Snapshot of the Clinical Trials Enterprise as revealed by ClinicalTrials.gov

Download date: 27 Sept 2010
Background

- What is ClinicalTrials.gov?
- ClinicalTrials.gov history
- Key reporting requirements
- Rationale for reporting clinical trials
- Basic uses of ClinicalTrials.gov
- Creation of AACT database
- Analysis of studies registered at ClinicalTrials.gov
What is ClinicalTrials.gov?

ClinicalTrials.gov is a web site that provides patients, their family members, and health care professionals easy access to information about clinical studies on a range of diseases and conditions.

Information is provided and updated by the sponsor or principal investigator of a clinical study, and the web site is maintained by the U.S. National Library of Medicine (NLM) at the National Institutes of Health (NIH).
# ClinicalTrials.gov History

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nov 21, 1997</td>
<td>Food and Drug Modernization Act of 1997 (FDAMA) section 113 enacted</td>
<td>Mandated the creation of the ClinicalTrials.gov registry for efficacy trials in serious and life-threatening conditions and interventions regulated by the FDA</td>
</tr>
<tr>
<td>Feb 29, 2000</td>
<td>First version of ClinicalTrials.gov publicly available</td>
<td></td>
</tr>
<tr>
<td>September 2004</td>
<td>Internal Committee of Medical Journal Editors’ (ICMJE) policy established</td>
<td>Required studies published in their journals be registered in ClinicalTrials.gov or other equivalent publicly available registries</td>
</tr>
<tr>
<td>September 27, 2007</td>
<td>FDA Amendments Act (FDAAA) section 801 enacted</td>
<td>Created a legal requirement for the registration of the trials of drugs, biologics, and devices</td>
</tr>
<tr>
<td>September 23, 2008</td>
<td>Results reporting launched</td>
<td></td>
</tr>
<tr>
<td>September 28, 2009</td>
<td>Adverse Event reporting launched</td>
<td></td>
</tr>
</tbody>
</table>
Key Trial Reporting Requirements

- Register at trial initiation for interventional studies of drugs, biologics, and devices
  - (Phase 1 excluded)
- Studies under an IND/IDE or with US site
- To meet ICMJE requirement of registration
  [http://www.icmje.org/publishing_10register.html](http://www.icmje.org/publishing_10register.html)
- Keep all entries up to date
  - Changes are tracked on public site
Key Trial Results Reporting Requirements

- Report summary results at trial completion for
  - Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation
  - Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies
Basic uses of ClinicalTrials.gov

- Identify trials of potential interest for specific individual
- Track progress of specific trial including access to summary results
- Identify all trials that are ongoing or completed for a given set of conditions or interventions
- Identify investigators and/or research centers participating in studies for given set of conditions or interventions
Database for the Aggregate Analysis of ClinicalTrials.gov (AACT)

Design

- Downloaded XML dataset of all clinical studies registered with ClinicalTrials.gov as of September 27, 2010
- Designed and implemented relational database to facilitate aggregate analysis of data

Uses of Aggregate Data

- Examine the “Clinical Research Enterprise”
- Provide information to specific user communities
- Examine the quality and completeness of reporting
Database for Aggregate Analysis of ClinicalTrials.gov (AACT)

Studies registered at ClinicalTrials.gov

Studies registered through 27 Sept 2010
N=96,346

Interventional Studies
N=79,413

Observational Studies
N=16,506

Expanded Access Studies
N=107

Study Type missing
N=320

Registered through Sept 2007
N=38,443

Registered 1 Oct 2007 through 27 Sept 2010
N=40,970

Snapshot analysis is focused on these studies.
Overview

- Funding
- Study Phase
- Intervention Types
- Therapeutic area
  - Oncology
  - Cardiovascular
  - Mental Health
## Funding

- Derived as follows:

<table>
<thead>
<tr>
<th>Lead Sponsor</th>
<th>Collaborators</th>
<th>Derived</th>
</tr>
</thead>
<tbody>
<tr>
<td>Industry</td>
<td>No restrictions</td>
<td>Industry</td>
</tr>
<tr>
<td>Not NIH</td>
<td>At least one from Industry, none from NIH</td>
<td>Industry</td>
</tr>
<tr>
<td>NIH</td>
<td>No restrictions</td>
<td>NIH</td>
</tr>
<tr>
<td>Not industry</td>
<td>At least one from NIH</td>
<td>NIH</td>
</tr>
<tr>
<td>Not industry, not NIH</td>
<td>None from industry, none from NIH</td>
<td>Other</td>
</tr>
</tbody>
</table>
Funding

# studies

Registration Date

* through Sept 27, 2010
Clinical Therapeutic Area

- Clinical specialists at Duke University Medical Center reviewed a subset of the 2010 MeSH* thesaurus and frequently-occurring free-text condition terms

- Specialists annotated terms for relevance to
  - Oncology
  - Cardiovascular
  - Mental Health

- For each therapeutic area, we algorithmically searched for studies with at least one relevant term in the following fields:
  - Condition terms entered by data submitters
  - MeSH condition terms generated by the National Library of Medicine


* MeSH: Medical Subject Headings
Therapeutic Area

A study may be counted in more than one therapeutic area

* through Sept 27, 2010
Funding by Therapeutic Area

# studies

- **Oncology**
  - Industry
  - NIH
  - Other

- **Cardiovascular**
  - Industry
  - NIH
  - Other

- **Mental Health**
  - Industry
  - NIH
  - Other
Study Phase

# studies

<table>
<thead>
<tr>
<th>Registration Date</th>
<th>Phase 0</th>
<th>Phase 1</th>
<th>Phase 1/2 &amp; 2</th>
<th>Phase 2/3 &amp; 3</th>
<th>Phase 4</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct07 - Sep08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Oct08 - Sep09</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Oct09 - Sep10*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* through Sept 27, 2010
Funding by Phase

# studies

- **Phase 0**: Industry (Blue), NIH (Red), Other (Green)
- **Phase 1**: Industry (Blue), NIH (Red), Other (Green)
- **Phase 1/2 & 2**: Industry (Blue), NIH (Red), Other (Green)
- **Phase 2/3 & 3**: Industry (Blue), NIH (Red), Other (Green)
- **Phase 4**: Industry (Blue), NIH (Red), Other (Green)
- **N/A**: Industry (Blue), NIH (Red), Other (Green)
Therapeutic Area by Phase

# studies

- Oncology
- Cardiovascular
- Mental Health

Phases:
- Phase 0
- Phase 1
- Phase 1/2 & 2
- Phase 2/3 & 3
- Phase 4
- N/A
Intervention Types

A study may have more than one intervention type
Intervention Types

Studies of drugs, biologics and devices in phases 2-4 are required to be registered by FDAAA. + Includes behavioral, radiation, dietary supplement, in addition to other interventions * through Sept 27, 2010
Intervention Types by Phase

Studies of drugs, biologics and devices in phases 2-4 are required to be registered by FDAAA.
+ Includes behavioral, radiation, dietary supplement, in addition to other interventions
Studies of drugs, biologics and devices in phases 2-4 are required to be registered by FDAAA. + Includes behavioral, radiation, dietary supplement, in addition to other interventions * Percent calculated within each therapeutic area
Sites/Participants

- Single- and multi-center studies
- Number of sites for multi-center studies
- Enrollment
- Location of sites
- Eligibility: sex
- Eligibility: age restrictions and exclusions
Single-Center and Multi-center Studies

N=3,450 studies missing center information
* through Sept 27, 2010
Single-Center and Multi-center Studies

### Single-Center

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th># studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>2000</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1500</td>
</tr>
<tr>
<td>Mental Health</td>
<td>1000</td>
</tr>
</tbody>
</table>

**Registration Date**

- Oct07 - Sep08
- Oct08 - Sep09
- Oct09 - Sep10*

* through Sept 27, 2010

### Multi-center

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
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<tr>
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**Registration Date**

- Oct07 - Sep08
- Oct08 - Sep09
- Oct09 - Sep10*
Single-center and Multi-center Studies by Phase

# studies

N=3,450 studies missing center information
Median Number of Sites/Study for Multi-center Studies

Based on N=12,732 multi-center studies
N=3,450 studies missing center information
* through Sept 27, 2010
Median Number of Sites/Study for Multi-center Studies

Median # sites/study

Registration Date

* through Sept 27, 2010
Number of Subjects/Study
(Anticipated or Actual enrollment)

604 studies have missing enrollment
Median Enrollment by Phase

<table>
<thead>
<tr>
<th>Phase</th>
<th>Oct07 - Sep08</th>
<th>Oct08 - Sep09</th>
<th>Oct09 - Sep10*</th>
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<tbody>
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<tr>
<td>Phase 4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

604 studies have missing enrollment
* through Sept 27, 2010
Median Enrollment by Funding

# research participants / study

Registration Date

604 studies have missing enrollment
* through Sept 27, 2010
Median Enrollment by Therapeutic Area

# research participants / study

Registration Date

* through Sept 27, 2010
Location of Study Sites

N=3,450 studies have missing center information

A study can have sites in multiple regions
Regions are defined according to http://www.clinicaltrials.gov/ct2/search/browse?brwse=loecn_cat
Central and South America combined into C&S America Pacifica, and East, North, South, and Southeast Asia combined into Pacifica/Asia
Studies with Sites in U.S. and Rest of World (R.O.W.)

N=3,450 studies have missing center information
* through Sept 27, 2010
Location of Studies by Therapeutic Area

# studies

- Oncology
- Cardiovascular
- Mental Health

Sites in US only
Sites in US and ROW
Sites in ROW only
Eligibility: Sex

# studies

<table>
<thead>
<tr>
<th>Registration Date</th>
<th>Female only</th>
<th>Male only</th>
<th>Both</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* through Sept 27, 2010
Sex Eligibility by Therapeutic Area

# studies

- **Oncology**: 9000 studies
- **Cardiovascular**: 3000 studies
- **Mental Health**: 3000 studies

- **Female only**: 1000 studies
- **Male only**: 1000 studies
- **Both**: 7000 studies
Eligibility: Age Restrictions

% studies+

Registration Date

+ All studies under consideration (N=40,970) provided information on minimum and maximum age restrictions, although some indicated that there were no restrictions (responded “N/A”). The % of studies with restrictions was calculated among all studies.

* through Sept 27, 2010
Age Restrictions by Therapeutic Area

% studies*

- Restricted to children
- Restricted to age >= 65
- Restricted to age >= 75

* Percent calculated within each therapeutic area
Eligibility: Age Exclusions

% studies+

- Excludes children
- Excludes age >= 65
- Excludes age >= 75

Registration Date

+ All studies under consideration (N=40,970) provided information on minimum and maximum age restrictions, although some indicated that there were no restrictions (responded “N/A”). The % of studies with restrictions was calculated among all studies.

* through Sept 27, 2010
Age Exclusions by Therapeutic Area

% studies*

- Excludes children
- Excludes age >= 65
- Excludes age >= 75

* Percent calculated within each therapeutic area
Study Characteristics

- Primary Purpose
- Masking — knowledge of intervention assignments (open label, single-blind, or double-blind)
- Randomization
- Number of arms
- Data Monitoring Committee — whether a data monitoring committee was appointed for this study
Primary Purpose

N=2,771 studies have missing primary purpose
+ Includes the categories supportive care, screening, health services research, and basic science
* through Sept 27, 2010
Primary Purpose by Phase

N=2,771 studies have missing primary purpose
+ Includes the categories supportive care, screening, health services research, and basic science
Primary Purpose by Therapeutic Area

# studies

- **Oncology**: 8000 studies
- **Cardiovascular**: 3000 studies
- **Mental Health**: 2000 studies

- **Treatment**
- **Prevention**
- **Diagnostic**
- **Other+**

+ Includes the categories supportive care, screening, health services research, and basic science
N=1,099 studies have missing masking information
* through Sept 27, 2010
Masking by Phase

N=1,099 studies have missing masking information
Randomization

N=1,730 studies have missing randomization information
* through Sept 27, 2010
Randomization by Phase

N=1,730 studies have missing randomization information
Randomization by Therapeutic Area

# studies

- Oncology
- Cardiovascular
- Mental Health

Randomized Non-randomized
Number of Arms

N=1,727 studies have missing information on number of arms
* through Sept 27, 2010

Registration Date
Number of Arms by Phase

N=1,727 studies have missing information on number of arms
Number of Arms by Therapeutic Area

# studies

- Oncology
- Cardiovascular
- Mental Health

Legend:
- Blue: One
- Red: Two
- Green: Three or more
Data Monitoring Committee (DMC)

Registration Date

# studies

- DMC = Yes
- DMC = No
- DMC unknown

* through Sept 27, 2010
DMC by Phase

# studies

- **DMC = Yes**
- **DMC = No**
- **DMC unknown**

Phase 0: 0 studies
Phase 1: 0 studies
Phase 1/2 & Phase 2/3: 0 studies
Phase 4: 0 studies
N/A: 0 studies
DMC use by Therapeutic Area

# studies

![Bar chart showing DMC use by therapeutic area.](chart.png)

- **Oncology**
  - DMC = Yes: Approximately 4,500
  - DMC = No: Approximately 2,500
  - DMC unknown: Approximately 2,000

- **Cardiovascular**
  - DMC = Yes: Approximately 1,500
  - DMC = No: Approximately 1,000
  - DMC unknown: Approximately 500

- **Mental Health**
  - DMC = Yes: Approximately 1,000
  - DMC = No: Approximately 1,000
  - DMC unknown: Approximately 500
Regression Analyses of DMC use, Blinding, and Randomization

- Associations Between Study Characteristics and DMC use, blinding, and randomization
  - Logistic regression analysis of
    - DMC use (yes versus no)
    - Blinding (single- or double-blind masking versus unblinded)
    - Randomization (yes versus no)
### DMC Use: Multivariable Odds Ratios

<table>
<thead>
<tr>
<th>Category</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study size</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Oncology</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mental Health</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Start year</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Funding</strong> (vs. Industry)</td>
<td>NIH</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td><strong>Phase</strong> (vs. Phase 3)</td>
<td>&lt; Phase 3</td>
</tr>
<tr>
<td></td>
<td>Phase 4</td>
</tr>
<tr>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Intervention</strong> (vs. Drug/Biological)</td>
<td>Proc/device</td>
</tr>
<tr>
<td></td>
<td>Behavioral</td>
</tr>
<tr>
<td></td>
<td>Dietary Suppl</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td><strong>Purpose</strong> (vs. Treatment)</td>
<td>Prevention</td>
</tr>
<tr>
<td></td>
<td>Diagnostic</td>
</tr>
<tr>
<td></td>
<td>Other+</td>
</tr>
</tbody>
</table>

* Per 1000 participants; # Per increment of 1 yr; + Includes supportive care, screening, health services research, and basic science.
**Blinding: Multivariable Odds Ratios**

- **Funding (vs. Industry)**
  - NIH
  - Other

- **Phase (vs. Phase 3)**
  - < Phase 3
  - Phase 4
  - N/A

- **Intervention (vs. Drug/Biological)**
  - Proc/device
  - Behavioral
  - Dietary Suppl
  - Other

- **Purpose (vs. Treatment)**
  - Prevention
  - Diagnostic
  - Other+

* Per 1000 participants; # Per increment of 1 yr; + Includes supportive care, screening, health services research, and basic science
Randomization: Multivariable Odds Ratios

<table>
<thead>
<tr>
<th>Funding (vs. Industry)</th>
<th>NIH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase (vs. Phase 3)</td>
<td>&lt; Phase 3</td>
<td>Phase 4</td>
</tr>
<tr>
<td>Intervention (vs. Drug/Biological)</td>
<td>Proc/device</td>
<td>Behavioral</td>
</tr>
<tr>
<td>Purpose (vs. Treatment)</td>
<td>Prevention</td>
<td>Diagnostic</td>
</tr>
</tbody>
</table>

* Per 1000 participants; # Per increment of 1 yr; + Includes supportive care, screening, health services research, and basic science
Conclusions

- ClinicalTrials.gov is a rich source of data about the clinical trials enterprise
- Significant heterogeneity exists in the use of common methods, sample sizes, trial location and oversight
- Examination of this heterogeneity in more detail may offer a means of improving the enterprise
- The creation of a publicly accessible file for analysis could enable research sponsors, investigators, government agencies and patients/patient advocates to assess the progress of the clinical trials enterprise as it relates to their areas of interest
Funding Disclosure

Financial support for this work was provided by grant U19FD003800 from the U.S. Food and Drug Administration awarded to Duke University for the Clinical Trials Transformation Initiative