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

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

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***
- 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)

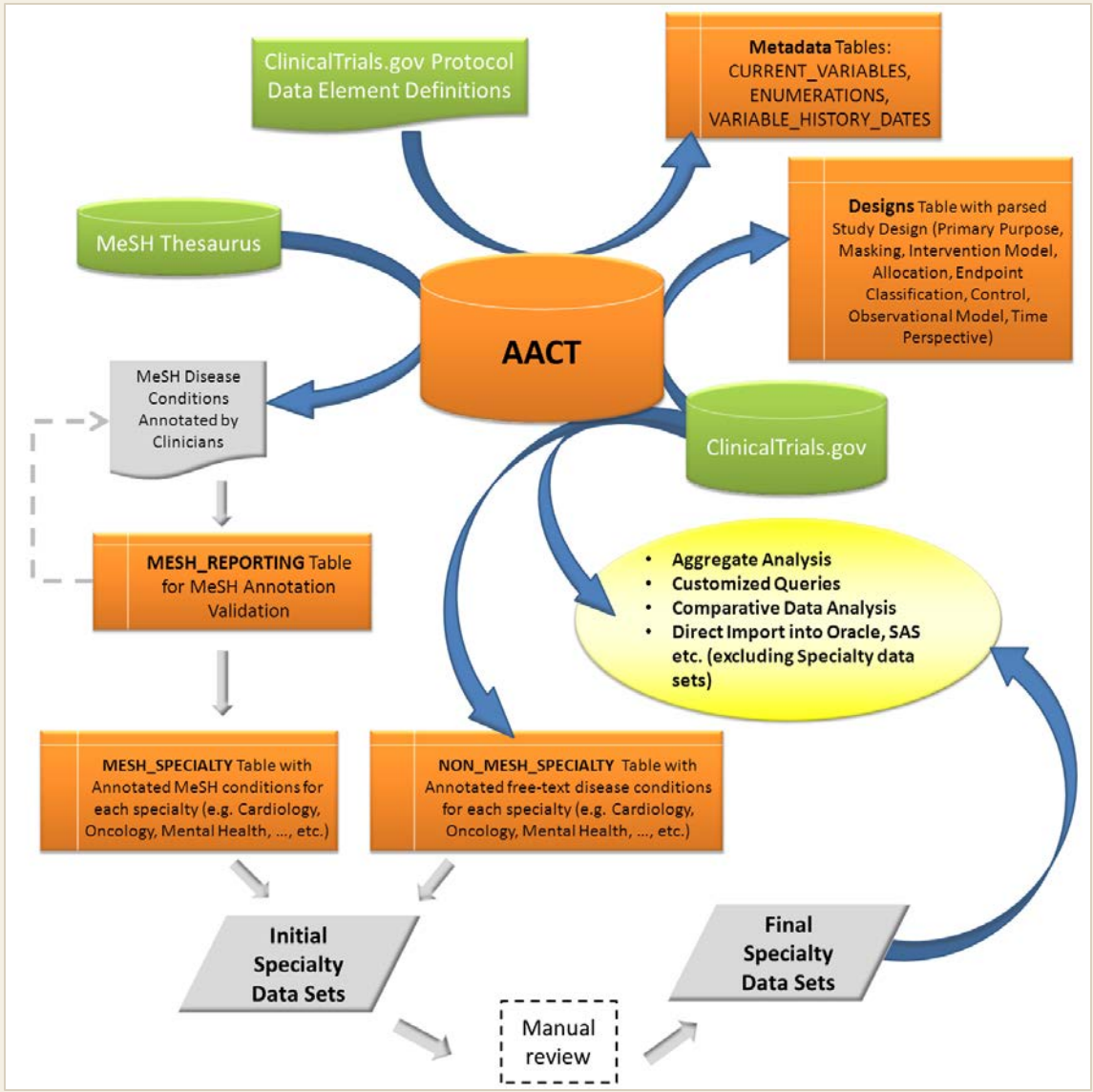
Design

- 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

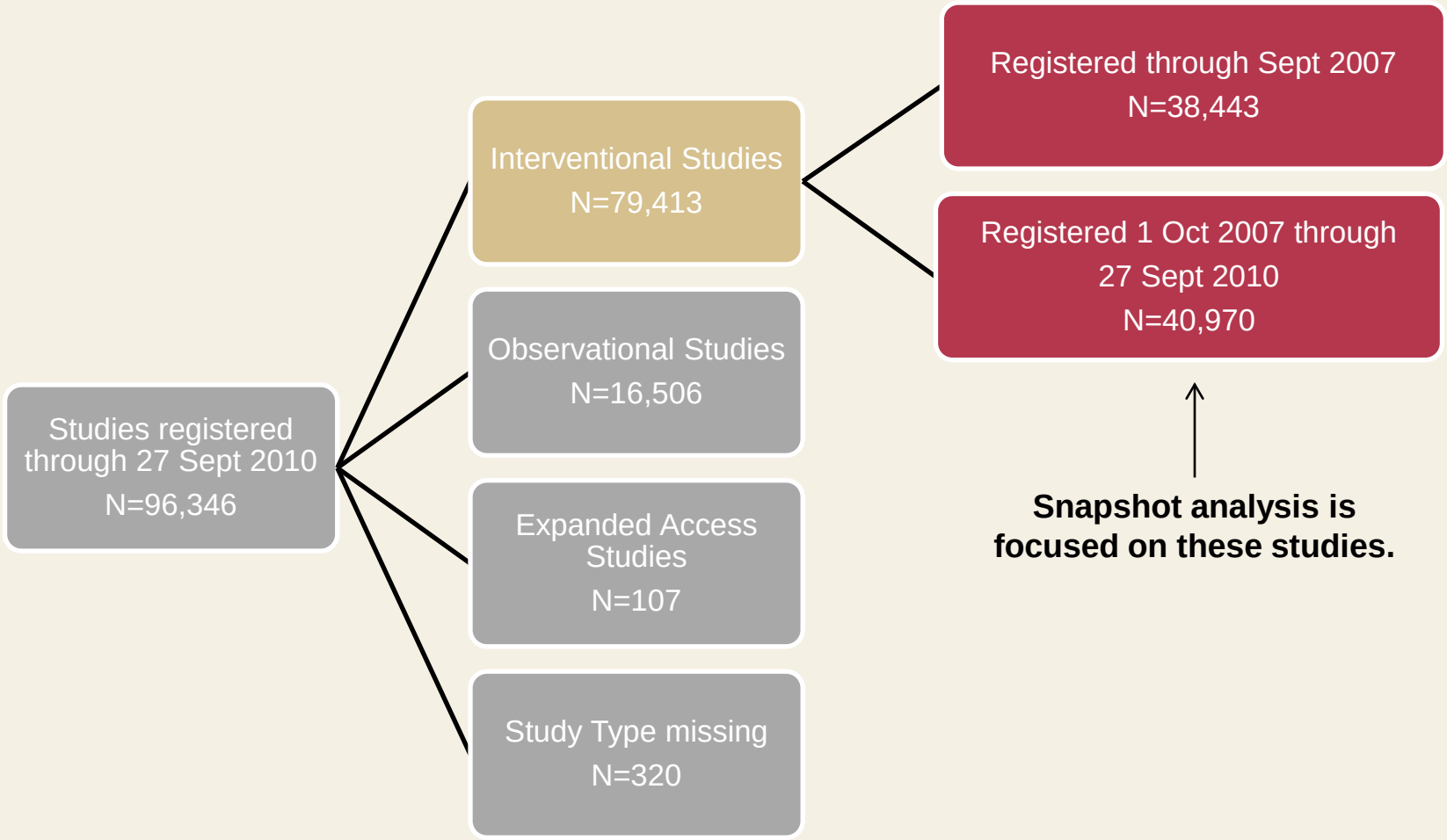
- Examine the “Clinical Research Enterprise”
- Provide information to specific user communities
- Examine the quality and completeness of reporting

Database for Aggregate Analysis of ClinicalTrials.gov (AACT)



Tasneem A, Aberle L, Ananth H, Chakraborty S, Chiswell K, et al. (2012) The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty. PLoS ONE 7(3): e33677. doi:10.1371/journal.pone.0033677

Studies registered at ClinicalTrials.gov



Overview

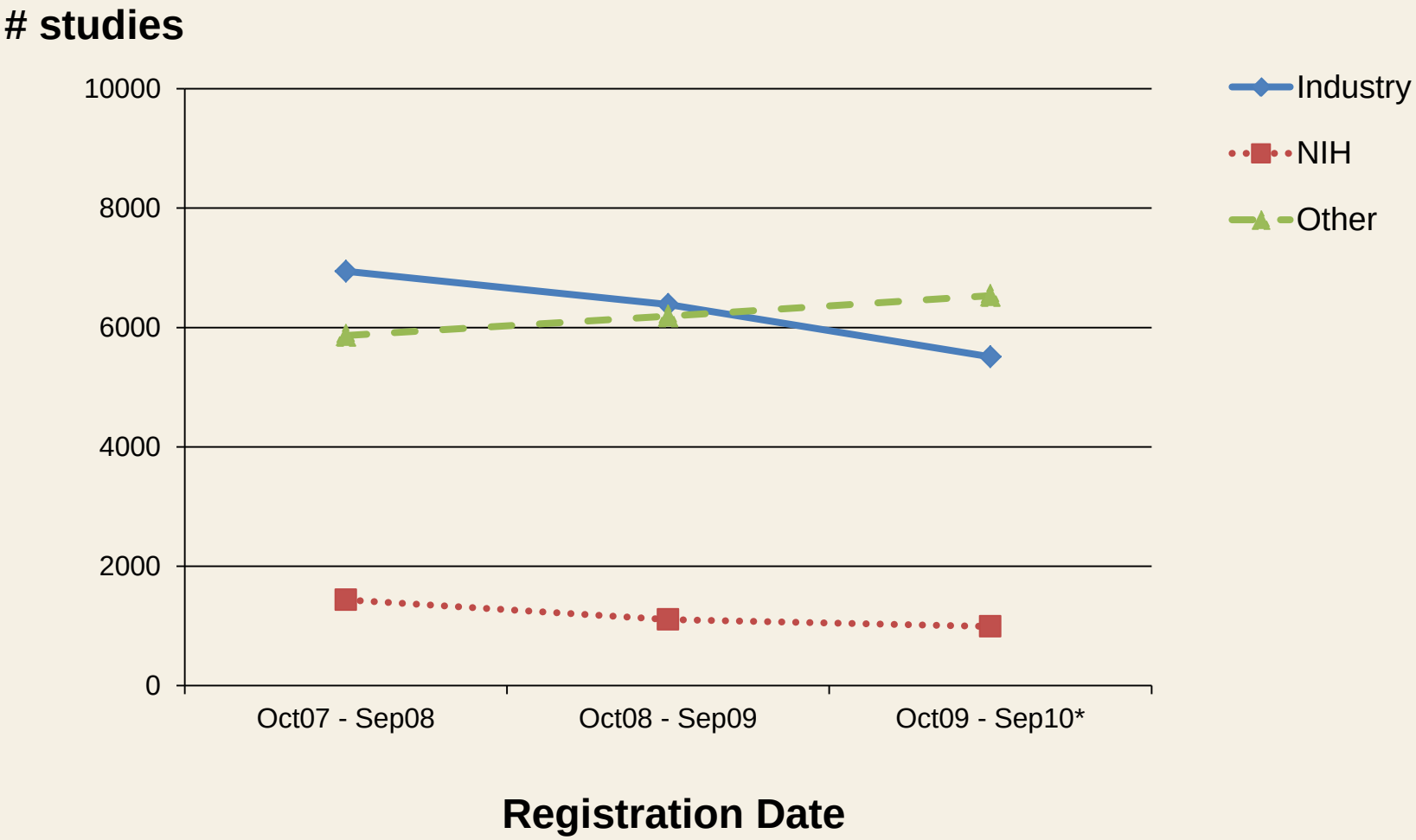
- Funding
- Study Phase
- Intervention Types
- Therapeutic area
  - Oncology
  - Cardiovascular
  - Mental Health

Funding

- Derived as follows:

	Submitted information	Derived
Lead Sponsor	**Collaborators**	**Funding**
Industry	No restrictions	Industry
Not NIH	At least one from Industry, none from NIH	Industry
NIH	No restrictions	NIH
Not industry	At least one from NIH	NIH
Not industry, not NIH	None from industry, none from NIH	Other

Funding



*** through Sept 27, 2010**

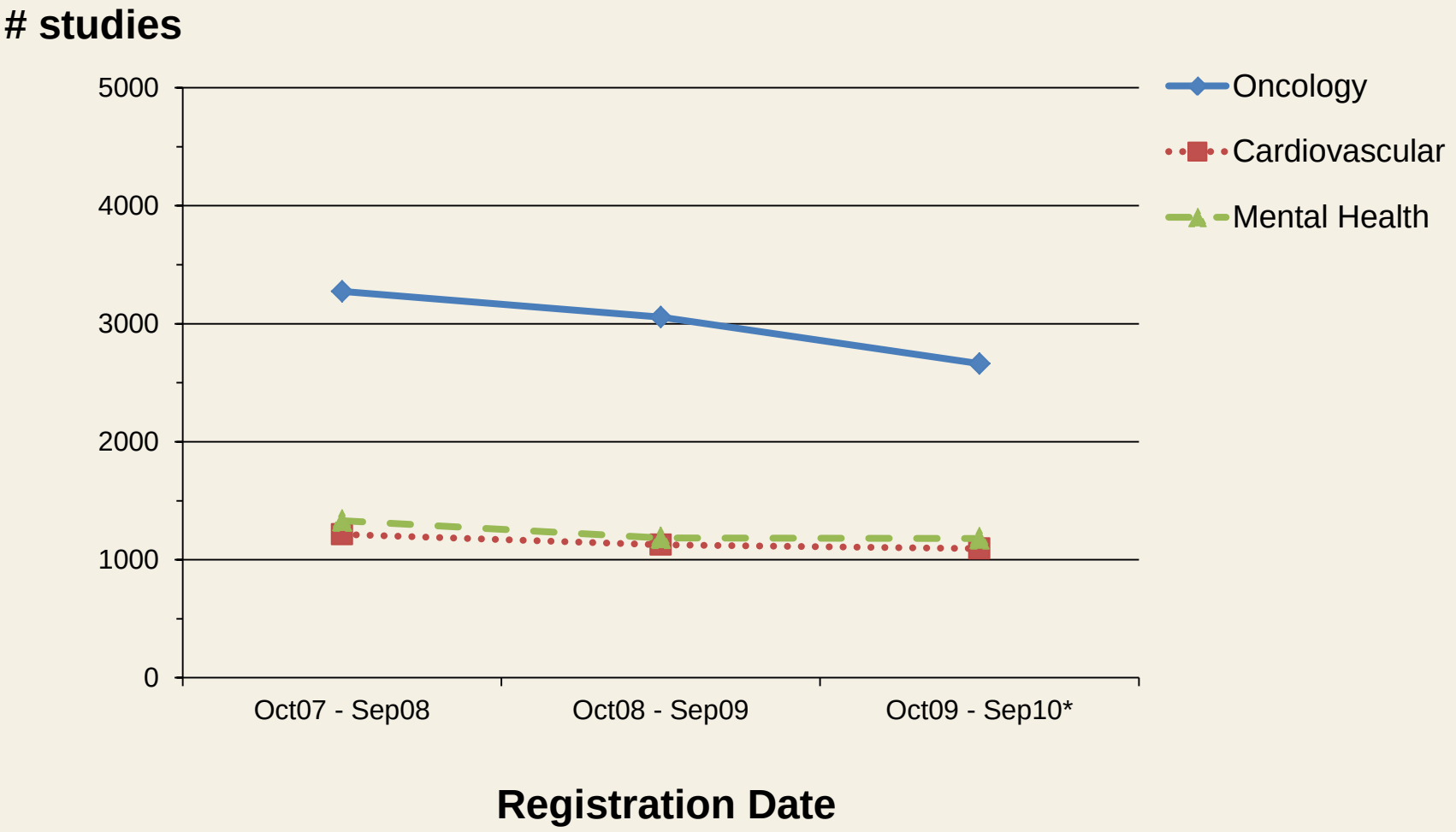
Clinical Therapeutic Area

- 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

Further details: Tasneem A, Aberle L, Ananth H, Chakraborty S, Chiswell K, et al. (2012) The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty. PLoS ONE 7(3): e33677. doi:10.1371/journal.pone.0033677

* MeSH: Medical Subject Headings

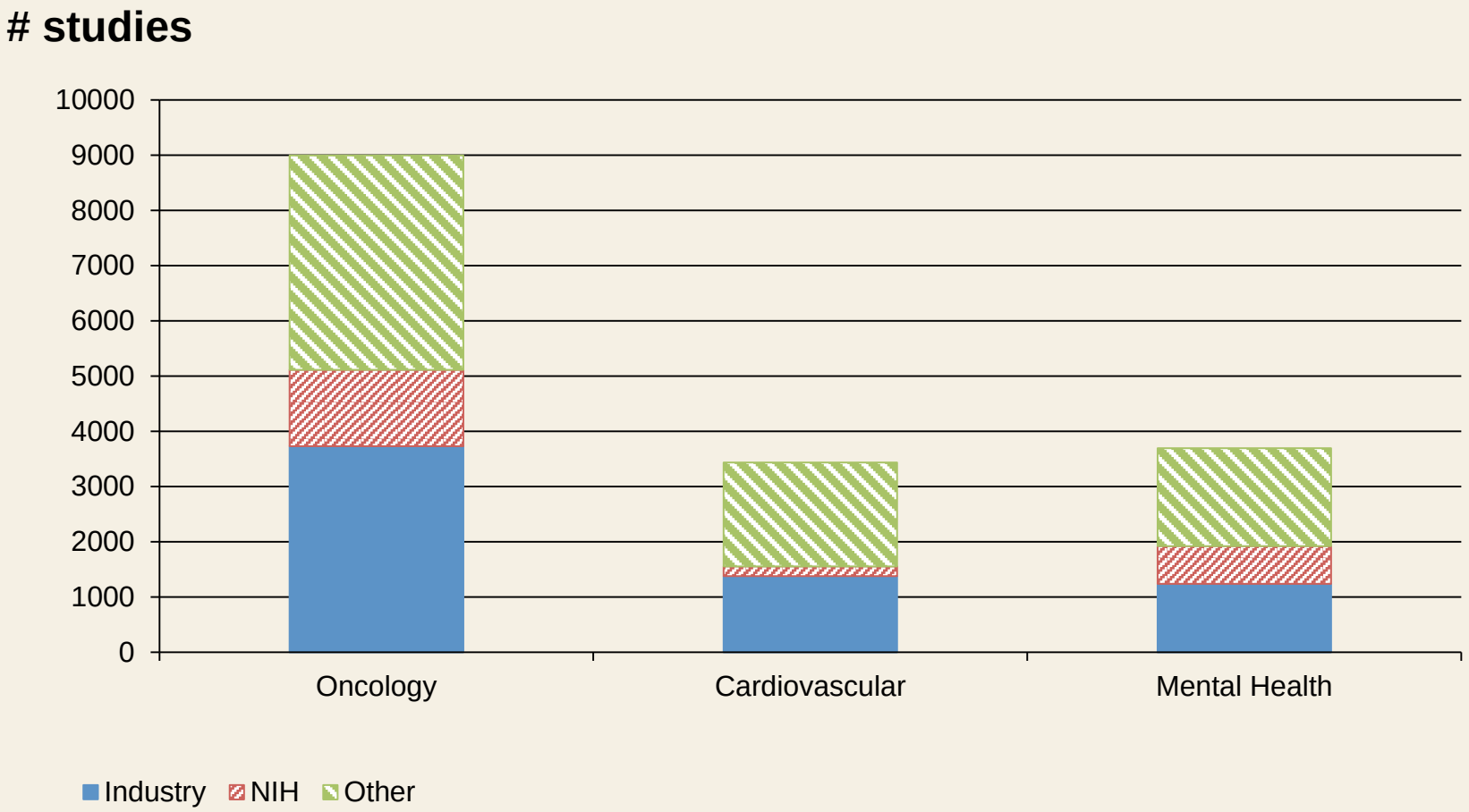
Therapeutic Area



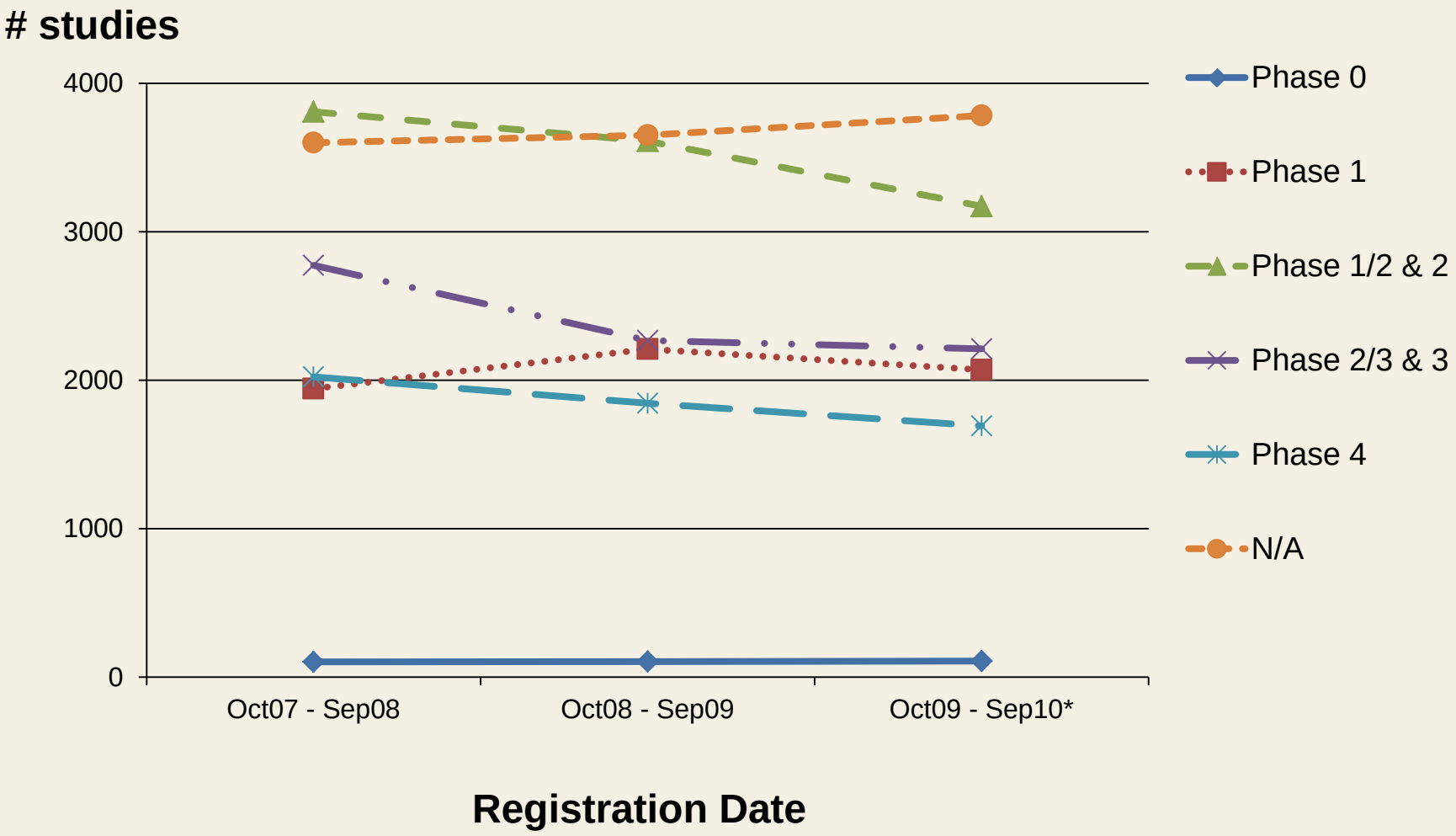
A study may be counted in more than one therapeutic area

*** through Sept 27, 2010**

Funding by Therapeutic Area

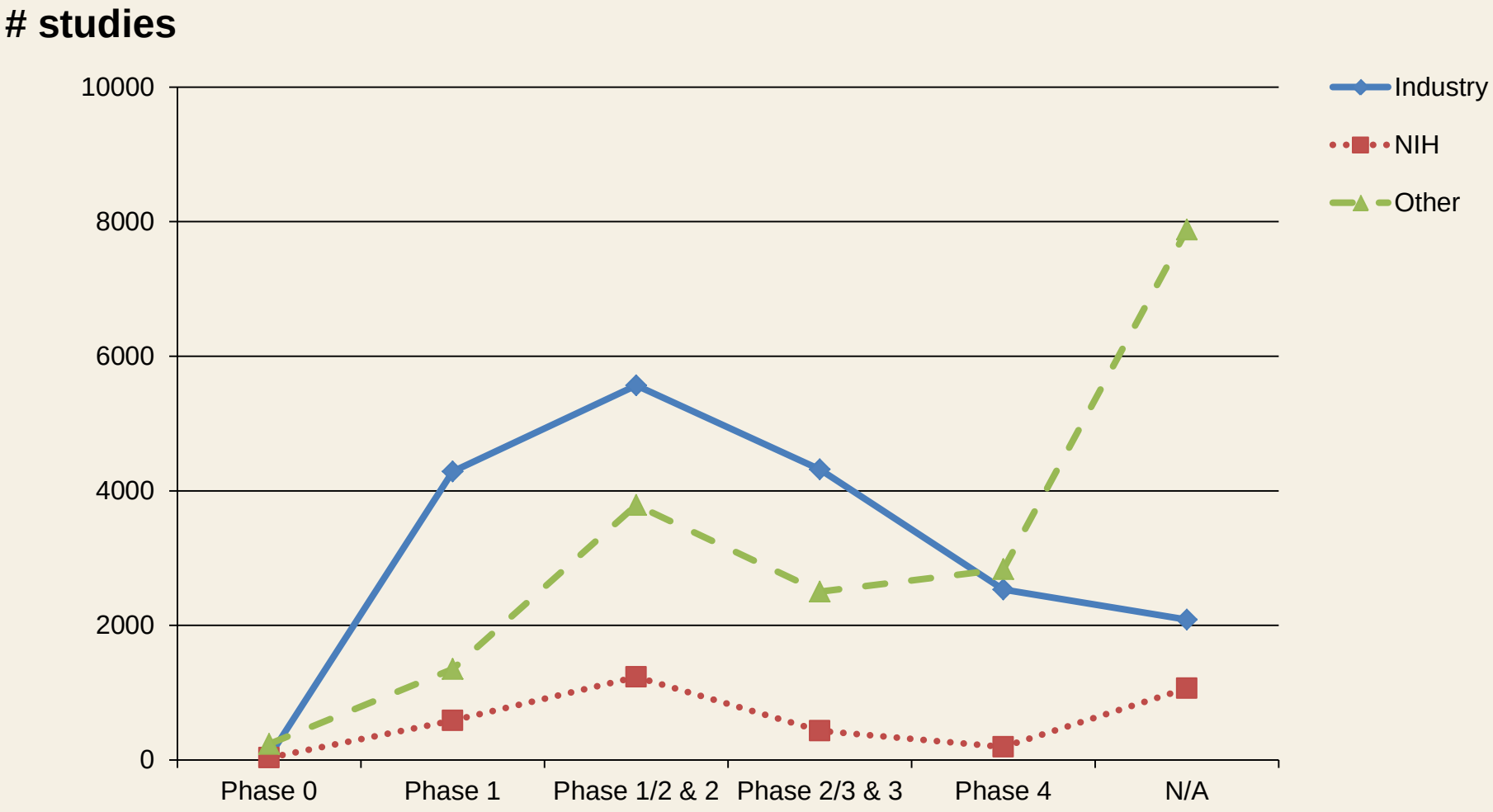


Study Phase

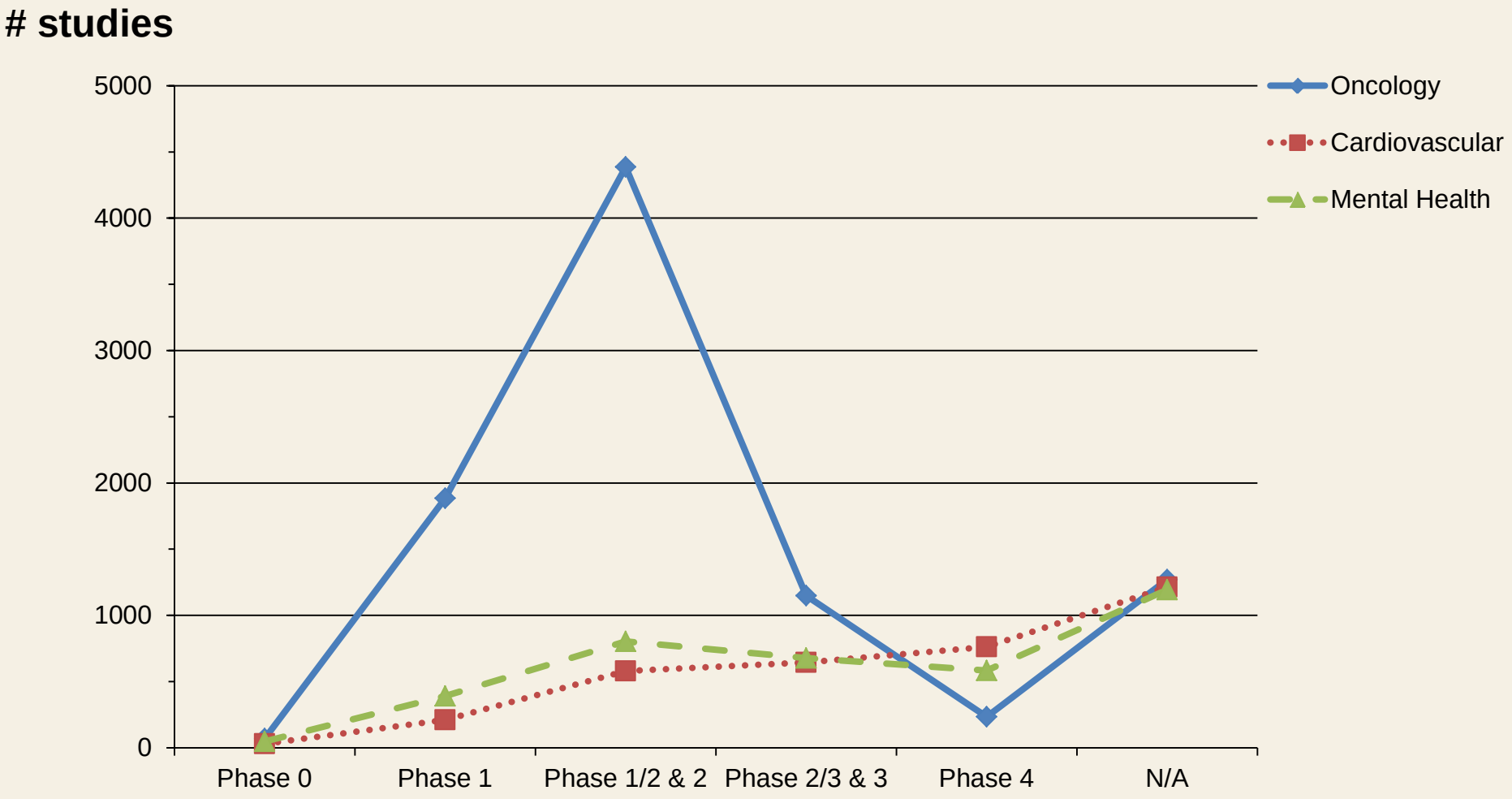


*** through Sept 27, 2010**

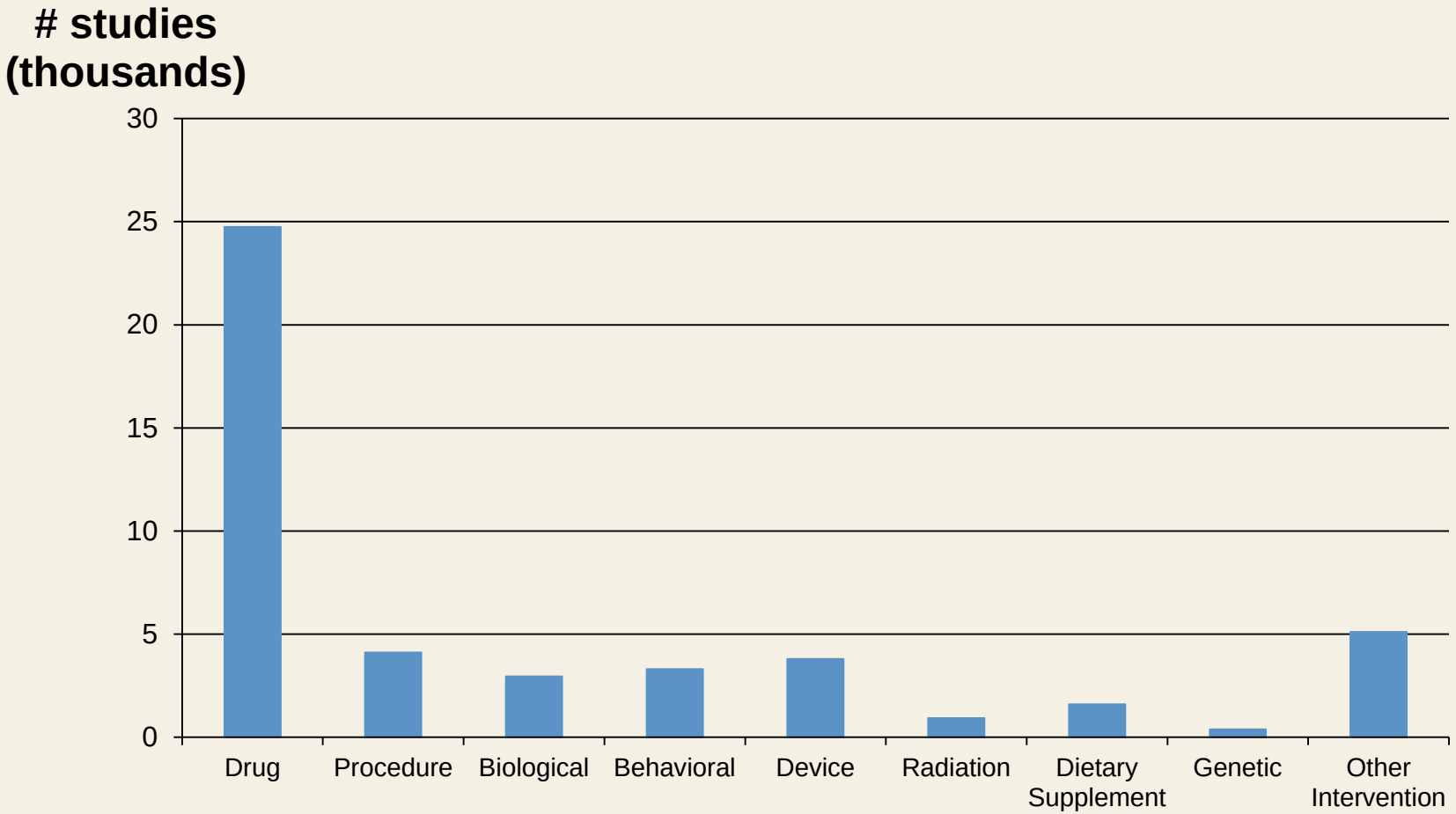
Funding by Phase



Therapeutic Area by Phase

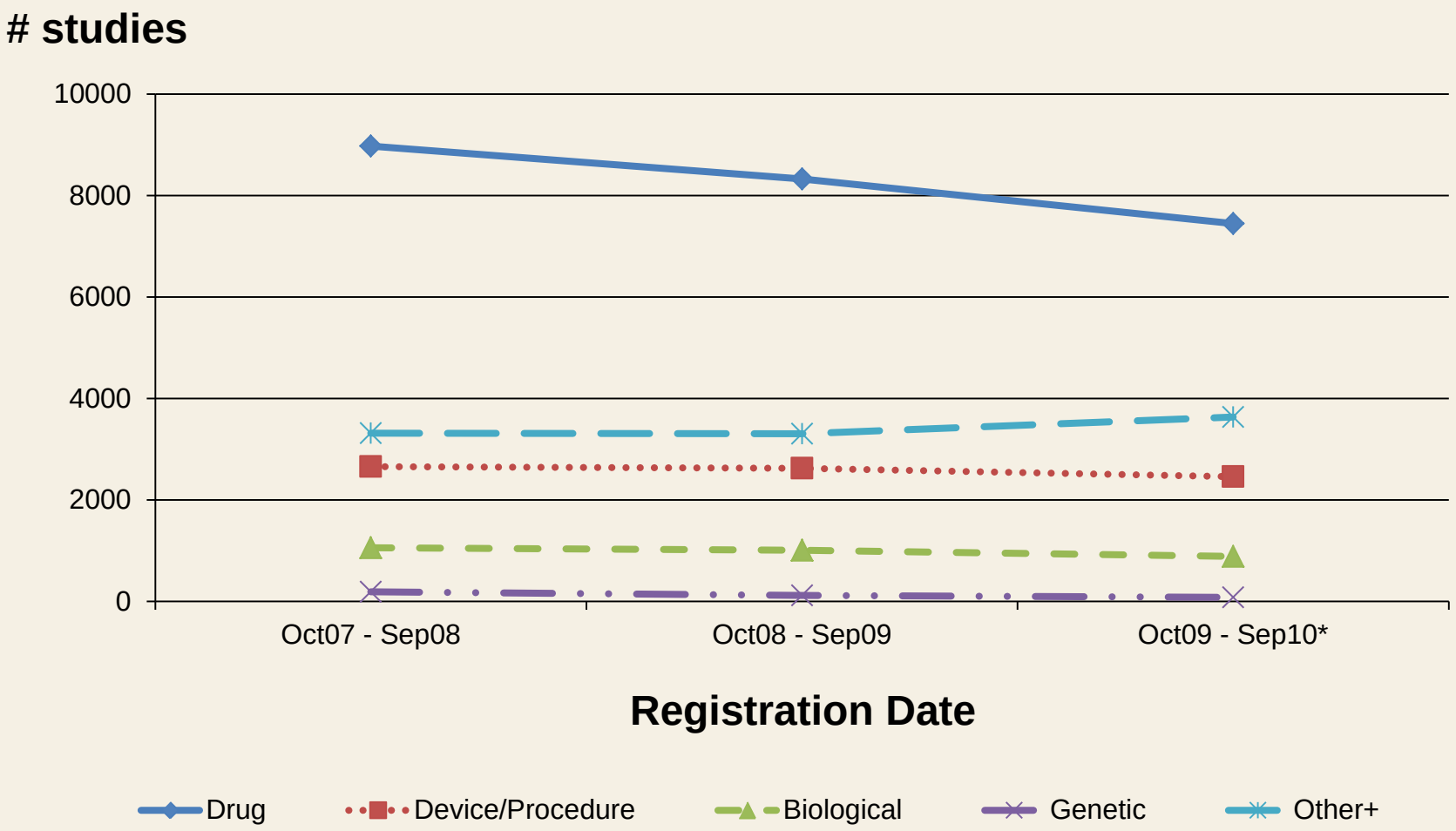


Intervention Types



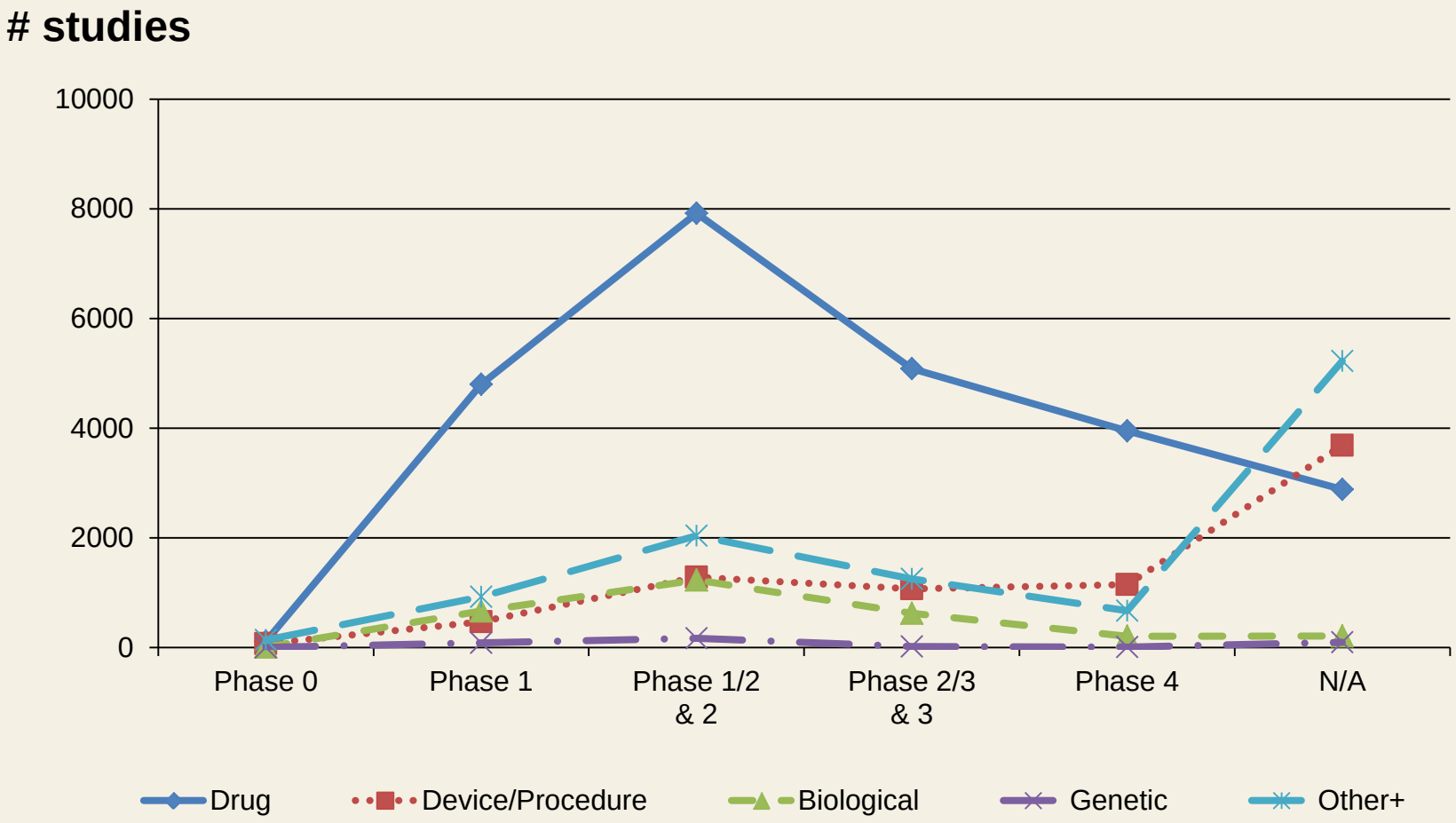
A study may have more than one intervention type

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**

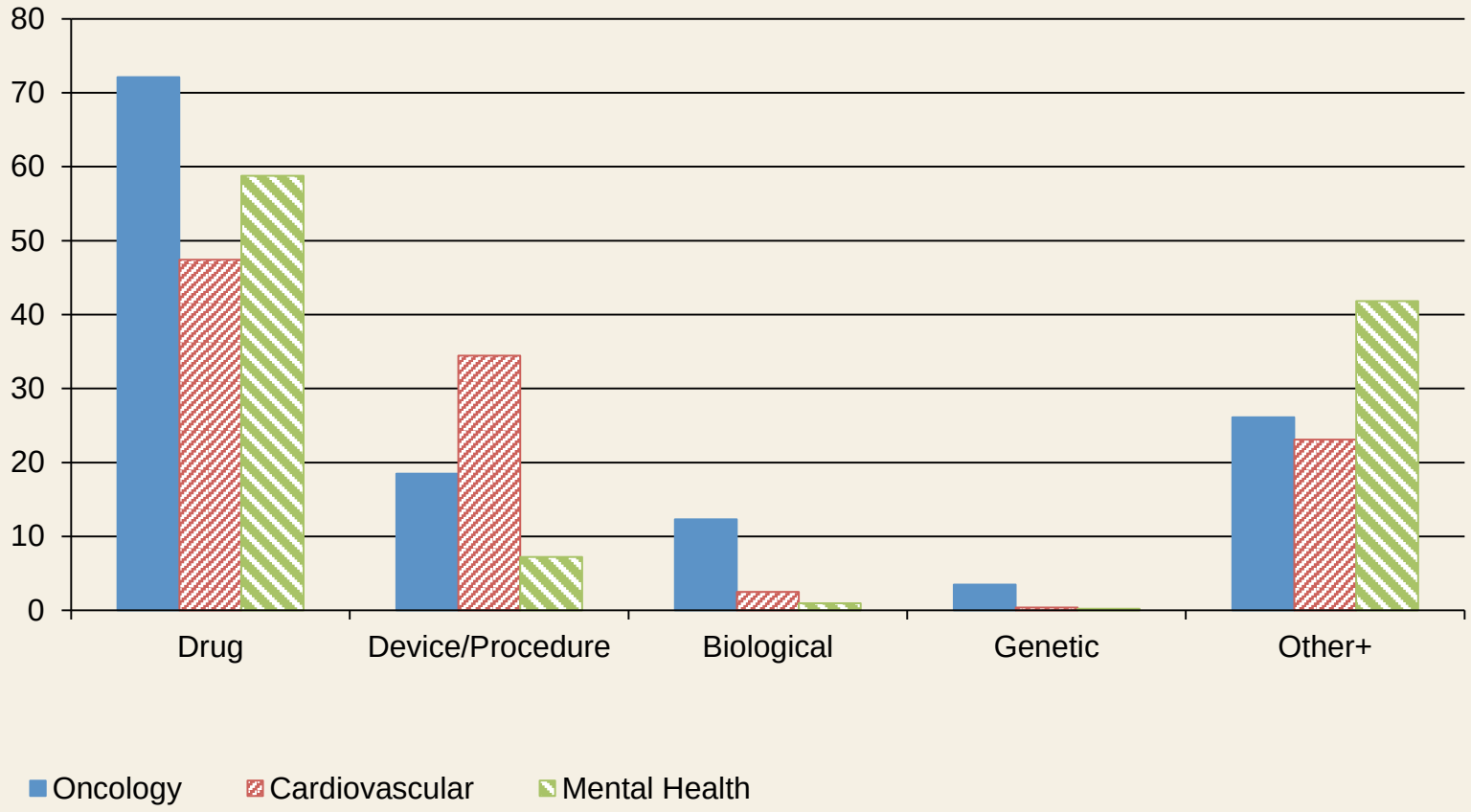
Intervention Types by Phase



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

Intervention Types by Therapeutic Area

% studies*



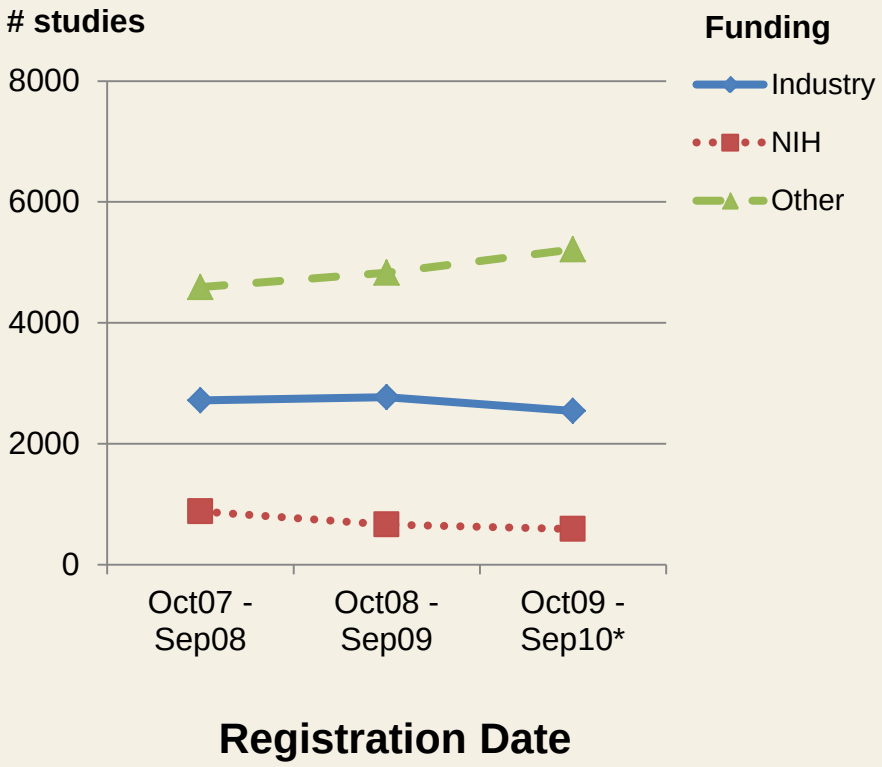
Studies of drugs, biologics and devices in phases 2-4 are required to be registered by FDAAA.
+ Includes behavioral, radiation, dietary supplement, in addition to other interventions
*** Percent calculated within each therapeutic area**

Sites/Participants

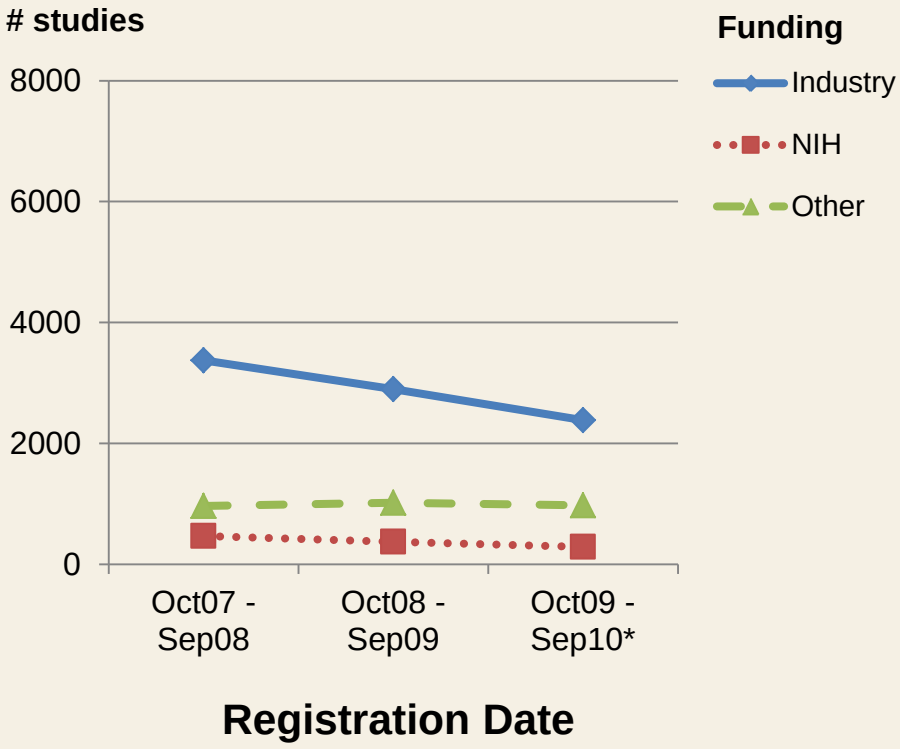
- Single- and multi-center studies
- Number of sites for multi-center studies
- Enrollment
- Location of sites
- Eligibility: sex
- Eligibility: age restrictions and exclusions

Single-Center and Multi-center Studies

Single-Center



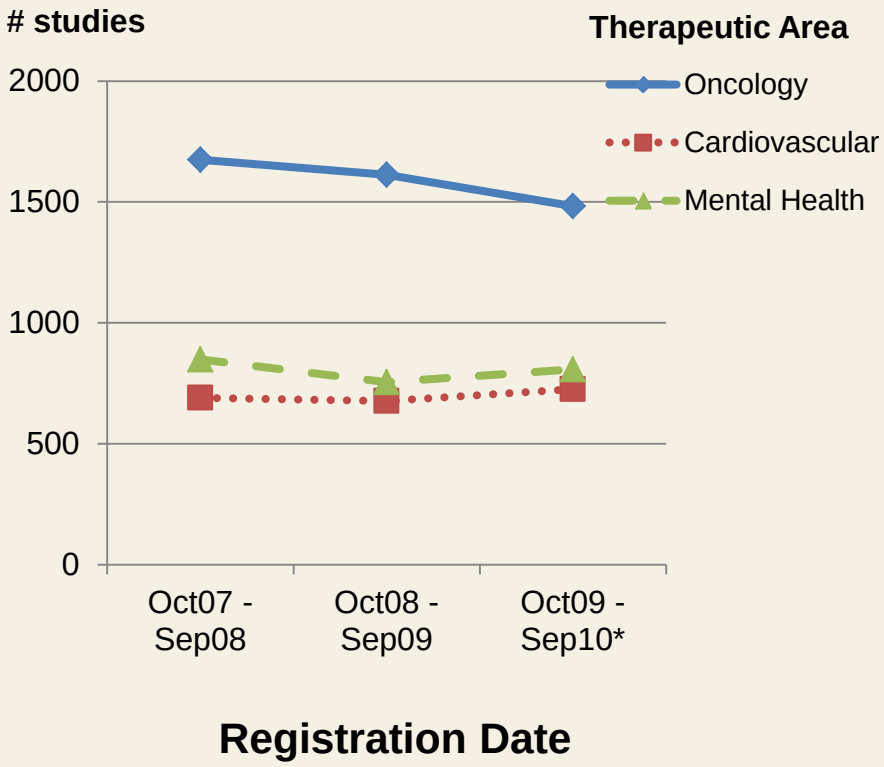
Multi-center



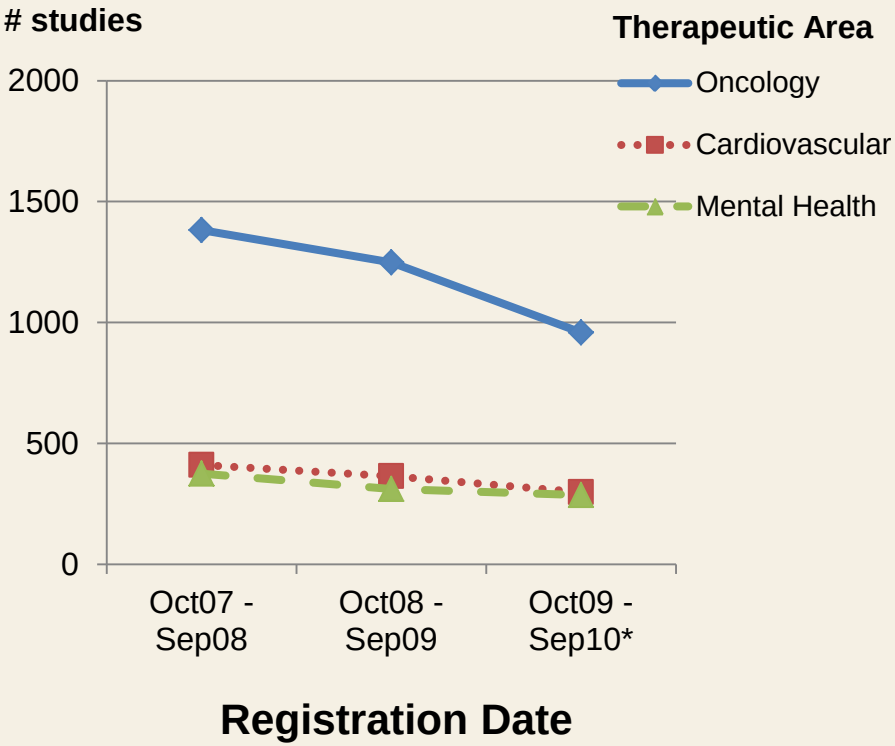
N=3,450 studies missing center information
*** through Sept 27, 2010**

Single-Center and Multi-center Studies

Single-Center

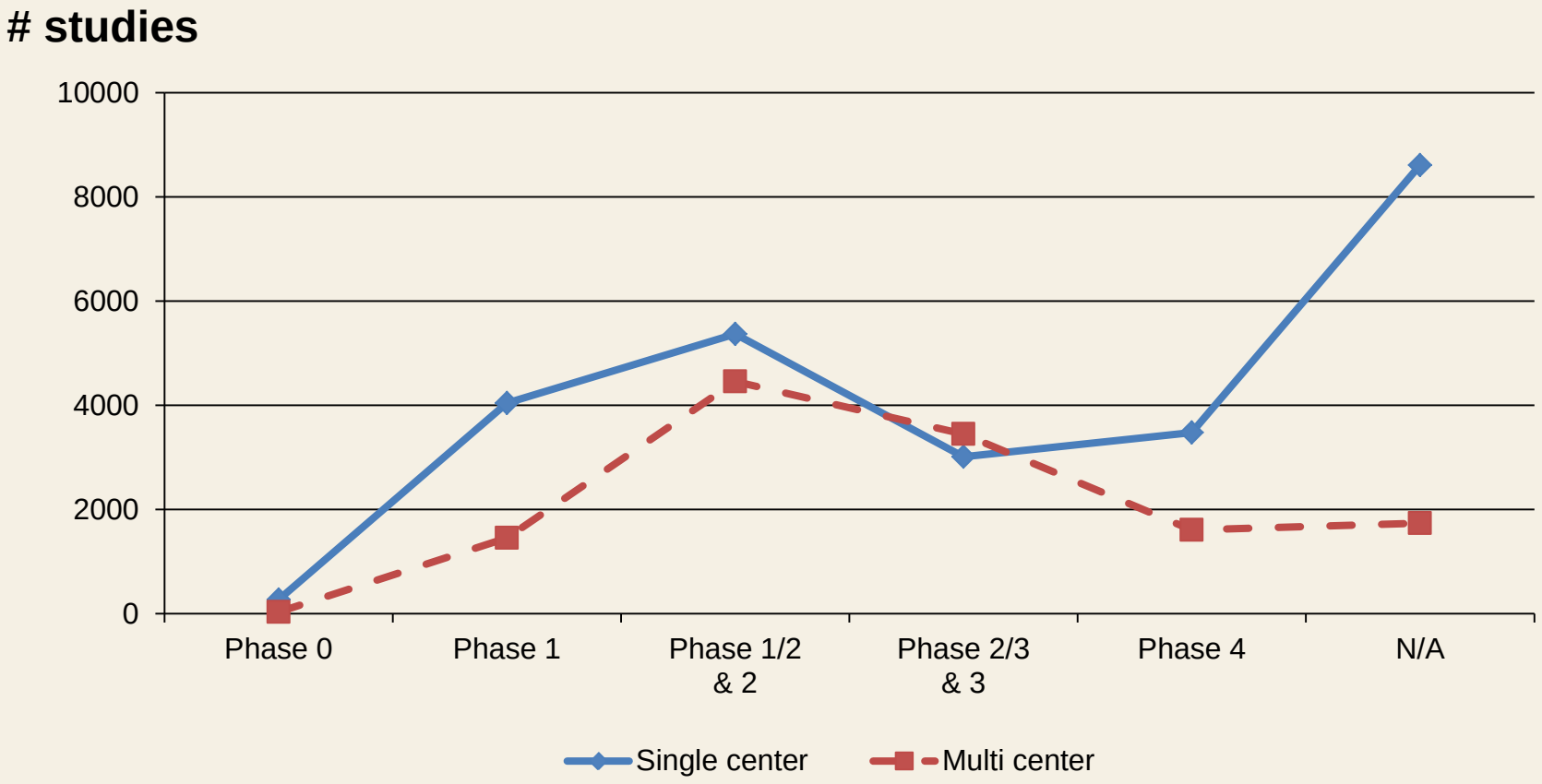


Multi-center



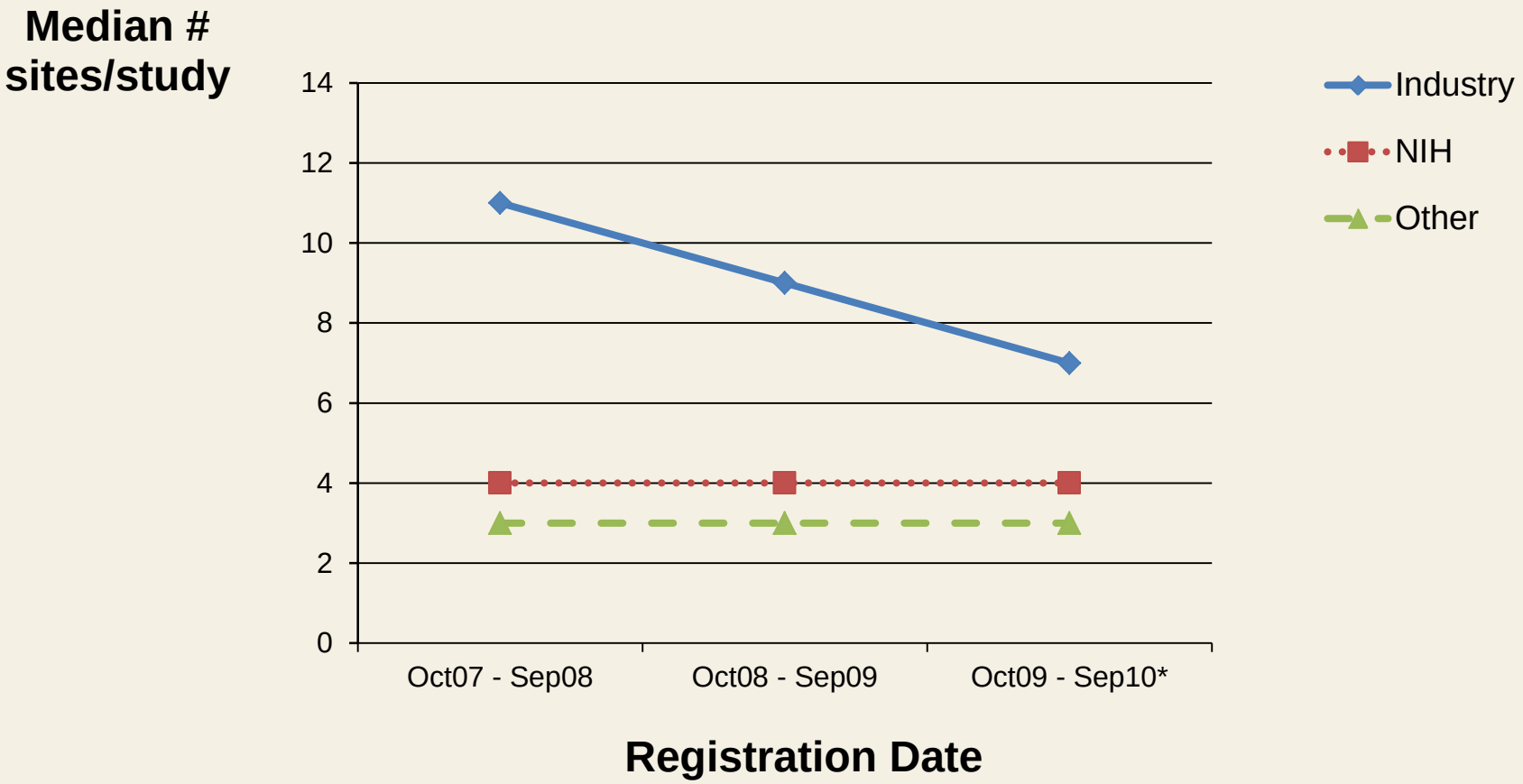
*** through Sept 27, 2010**

Single-center and Multi-center Studies by Phase



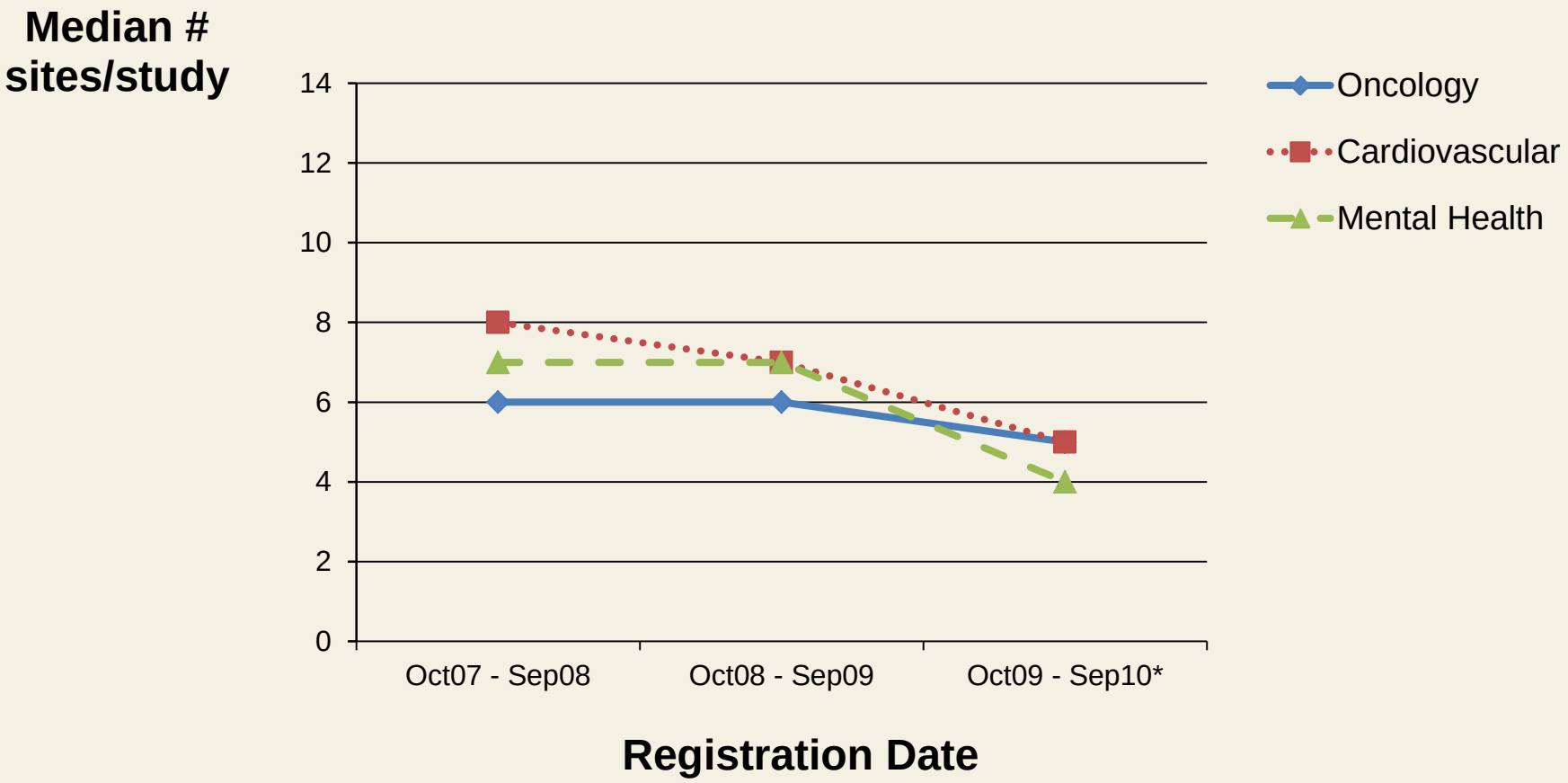
N=3,450 studies missing center information

Median Number of Sites/Study for Multi-center Studies



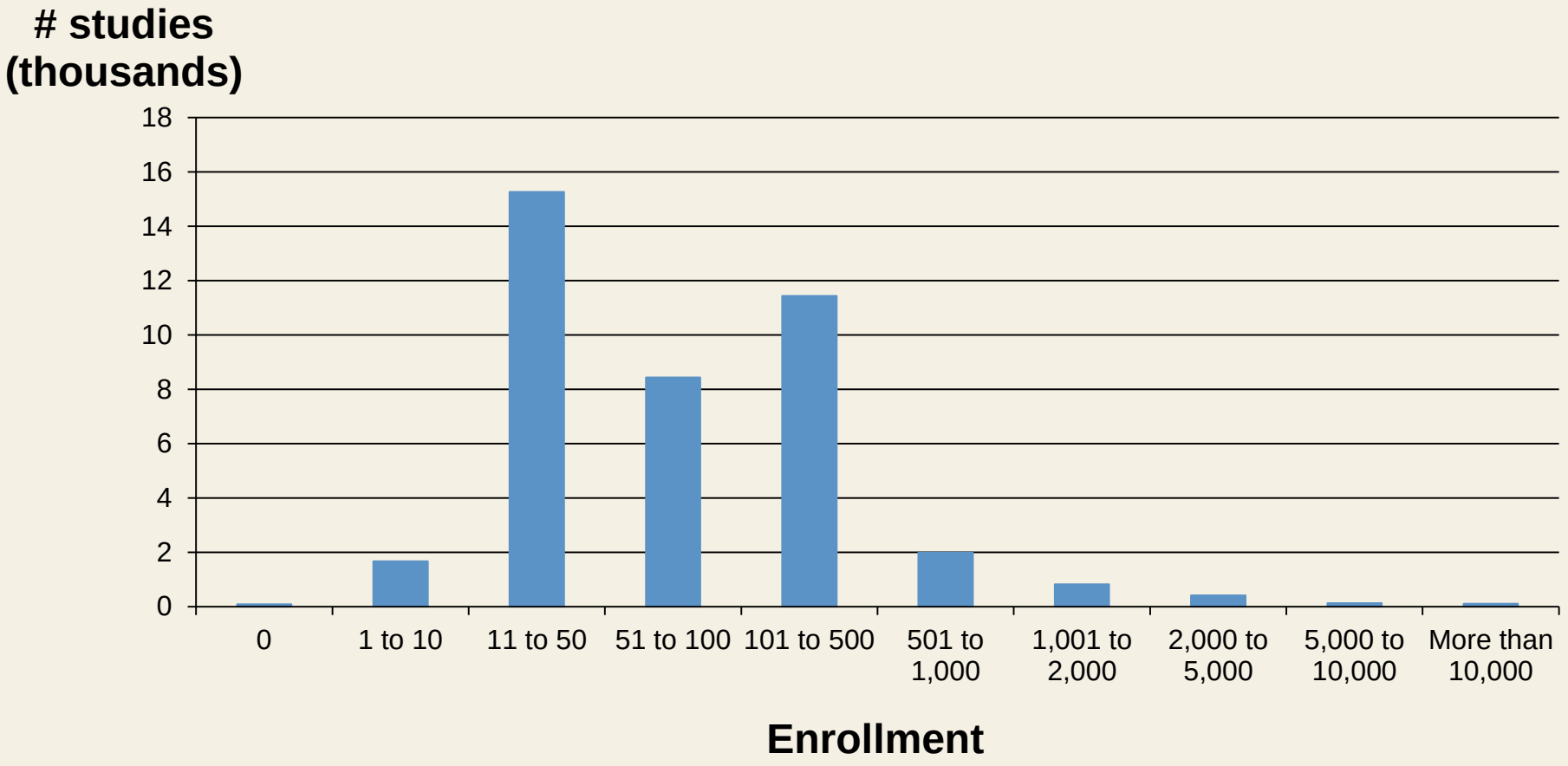
Based on N=12,732 multi-center studies
N=3,450 studies missing center information
*** through Sept 27, 2010**

Median Number of Sites/Study for Multi-center Studies



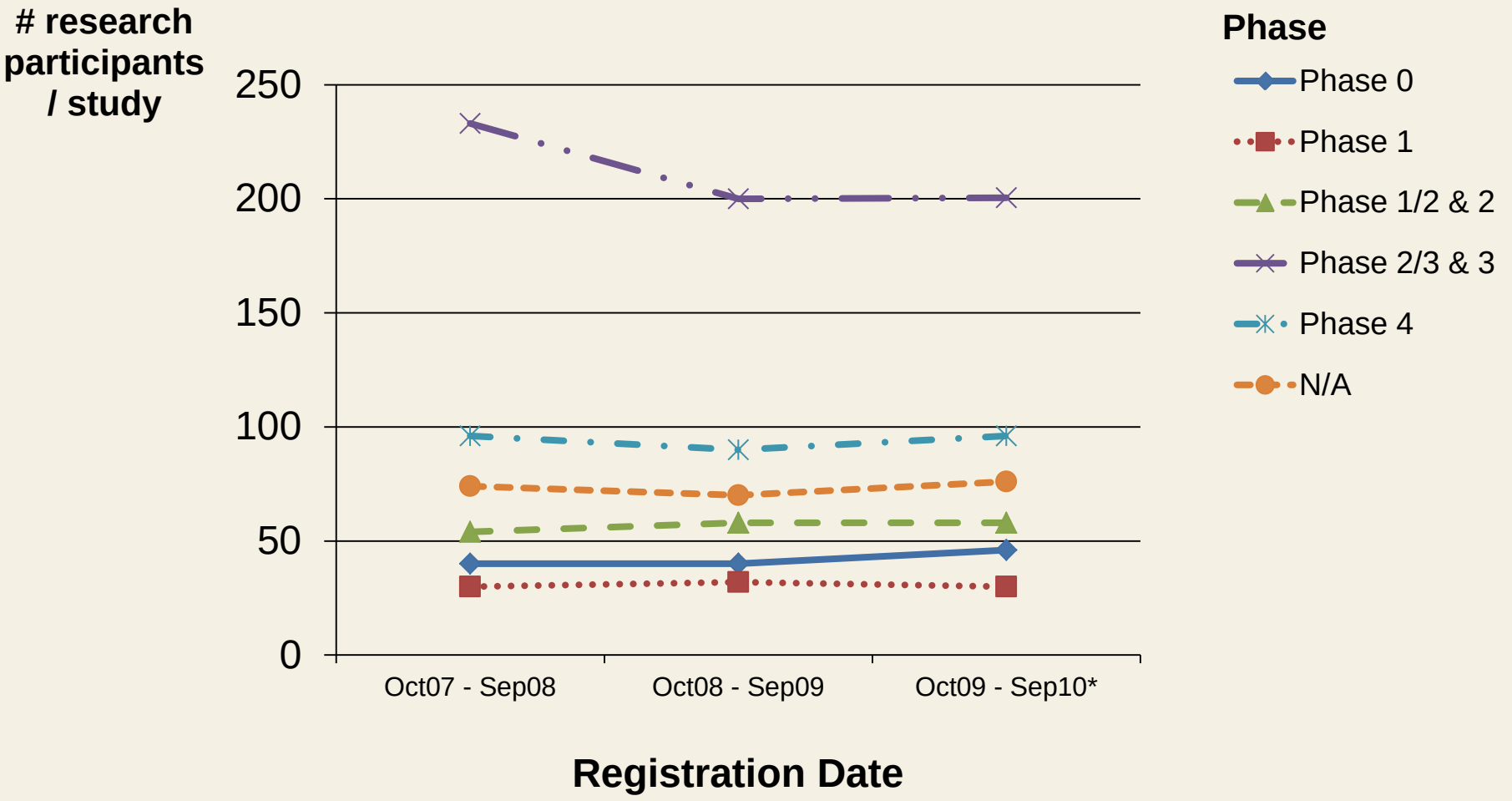
*** through Sept 27, 2010**

Number of Subjects/Study
(Anticipated or Actual enrollment)



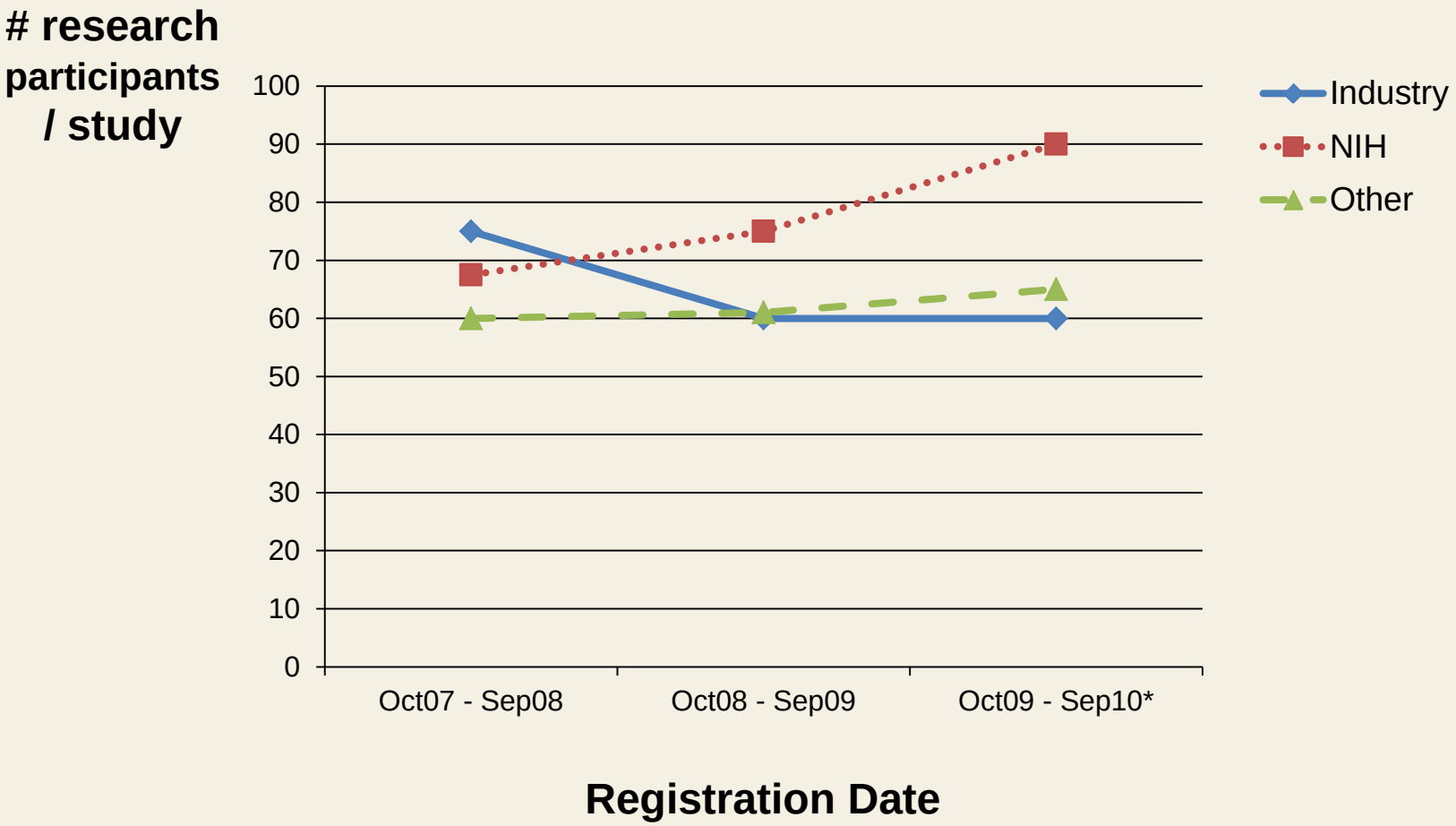
604 studies have missing enrollment

Median Enrollment by Phase



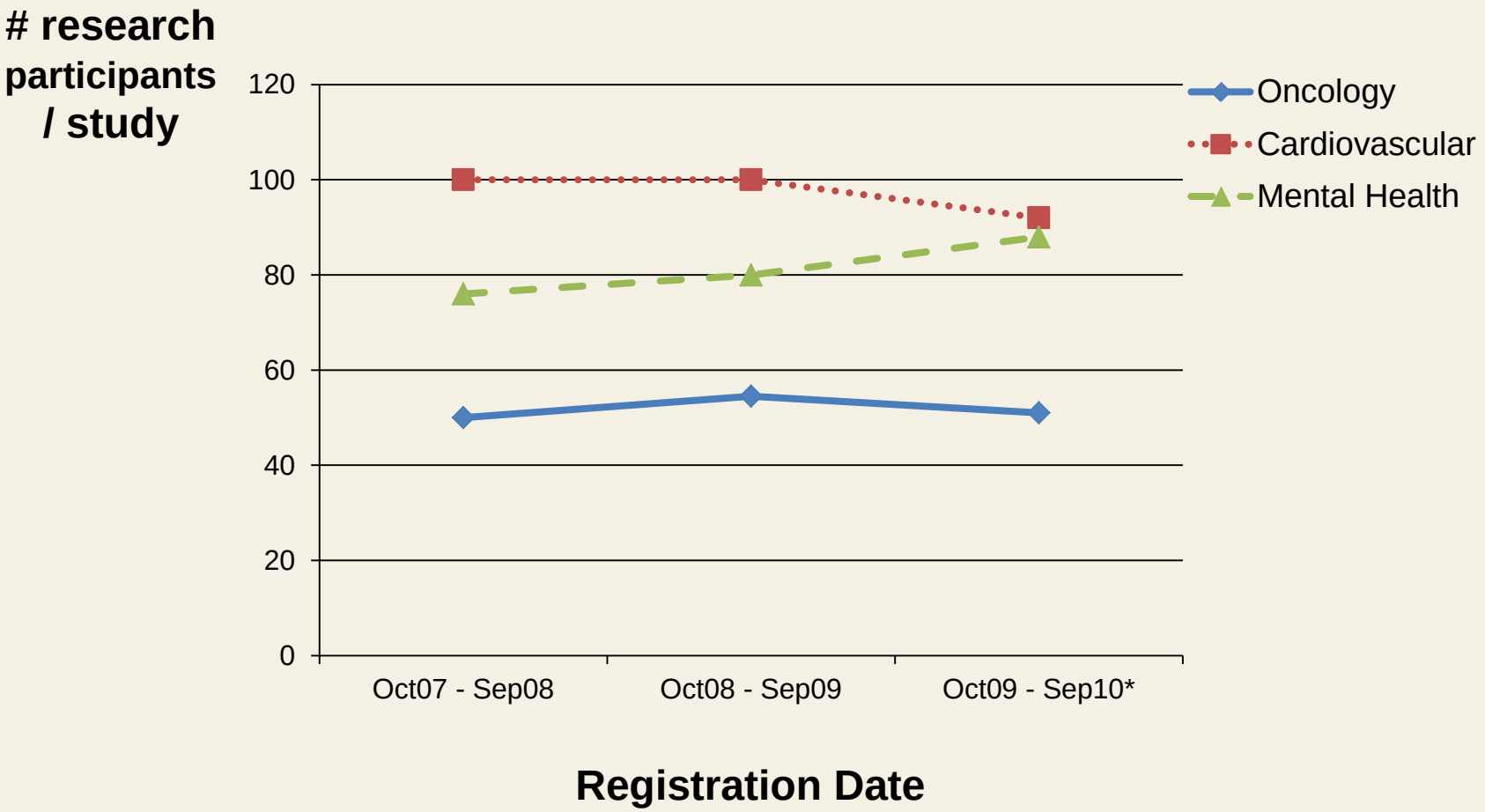
604 studies have missing enrollment
*** through Sept 27, 2010**

Median Enrollment by Funding



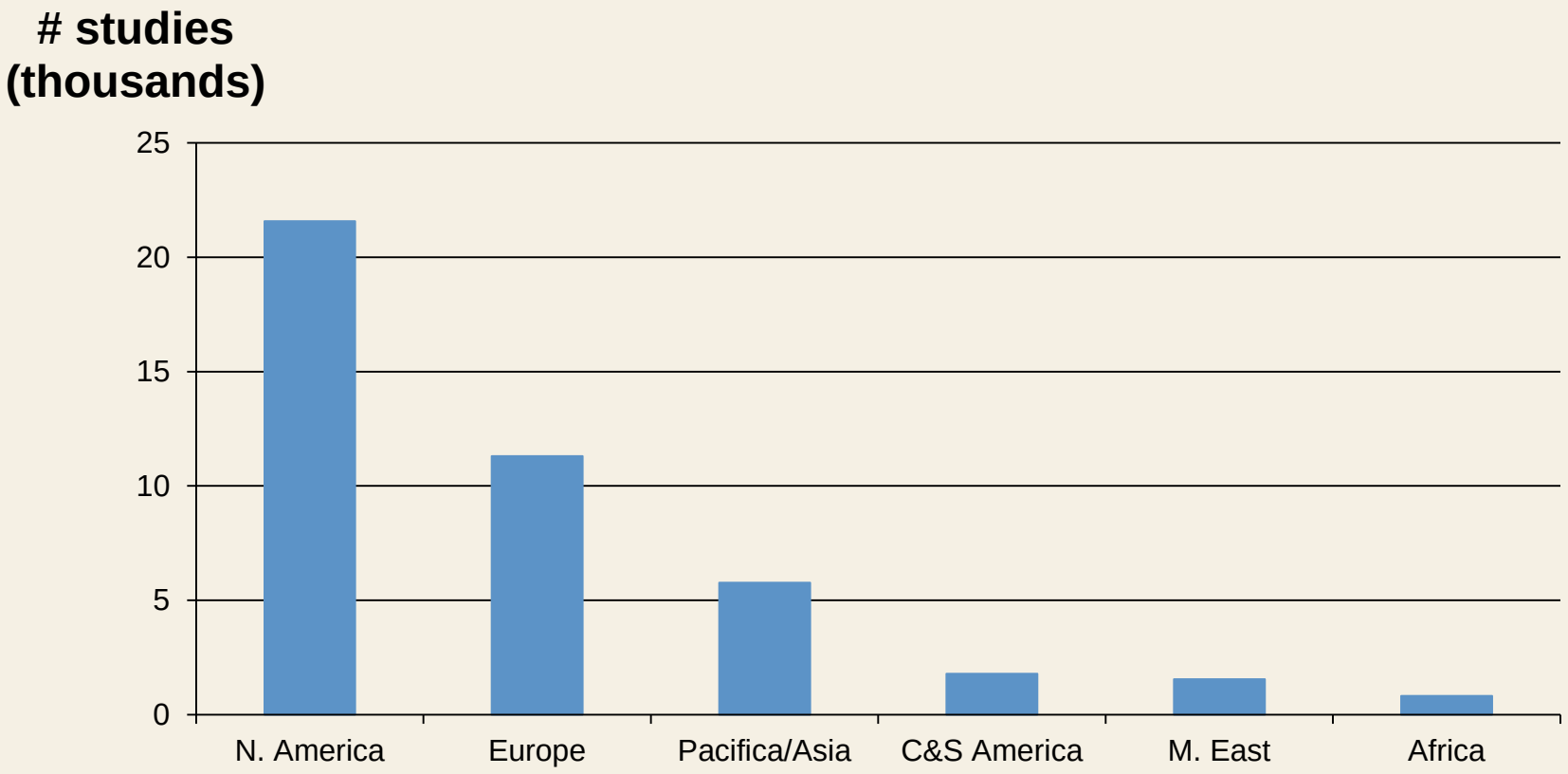
604 studies have missing enrollment
*** through Sept 27, 2010**

Median Enrollment by Therapeutic Area



*** through Sept 27, 2010**

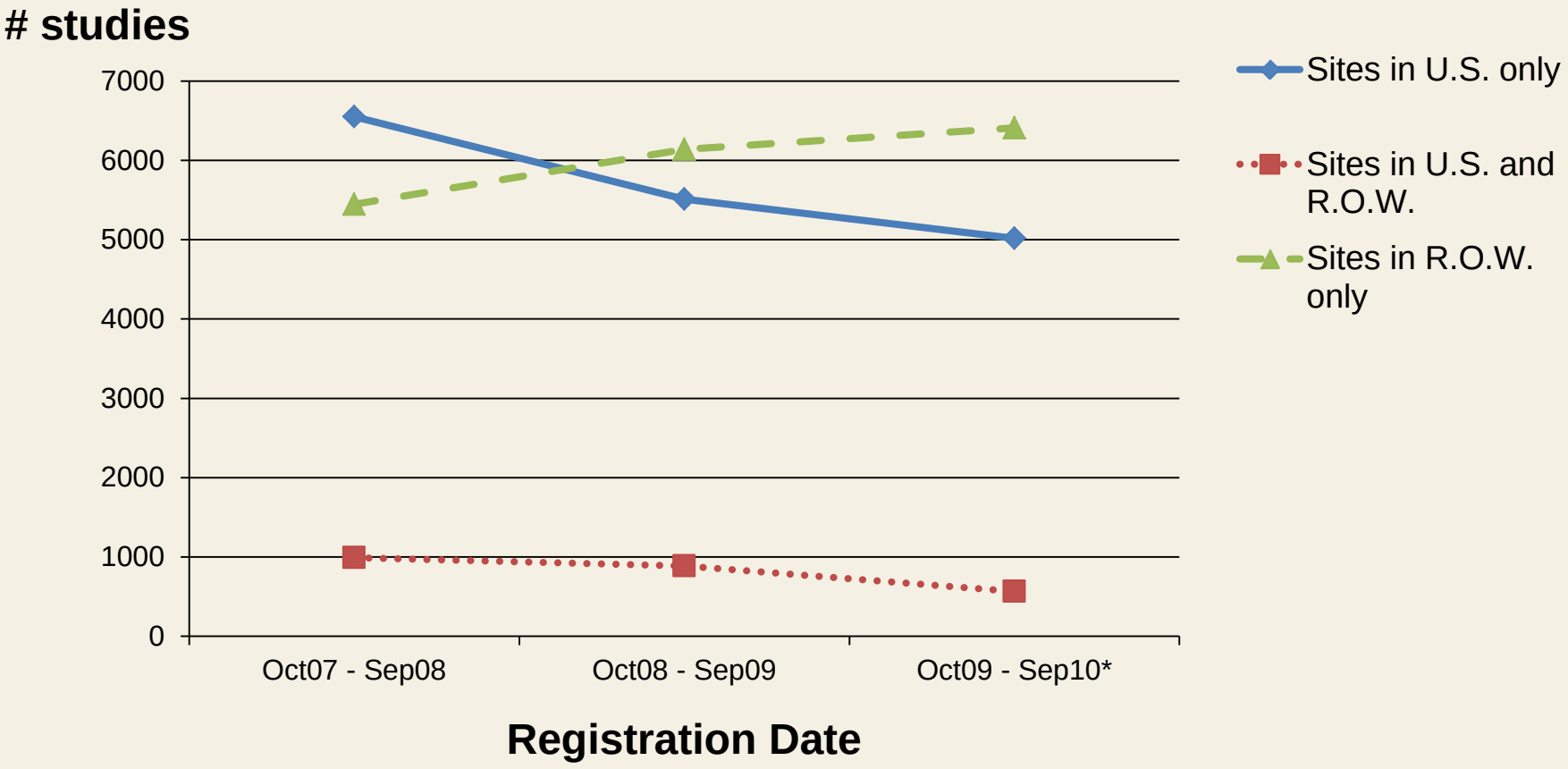
Location of Study Sites



N=3,450 studies have missing center information

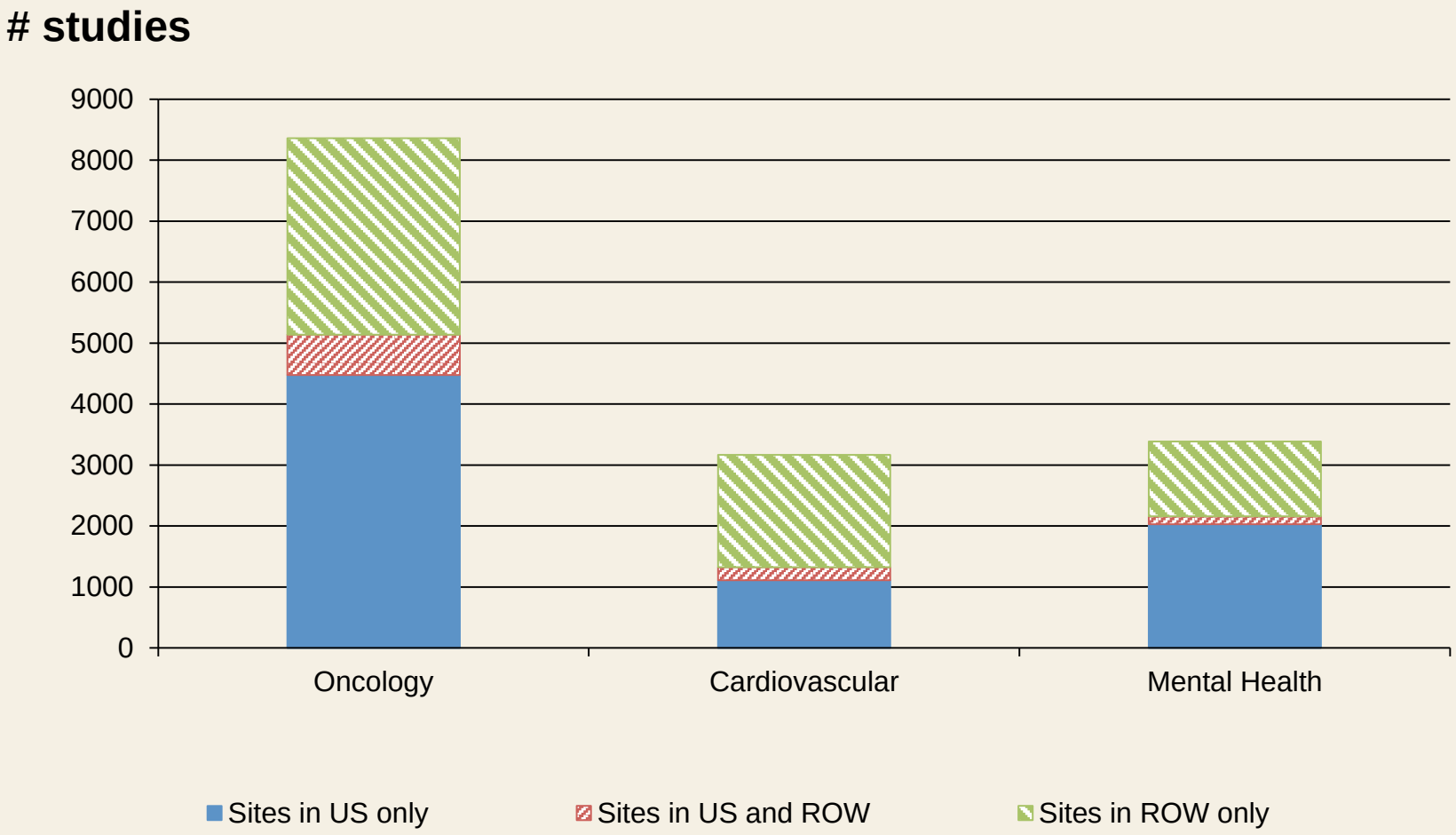
A study can have sites in multiple regions
Regions are defined according to http://www.clinicaltrials.gov/ct2/search/browse?brwse=locn_cat
Central and South America combined into C&S America Pacifica, and East, North, South, and Southeast Asia combined into Pacifica/Asia

Studies with Sites in U.S. and Rest of World (R.O.W.)

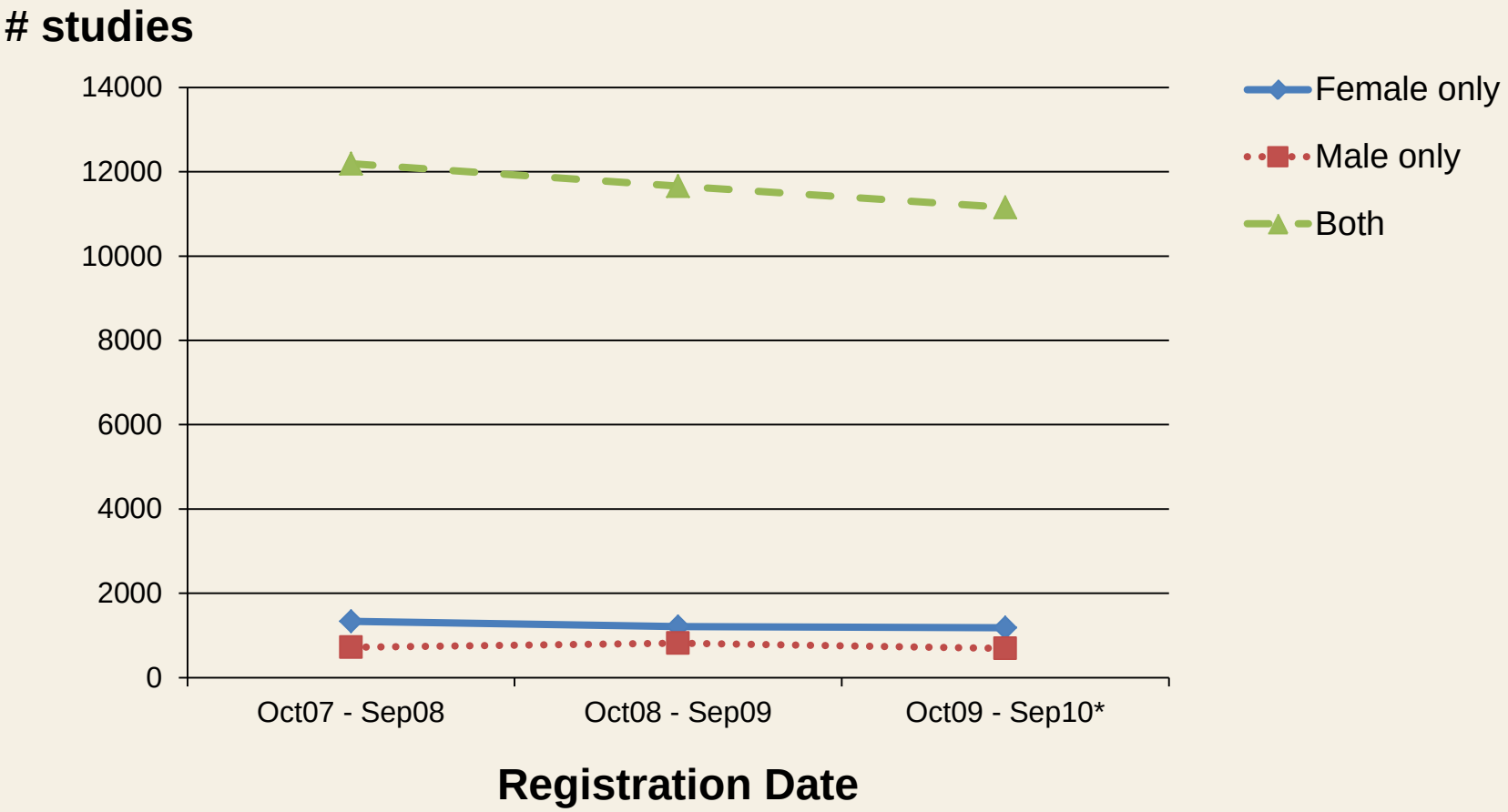


N=3,450 studies have missing center information
*** through Sept 27, 2010**

Location of Studies by Therapeutic Area

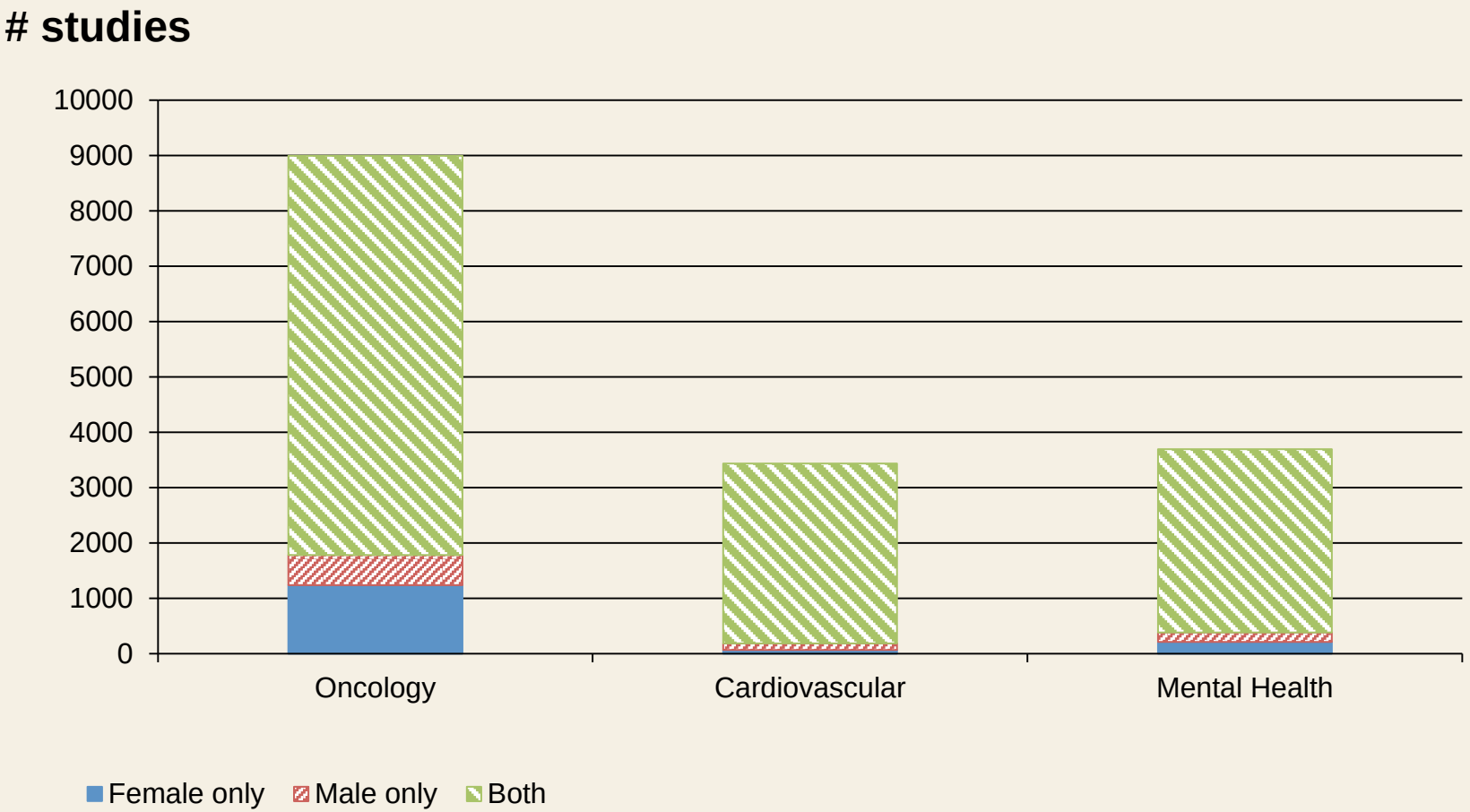


Eligibility: Sex

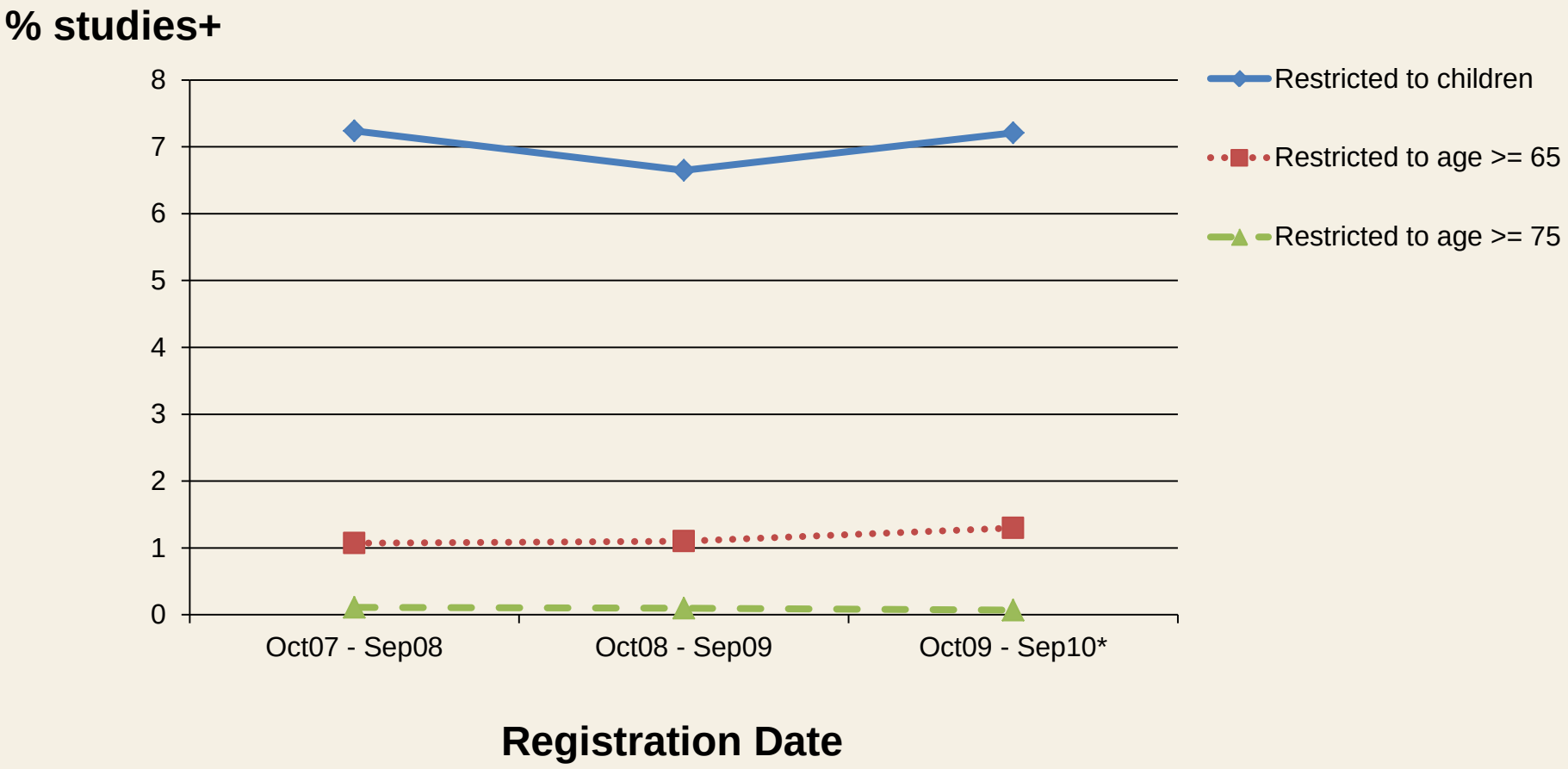


*** through Sept 27, 2010**

Sex Eligibility by Therapeutic Area



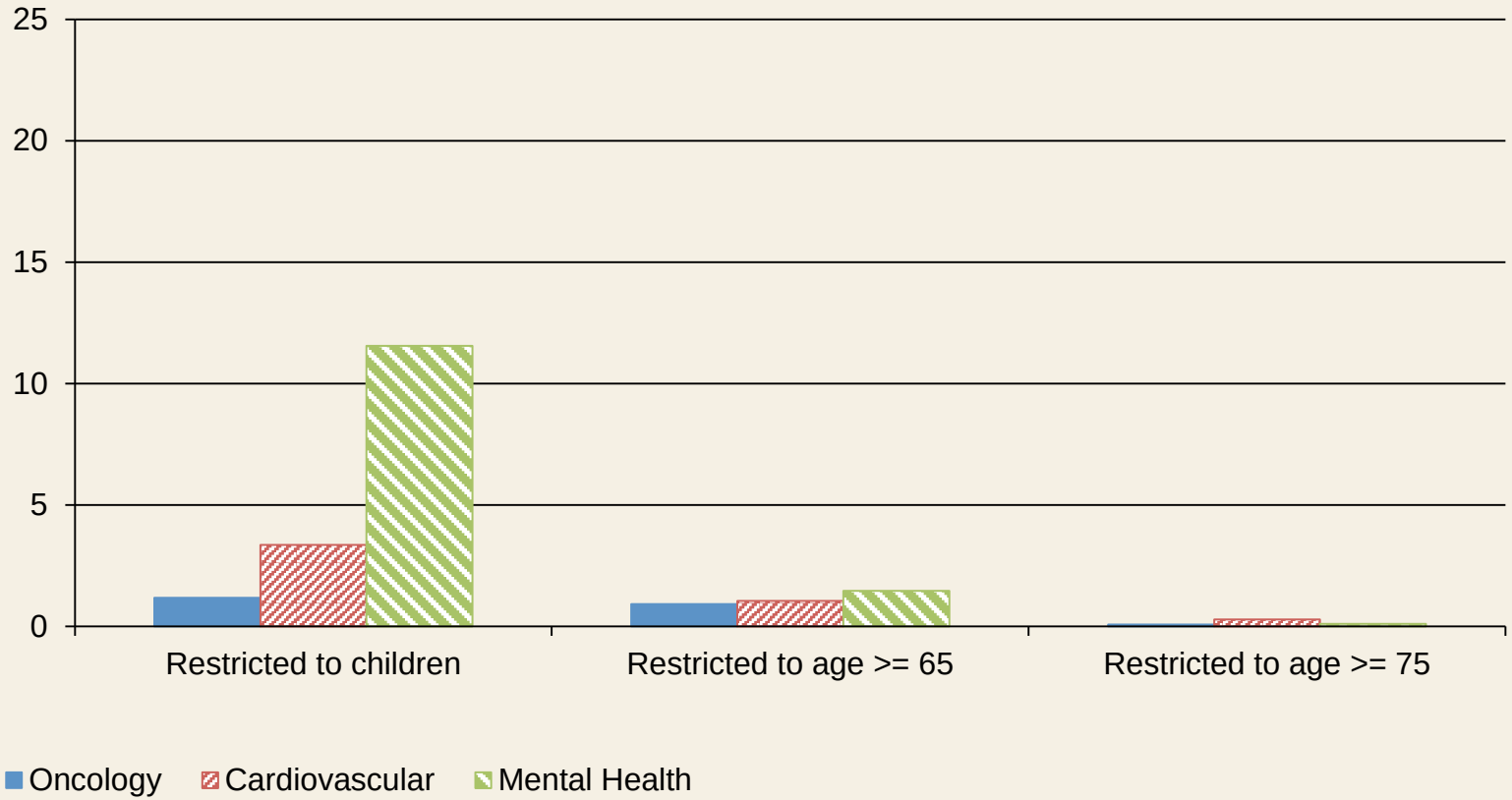
Eligibility: Age Restrictions



+ 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**

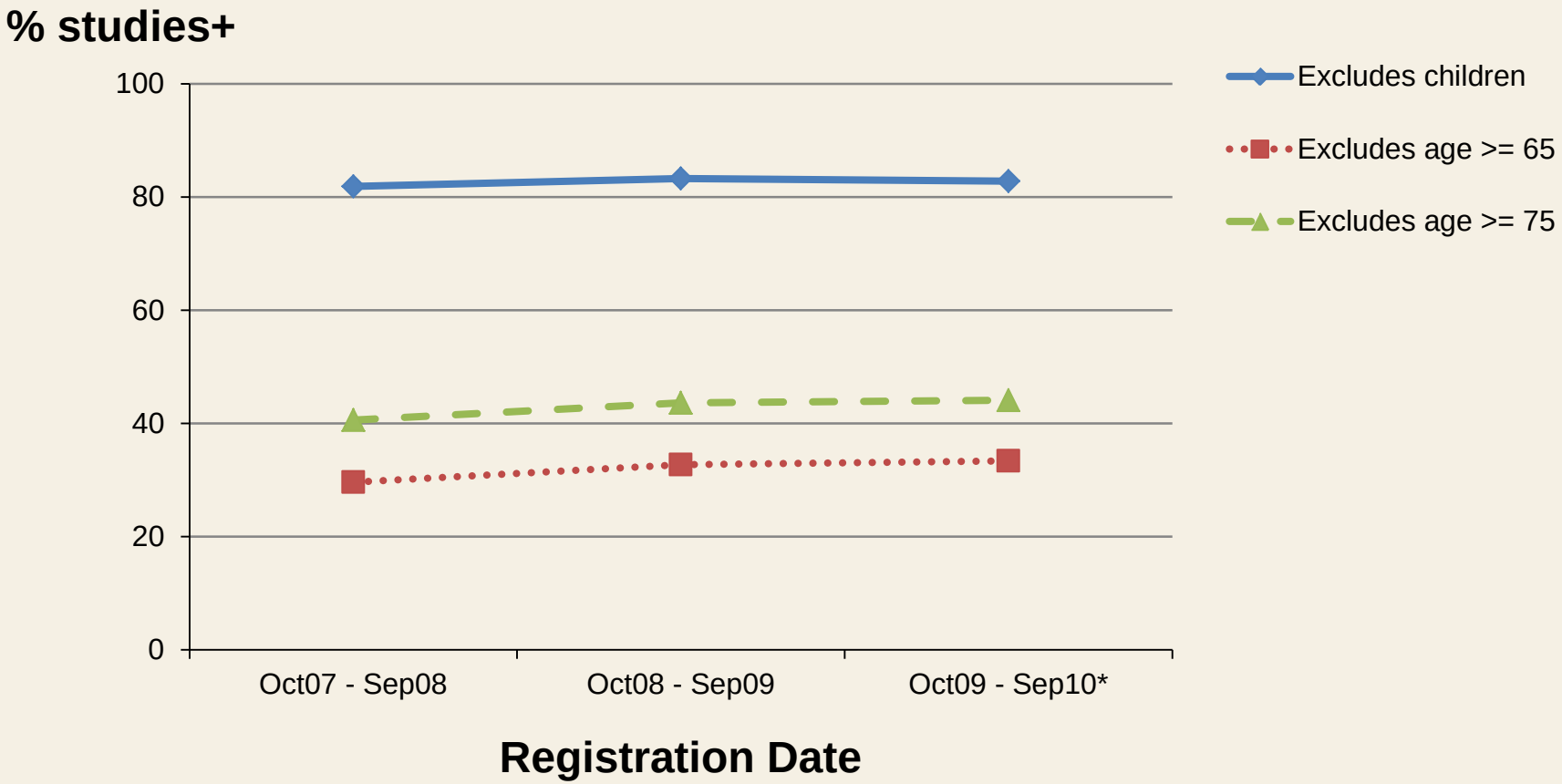
Age Restrictions by Therapeutic Area

% studies*



*** Percent calculated within each therapeutic area**

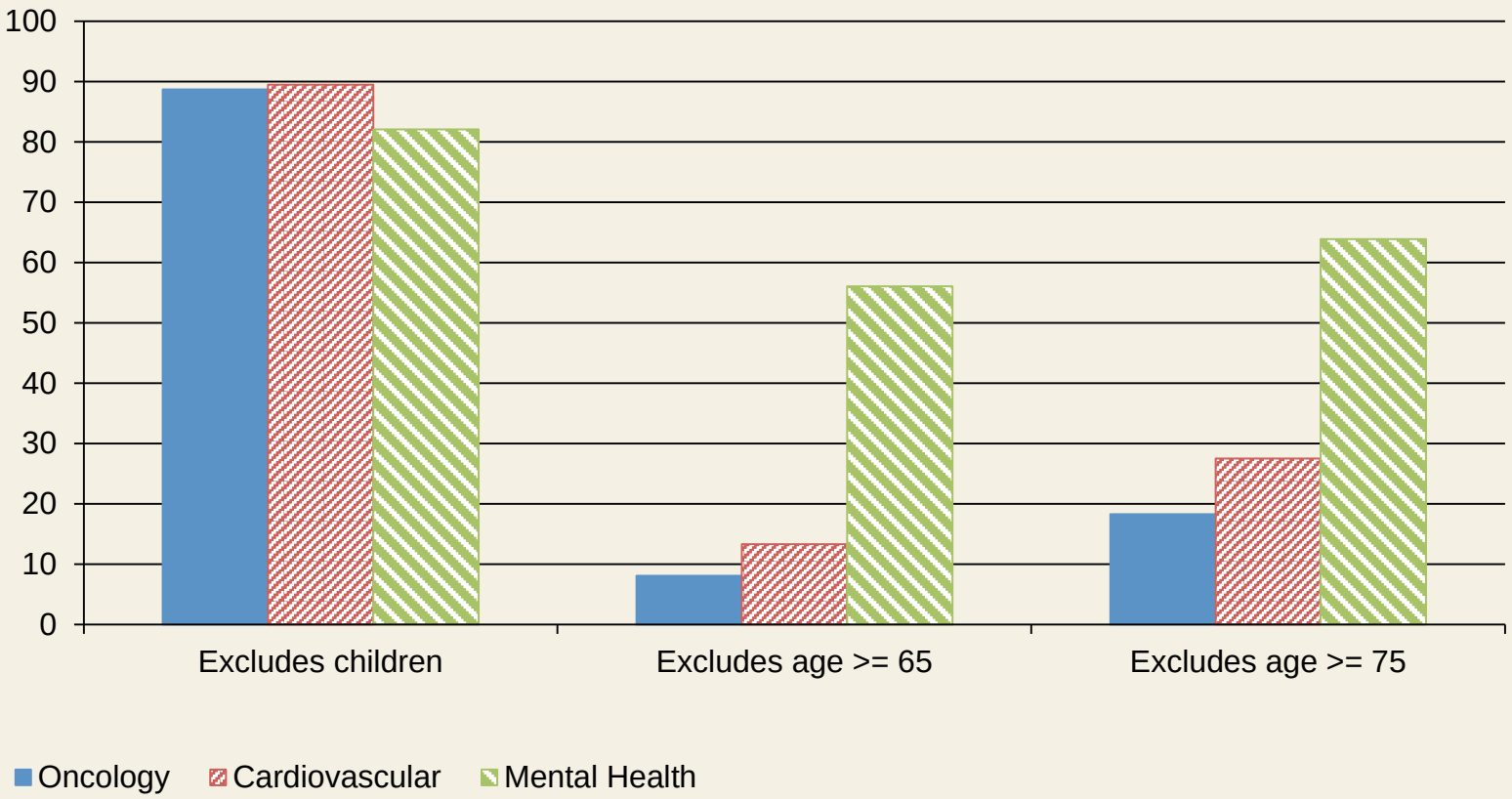
Eligibility: Age Exclusions



+ 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*

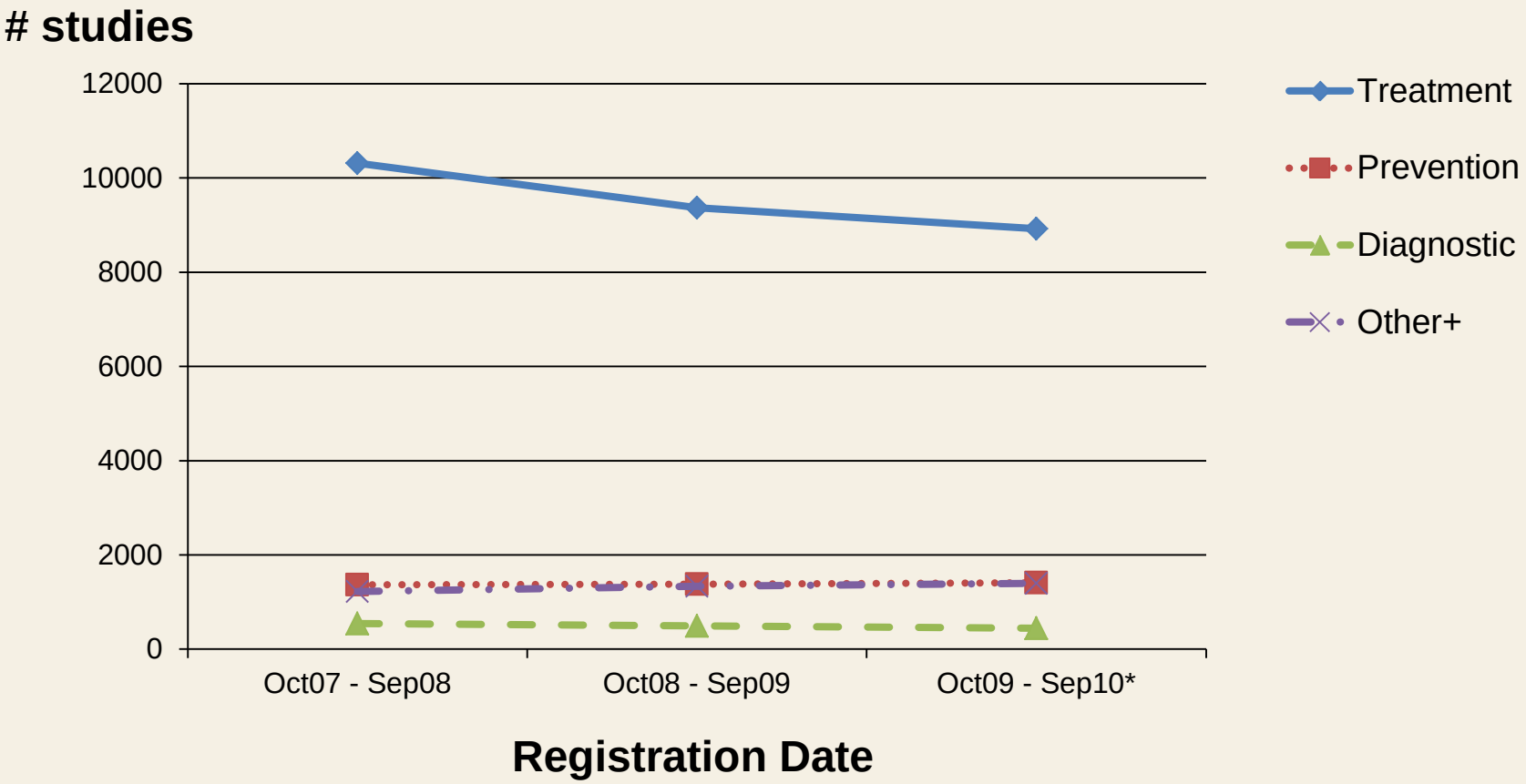


*** Percent calculated within each therapeutic area**

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

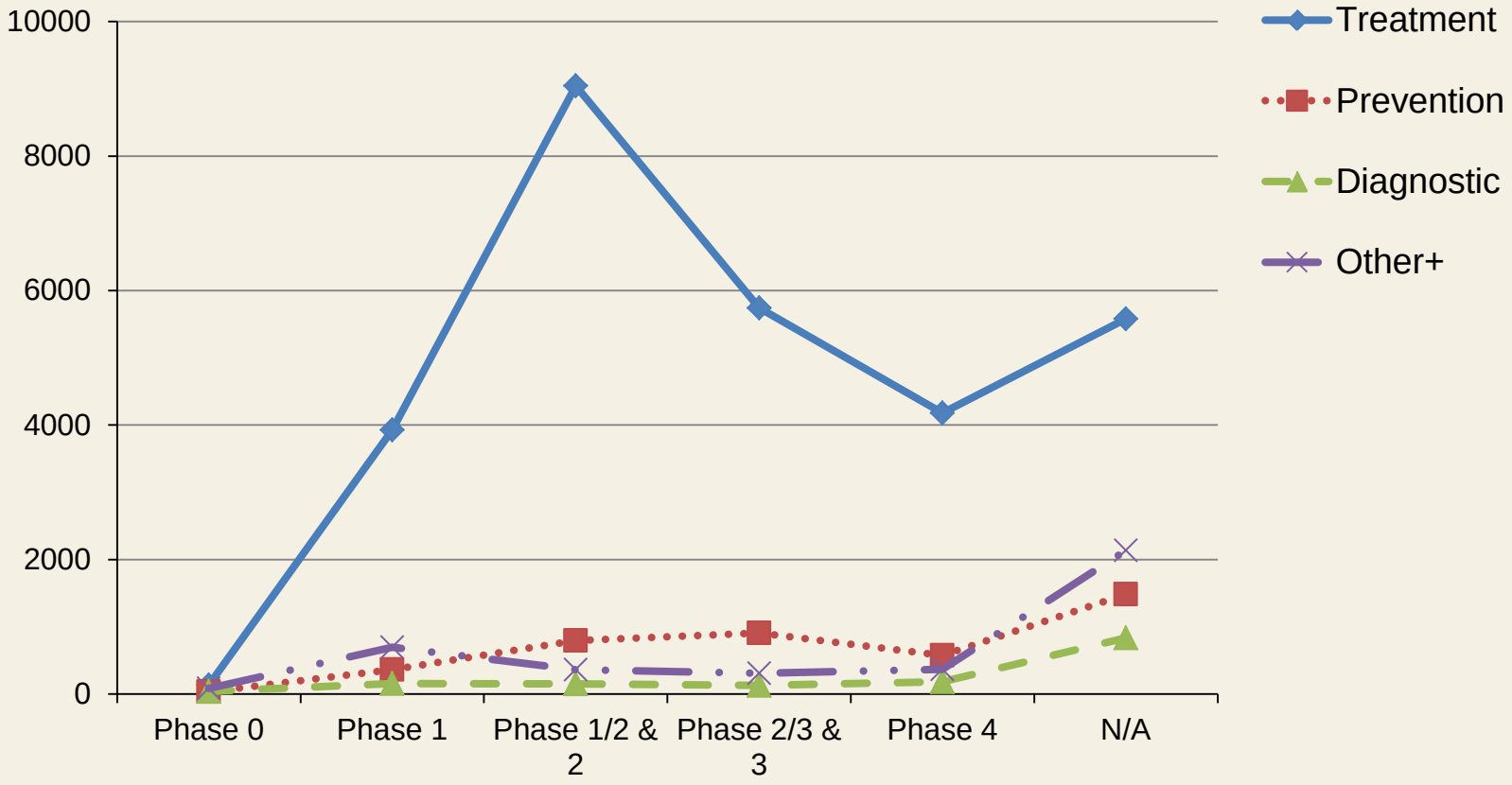
Primary Purpose



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

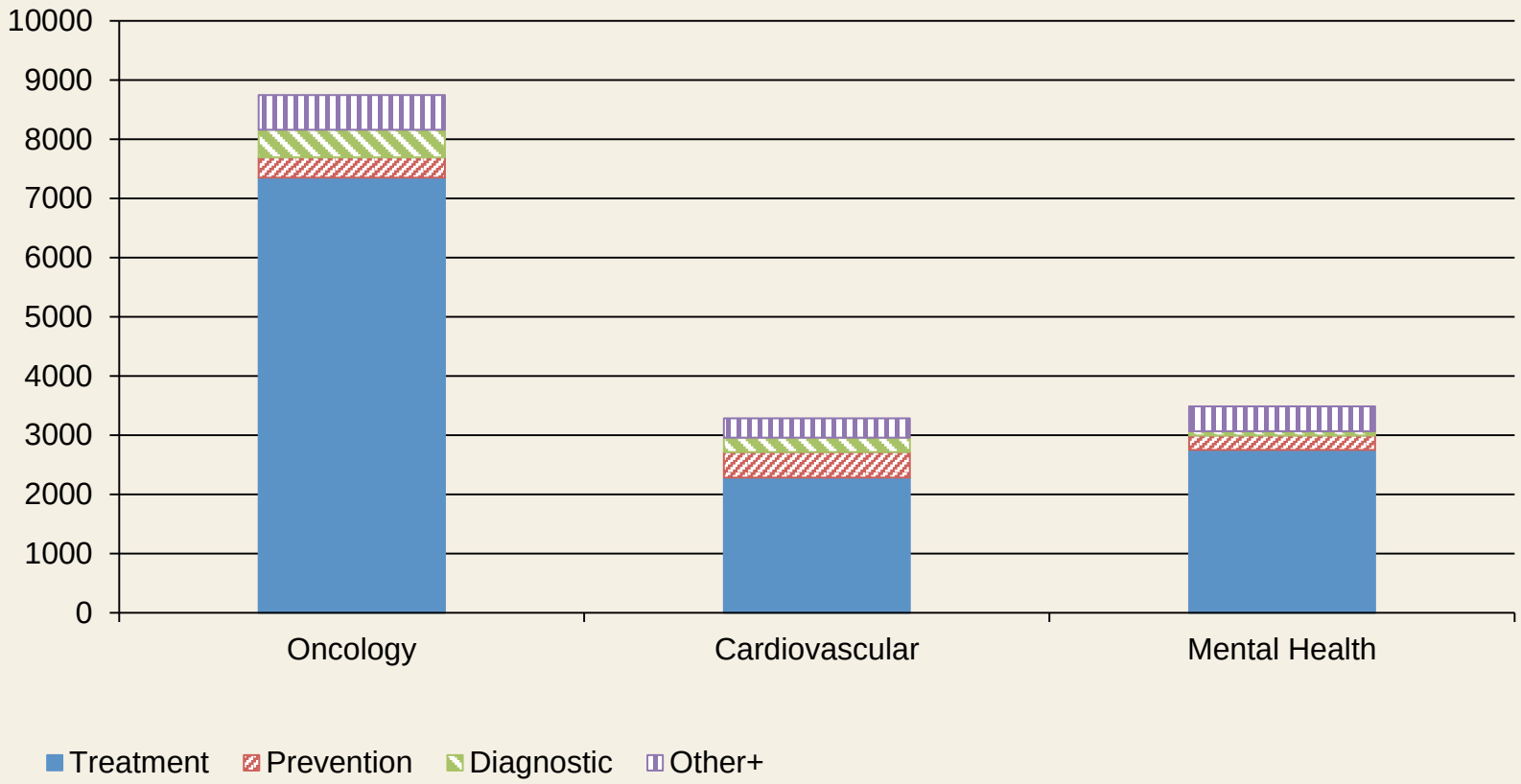
 # studies



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

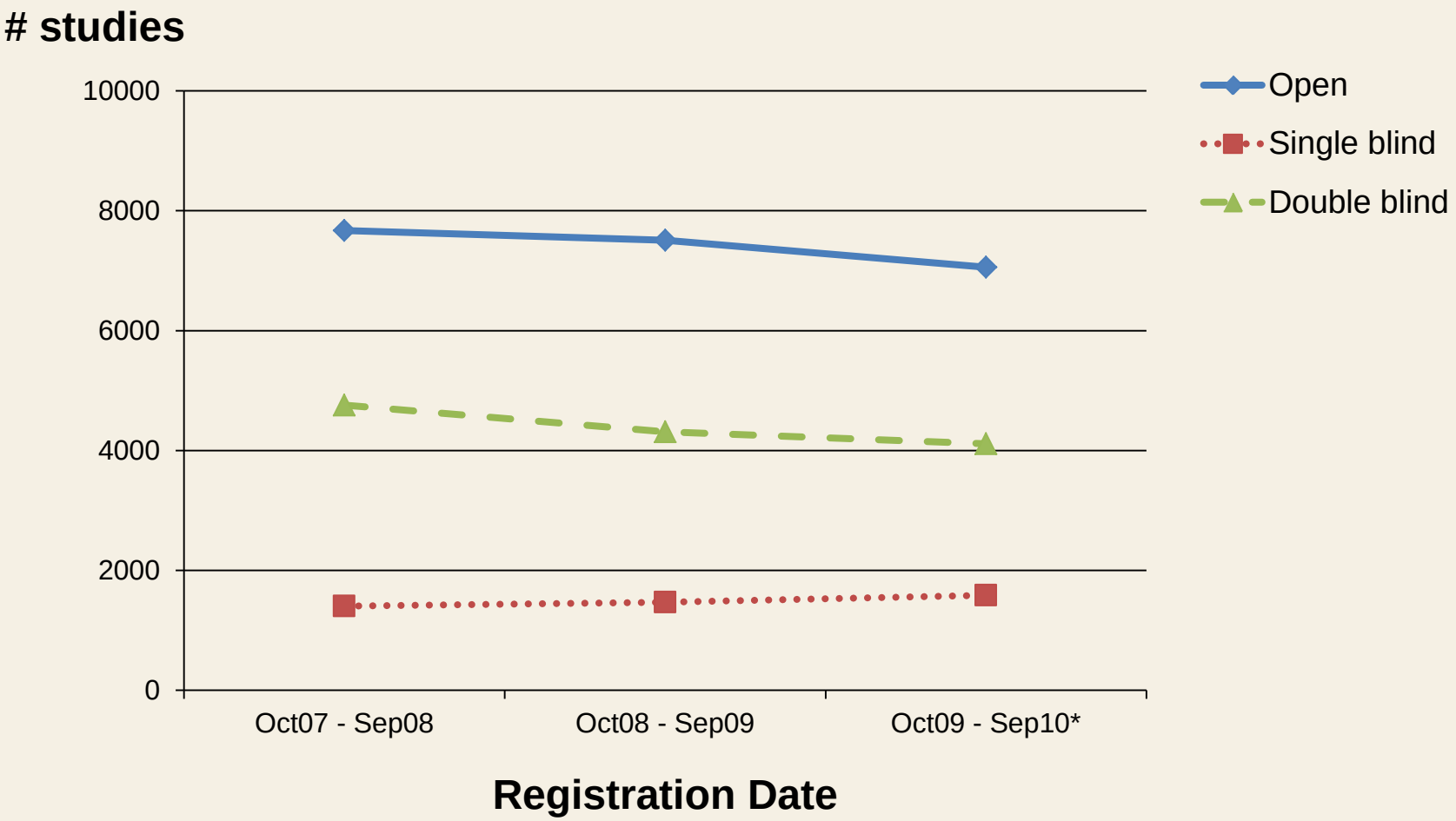
Primary Purpose by Therapeutic Area

 # studies



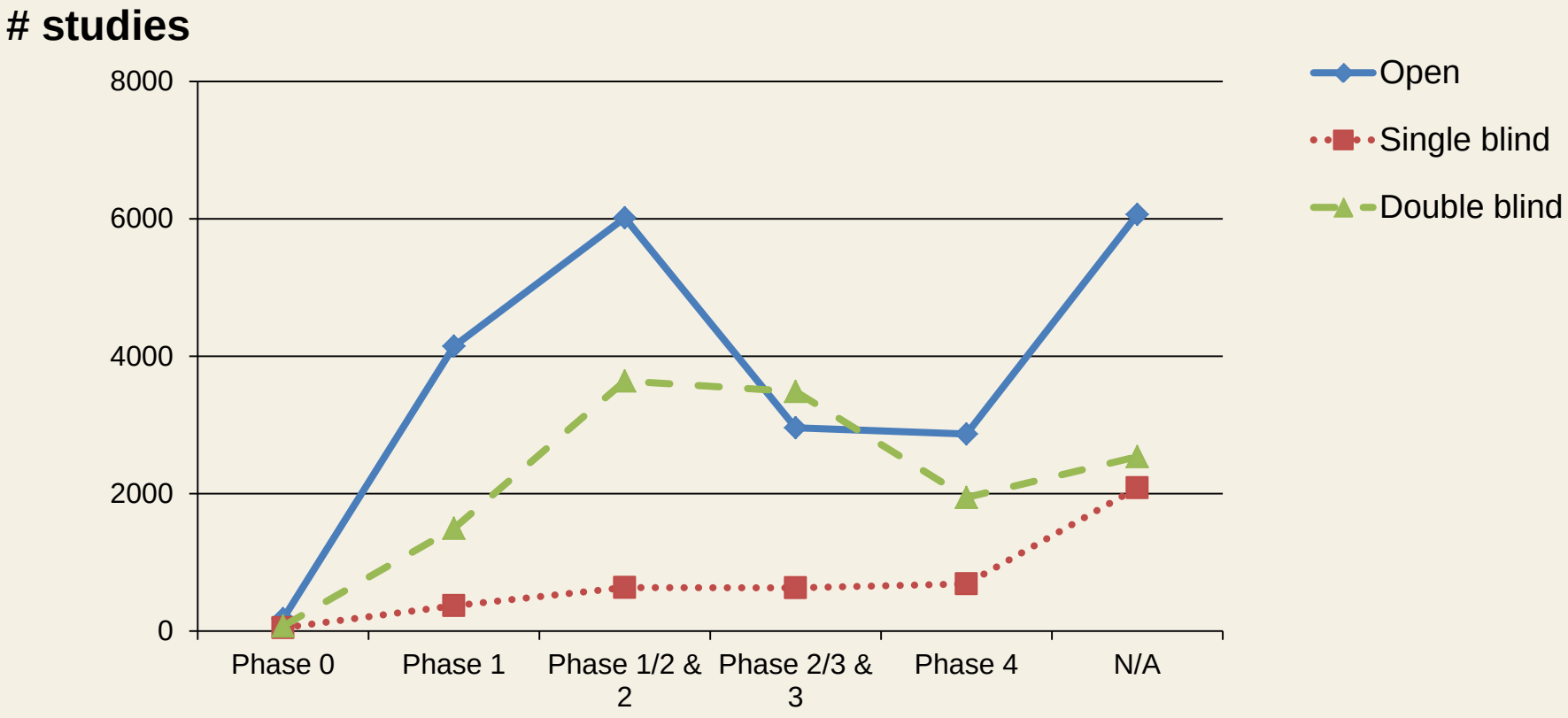
+ Includes the categories supportive care, screening, health services research, and basic science

Masking



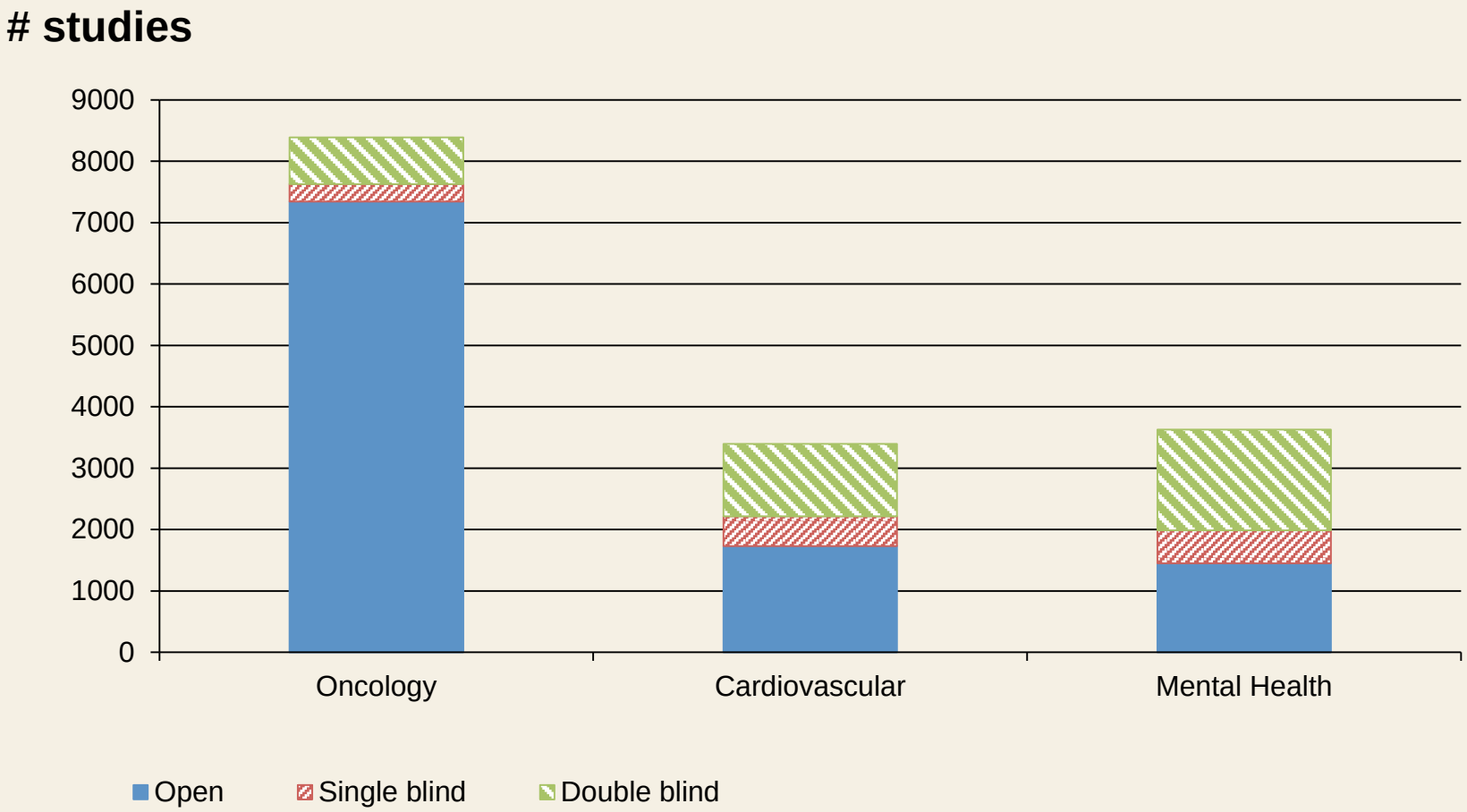
N=1,099 studies have missing masking information
*** through Sept 27, 2010**

Masking by Phase

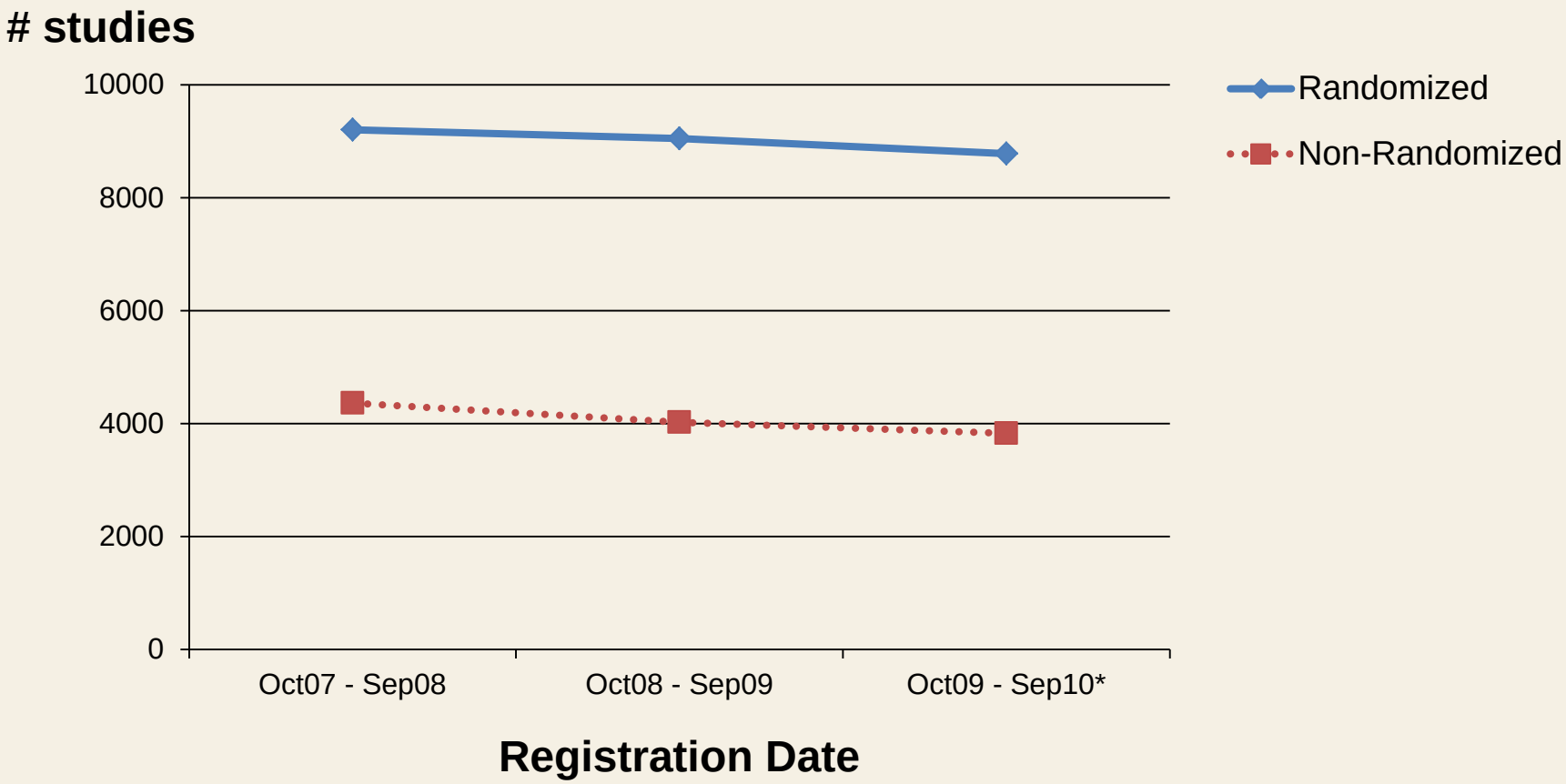


N=1,099 studies have missing masking information

Masking by Therapeutic Area

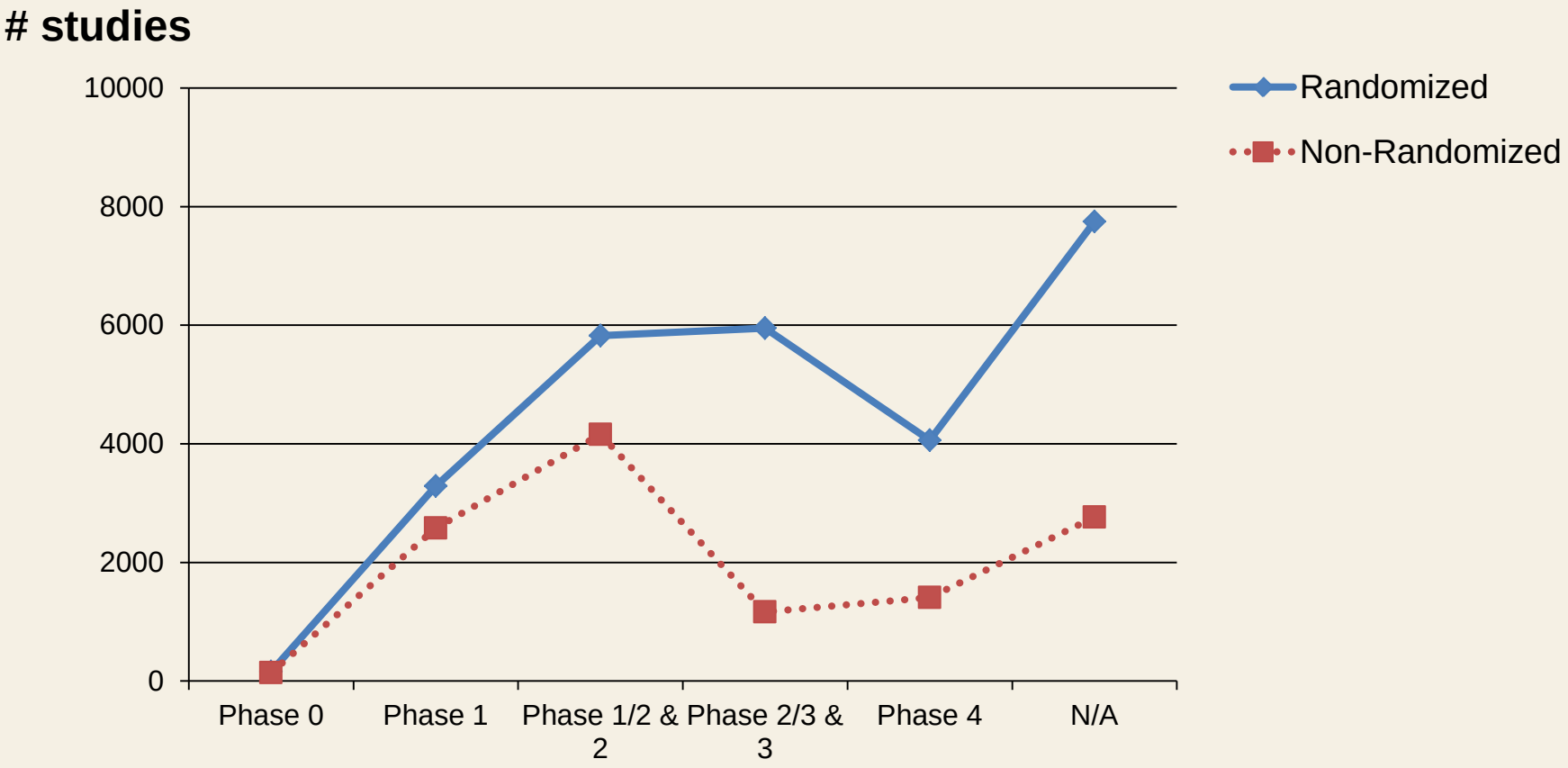


Randomization



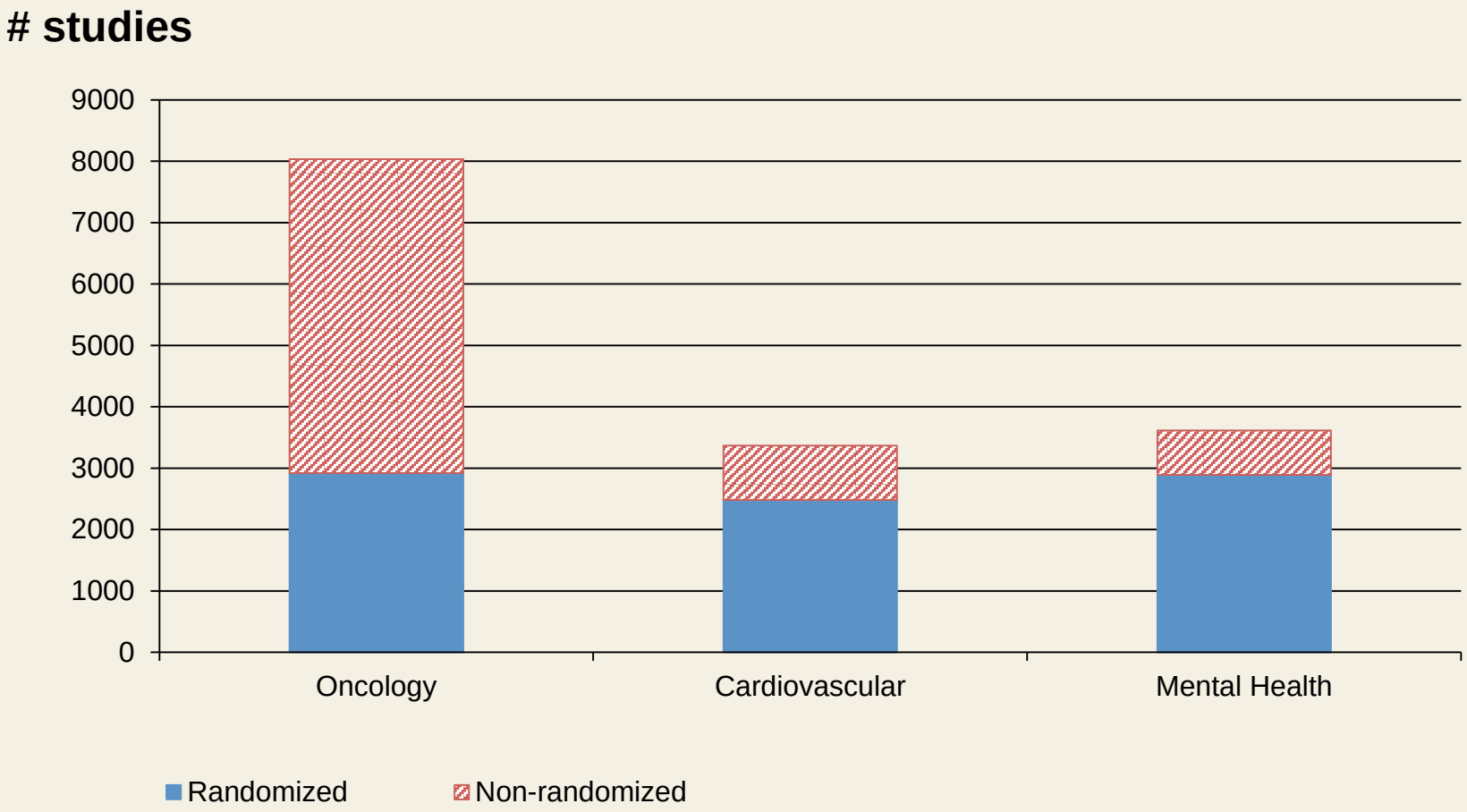
N=1,730 studies have missing randomization information
*** through Sept 27, 2010**

Randomization by Phase

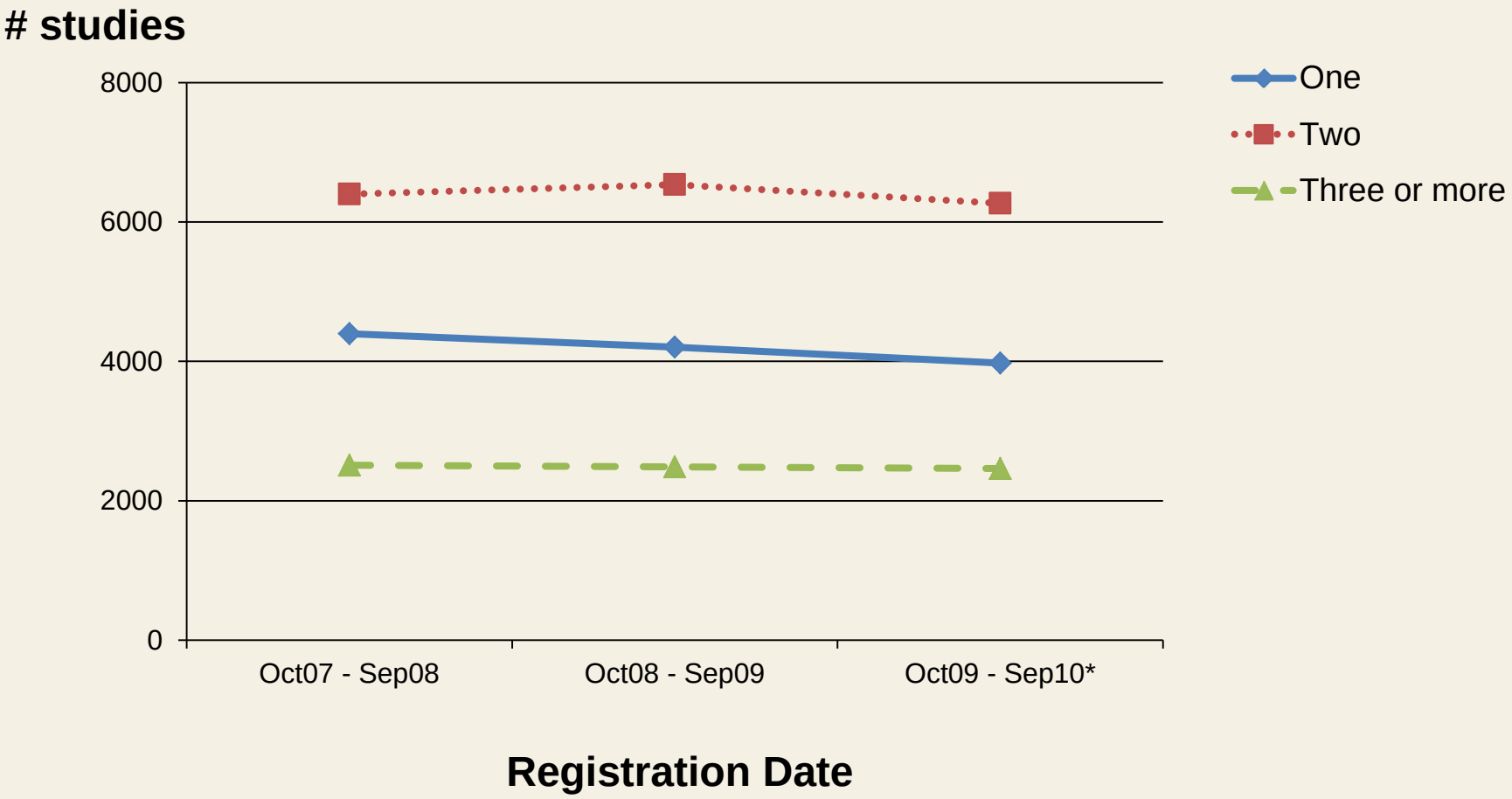


N=1,730 studies have missing randomization information

Randomization by Therapeutic Area

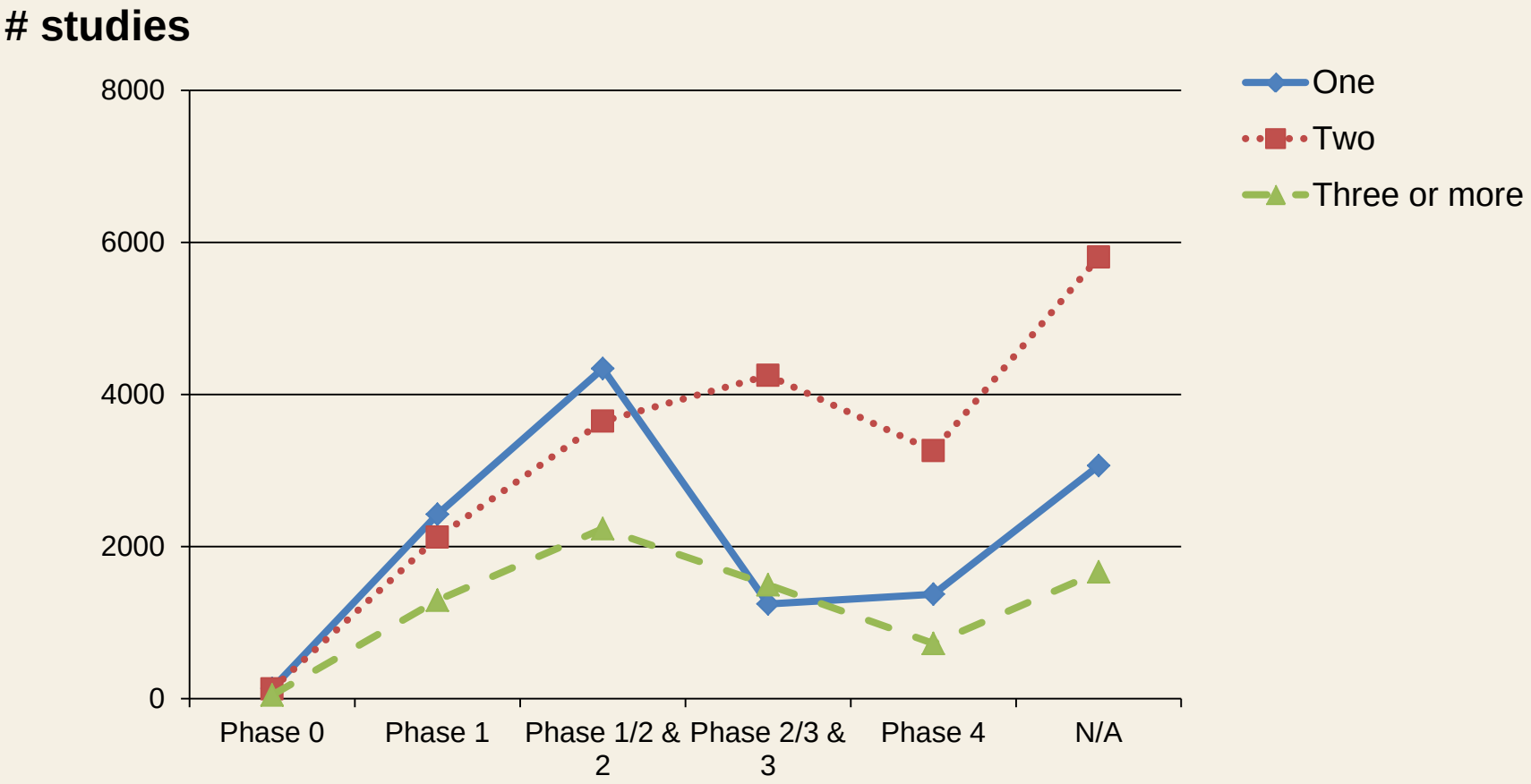


Number of Arms



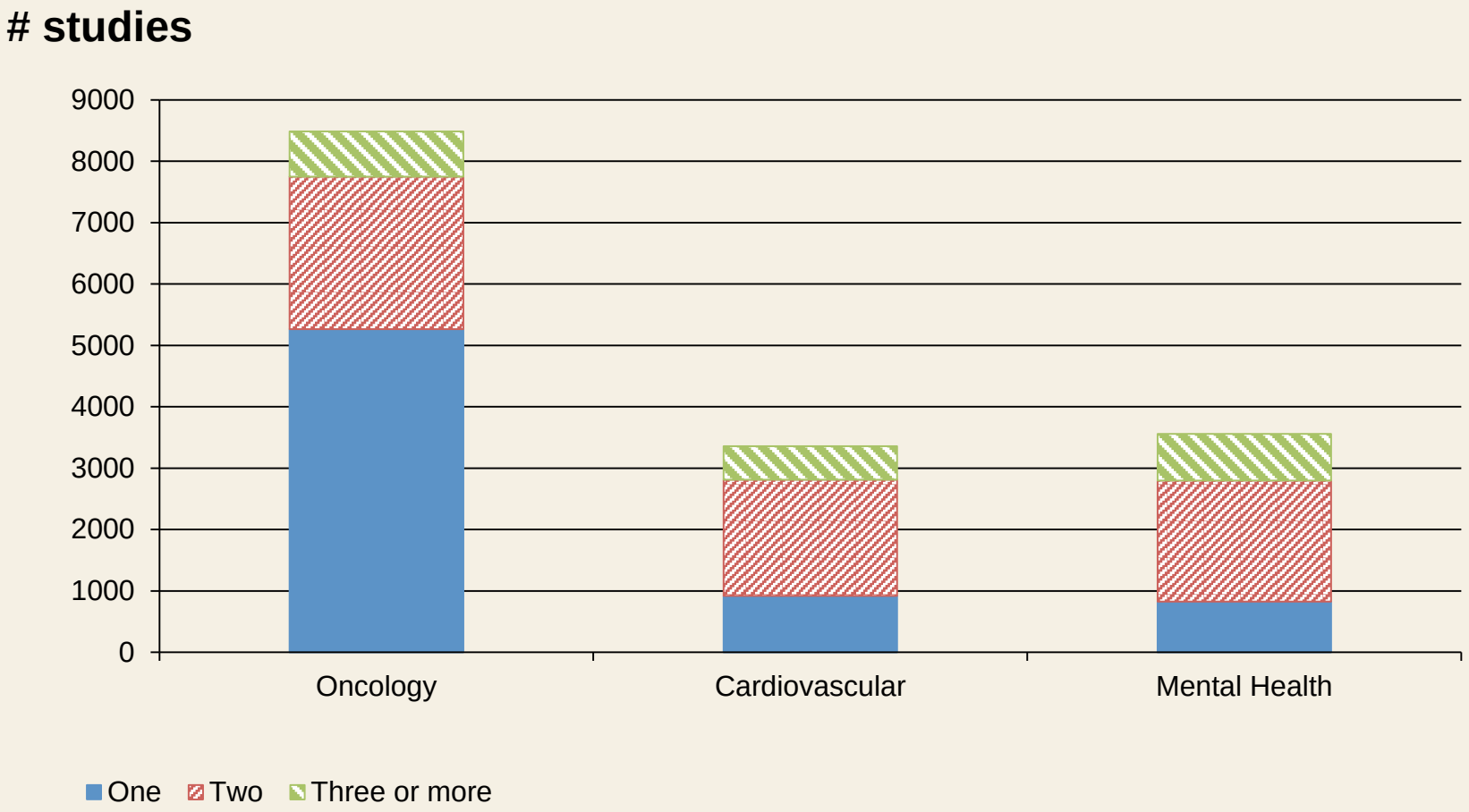
N=1,727 studies have missing information on number of arms
*** through Sept 27, 2010**

Number of Arms by Phase

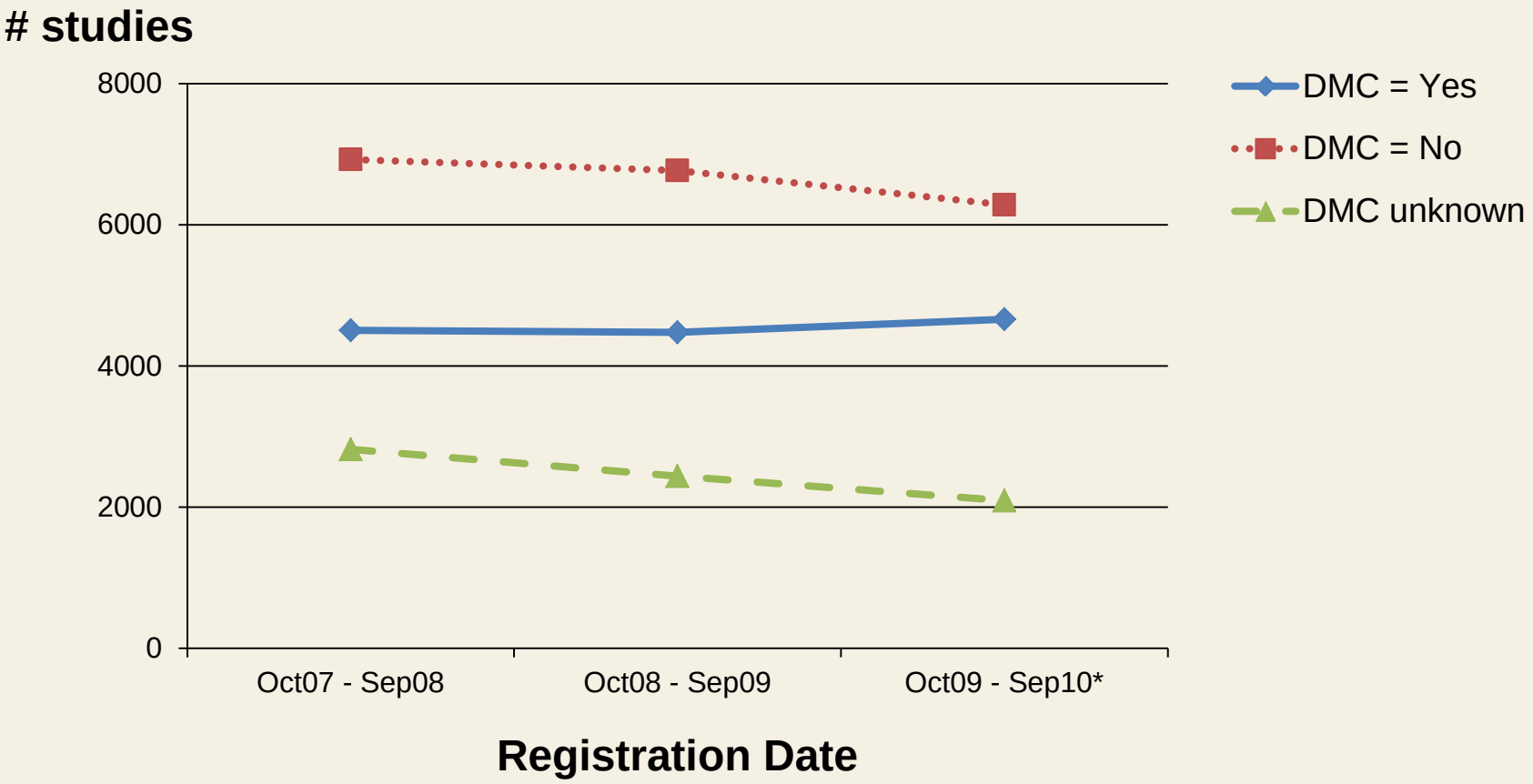


N=1,727 studies have missing information on number of arms

Number of Arms by Therapeutic Area

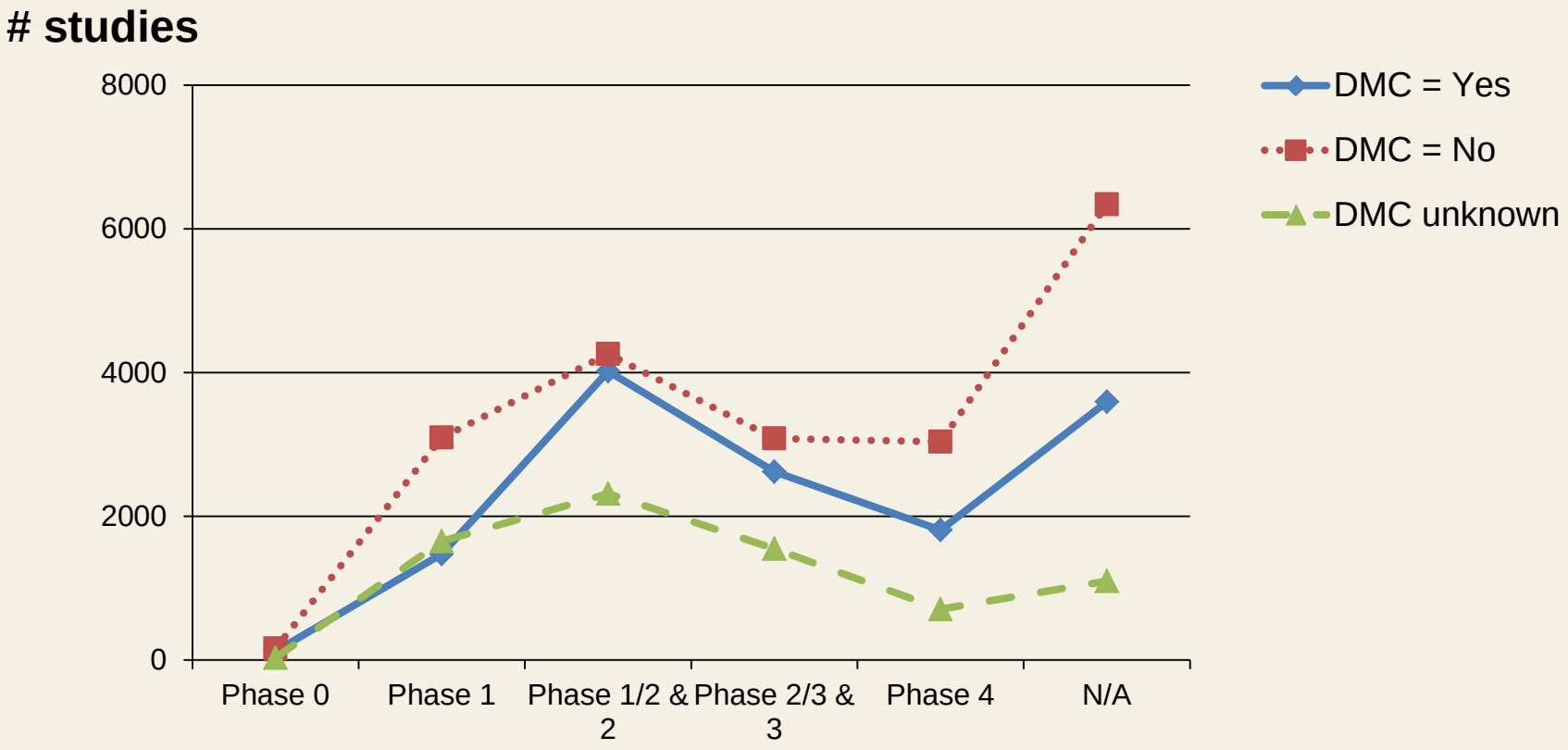


Data Monitoring Committee (DMC)

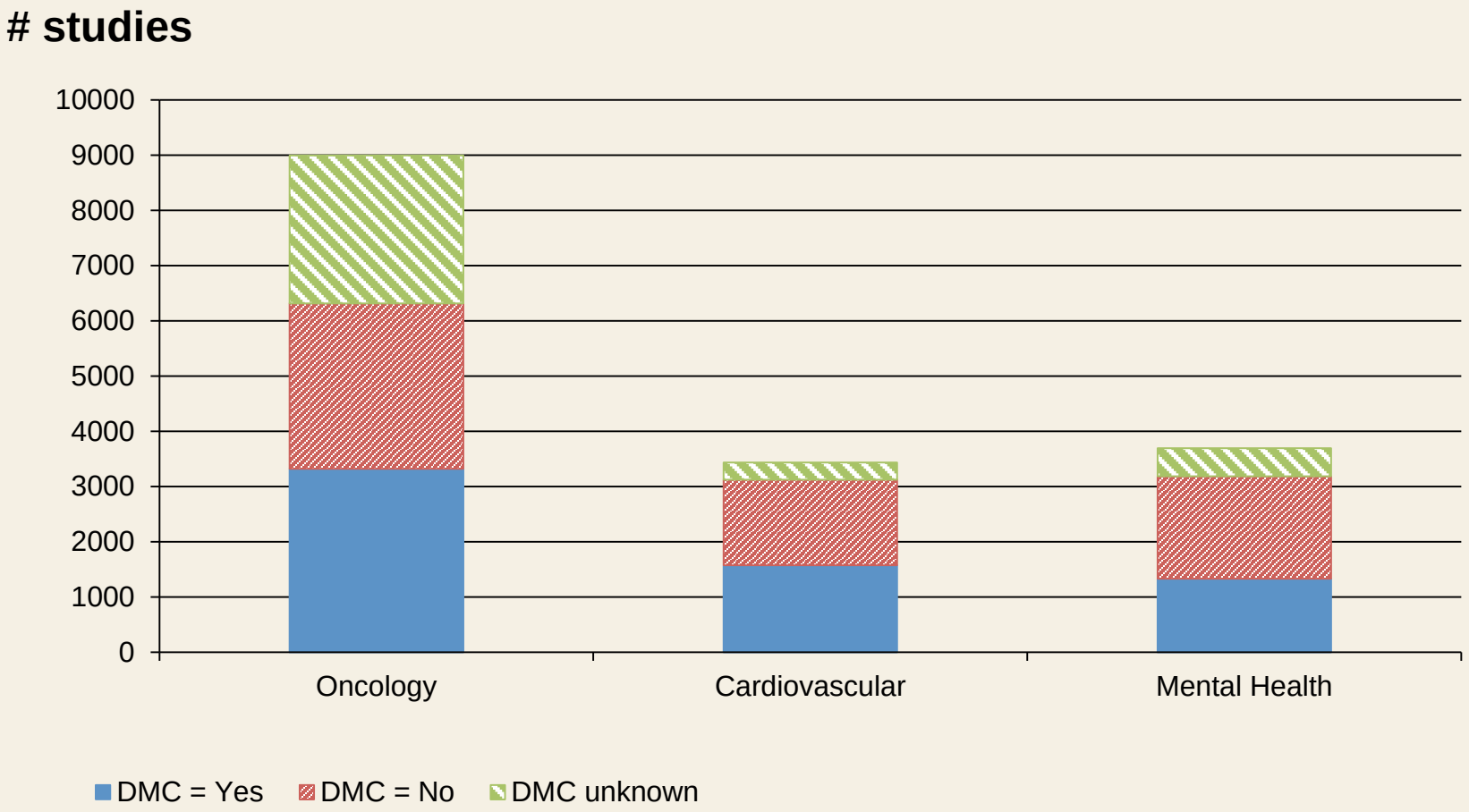


*** through Sept 27, 2010**

DMC by Phase


studies
8000
6000
4000
2000
0
Phase 0
Phase 1
Phase 1/2 & 2
Phase 2/3 & 3
Phase 4
N/A
DMC = Yes
DMC = No
DMC unknown

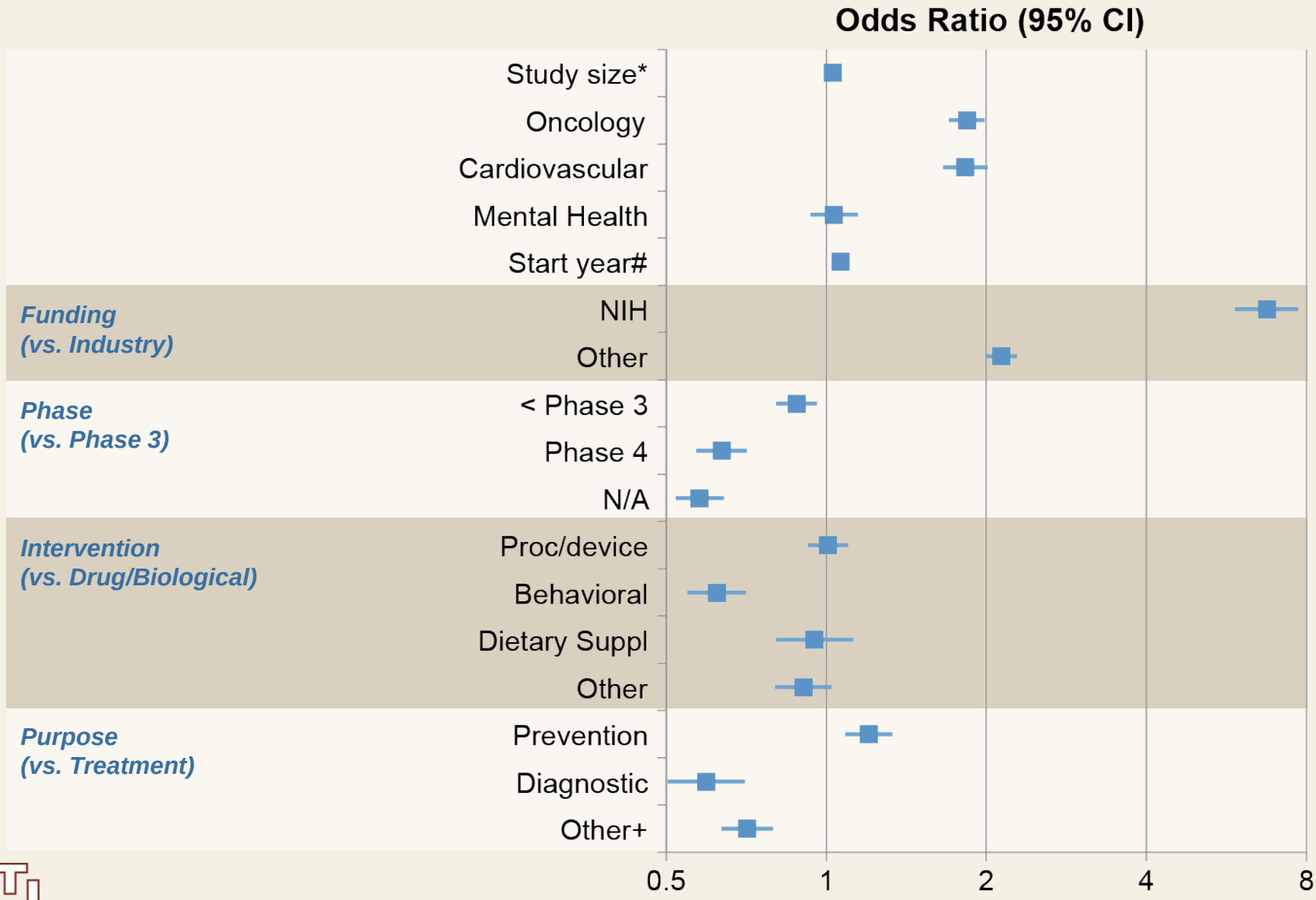
DMC use by Therapeutic Area



Regression Analyses of DMC use, Blinding, and Randomization

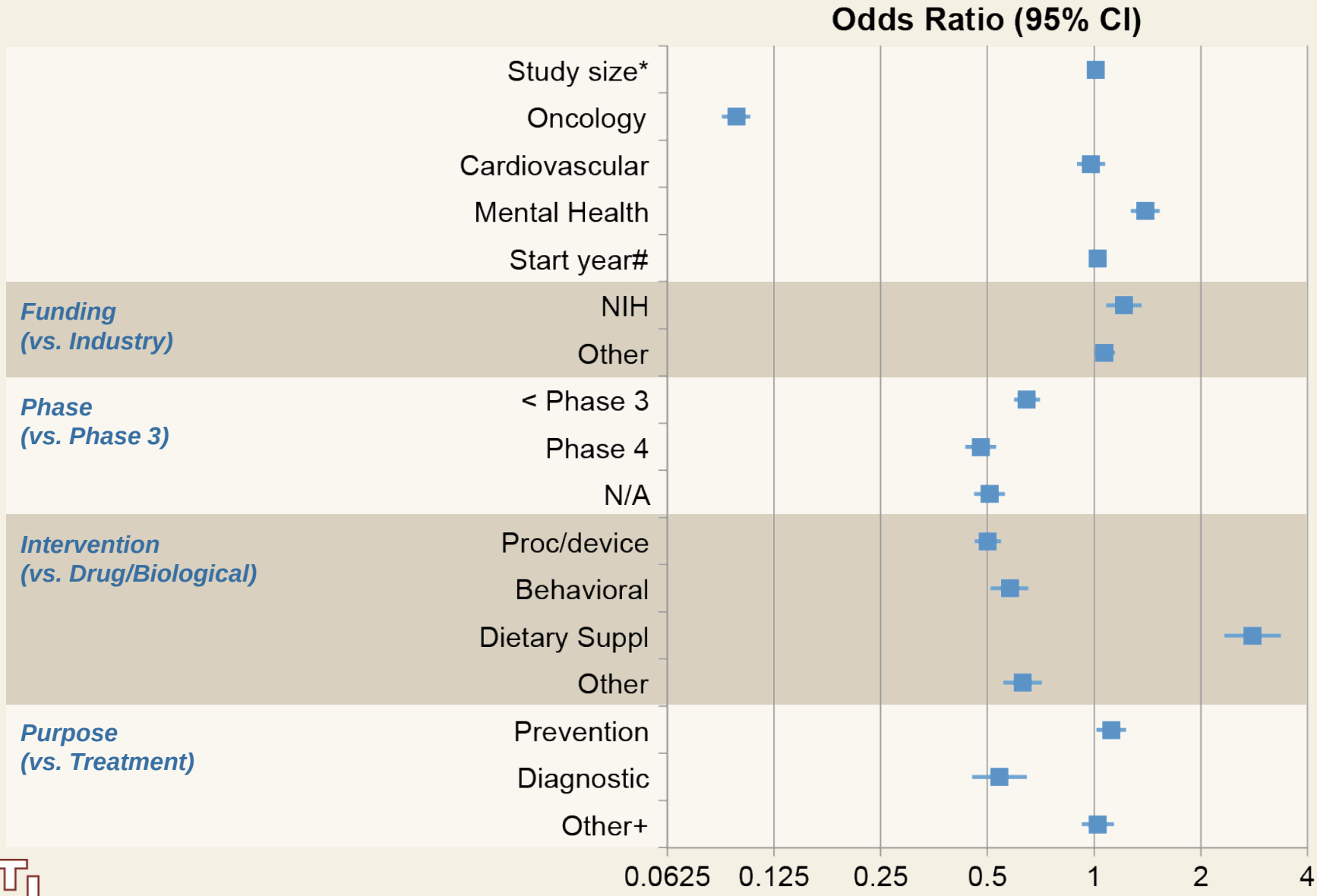
- **Associations Between Study Characteristics and DMC use, blinding, and randomization**
  - Logistic regression analysis of
    - DMC use (yes versus no)
    - Blinding (single- or double-blind masking versus unblinded)
    - Randomization (yes versus no)

DMC Use: Multivariable Odds Ratios



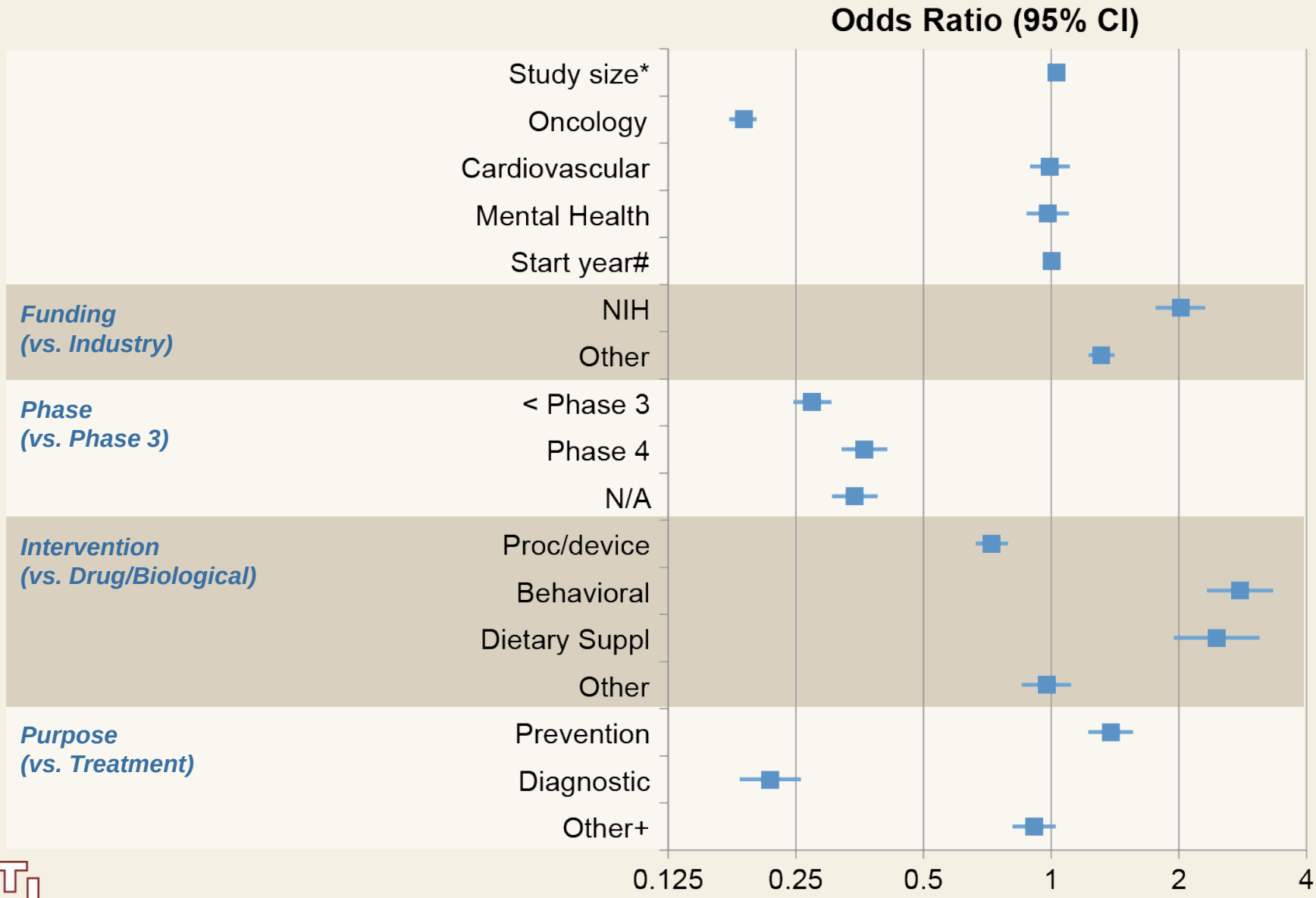
* Per 1000 participants; # Per increment of 1 yr; + Includes supportive care, screening, health services research, and basic science

Blinding: Multivariable Odds Ratios



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

Randomization: Multivariable Odds Ratios



* 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