Clinical Trials in Pulmonary, Critical Care, and Sleep Medicine (PCCSM): A Systematic Analysis

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Disclosures

- No disclosures related to commercial interests, non-commercial interests, tobacco industry, or off-label product use.
# Milestones in Clinical Trial Registration

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>November 1997</td>
<td>FDAMA section 113 requires registry of clinical trials</td>
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<tr>
<td>February 2000</td>
<td>ClinicalTrials.gov registry is made publicly available</td>
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<tr>
<td>September 2004</td>
<td>ICMJE published policy making publication of interventional trials conditional upon registration</td>
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<tr>
<td>September 2007</td>
<td>FDAAA section 801 mandates registration of interventional trials involving drug, biologic, or device</td>
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<tr>
<td>September 2008</td>
<td>Reporting of summary trial results mandated</td>
</tr>
<tr>
<td>September 2009</td>
<td>Reporting of adverse events mandated</td>
</tr>
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</table>

FDAMA = Food and Drug Administration Modernization Act  
ICMJE = International Committee of Medical Journal Editors  
FDAAA = Food and Drug Administration Amendments Act
Study Background and Objectives

CTTI is a partnership established between the FDA and Duke to transform information contained in ClinicalTrials.gov into a high quality database suitable for aggregate analysis.

- www.ctti-clinicaltrials.org

Our goal was to leverage this database to better understand the current portfolio of interventional clinical research in PCCSM with an emphasis on:

- Trial characteristics
- Disease distribution
- Primary outcomes
- Funding sources
Methods

- Studies were identified as PCCSM using source data from ClinicalTrials.gov and NLM expanded MeSH terms*

- Studies were subcategorized to determine
  - **Disease** - condition terms occurring ≥ 2 times manually reviewed, clustered into clinically relevant diagnosis groups
  - **Primary outcome** - free text entered by submitter manually reviewed, general outcome categories assigned
  - **Funding source** - derived from submitted lead sponsor/collaborator
    - Industry, NIH, “Other”

- Descriptive statistics were used to characterize the portfolio

Results

40,970 “interventional” trials registered from October 2007 to September 2010

Restricted to 2,888 potential PCCSM studies using annotated disease condition terms

38,082 pertained to other medical specialties

Restricted to 2,226 PCCSM studies after manual review of full study record at CT.gov

662 trials non-PCCSM related
PCCSM Trials Represent A Small Fraction of Interventional Clinical Trials, 10/2007–9/2010

- **PCCSM, 5.4%**
- **Oncology, 21.9%**
- **Mental Health, 9.0%**
- **CV Disease, 8.4%**
- **Other, 55.3%**
Design Characteristics of PCCSM Studies

- **Phase**
  - I, 11.6%
  - II, 33.6%
  - III, 32.2%
  - IV, 22.6%

- **Interventional model**
  - Parallel groups, 59.3%
  - Single group, 20.7%
  - Crossover, 18.6%
  - Factorial, 1.3%

- **Allocation**
  - Randomized, 79.0%
  - Non-randomized, 21.0%

- **Blinding**
  - Double blind, 47.2%
  - Single blind, 11.5%
  - Open label, 41.3%
Most PCCSM Trials Report Anticipated or Actual Enrollment < 100 Patients*

*Anticipated enrollment for active trials
Actual enrollment for completed trials
## Distribution of PCCSM Trials by Disease Condition

<table>
<thead>
<tr>
<th>Condition</th>
<th>% of Total, N=2,121†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>27.4%</td>
</tr>
<tr>
<td>COPD</td>
<td>21.8%</td>
</tr>
<tr>
<td>Sleep Disordered Breathing</td>
<td>9.8%</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>7.4%</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>6.5%</td>
</tr>
<tr>
<td>Sepsis and Shock</td>
<td>6.4%</td>
</tr>
<tr>
<td>Non-Hypoxic Respiratory Failure</td>
<td>5.3%</td>
</tr>
<tr>
<td>Hypoxic Respiratory Failure</td>
<td>4.7%</td>
</tr>
<tr>
<td>Critical Care, Other</td>
<td>3.3%</td>
</tr>
<tr>
<td>Intubation and Airway Management</td>
<td>2.5%</td>
</tr>
<tr>
<td>Interstitial Lung Disease</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

*Studies may indicate more than one condition of interest
† Using the described methodology, at least one condition was identified for 95.3% (2121/2226) of studies in the PCCSM data set.
**Top Ten Primary Outcomes in PCCSM Trials**

<table>
<thead>
<tr>
<th>Primary Outcome*</th>
<th>% of Total, N=2,193†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Function</td>
<td>18.3</td>
</tr>
<tr>
<td>Safety and Tolerability</td>
<td>9.3</td>
</tr>
<tr>
<td>Cytokines and Biomarkers</td>
<td>6.8</td>
</tr>
<tr>
<td>Change in Vital Signs/Serum Parameters</td>
<td>4.7</td>
</tr>
<tr>
<td>Mortality</td>
<td>4.6</td>
</tr>
<tr>
<td>Pharmacodynamics/kinetics</td>
<td>4.4</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>3.1</td>
</tr>
<tr>
<td>Exercise Capacity, other than 6MWD</td>
<td>2.7</td>
</tr>
<tr>
<td>Exacerbation</td>
<td>2.6</td>
</tr>
<tr>
<td>6MWD</td>
<td>2.5</td>
</tr>
</tbody>
</table>

6MWD = 6 minute walk distance

*Studies may indicate more than one primary outcome
† No outcome could be determined for 33 studies based on the information submitted at ClinicalTrials.gov
PCCSM Trial Characteristics Vary by Funding Source

- Funding source
  - Industry, 43.5%
  - NIH, 5.4%
  - Other, 51.1% Universities, health care institutions, foundations
    - Cystic Fibrosis Foundation (CFF) #1 collaborator

- Asthma and COPD top two disease priorities for all funders
  - Variations in priorities for less common diseases

- Industry trials
  - More likely to include >500 patients
  - Less heterogeneity in primary outcome measures
    - Emphasis on lung function, 30.8% vs. 15.1% (NIH), 7.9% (other)
Conclusions

- PCCSM trials represent a relatively small proportion of all interventional clinical trials registered at ClinicalTrials.gov

- Characteristics of the current PCCSM portfolio
  - Relatively small study sample sizes
  - Driven by asthma and COPD
  - Use lung function as the primary outcome
  - Industry is single largest identifiable funding source

- Interesting variations in trial characteristics by funder
Limitations

- Comprehensiveness
  - ClinicalTrials.gov likely to be most complete for trials of drugs or devices that are sponsored by US based or multinational organizations

- Quality of data registered at ClinicalTrials.gov
  - Free text, prone to errors that later limit aggregate analysis
  - Lack of standard ontology for important data elements

- Funding source, derived variable
  - NIH funded trials may be underidentified
Implications

- Disparity between the growing public health burden of chronic lung disease and quantity and quality of available PCCSM interventional research

- Advocacy groups and private foundations can positively impact the research landscape (e.g. CFF)

- Opportunities to expand NIH investment in interventional PCCSM research

- Need to rapidly improve and standardize data at ClinicalTrials.gov
Acknowledgements

- 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.

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  - Scott M. Palmer, MD, MHS Director Pulmonary Research, DCRI
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- Dr. Judith Kramer – Executive Director, CTTI
- Dr. Robert M. Califf – Principal Investigator, CTTI
- Jean Bolte – Project Leader, CTTI
- Sara Calvert – Project Leader, CTTI
- Dr. Deborah Zarin – Director, ClinicalTrials.gov
- Nick Ide – National Library of Medicine