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

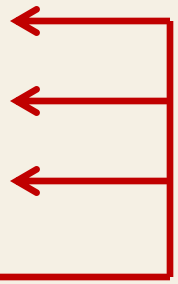
November 1997	FDAMA section 113 requires registry of clinical trials
February 2000	ClinicalTrials.gov registry is made publicly available
September 2004	ICMJE published policy making publication of **interventional** trials conditional upon registration
September 2007	FDAAA section 801 mandates registration of interventional trials involving **drug, biologic, or device**
September 2008	Reporting of summary trial results mandated
September 2009	Reporting of adverse events mandated

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

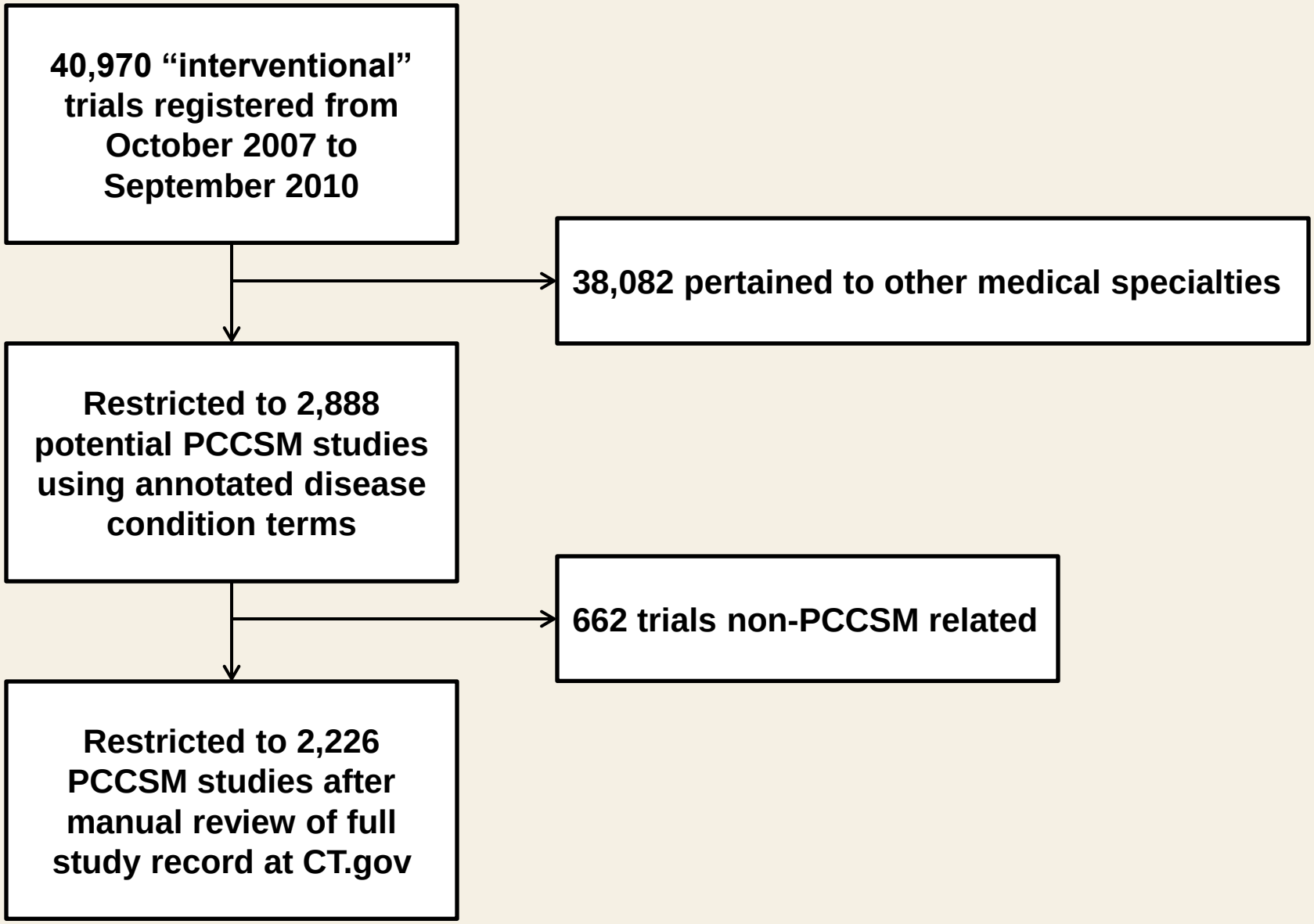
- Studies were identified as PCCSM using source data from ClinicalTrials.gov and NLM expanded MeSH terms*

- 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”

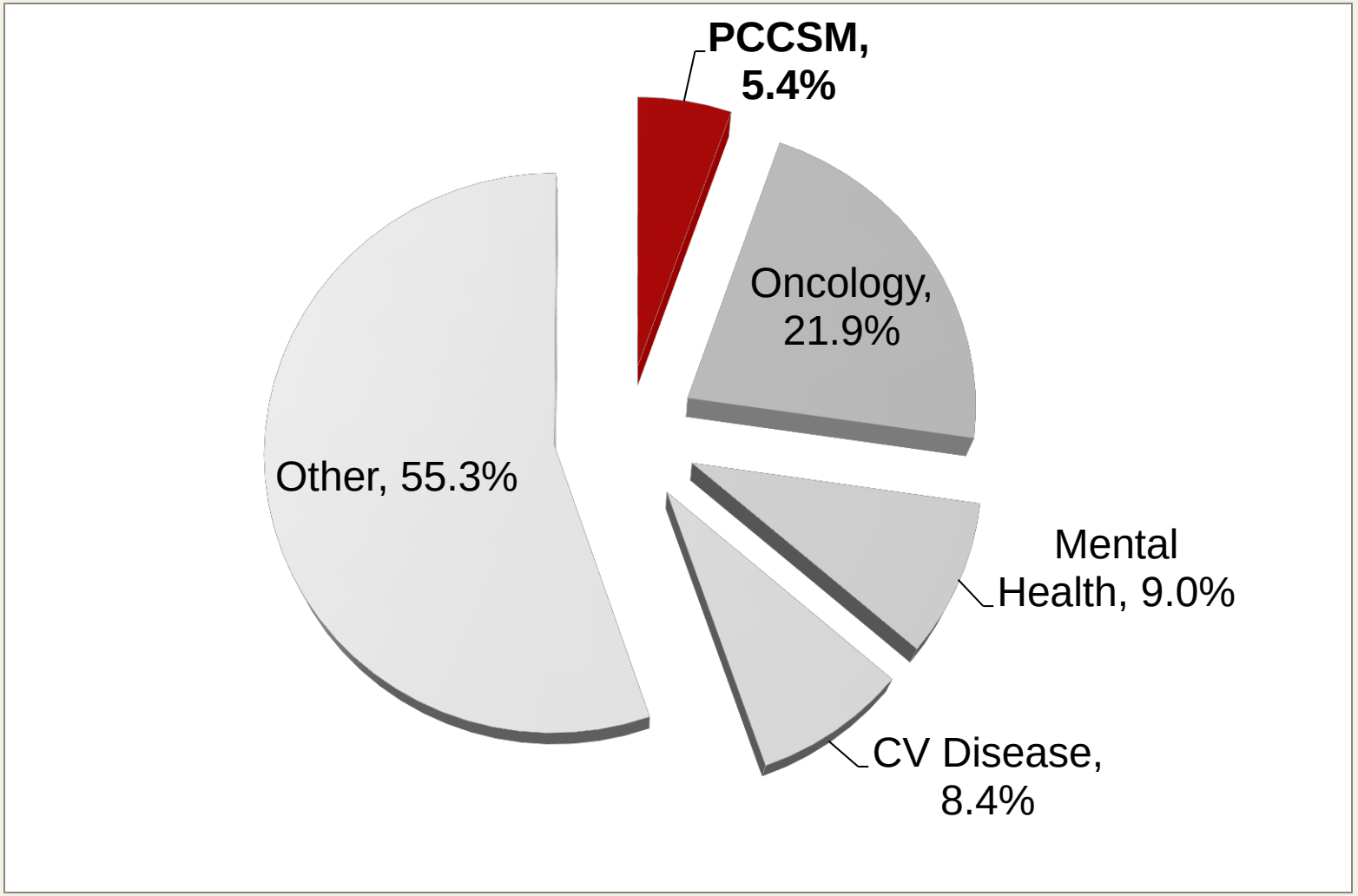
- Descriptive statistics were used to characterize the portfolio

*Tasneem A et al. *PLoS One* 2012;7(3):e33677

Results


40,970 “interventional” trials registered from October 2007 to September 2010
38,082 pertained to other medical specialties
Restricted to 2,888 potential PCCSM studies using annotated disease condition terms
662 trials non-PCCSM related
Restricted to 2,226 PCCSM studies after manual review of full study record at CT.gov

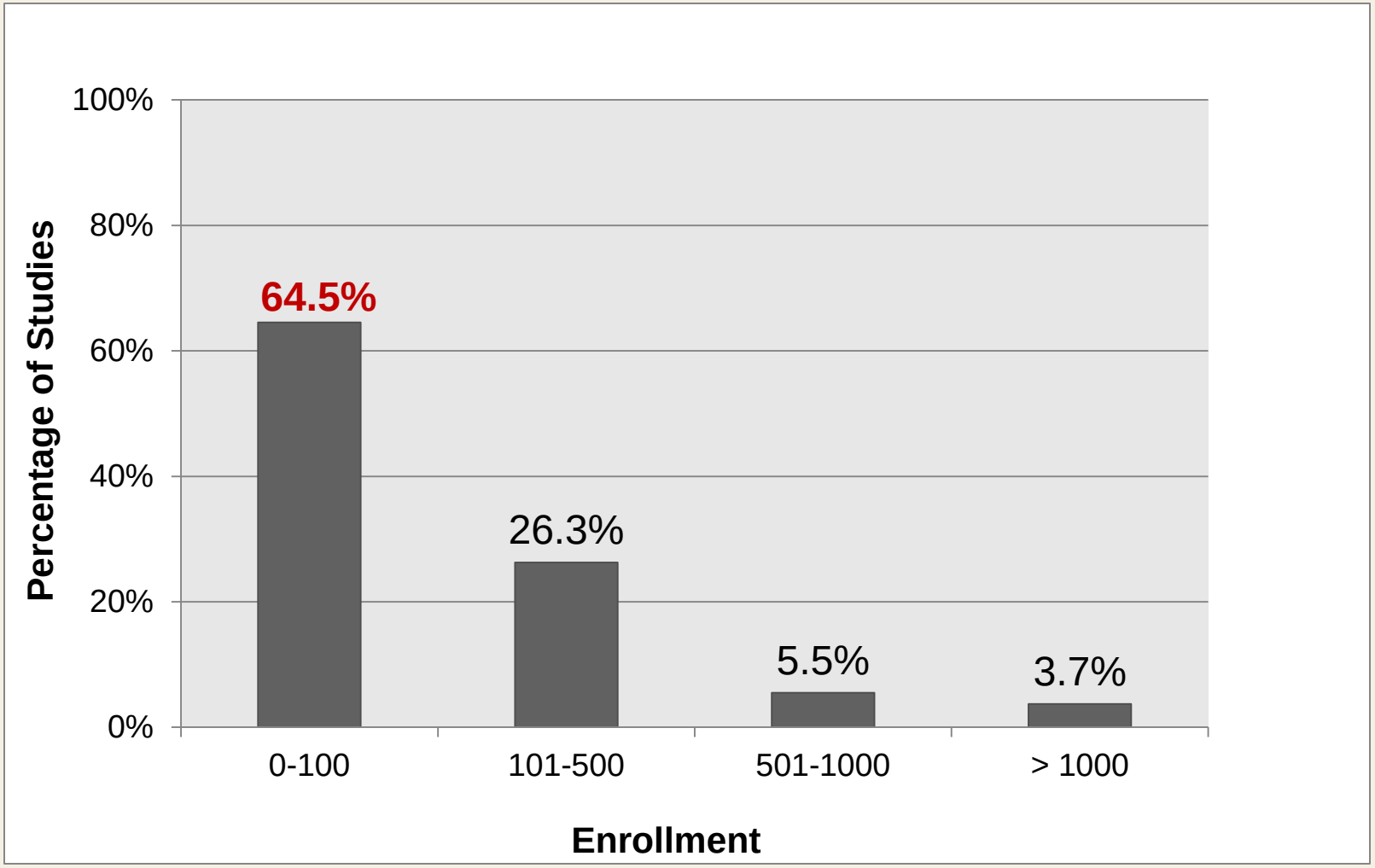
PCCSM Trials Represent A Small Fraction of Interventional Clinical Trials, 10/2007–9/2010



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

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

*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

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

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

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- Co-authors
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