Registration of Observational Studies

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National Library of Medicine

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.”

http://prsinfo.clinicaltrials.gov/definitions.html
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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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. However, observational studies, like interventional studies (clinical trials), are subject to publication bias and reporting bias. Registration of clinical trials is a widely recognized tool for facilitating complete public reporting. Registration of observational studies has received less attention, although interest is growing. 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 trials applies to the registration of observational studies (Table 1). 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. 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. 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. 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.

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” in response to a published observational study associating abacavir and didanosine with an increased risk of cardiovascular and cerebrovascular events. The authors of the study noted that, although a randomized controlled trial is necessary to prove 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 studies, 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 mimicking similar studies, identifying gaps in research or seeking collaborators. 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 Maine and the corporate policies of some drug manufacturers address disclosure of observational studies. Recently, an international workshop was held on the topic, and several medical journals published editorials on the registration of observational studies. Some have suggested that ethics review boards should require prospective registration of any study involving human participants, 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. The European Medicines Agency recently issued a work plan to create a registry of post-authorization safety studies that would include observational studies, and a draft report by the Agency for Healthcare Research and Quality considered the utility of creating a "registry of

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.

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

<table>
<thead>
<tr>
<th>Rationale for registration of clinical trials</th>
<th>Application to observational studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respect for human participants</td>
<td>Observational studies involve human participants and thereby entail ethical obligations. Individuals deserve to know that the study will result in information that will advance medical knowledge.</td>
</tr>
<tr>
<td>Evidence-based medicine</td>
<td>Complete set of evidence is required to practise evidence-based medicine. Observational studies are considered to be part of the complete set of evidence.</td>
</tr>
<tr>
<td>Mitigation of publication bias and detection of deviations</td>
<td>Studies or outcomes with positive or statistically significant results may be more likely to be published (or suppressed). Unacknowledged changes to protocol could lead to misinterpretation of findings.</td>
</tr>
<tr>
<td>Clear documentation of prespecified study design</td>
<td>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.</td>
</tr>
<tr>
<td>Identification of gaps in research</td>
<td>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).</td>
</tr>
<tr>
<td>Avoidance of duplication</td>
<td>Support and conduct of redundant research studies are avoided. Funding through grants and allocation of limited research resources are optimized.</td>
</tr>
<tr>
<td>Public record</td>
<td>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.</td>
</tr>
</tbody>
</table>
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)

- 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.
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)
Advanced Search

Fill in any or all of the fields below.

Click on a label to the left for further explanation or read the Help.

Search Terms: 

Recruitment: All Studies

Study Results: All Studies

Study Type: Observation Studies

Targeted Search: Observation Studies

Conditions:

Interventions:

Title Acronym/Titles:

Outcome Measures:

Sponsor/Collaborators:

Sponsor (Lead):

Study IDs:

Locations:

State 1: Optional

Country 1: Optional
# ClinicalTrials.gov Stats
(as of 07/24/13)

## Study Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Registry # Records</th>
<th>Results Database</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventional</td>
<td>120,941 (81%)</td>
<td>8,868</td>
<td></td>
</tr>
<tr>
<td>Observational</td>
<td>27,666 (19%)</td>
<td>603</td>
<td></td>
</tr>
</tbody>
</table>

## Sponsor-Collaborator Class

<table>
<thead>
<tr>
<th>Class</th>
<th>Registry # Records</th>
<th>Results Database</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH</td>
<td>5,285 (19%)</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Industry</td>
<td>6,362 (23%)</td>
<td>486</td>
<td></td>
</tr>
<tr>
<td>Other (Not NIH and Not Industry)</td>
<td>16,019 (58%)</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

## Time Perspective

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Registry # Records</th>
<th>Results Database</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>18,264</td>
<td>449</td>
<td></td>
</tr>
<tr>
<td>Cross-Sectional</td>
<td>3,050</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Retrospective</td>
<td>2,758</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

## Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>Registry # Records</th>
<th>Results Database</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>9,732</td>
<td>225</td>
<td></td>
</tr>
<tr>
<td>Case Control</td>
<td>3,383</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Defined Population</td>
<td>689</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Natural History</td>
<td>418</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
### Observational Studies: 1 Nov 07 to 22 Jul 13 (as of 7/24/13)

#### Time Perspective

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

*Time perspective and study design (ClinicalTrials.gov data element – Observational Study Model) definitions available at: [http://prsinfo.clinicaltrials.gov/definitions.html](http://prsinfo.clinicaltrials.gov/definitions.html).*  
†Includes: case-crossover, ecologic or community, family based, and other.
**Tracking Information**

<table>
<thead>
<tr>
<th>Tracking Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Received Date</strong>: March 24, 2009</td>
</tr>
<tr>
<td><strong>Last Updated Date</strong>: August 23, 2012</td>
</tr>
<tr>
<td><strong>Start Date</strong>: May 2004</td>
</tr>
<tr>
<td><strong>Primary Completion Date</strong>: January 2010 (final data collection date for primary outcome measure)</td>
</tr>
</tbody>
</table>

**Current Primary Outcome Measures**

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**

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

<table>
<thead>
<tr>
<th>Description</th>
<th>Warfarin Use Short Duration</th>
<th>2 - Warfarin Use Intermediate</th>
<th>3 - Warfarin Use Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Use Short Duration</td>
<td>Warfarin use for less than 6 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 - Warfarin Use Intermediate</td>
<td>Warfarin use for 6 to 24 months in duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 - Warfarin Use Chronic</td>
<td>Warfarin use &gt;24 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Measured Values

<table>
<thead>
<tr>
<th>Description</th>
<th>Warfarin Use Short Duration</th>
<th>2 - Warfarin Use Intermediate</th>
<th>3 - Warfarin Use Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Participants Analyzed [units: participants]</td>
<td>31</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>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]</td>
<td>175 ± 285</td>
<td>289 ± 382</td>
<td>426 ± 789</td>
</tr>
<tr>
<td>Mean ± Standard Deviation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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