

Registration of Observational Studies

July 2013

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<http://ClinicalTrials.gov>

ClinicalTrials.gov Definitions

- **Observational Study:** “studies in human beings in which biomedical and/or health outcomes are assessed in pre-defined groups of individuals. Subjects in the study may receive diagnostic, therapeutic, or other interventions, but the investigator does not assign specific interventions to the subjects of the study.”
- **Interventional Study:** “studies in human beings in which individuals are assigned by an investigator based on a protocol to receive specific interventions. Subjects may receive diagnostic, therapeutic or other types of interventions. The assignment of the intervention may or may not be random. The individuals are then followed and biomedical and/or health outcomes are assessed.”

Key Policies for Interventional Studies

- ICMJE (Registration only)
 - Interventional trials
 - All intervention types
 - All phases
- FDAAA (Registration and Results)
 - Interventional trials
 - Drugs, biologics, devices
 - Not phase 1
 - US FDA jurisdiction (e.g., IND/IDE or US site)
 - Specific enforcement mechanisms
- European Medicines Agency (EMA)
(Registration and Results)

Reasons to Register Clinical Trials and Report Results

- Human Subject Protections
 - Allows potential participants to find studies
 - Assists ethical review boards and others to determine appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
 - Promote fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge
- Research Integrity
 - Facilitates tracking of protocol changes
 - Increases transparency of research enterprise
- Evidence Based Medicine
 - Facilitates tracking of studies and outcome measures
 - Allows for more complete identification of relevant studies
- Allocation of Resources
 - Promotes more efficient allocation of resources

Registration of observational studies: Is it time?

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Previously published at www.cmaj.ca

Observational studies form an important part of the medical evidence base, particularly for assessing rare adverse events and long-term effectiveness of medications and devices.¹ However, observational studies, like interventional studies (clinical trials), are subject to publication bias and reporting bias.²⁻⁴ Registration of clinical trials is a widely recognized tool for facilitating complete public reporting.⁵ Registration of observational studies has received less attention, although interest is growing.⁶⁻⁸ Because existing registries (e.g., ClinicalTrials.gov) accommodate observational studies, and the rationale and benefits of registration are similar, we ask the scientific community and other stakeholders to consider the systematic, prospective registration of observational studies.

Why register observational studies?

Much of the rationale for the prospective registration of clinical trials⁹ applies to the registration of observational studies (Table 1).⁷ For example, observational studies in which researchers acquire data directly from human participants entail ethical obligations to participants, even though such research generally involves less risk than interventional studies.¹⁰ These obligations include oversight by ethical review boards, informed consent, and public release of the study findings to advance biomedical knowledge. As with clinical trials, incomplete reporting of observational studies has been documented.³ Some researchers suggest that observational studies are also at increased risk for publication bias or other types of bias, including misrepresentation of prespecified analyses or phenotype definitions.^{2,4} Such biases are a concern because they undermine the validity of observational studies, which are an important component of the medical evidence base in areas of public health, such as detection of rare adverse events.^{1,16}

Observational studies of medications and devices are playing a more visible role at the United States Food and Drug Administration (FDA) (Table 2). For instance, the FDA posted an "Early communication about an ongoing safety review"¹⁸ in response to a published observational study associating abacavir and didanosine with an increased risk of cardiovascular and cerebrovascular events.¹⁹ The authors of the study noted that, although a randomized controlled trial is necessary to show a causal association, such a trial design is "unlikely to be feasible," given that it would require more than 10 000 participants to be followed for at least two years. In addition, there may be ethical concerns in conducting a randomized controlled trial if harms are expected. Given that this and other associations between marketed products and possible harms are likely to be investigated further using observational stud-

Key points

- Clinical trial registries are established tools for improving access to information on trials and for addressing publication bias and reporting bias.
- Much of the ethical and scientific rationale for registering clinical trials also applies to observational studies.
- The existing infrastructure for trial registration is being used for observational studies, which make up 17% of the studies registered in ClinicalTrials.gov.
- Further discussion is necessary to assess the scope and specific implementation-related issues of systematic registration of observational studies.

ies, a registry containing summary protocol information would allow researchers to track such studies from initiation to completion. Such a tool could be useful to researchers who are evaluating the current evidence, considering initiating similar studies, identifying gaps in research or seeking collaborators.¹⁵ Similarly, a database of summary results could improve access to information about published and unpublished observational study analyses (whether prespecified or post hoc), thereby mitigating publication bias and incomplete reporting of results.

Given these potential benefits, observational studies are already being registered for various reasons, and there is increasing attention given to this practice. For example, the state of Maine requires registration and reporting of results of postmarketing observational studies of medications and biological products marketed in Maine²⁰ and the corporate policies of some drug manufacturers address disclosure of observational studies.²¹ Recently, an international workshop was held on the topic,⁶ and several medical journals published editorials on the registration of observational studies.^{7,8,22} Some have suggested that ethics review boards should require prospective registration of any study involving human participants,¹² whereas others have proposed that observational studies under the mandate of the FDA should be subject to the same requirements for registration and reporting of results as those for clinical trials.^{17,23} The European Medicines Agency recently issued a work plan to create a registry of post-authorization safety studies that would include observational studies,²⁴ and a draft report by the Agency for Healthcare Research and Quality considered the utility of creating a "registry of

From the National Library of Medicine, National Institutes of Health, United States Department of Health and Human Services, Bethesda, USA

CMAJ 2010. DOI:10.1503/cmaj.092252

DOI:10.1503/cmaj.092252

Rationale for registration of clinical trials

Application to observational studies

Respect for human participants

Observational studies involve human participants and thereby entail ethical obligations.¹⁰ Individuals deserve to know that the study will result in information that will advance medical knowledge.

Evidence-based medicine

Complete set of evidence is required to practise evidence-based medicine. Observational studies are considered to be part of the complete set of evidence.¹¹

Mitigation of publication bias and detection of deviations

Studies or outcomes with positive or statistically significant results may be more likely to be published (or suppressed).^{4,12,13} Unacknowledged changes to protocol could lead to misinterpretation of findings.

Clear documentation of prespecified study design

Interpretation of findings requires clear documentation of research methods. Reporting guidelines, such as STROBE (Strengthening the Reporting of Observational Studies in Epidemiology), identify protocol-related items that can be prespecified and are essential for interpreting the methods and results of an observational study.¹⁴

Identification of gaps in research

Gaps in evidence base are identified and opportunities for collaborative research provided. Records could signal a need for research or provide opportunities for collaborative research (e.g., assembling large cohorts to conduct genome-wide association studies).¹⁵

Avoidance of duplication

Support and conduct of redundant research studies are avoided. Funding through grants and allocation of limited research resources are optimized.

Public record

Registration is a permanent, public record of the study. The ClinicalTrials.gov unique identifier (NCT number) can be used in all publications and future discourse, including systematic reviews, regarding the study.

Registration of Observational Studies

- Clinical trial registries are established tools for improving access to information on trials and for addressing publication bias and reporting bias.
- Much of the ethical and scientific rationale for clinical trials also applies to observational studies, **especially collection of primary, prospective data.**
- The existing infrastructure for trial registration is being used for observational studies, which make up 19% of the studies registered in ClinicalTrials.gov.
- Further discussion is necessary to assess the scope and specific implementation-related issues.

Selected Recent Articles (Pro and Con)

- Onukwugha E. Improving confidence in observational studies : should statistical analysis plans be made publicly available? *Pharmacoeconomics*. 2013 Mar;31(3):177-9.
- Lash TL, Vandembroucke JP. Should preregistration of epidemiologic study protocols become compulsory? Reflections and a counterproposal. *Epidemiology*. 2012 Mar;23(2):184-8.
- Ioannidis JP. The importance of potential studies that have not existed and registration of observational data sets. *JAMA*. 2012 Aug 8;308(6):575-6.
- Savitz DA. Registration of observational studies does not enhance validity. *Clin Pharmacol Ther* 2011;90(5):646-8
- Loder E, Groves T, Macauley D. Registration of observational studies. *BMJ* 2010;340:c950.
- Editors. Should protocols for observational research be registered? *Lancet* 2010;375(9712):348.

Current Landscape

- Certain journals encourage or “require” registration
 - BMJ, Lancet
- EMA requires “registration” of protocols and abstracts for certain “post-authorization safety studies”—some of these are observational
- ClinicalTrials.gov has always accepted and encouraged registration of full range of observational studies
- Certain other registries accept observational studies (e.g., UMIN in Japan)

Issues to Consider

- What is a “study”? (unit of registration)
 - Prespecified protocol vs. broad plan for data analysis
 - Handling substudies & secondary studies
 - How to define start and end dates
- What study designs?
 - Prospective vs. retrospective studies
 - Secondary data analyses
- What about “registries” with “progeny studies?”

Observational Studies and ClinicalTrials.gov

ClinicalTrials.gov Data Elements Specific to Observational Studies

- **Observational Study Model** – primary strategy for subject identification and follow-up. Select one. (e.g., Cohort, Case-Control)
- **Time Perspective** – temporal relationship of observation period to time of subject enrollment. Select one. (e.g., Prospective)
- **Study Population Description** – a description of the population from which the groups or cohorts will be selected (e.g., primary care clinic).
- **Sampling Method** – select one (i.e., Probability or Non-probability)
- **Biospecimen Retention** – select one (e.g., Samples with DNA)
- **Biospecimen Description** – Specify all types of biospecimens to be retained (e.g., whole blood)

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ClinicalTrials.gov Stats

(as of 07/24/13)

<u>Study Characteristics</u>	<u># Records</u>	
	<u>Registry</u>	<u>Results Database</u>
Interventional	120,941 (81%)	8,868
Observational	27,666 (19%)	603
Sponsor-Collaborator Class		
NIH	5,285 (19%)	16
Industry	6,362 (23%)	486
Other (Not NIH and Not Industry)	16,019 (58%)	101
Time Perspective		
Prospective	18,264	449
Cross-Sectional	3,050	39
[Retrospective	2,758	99]
Study Design		
Cohort	9,732	225
Case Control	3,383	39
Defined Population	689	0
Natural History	418	0

Observational Studies: 1 Nov 07 to 22 Jul 13 (as of 7/24/13)

Study Design	Time Perspective				
	Prospective	Cross-Sectional	Retrospective	Missing	Total
Cohort	7,859	686	1,031	294	9,870
Case only	2,535	480	426	106	3,547
Case-Control	2,219	649	331	96	3,295
Other	346	175	60	31	612
Missing	1,881	309	345	904	3,439
Total	14,840	2,299	2,193	1,431	20,763

*Time perspective and study design (ClinicalTrials.gov data element – Observational Study Model) definitions available at: <http://prsinfo.clinicaltrials.gov/definitions.html>.

†Includes: case-crossover, ecologic or community, family based, and other.

Warfarin and Coronary Calcification Project (WACC)

This study has been completed.

Sponsor:

Walter Reed Army Medical Center

Information provided by (Responsible Party):

Todd C. Villines, Walter Reed Army Medical Center

ClinicalTrials.gov Identifier:

NCT00868712

First received: March 24, 2009

Last updated: August 23, 2012

Last verified: August 2012

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Tracking Information		Study Type ^{ICMJE}	Observational
First Received Date ^{ICMJE}	March 24, 2009	Study Design ^{ICMJE}	Observational Model: Cohort Time Perspective: Prospective
Last Updated Date	August 23, 2012		
Start Date ^{ICMJE}	May 2004		
Primary Completion Date	January 2010 (final data collection date for primary outcome measure)		
Current Primary Outcome Measures ^{ICMJE} (submitted: August 23, 2012)	Coronary Calcification (Presence and Degree as Measured by Agatston Score) Attributed to Duration of Warfarin Use in Months After Controlling for Standard Cardiovascular Risk Factors to Include the Framingham Risk Score [Time Frame: EBCT scan is done at time of enrollment of patient into 1 of 3 groups based on warfarin use duration: <6 months; 6-24 months; >24 mos.] [Designated as safety issue: No] The Agatston score is calculated using a non-contrast computed tomography (CT) scan to measure for the presence and severity of coronary artery disease through identification of calcification in the coronary arteries. Scores can range from 0 to several thousands. The measure is without units. Score categories are as follows: 0 = no coronary disease; 1-100 = low amount of coronary artery disease; 101-400 = moderately elevated score / moderate coronary artery disease; 401-1000 = severely elevated score; >1000 very severely elevated score. Higher Agatston scores correlate with more coronary artery disease and predict a higher risk of coronary heart disease events and mortality.		
Original Primary Outcome Measures ^{ICMJE} (submitted: March 24, 2009)	Coronary calcification (presence and degree as measured by Agatston score) attributed to duration of warfarin use in months after controlling for standard cardiovascular risk factors to include the Framingham risk score [Time Frame: EBCT scan is done at time of enrollment of patient into 1 of 3 groups based on warfarin use duration: <6 months; 6-24 months; >24 mos.] [Designated as safety issue: No]		

Warfarin and Coronary Calcification Project (WACC)

This study has been completed.

ClinicalTrials.gov Identifier:
NCT00868712

Population Description

Explanation of how the number of participants for analysis was determined. Includes whether analysis was per protocol, intention to treat, or another method. Also provides relevant details such as imputation technique, as appropriate.

After interim analysis following n=70 showed no effect, further enrollment was halted.

Reporting Groups

	Description
Warfarin Use Short Duration	Warfarin use for less than 6 months
2 - Warfarin Use Intermediate	Warfarin use for 6 to 24 months in duration
3 - Warfarin Use Chronic	Warfarin use >24 months

Measured Values

	Warfarin Use Short Duration	2 - Warfarin Use Intermediate	3 - Warfarin Use Chronic
Number of Participants Analyzed [units: participants]	31	11	28
Coronary Calcification (Presence and Degree as Measured by Agatston Score) Attributed to Duration of Warfarin Use in Months After Controlling for Standard Cardiovascular Risk Factors to Include the Framingham Risk Score [units: Agatston Score] Mean \pm Standard Deviation	175 \pm 285	289 \pm 382	426 \pm 789

Sample Primary Outcome Measures

- Incidence Rate of Idiopathic Venous Thromboembolism
Number of Participants That Responded to Amlodipine/
Atorvastatin Treatment With Angina Pectoris
- Percent of Subjects That Achieved Controlled Serum
Phosphorous Levels on Calcium-based Phosphate Binder
Therapy
- Percentage of Participants With One or More
Adverse Drug Reactions (ADRs)
- Time From End of Surgery (End of Last Stitch) to
Extubation
- Type of Surgical Procedure Performed in
Study Participants

Policy Options

- All observational studies
 - Include retrospective studies?
 - Secondary analyses?
 - Registries?
- All studies involving drugs/devices
 - What does “involving” mean?
 - Based on regulatory status (e.g., post-marketing surveillance studies)
- Proposal: include studies requiring IRB review
 - No distinction between interventional and observational
 - External marker of study start and end dates
 - Oversight system in place