, Access to Clinical Trials Data and the Right to Health, 38 *Am J L & Med* 63 (2012) at 75. See also Rasmussen N, Lee K & Bero L, Association of Trial Registration with the results and conclusions of published trials of new oncology drugs, *Trials* (2009), 10:116.

[3] See sections 301 and 303, *Federal Food, Drug, and Cosmetic Act*, 21 U.S.C. § 331 and 21 U.S.C. § 333 (3)(A)(B), as amended by the *Food and Drug Administration Amendments Act (FDAAA) of 2007.*

[4] World Medical Association General Assembly, *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*, online at: <http://www.wma.net/en/30publications/10policies/b3/> (accessed: 25 Dec 2011).

[5] Canadian Institutes of Health Research, Natural Sciences and Engineering Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*, December 2010.

[6] Zarin DA et al, Trial Registration at ClinicalTrials.gov Between May and October 2005, 353 *New Eng J. Med* 2779 (2005); FDA Office of Special Health Issues, Department of Health and Human Services, FDAMA Section 113: Status Report on Implementation (August 2005), online at: <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ParticipatinginClinicalTrials/ucm143810.htm>; Gøtzsche P & Jørgensen AW, Opening Up Data at the European Drug Medicines Agency, 342 *Brit Med J* 1184 (2011); Trial Registration, *supra.*

[7] See note 3 *supra.* For an overview of the requirements and penalties, see *Registration at ClinicalTrials.gov: As Required by Public Law 110-85, Title VIII* (27 Oct 2009), online at: *<http://prsinfo.clinicaltrials.gov/s801-fact-sheet.pdf>*.

[8] Krleža-Jerić K et al, Principles for International Registration of Protocol Information and Results from Human Trials of Health Related Interventions: Ottawa Statement (part 1), 330 *Brit Med J* 956 (2005).

[9] Krleža-Jerić K, THE OTTAWA STATEMENT, PART 2 Principles of operationalisation for international trial registration (Draft, 6 Jan 2006), online at: <http://ottawagroup.ohri.ca/docs/draft_Ottawa_Statement_Part2.pdf>.

[10] Krumholz H, Open Science and Data Sharing in Clinical Research: Basing Informed Decisions on the Totality of the Evidence, *Circ Cardiovasc Qual Outcomes* (2012), 5:141; Easy Access, *supra*; Imperative, *supra*; Registering Clinical Trials, supra; Trial Registration, supra; Ross JS, Lehman R & Gross CP, The Importance of Clinical Trial Data Sharing: Toward More Open Science. *Circ Cardiovasc Qual Outcomes* (2012), 5:238; Spertus JA, The Double-Edged Sword of Open Access to Research Data, *Circ Cardiovasc Qual Outcomes* (2012), 5:143; Gøtzsche P, Strengthening and Opening Up Health Research by Sharing Our Raw Data, *Circ Cardiovasc Qual Outcomes* (2012), 5:236; The *PLoS Medicine* Editors, Best Practice in Systematic Reviews: The Importance of Protocols and Registration, *PLoS Med* (2011), 8(2): e1001009; Chang SM & Slutsky J, Debunking myths of protocol registration, *Systematic Reviews* 2012, 1:4 doi:10.1186/2046-4053-1-4, online at: <http://www.systematicreviewsjournal.com/content/1/1/4>; see also note 3 *supra.*

[11] ClinicalTrials.gov Protocol Data Element Definitions (Draft, Aug 2011), online at: <http://prsinfo.clinicaltrials.gov/definitions.html>.
[12] Zarin DA, Tse T, Williams RJ, Califf RM & Ide NC, The ClinicalTrials. gov results database—update and key issues, 364 *N Engl J Med* 852 (2011).
[13] Law MR, Kawasumi Y & Morgan SG, Despite Law, Fewer Than One In Eight Completed Studies Of Drugs And Biologics Are Reported On Time On ClinicalTrials.gov, 30 *Health Affairs* 2338 (2011).