‘START’ (Start-up Time And Readiness Tracking) Study

Working Group

FINAL REPORT

June 15, 2012

Boston, MA

Tufts CSDD:

Adam Mathias, Research Analyst

Mary Jo Lamberti, Senior Project Manager

Ken Getz, (PI) Senior Research Fellow, Assistant Professor

Tufts Center for the Study of Drug Development

TUFTS UNIVERSITY

Executive Summary

- **The majority of companies have no centralized study start-up teams or department in place.**
  - Those that have teams are staffed with an average of 6 FTE, have been in existence for about one year on average, and report into clinical operations.

- **Overall perceptions are that study initiation cycle times can be somewhat shortened and that shorter study initiation cycle times are very important to each company.**

- **All companies reported the existence of initiatives to speed up study initiation.**

Executive Summary *(continued)*

- **Each participating company initiated 87 Phase I-IV studies on average in 2011.**
- **In general, the most commonly utilized sites are those that are run by an independent researcher/physician as well as those that are affiliated with an academic institution.**
- **North America and Western Europe had the largest number of sites utilized per study.**
- **Overall, benchmark percentage of sites enrolling, percentage of sites non-enrolling, and percentage of sites dropped after initiation are 84%, 16%, and 14% respectively.**

Executive Summary *(continued)*

- **Companies varied in the sequence of activities completed prior to enrolling first patient in.**

- **The early stages of the site initiation process are areas where companies can potentially improve upon.**
  - "PSV" to "Contract Execution" accounts for the majority of cycle time
  - Little variation observed from "Contract Execution" to "First Patient In" across TA, type of site, and geographical region

- **Large variances in stages of the site initiation process might indicate that companies are not managing the process consistently.**

Executive Summary *(continued)*

- **Benchmark areas with *HIGHEST* variance:**
  - Protocol Approval to 25% Approved Sites Initiated
  - 50% to 100% Approved Sites Initiated
  - Pre-Visit to Contract/Budget Sent
  - Contract/Budget Sent to Contract Execution

- **Benchmark areas with *LOWEST* variance:**
  - 25% to 50% Approved Sites Initiated
  - Contract Execution to Site initiation
  - Site Initiation to First Patient In

- **Benchmark time from "Regulatory Submission" to "Regulatory Approval" was 2.8 months**
  - CNS studies require the most time to approval for patient enrollment
  - North America has the shortest time to approval

Executive Summary *(continued)*

- **Oncology and CNS therapeutic areas represented the longest cycle times to first patient in.**
  - 12.6 months for oncology and 12.2 months for CNS/Neuroscience
- **Academic institutions and government funded sites took longest to enrolling first patient in, while physician practices were fastest.**
  - 13.0 months (academic) and 12.6 months (government) vs. 7.2 months (physician practices)
- **Cycle time (to first patient in) in Latin America was more than twice that of North America.**
  - 16.1 months in Latin America vs. 7.4 months in North America

Study Methods

- **Phases I-IV**
- **Enrollment completed between 2008 and 2011**
- **Therapeutic Areas:**

Cardiovascular	Metabolics/Endocrine
Dermatology	Oncology
Gastrointestinal	CNS/Neuroscience
Hematology	Respiratory
Immunology	Transplant
Infectious disease	Other

- **Type of data collected:**
  - Company information, department structure, and overall perceptions
  - Study characteristics and metrics
    - **n= 105 studies**
      - 21 Phase I
      - 35 Phase II
      - 36 Phase III
      - 13 Phase IV
  - Site level metrics
    - **n= 5296 sites**
  - Country level metrics
    - **n= 774 submissions**

- **Study supported by an unrestricted grant from goBalto, Inc.**

Company Information and Department Structures

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Working Group Companies and Study Start-Up Teams

- **General Trends:**
  - Large pharma/biotech
  - Majority of companies have **NO** dedicated start-up team
  - Study teams report into Clinical Operations
    - If no team, start-up handled by study teams
  - Average group size is 6 FTE; average age of team is one year
  - Overall perceptions:
    - study initiation cycle times can be somewhat shortened
    - shorter study initiation cycle times are very important to each company

Company Challenges

Greatest challenges in initiating a study?

- Contract/Budget Negotiation
- Regulatory requirements
- Protocol amendments
- Site/country selection
- Resourcing/Site training/site experience
- Study materials

Perceptions about the Study Start-Up Process

What organizational resources or process changes would speed study initiation?

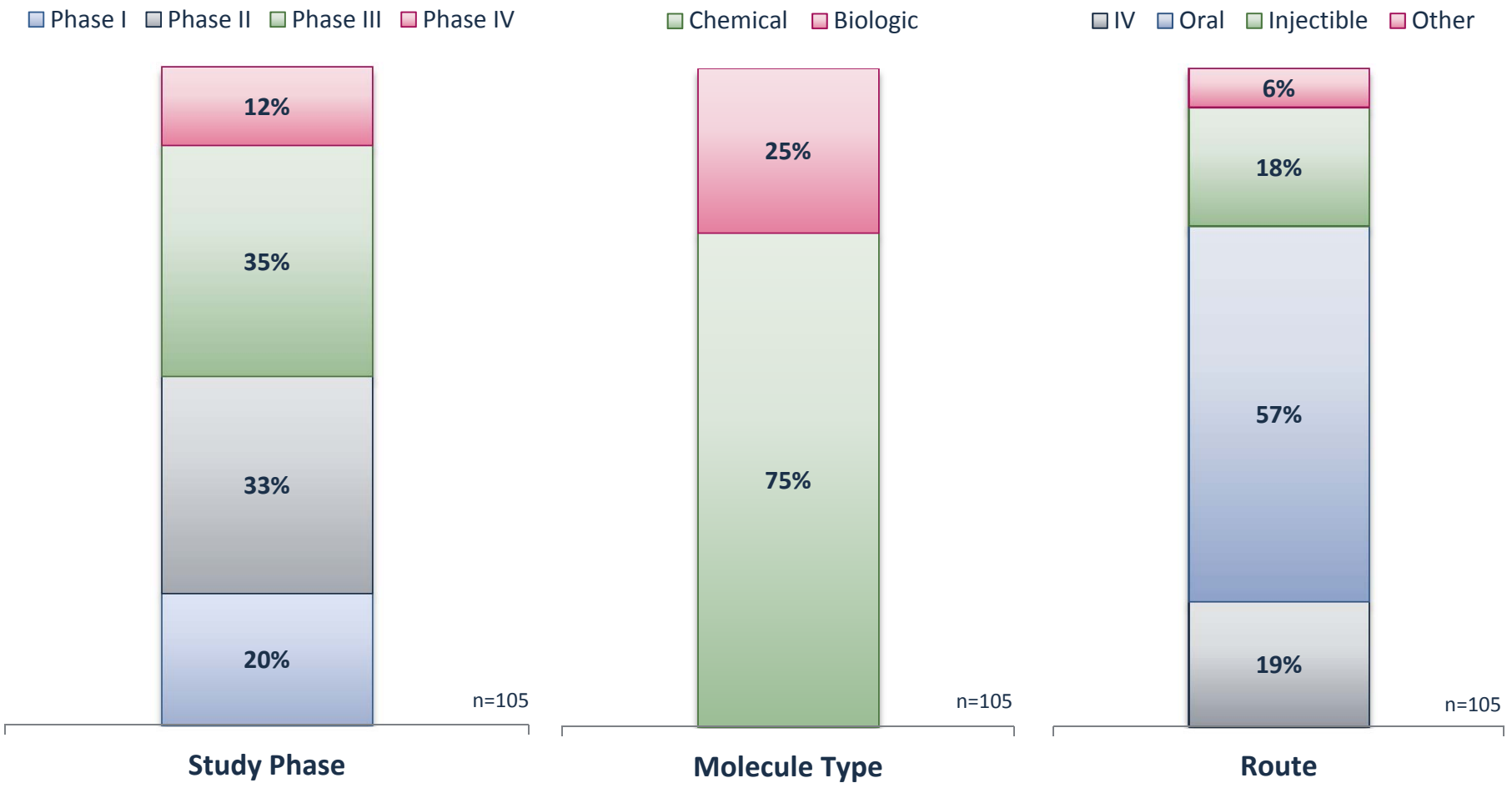
- More streamlined and data-driven site selection
- Electronic document/workflows and visibility
- Protocol Development
- Contract Negotiation
- Clearly integrated CRO/Sponsor processes

STUDY CHARACTERISTICS

Characteristics of Study Data Provided by Participating Companies

Phase II or III
Chemical; Oral
Adult; Adult and Senior
33 eligibility criteria
29 unique; 161 total procedures
42 months of treatment; 14 treatment visits; 11 procedures/visit
Enrollment timeline is 15 months
Actual enrollment timeline is equal to planned timeline on average
North American study sites
620 patients screened; 420 enrolled; 280 completed

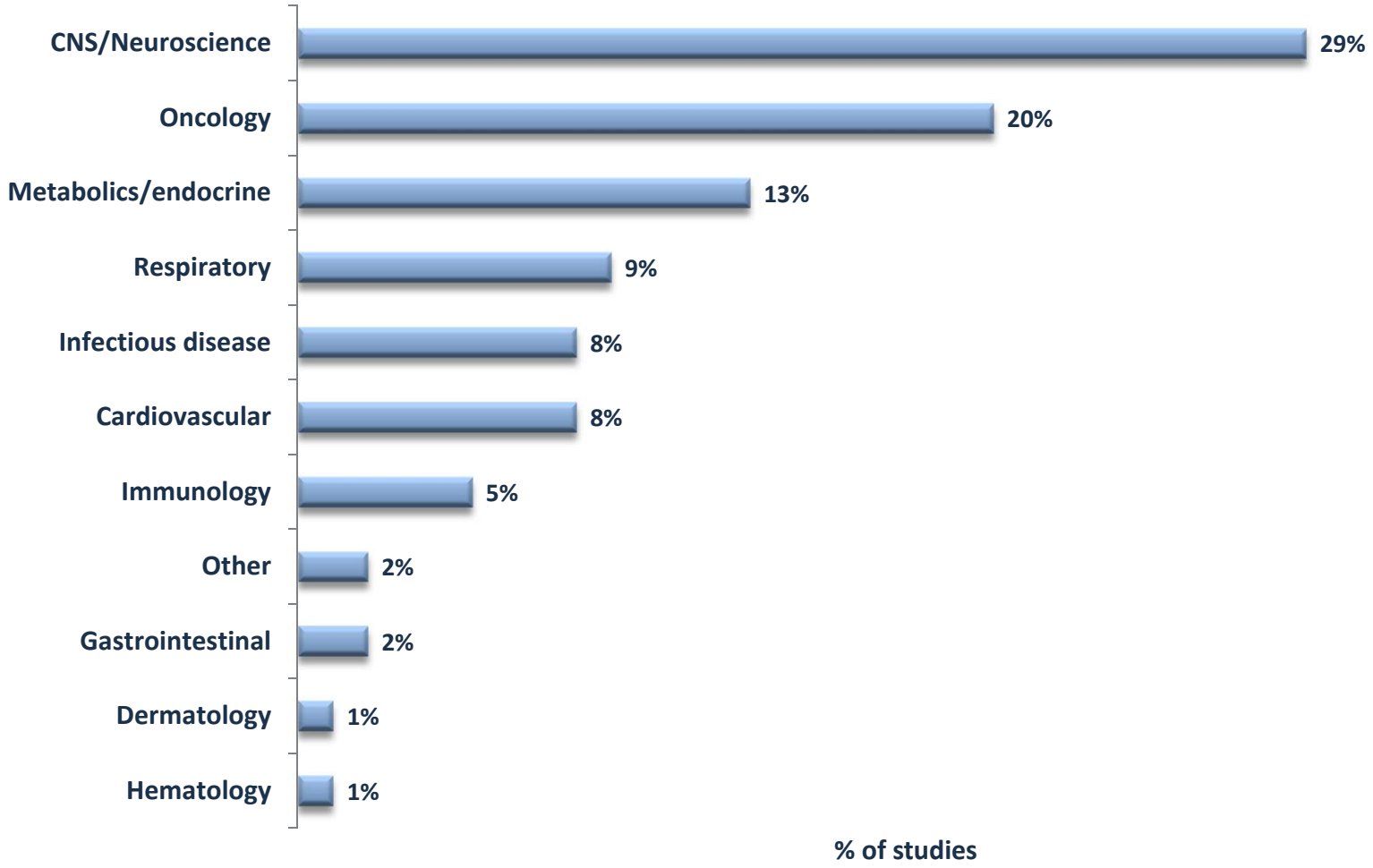
Study Phase, Molecule Type, and Route of Administration



NOTE: Majority of Phase I studies did not involve "healthy" patients

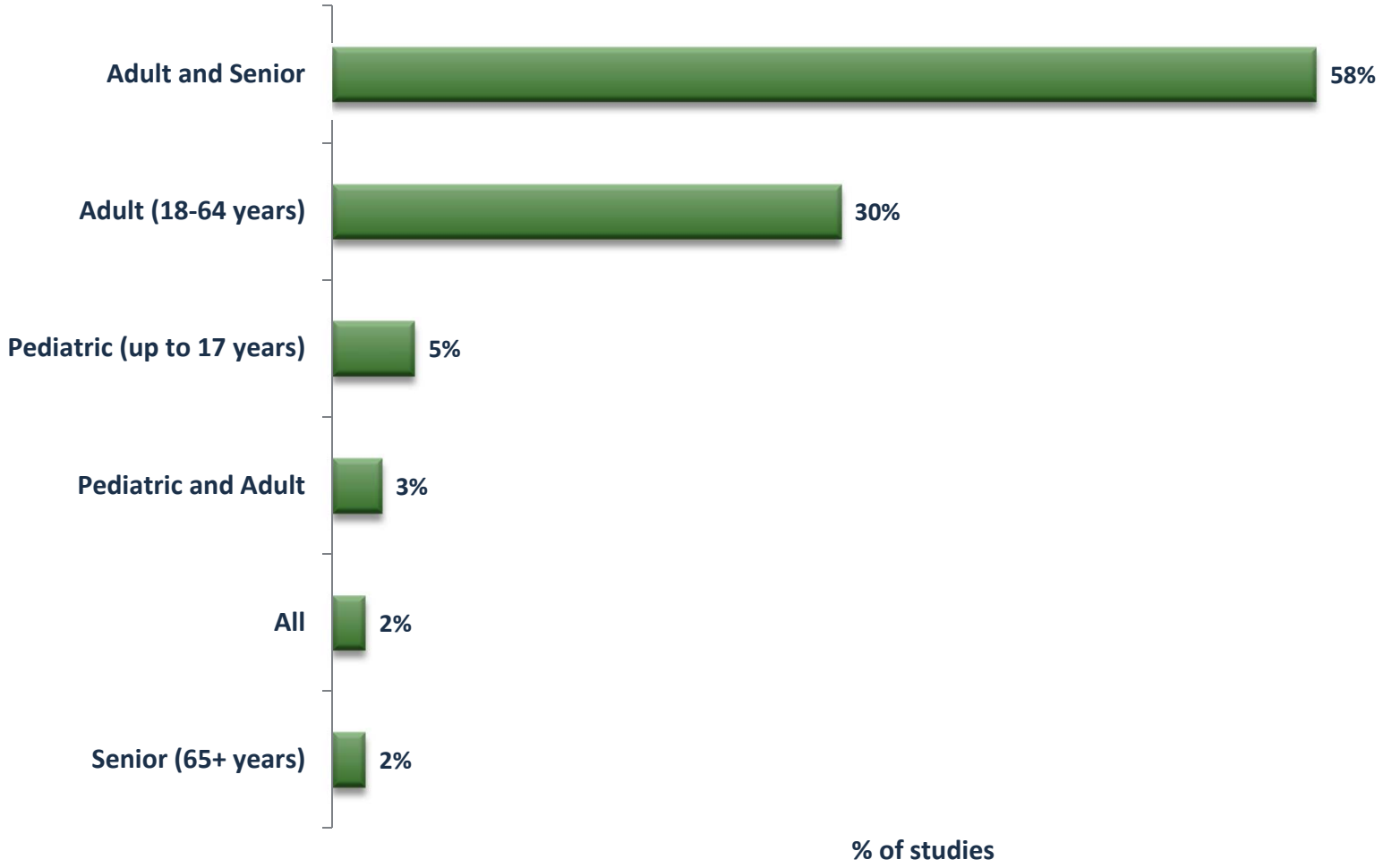
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Study Therapeutic Area



n=95

Age Group of Study Patients



n=103

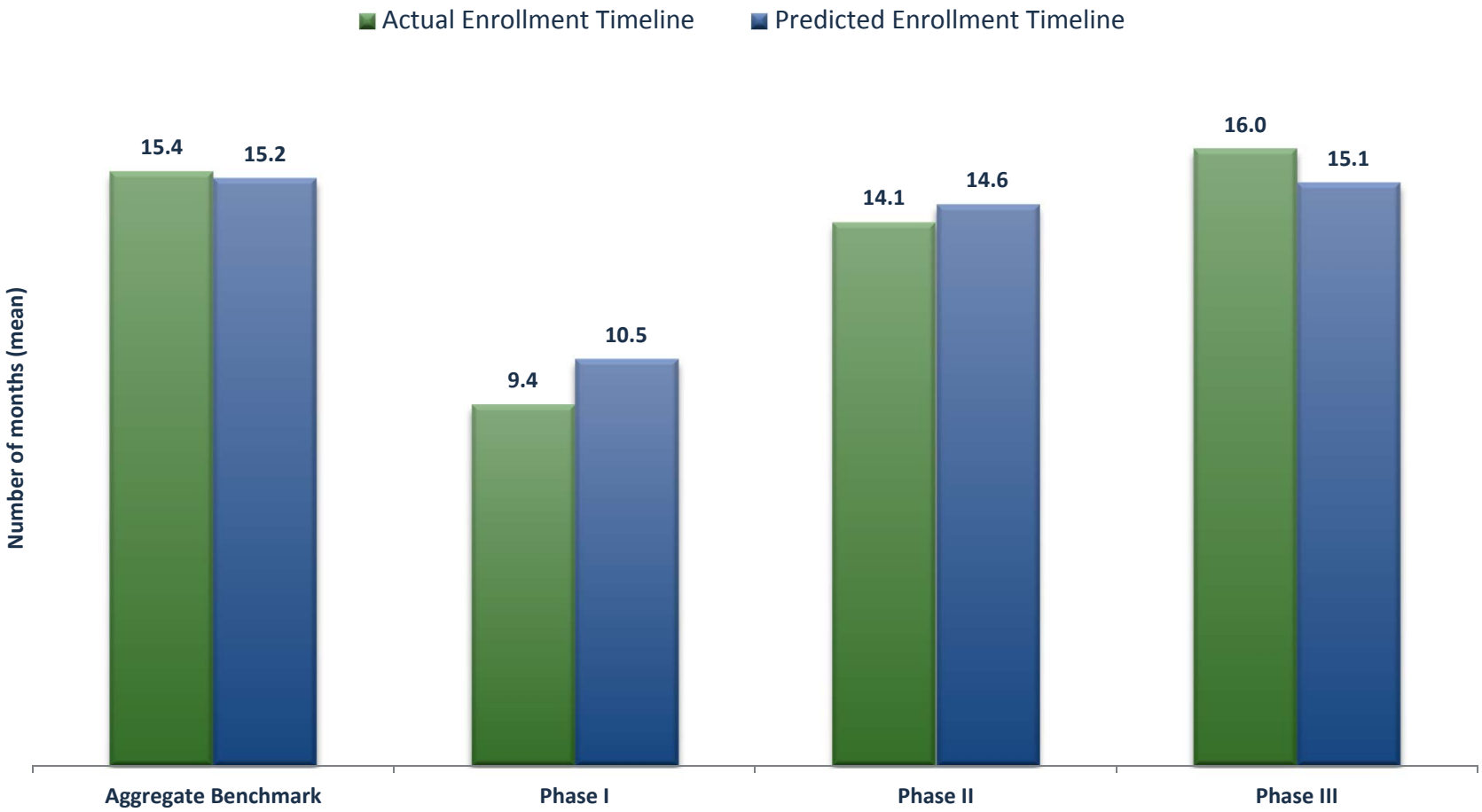
Treatment Procedures and Visit Frequency by Phase

	Phase I (n=18)	Phase II (n=34)	Phase III (n=34)	Phase IV (n=11)	**Aggregate Benchmark** (n=80)
# of Eligibility Criteria (mean)	32.6	33.6	31.4	33.4	**32.6**
# of Unique Procedures (mean)	20.8	27.9	30.8	27.7	**29.1**
Total Procedures (mean)	83.9	124.9	198.7	154.7	**161.3**

	Phase I (n=18)	Phase II (n=33)	Phase III (n=33)	Phase IV (n=11)	**Aggregate Benchmark** (n=78)
Length of Treatment in months (mean)	9.6	26.5	60.7	37.8	**42.7**
# of Treatment Visits (mean)	8.6	9.2	19.2	16.7	**14.6**
# of Total Procedures per Visit	9.7	13.5	10.3	9.3	**11.0**

NOTE: Aggregate benchmark excludes Phase 1

Enrollment Timelines by Phase



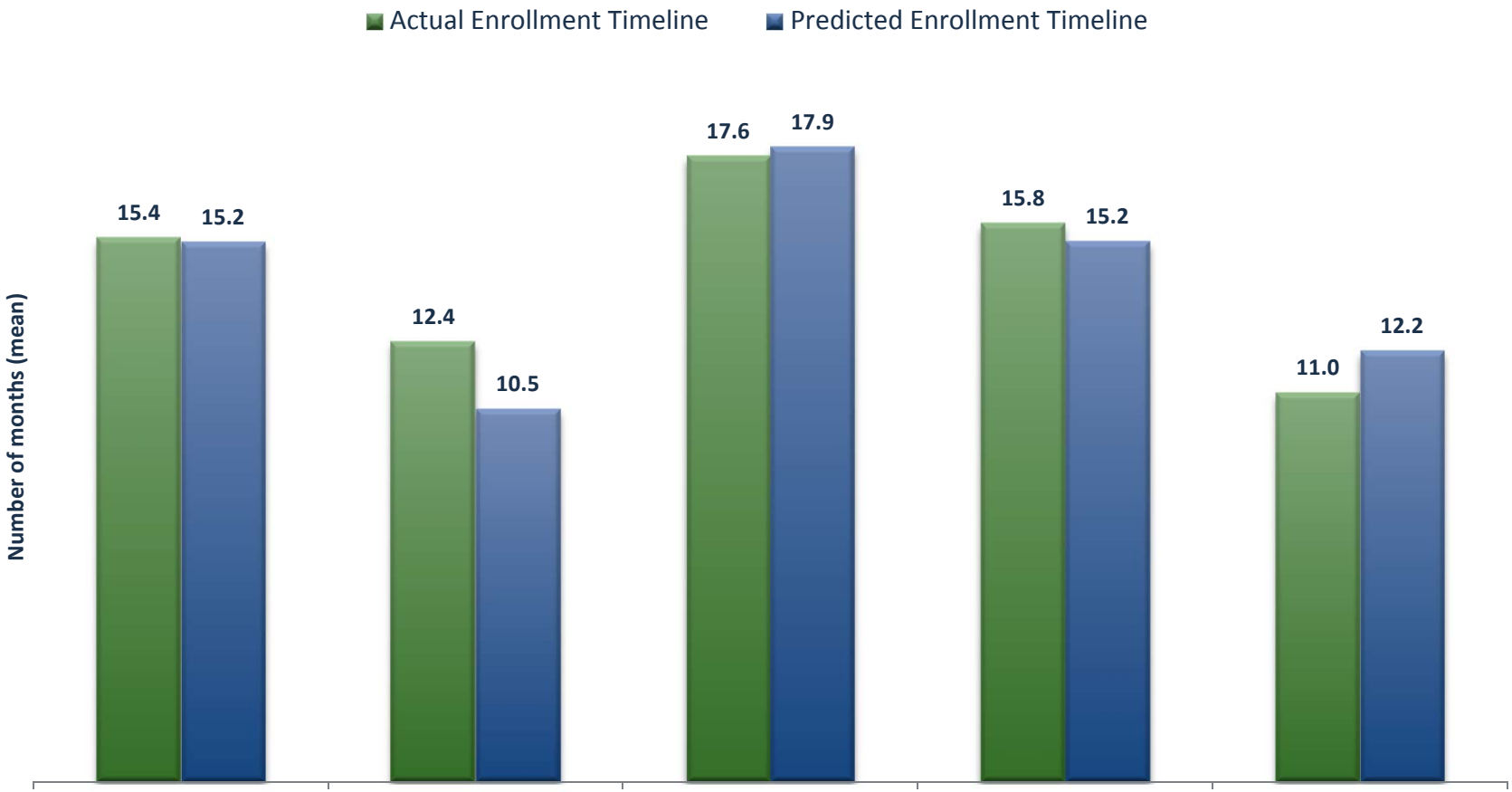
	Aggregate Benchmark	Phase I	Phase II	Phase III
Change in timeline	101%	89%	97%	106%
	n=70	n=22	n=35	n=34

NOTE: Aggregate benchmark excludes Phase 1

% Change in timeline = actual timeline/planned timeline

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Enrollment Timelines by TA



	Aggregate Benchmark	Infectious Disease	Oncology	CNS/Neuroscience	Respiratory
Change in timeline	101%	118%	99%	104%	90%
	n=70	n=11	n=23	n=36	n=12

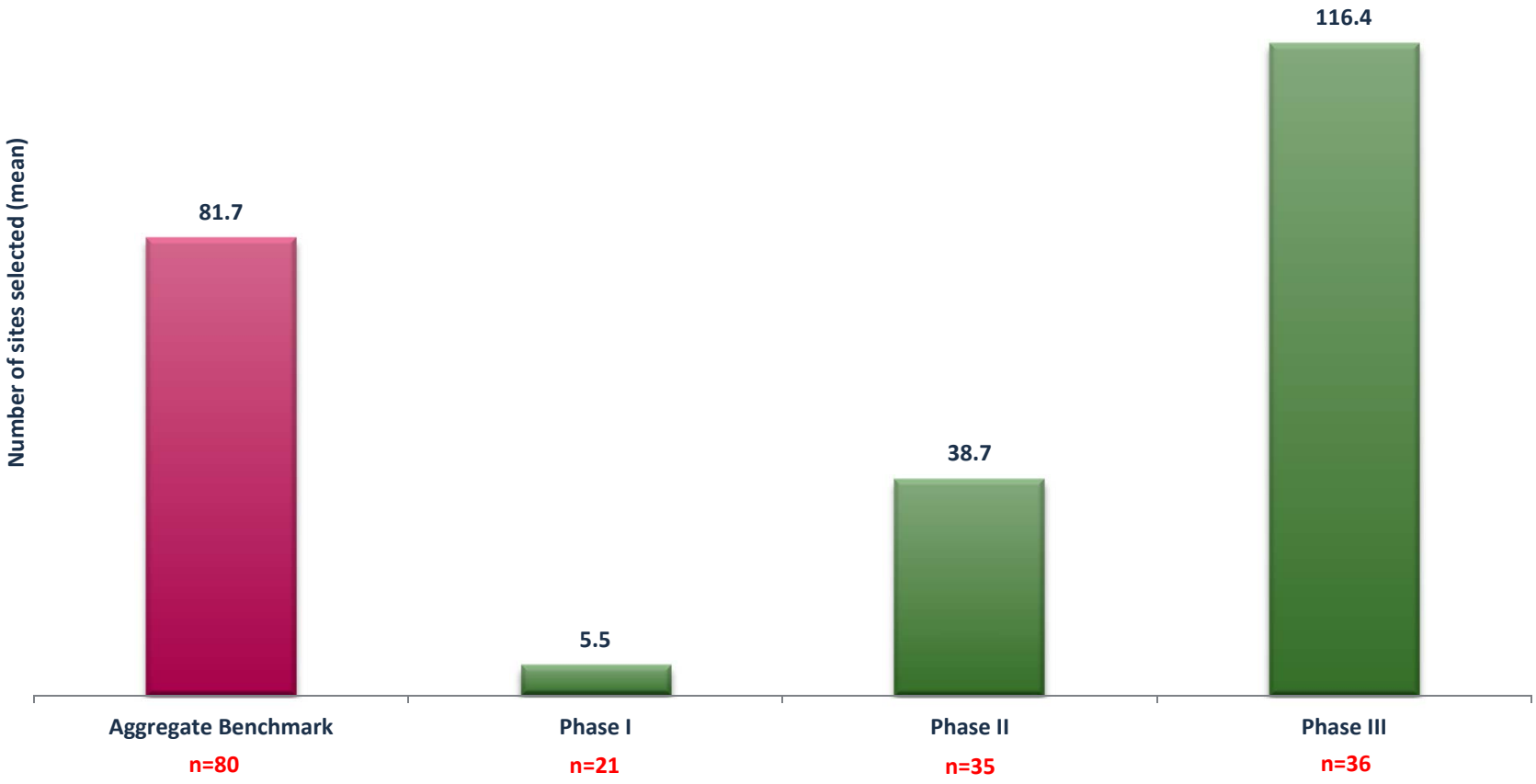
NOTE: Aggregate benchmark excludes Phase 1

% Change in timeline = actual timeline/planned timeline

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Study Level Metrics

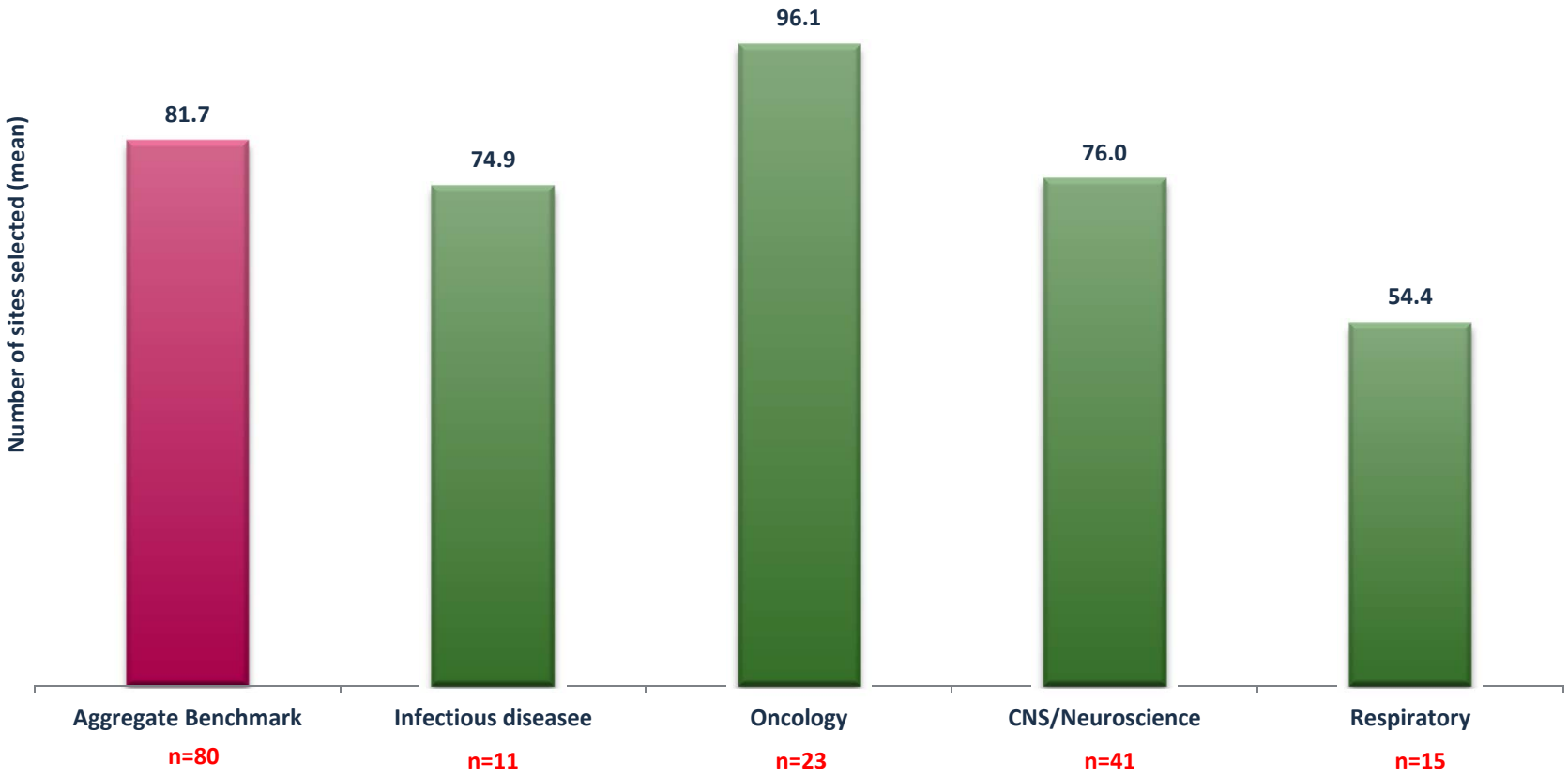
Site Selection by Phase



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

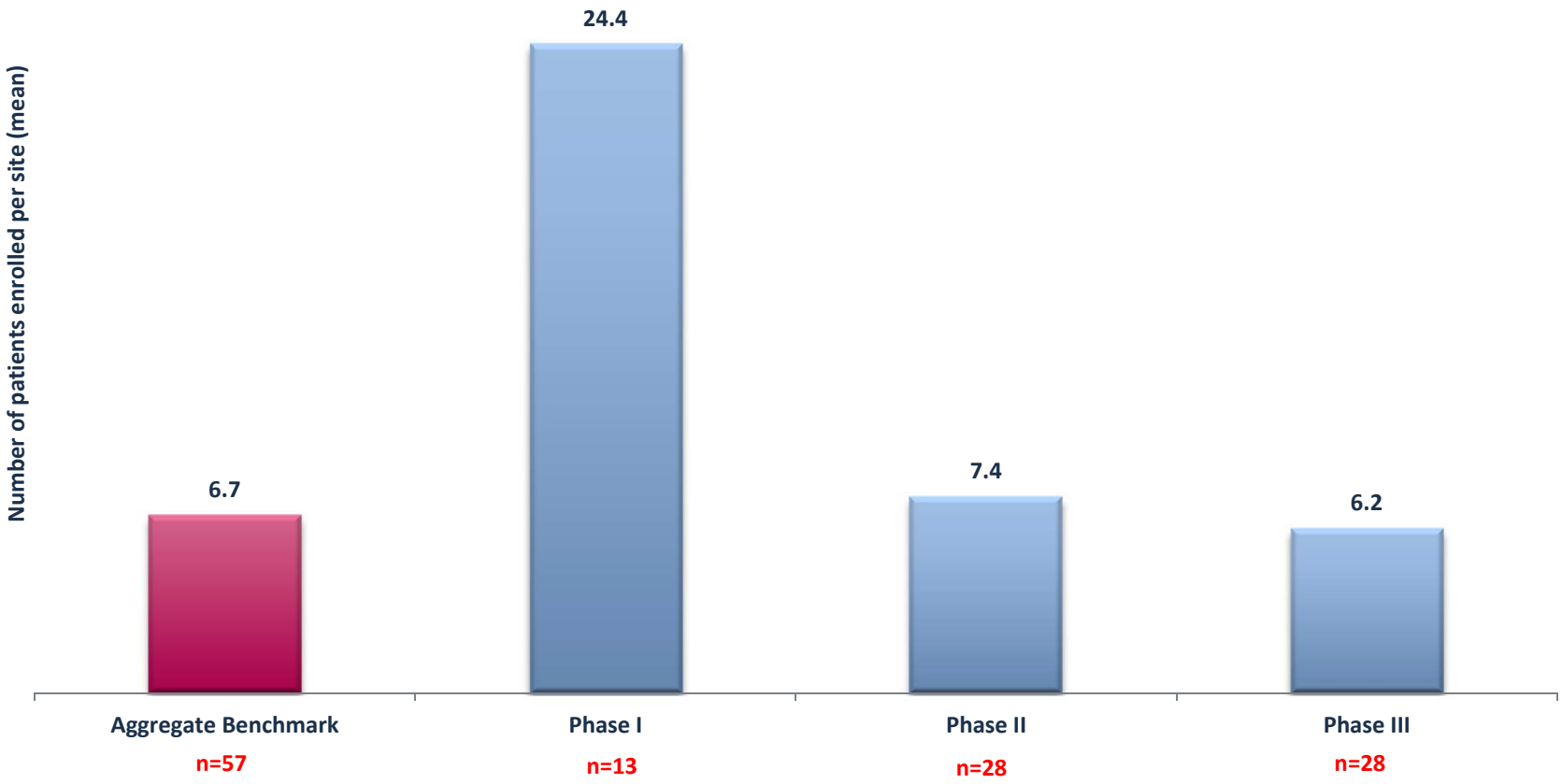
Site Selection by TA



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

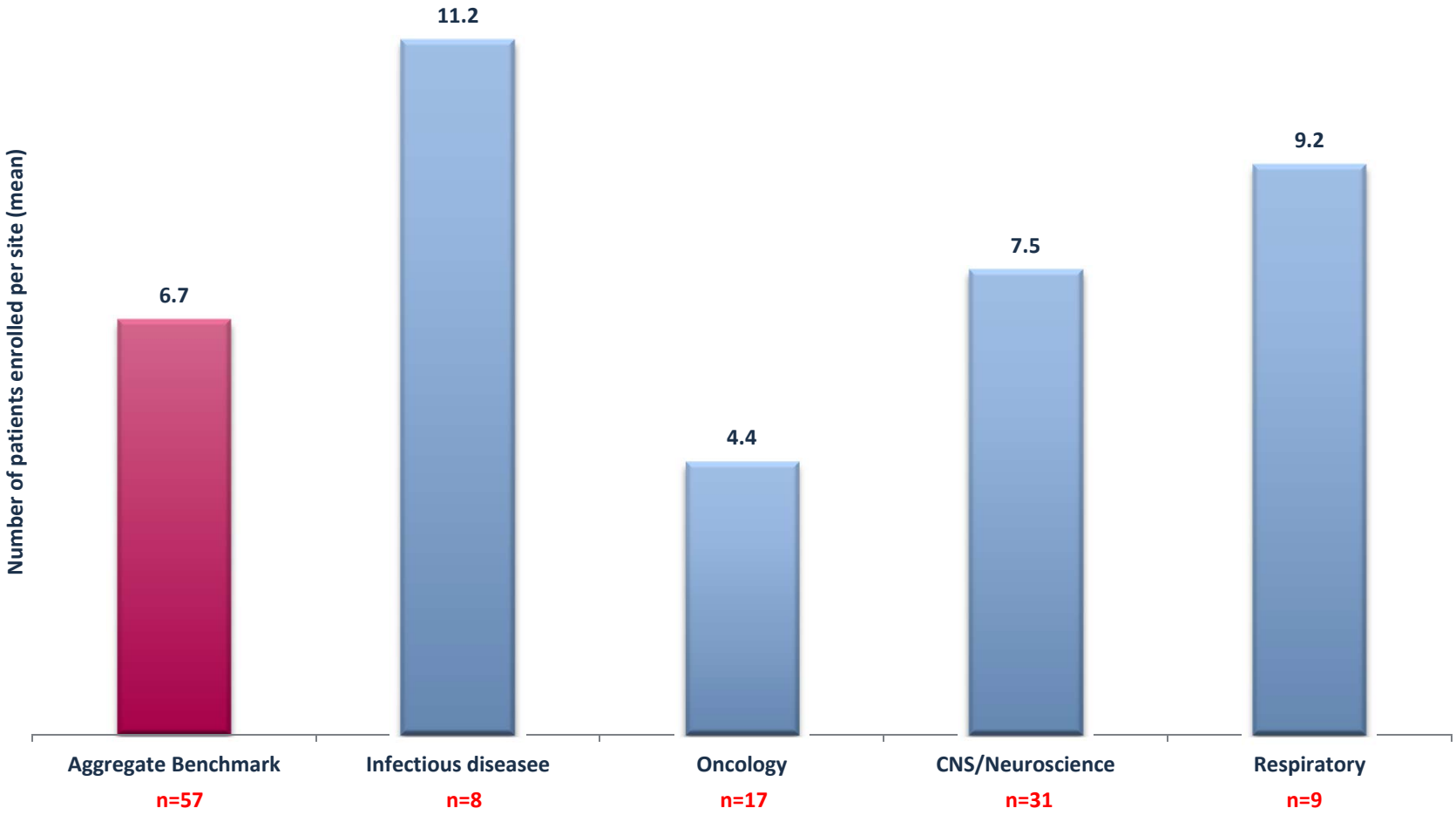
Patients Enrolled per Site by Phase



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

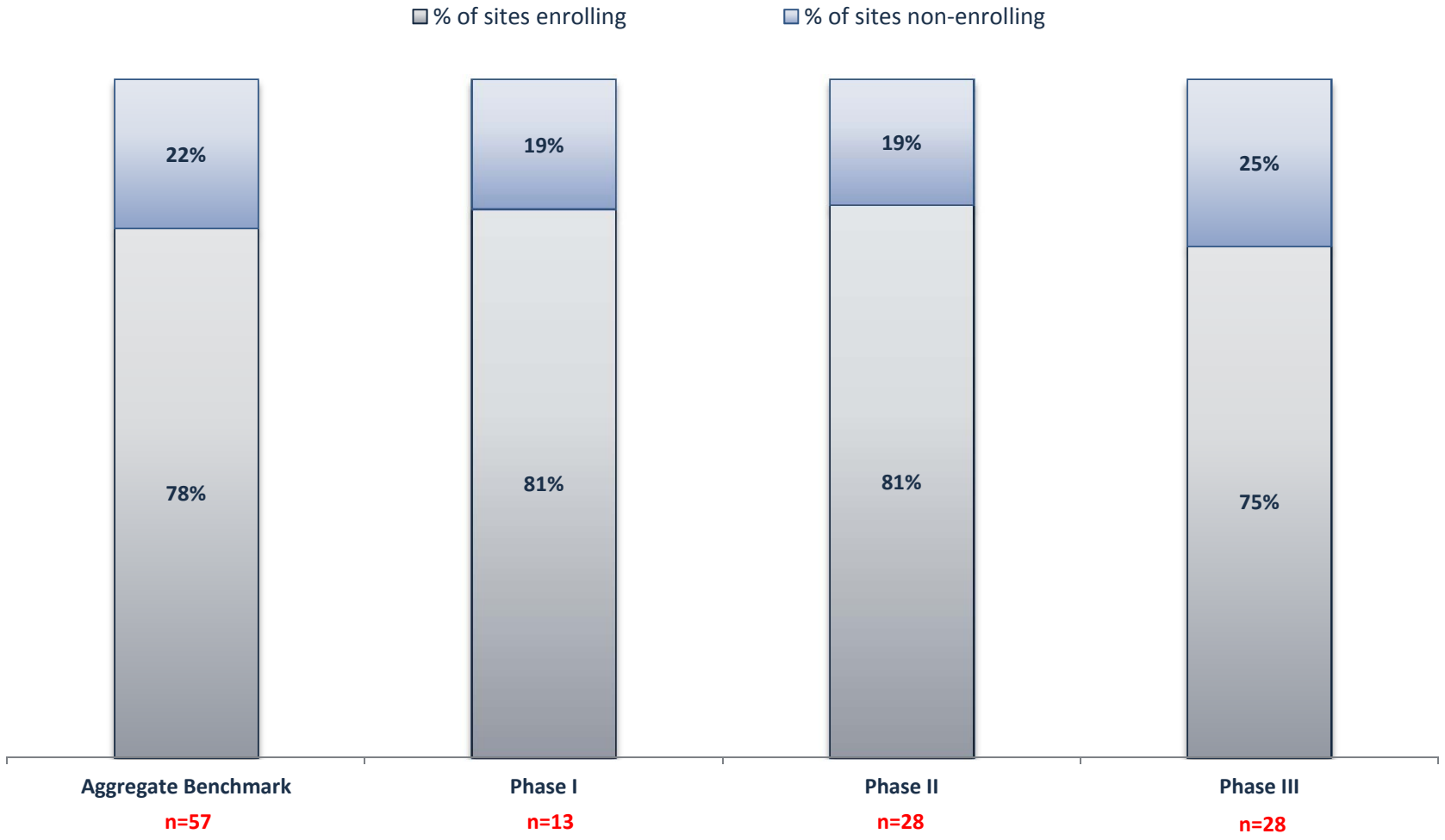
Patients Enrolled per Site by TA



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

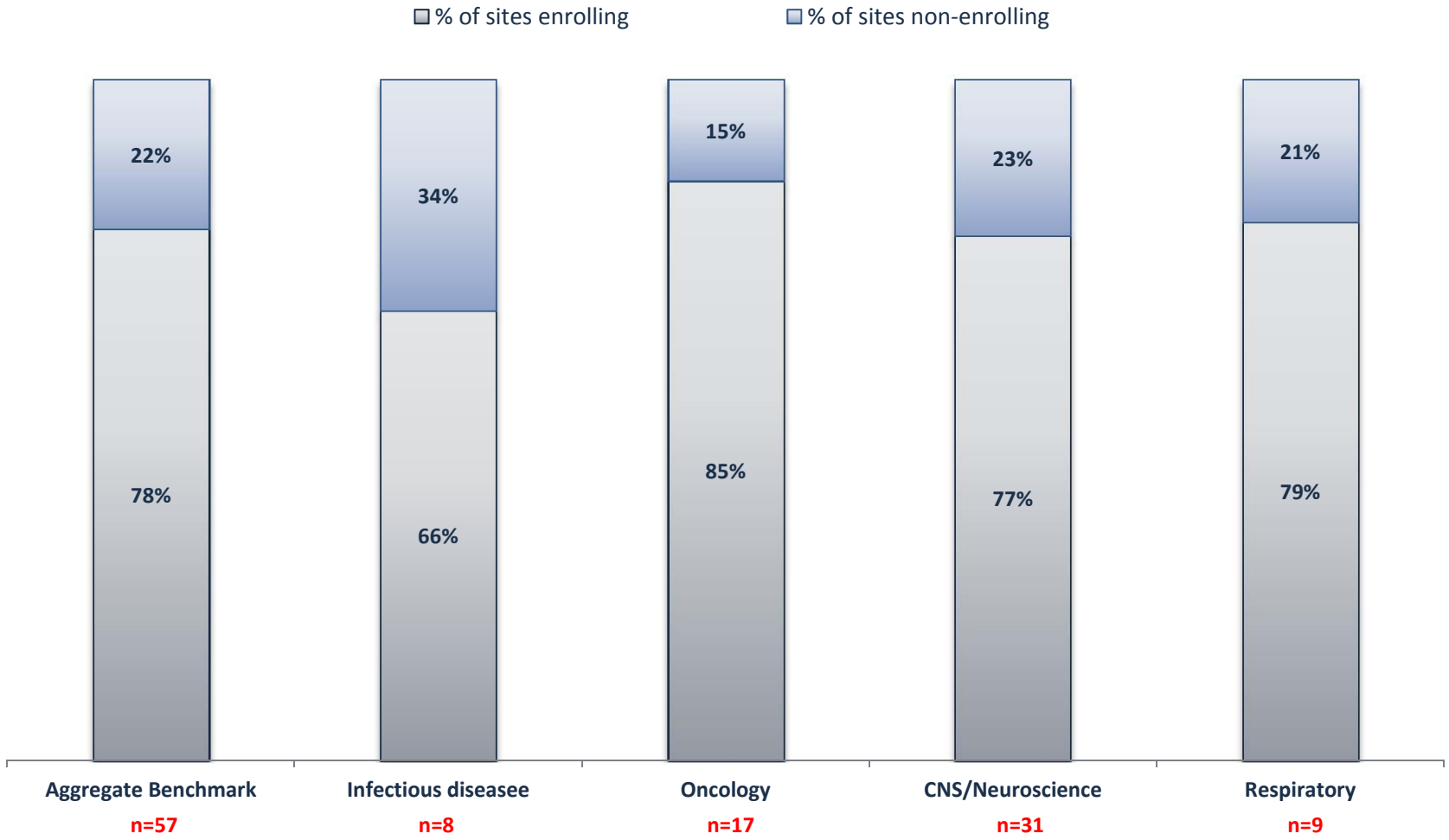
Site Breakdown by Phase



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

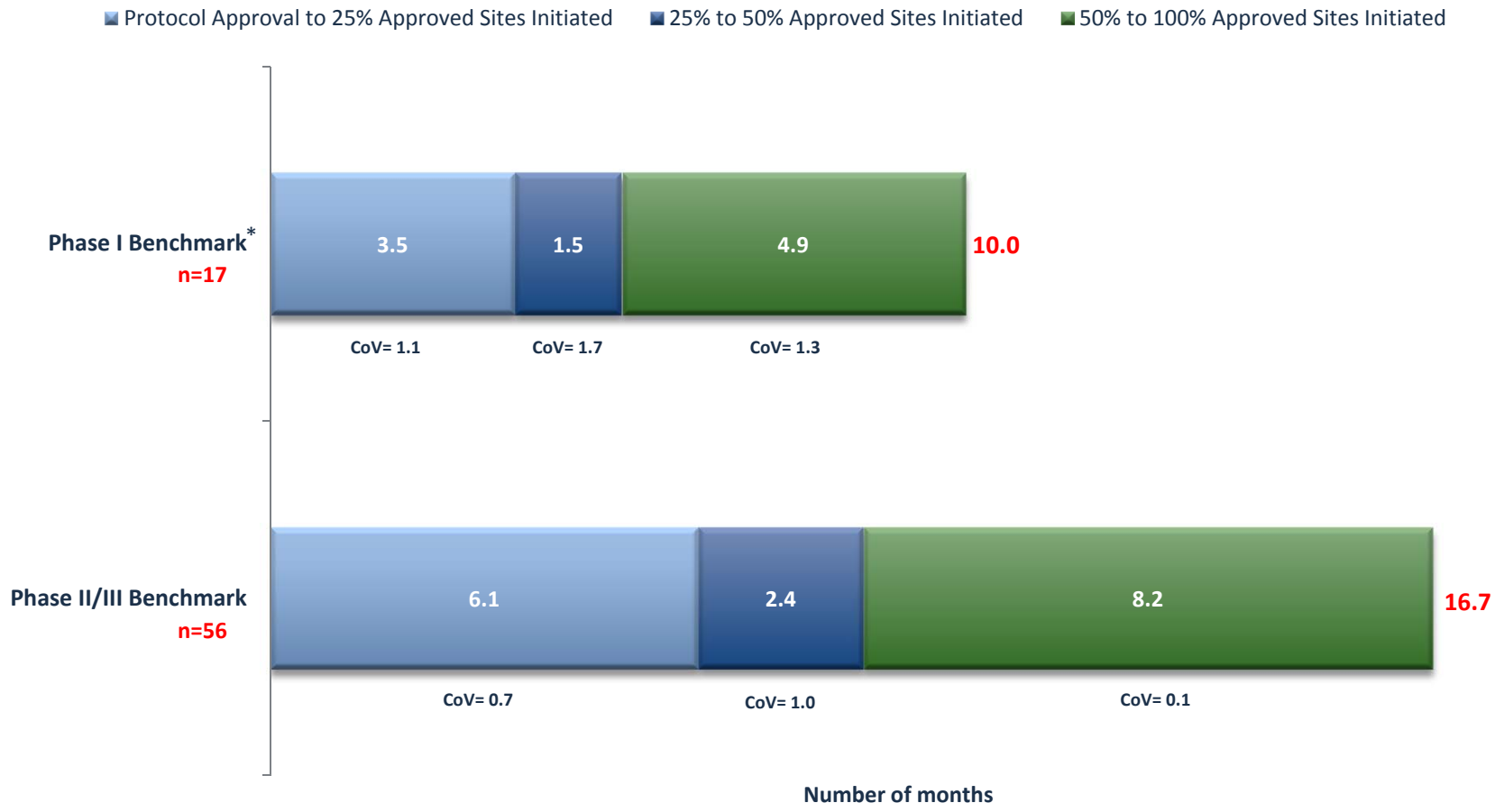
Site Breakdown by TA



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Site Initiation Timeline



* Interpret with caution due to low number of data points

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

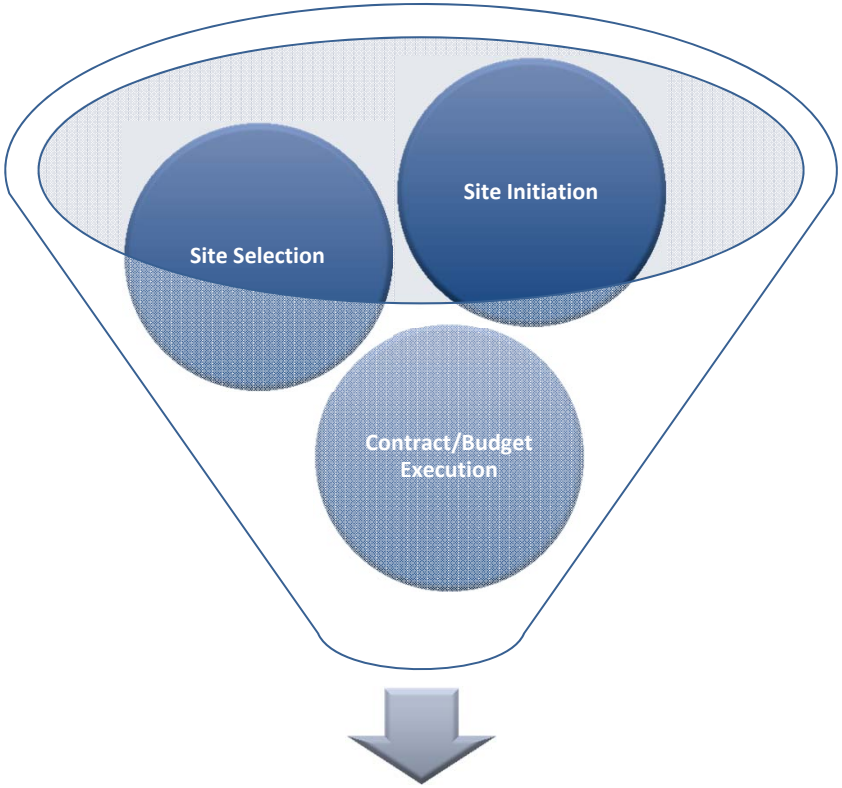
Site Initiation Timeline by TA

* Interpret with caution due to low number of data points

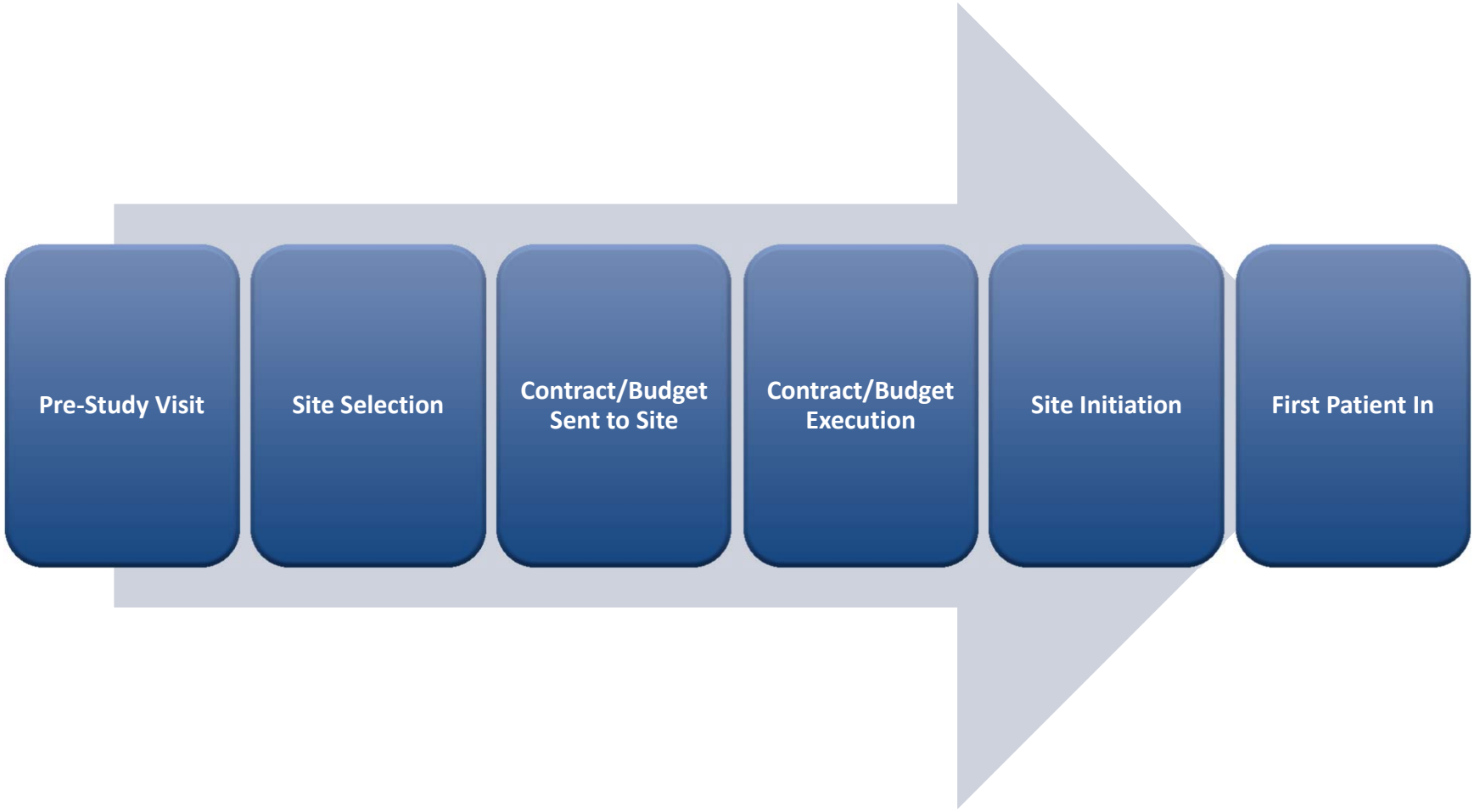
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Site Level Metrics

Variation in Site Initiation Process

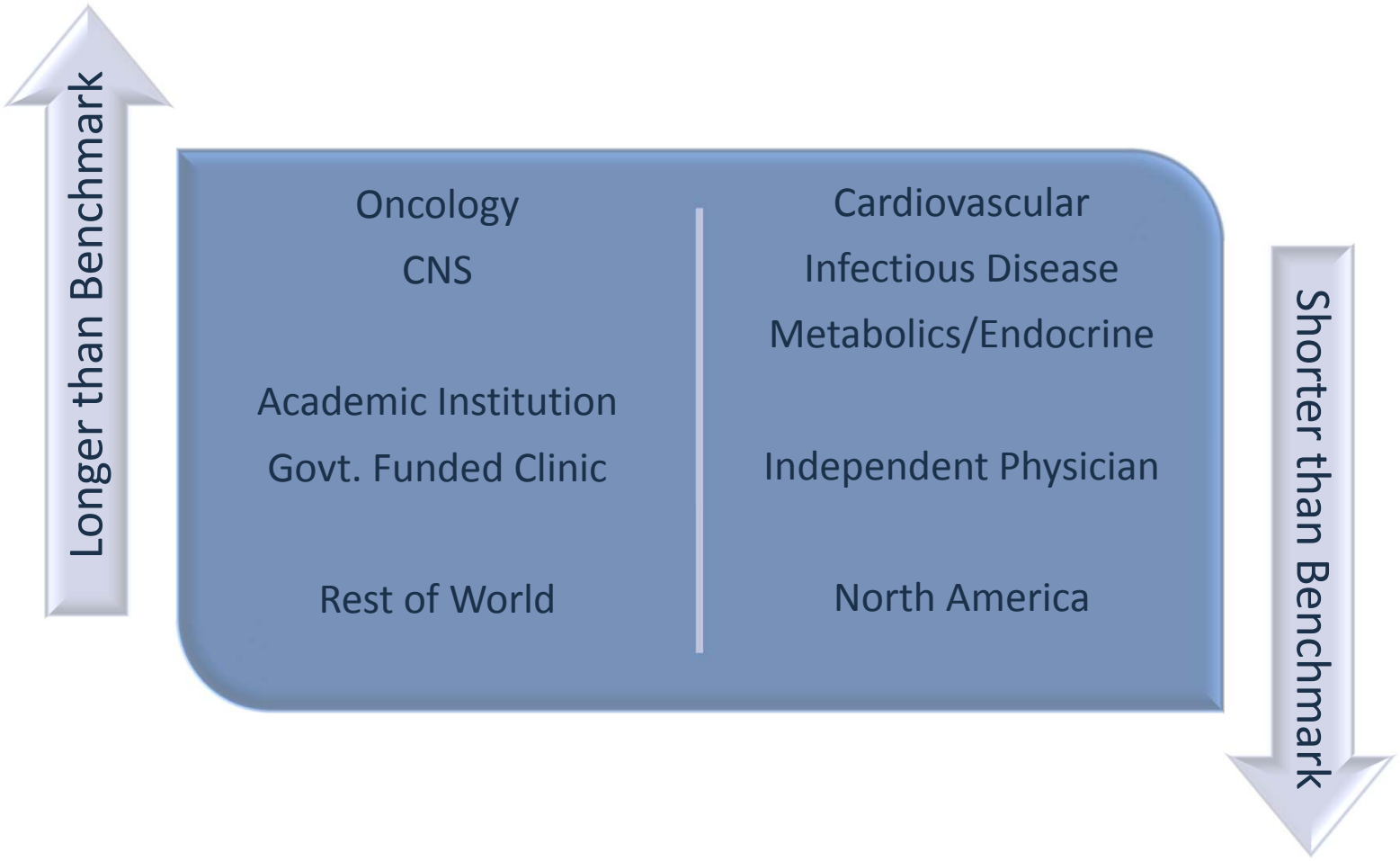


Most Common Process Flow



Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

“First Patient-In” Cycle Time

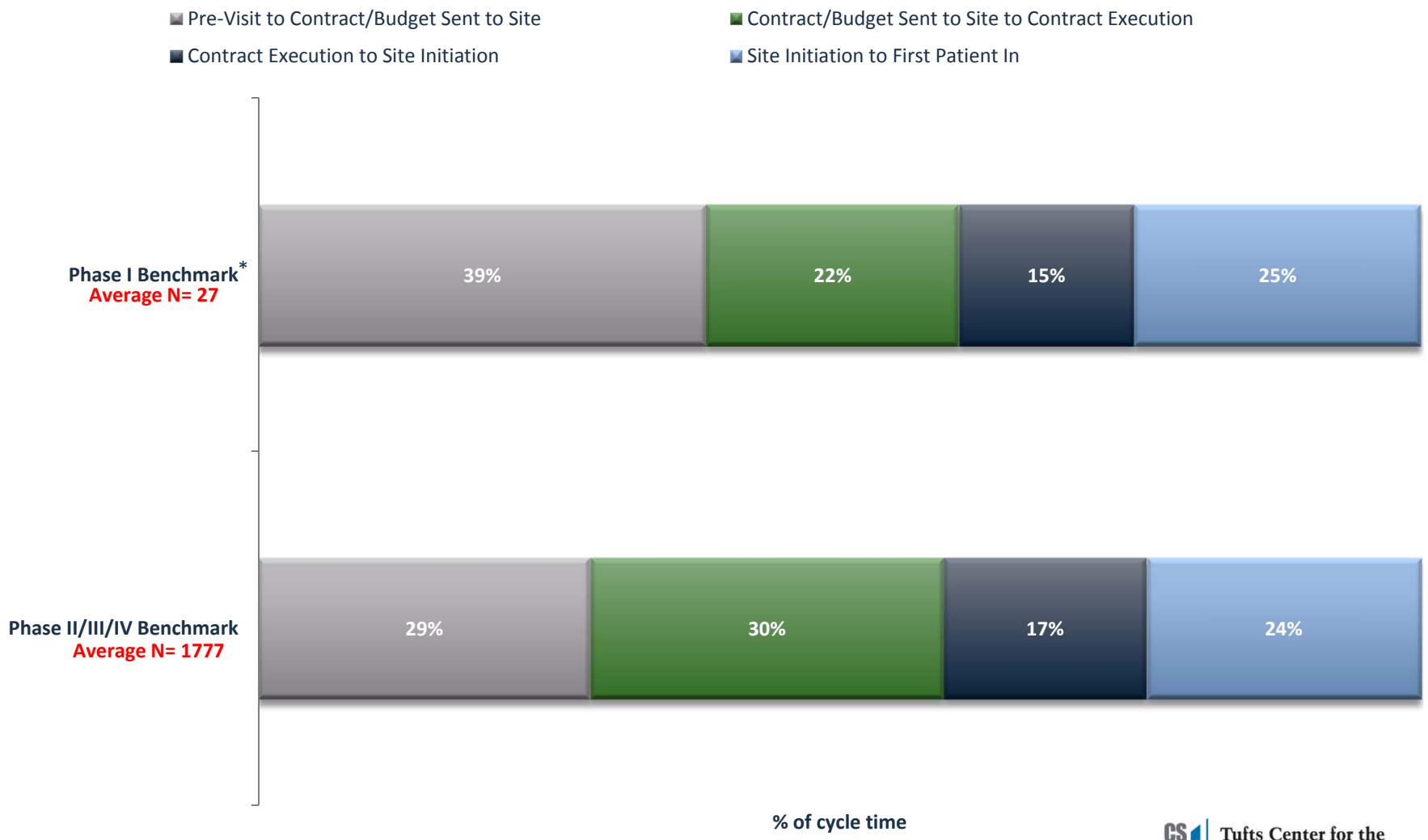


“First Patient-In” Cycle Time

* Interpret with caution due to low number of data points

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

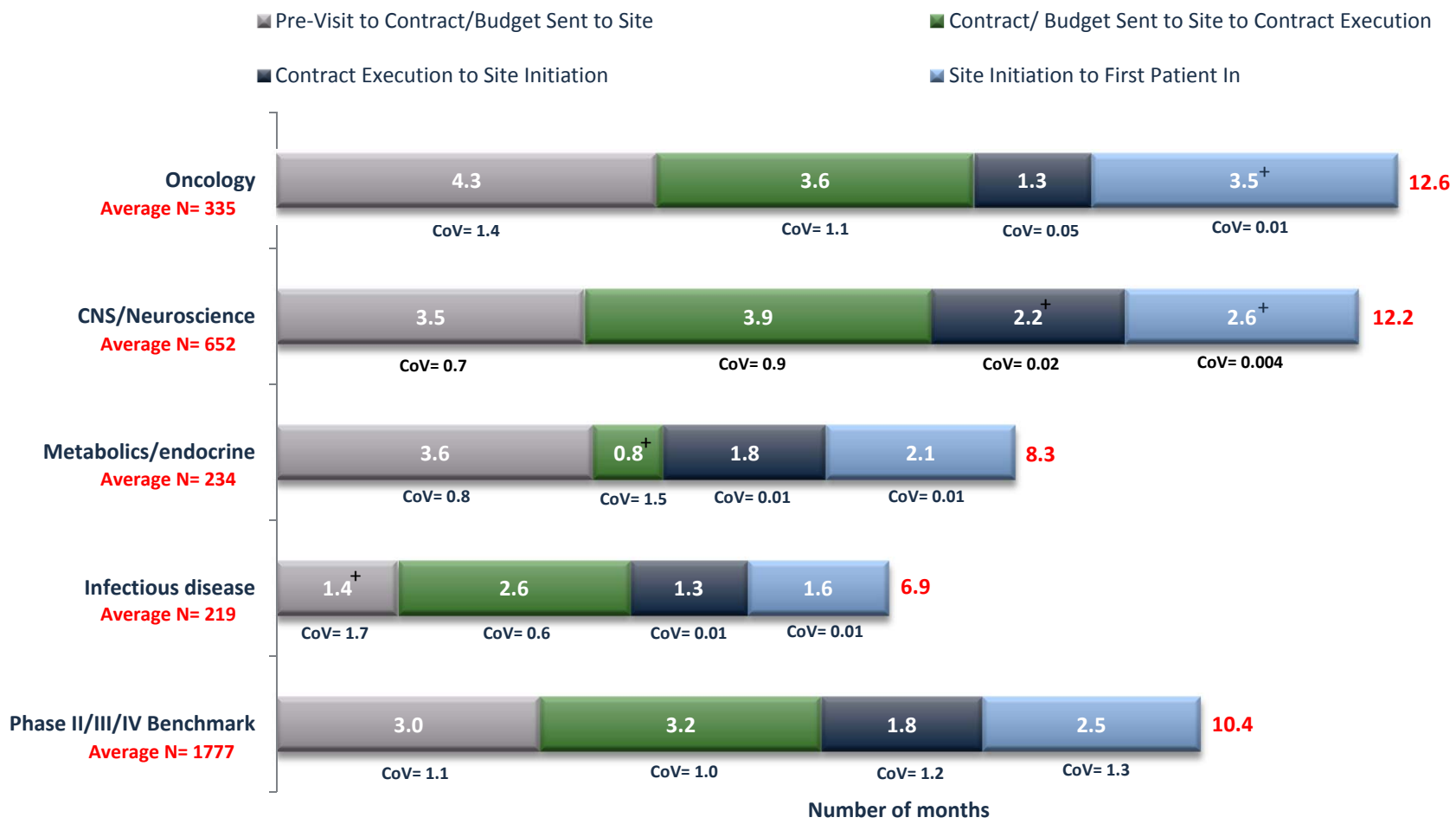
“First Patient-In” Cycle Time Breakdown



* Interpret with caution due to low number of data points

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

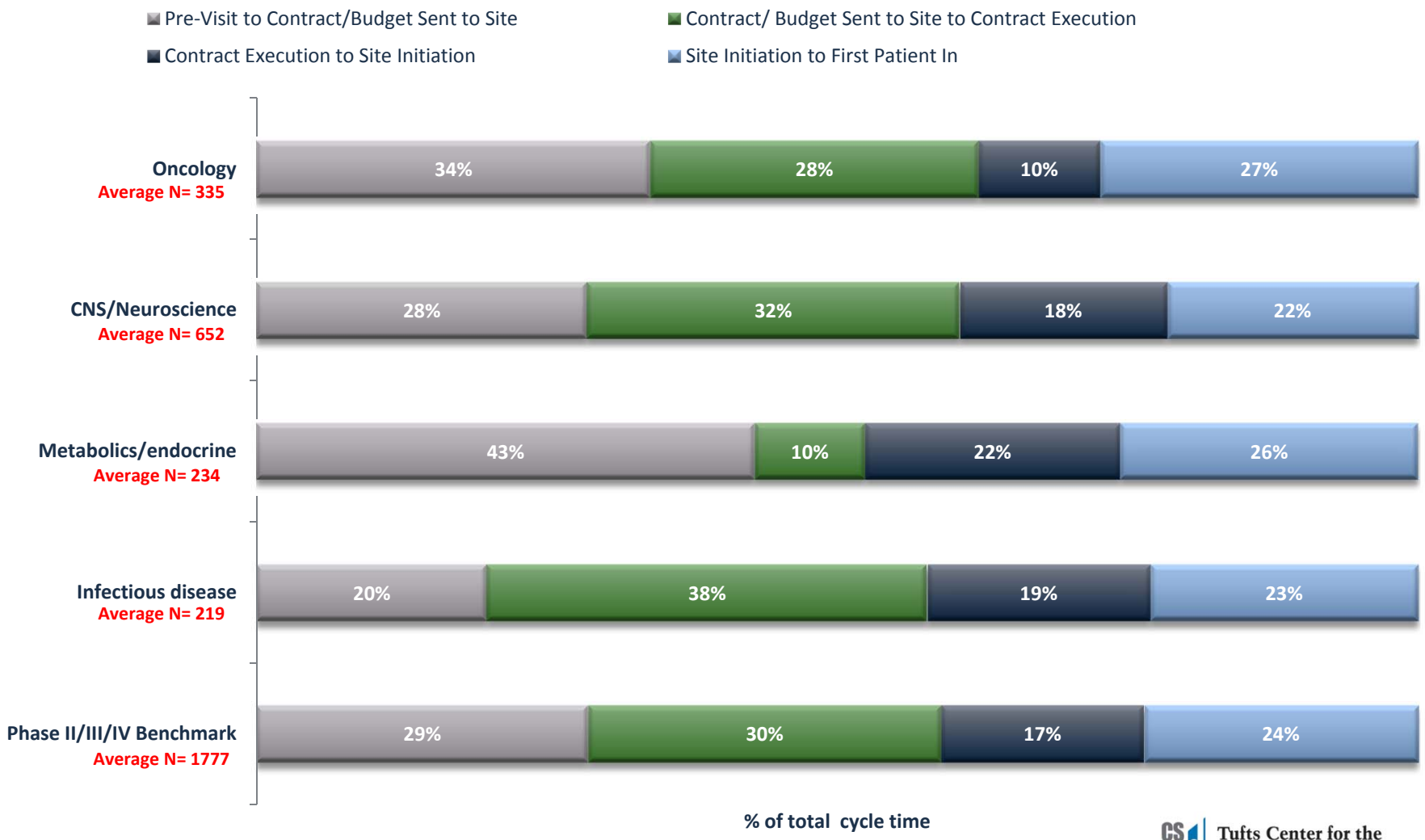
“First Patient-In” Cycle Time by TA



+ Statistically significant; P ≤ 0.05

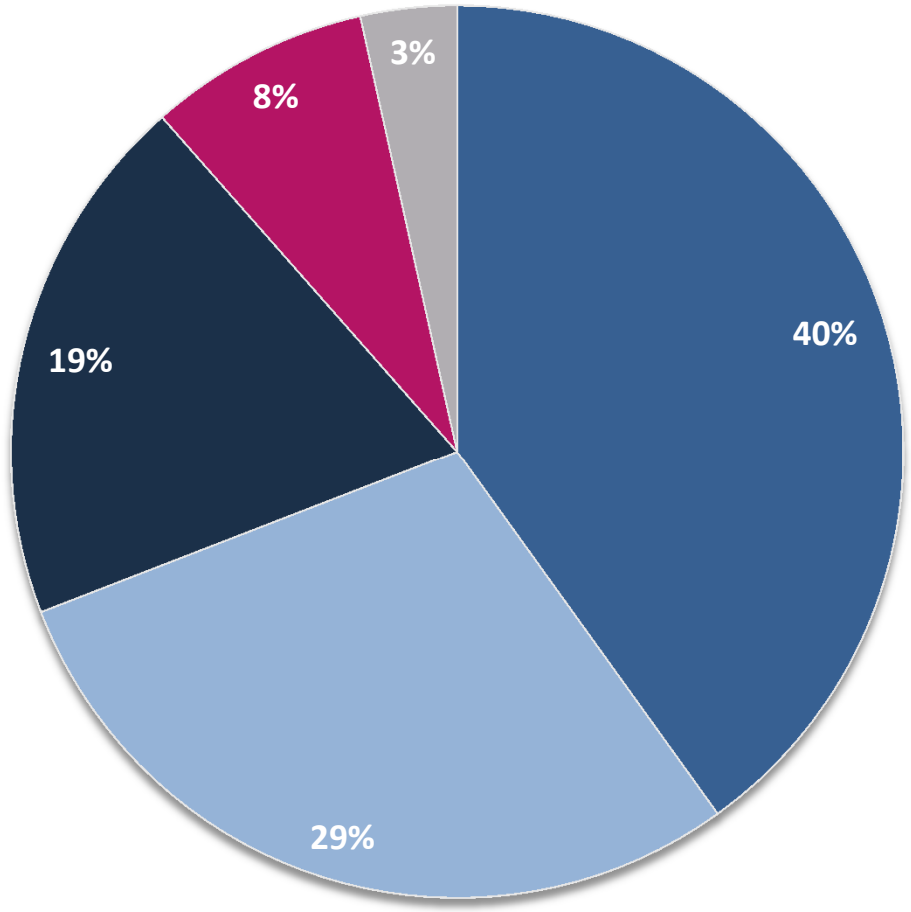
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

“First Patient-In” Cycle Time Breakdown by TA



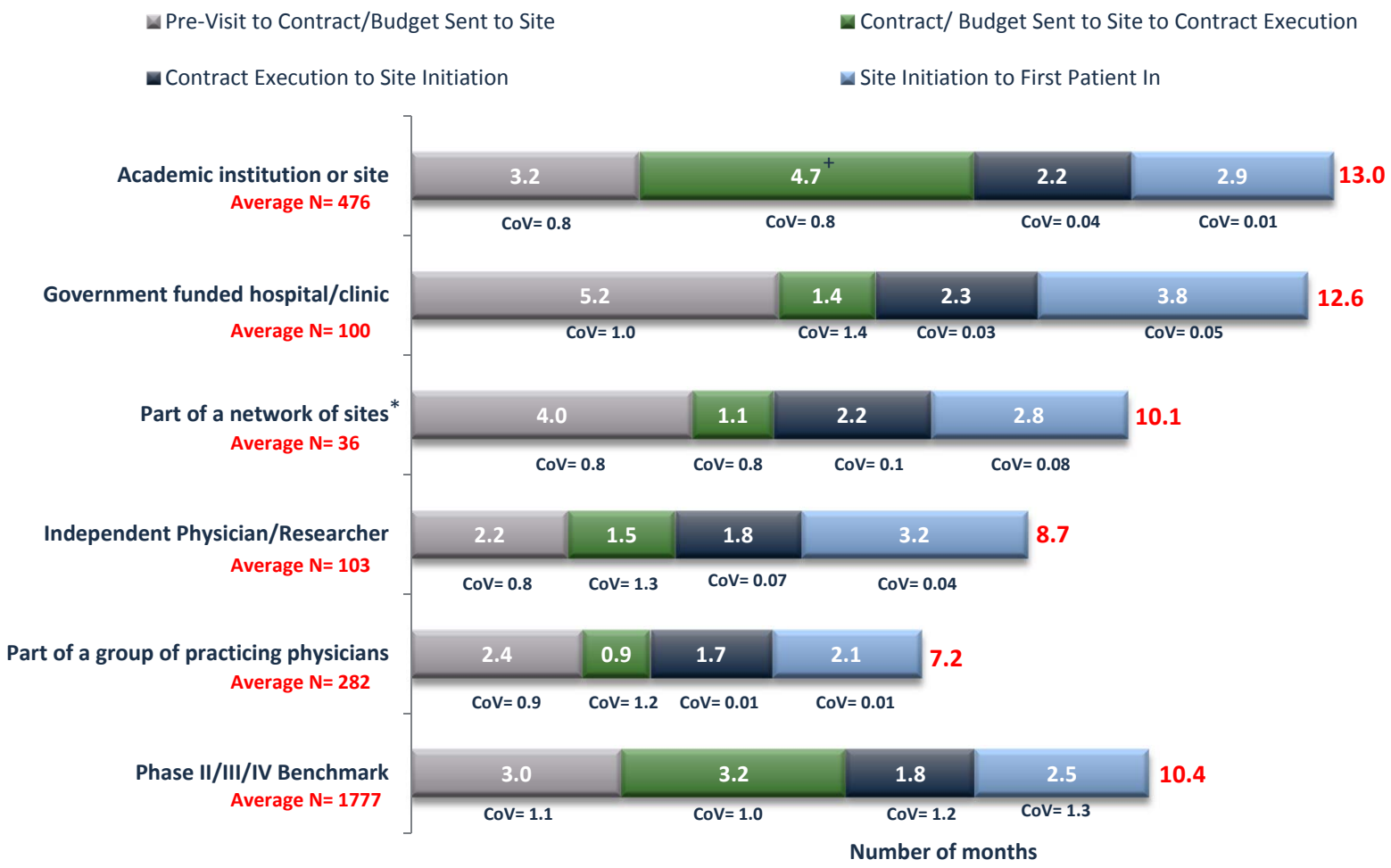
Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Type of Site Initiated



n=2679, 45% of all sites

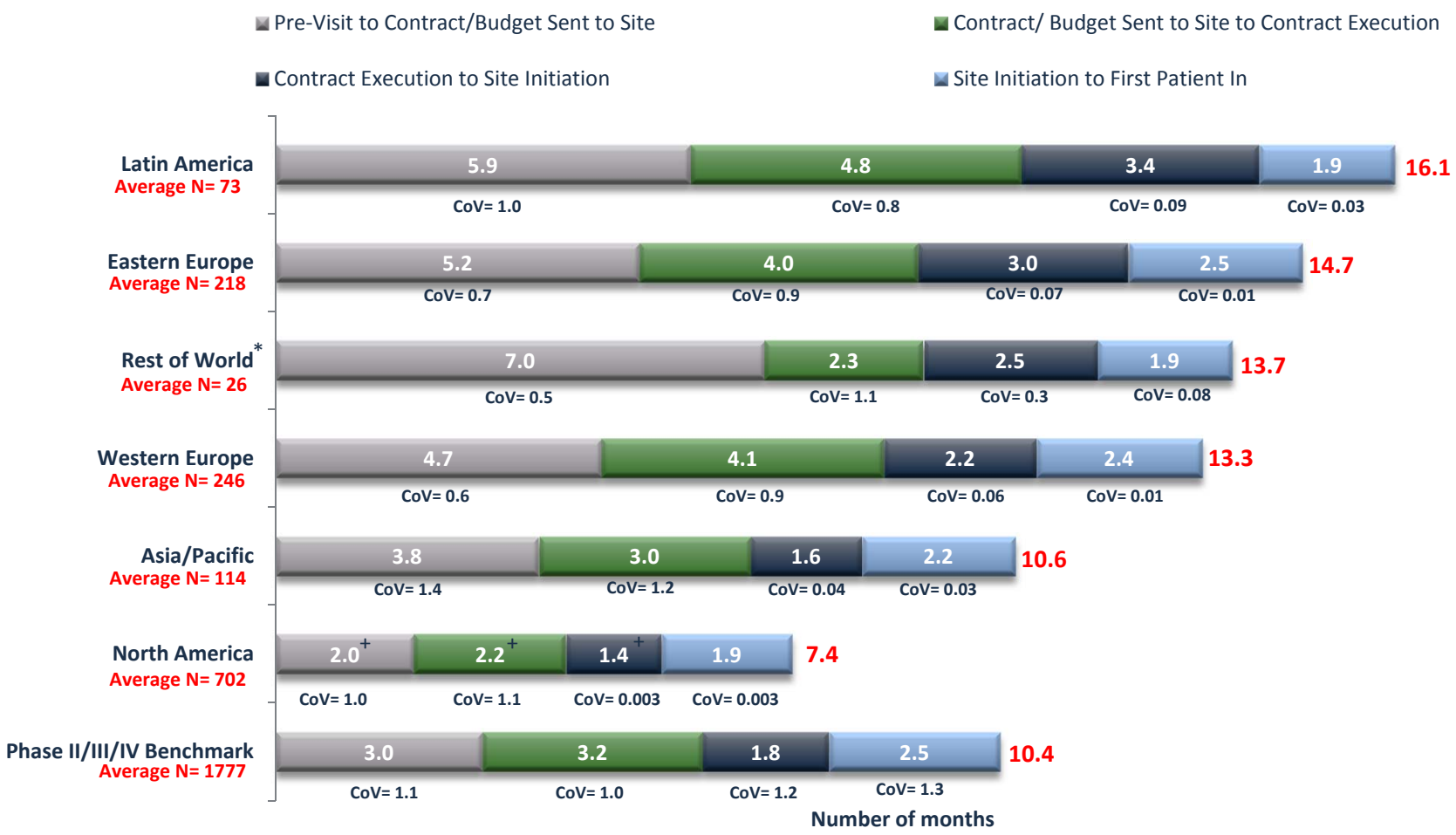
“First Patient-In” Cycle Time by Type of Site



* Interpret with caution due to low number of data points
\+ Statistically significant; P ≤ 0.05

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

“First Patient-In” Cycle Time by Region

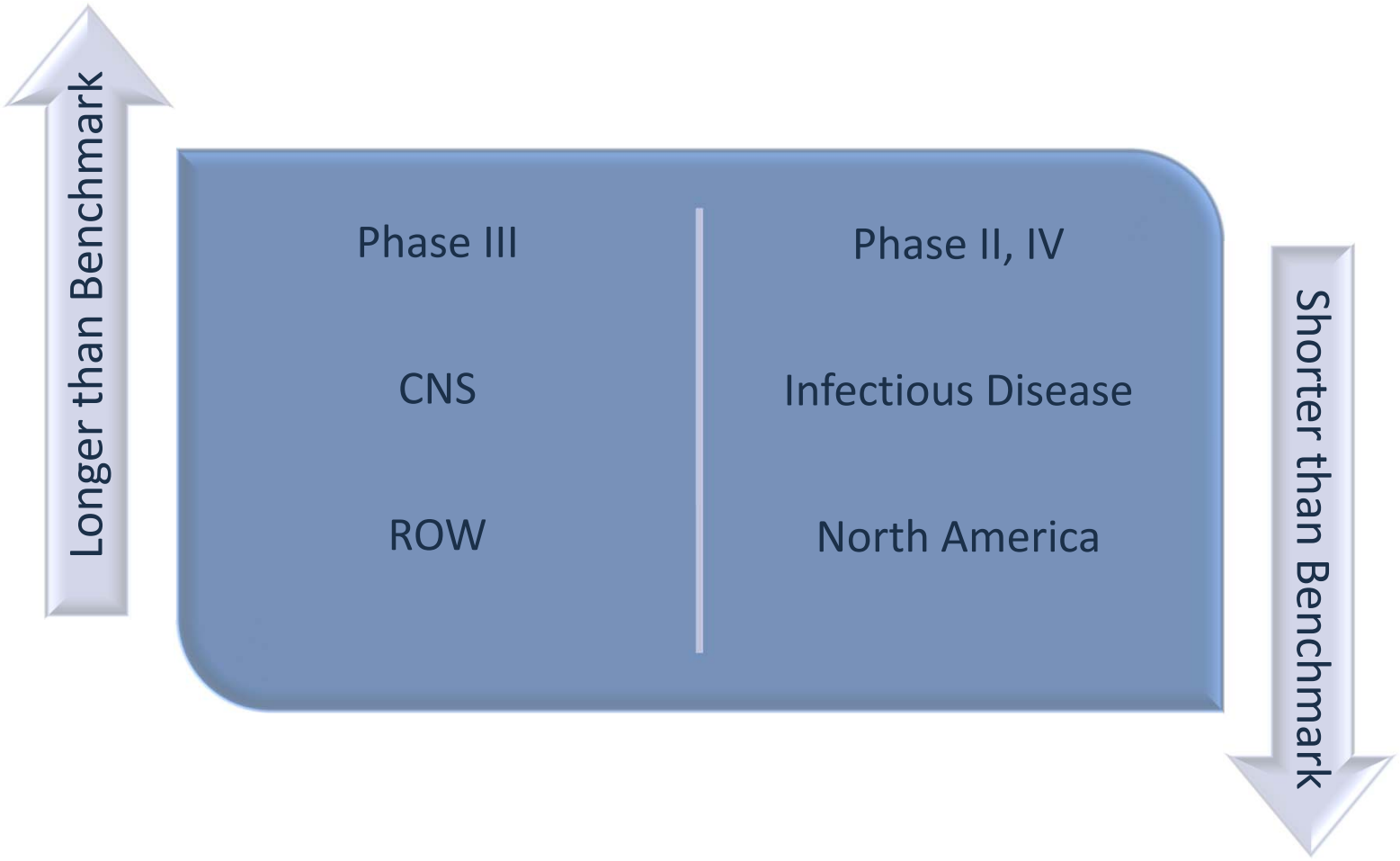


* Interpret with caution due to low number of data points
\+ Statistically significant; P ≤ 0.05

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

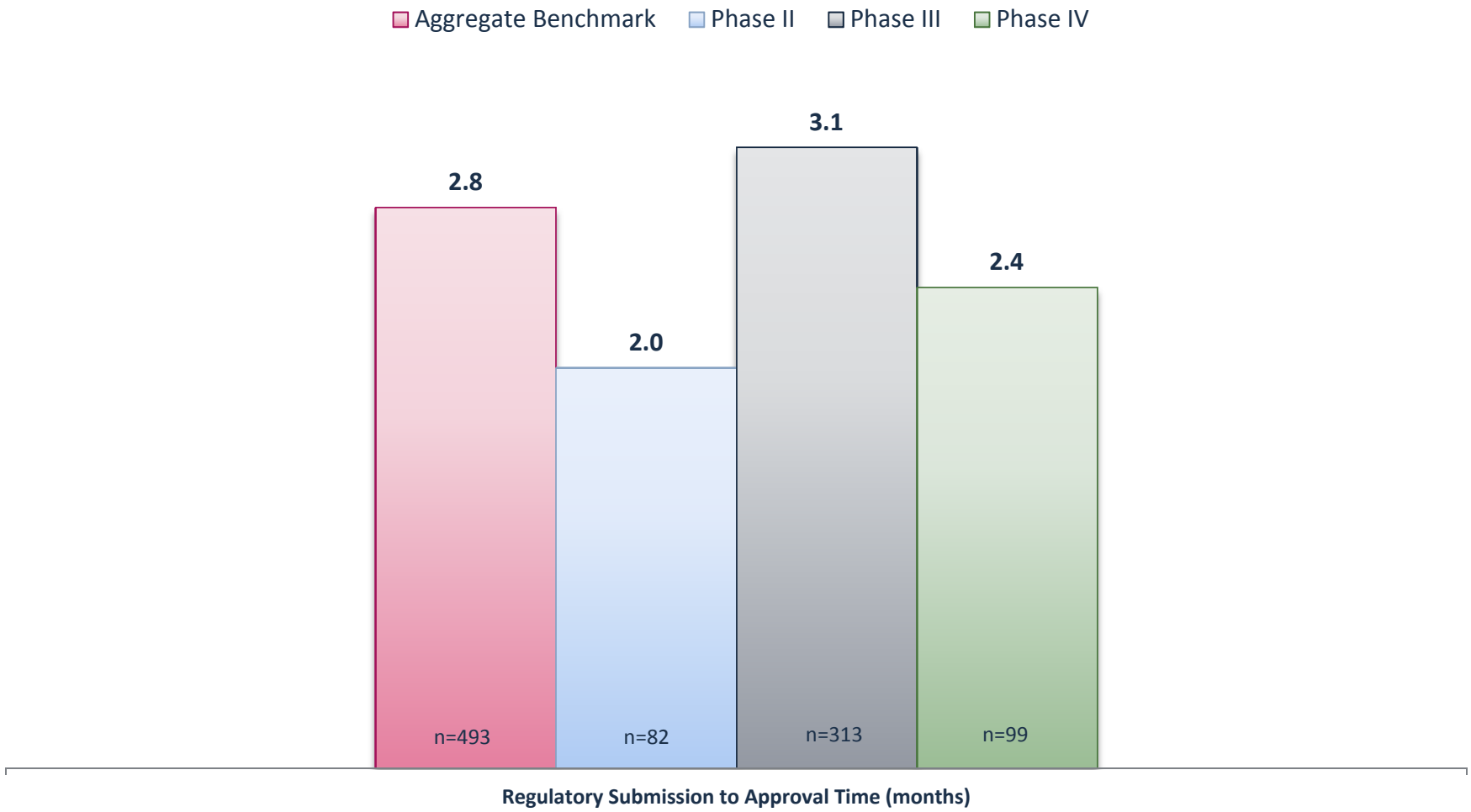
COUNTRY LEVEL METRICS

Regulatory Review and Approval



NOTE: 66% of regulatory submissions had both submission and approval dates

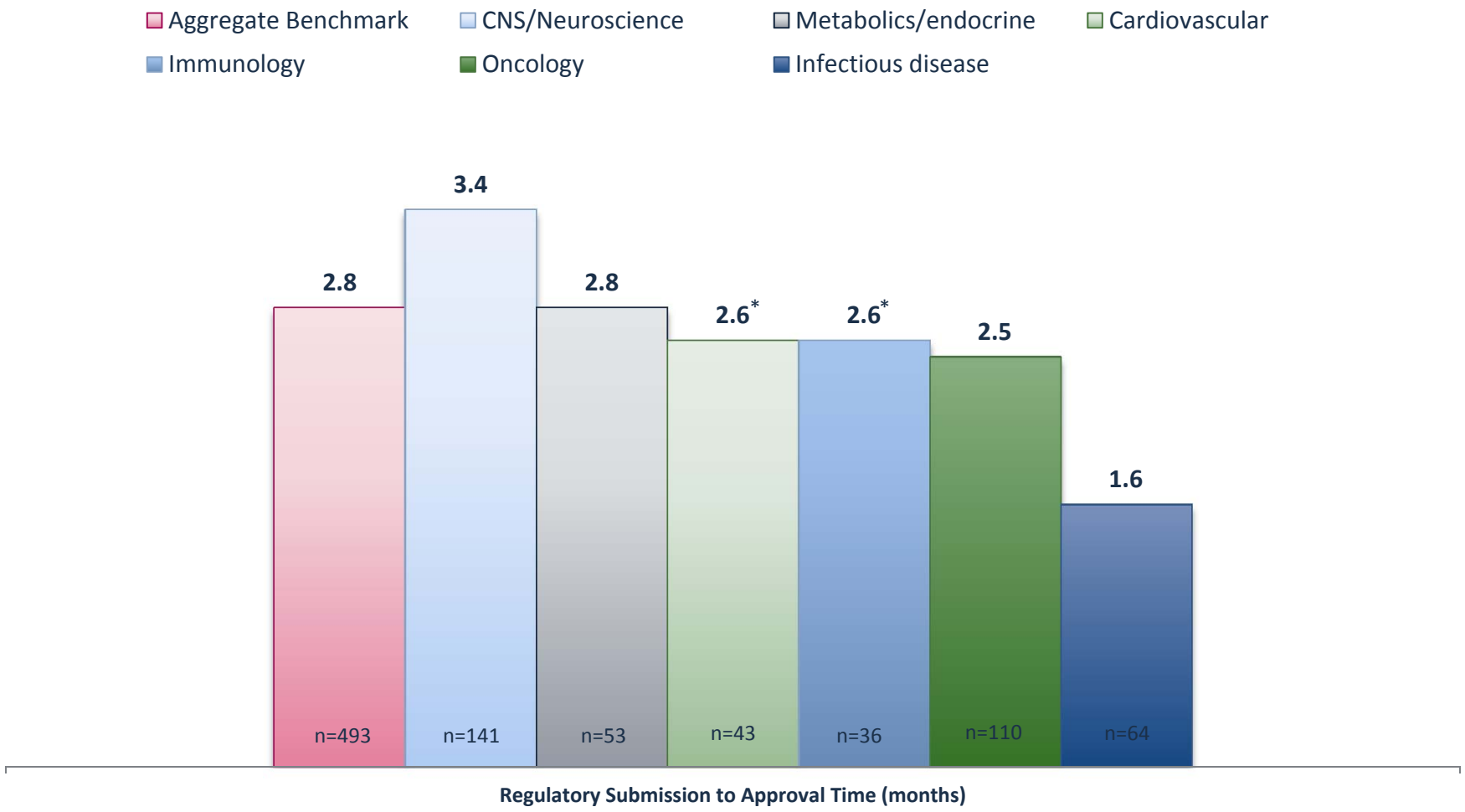
Regulatory Approval by Phase



NOTE: Aggregate benchmark excludes Phase 1

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Regulatory Approval by TA

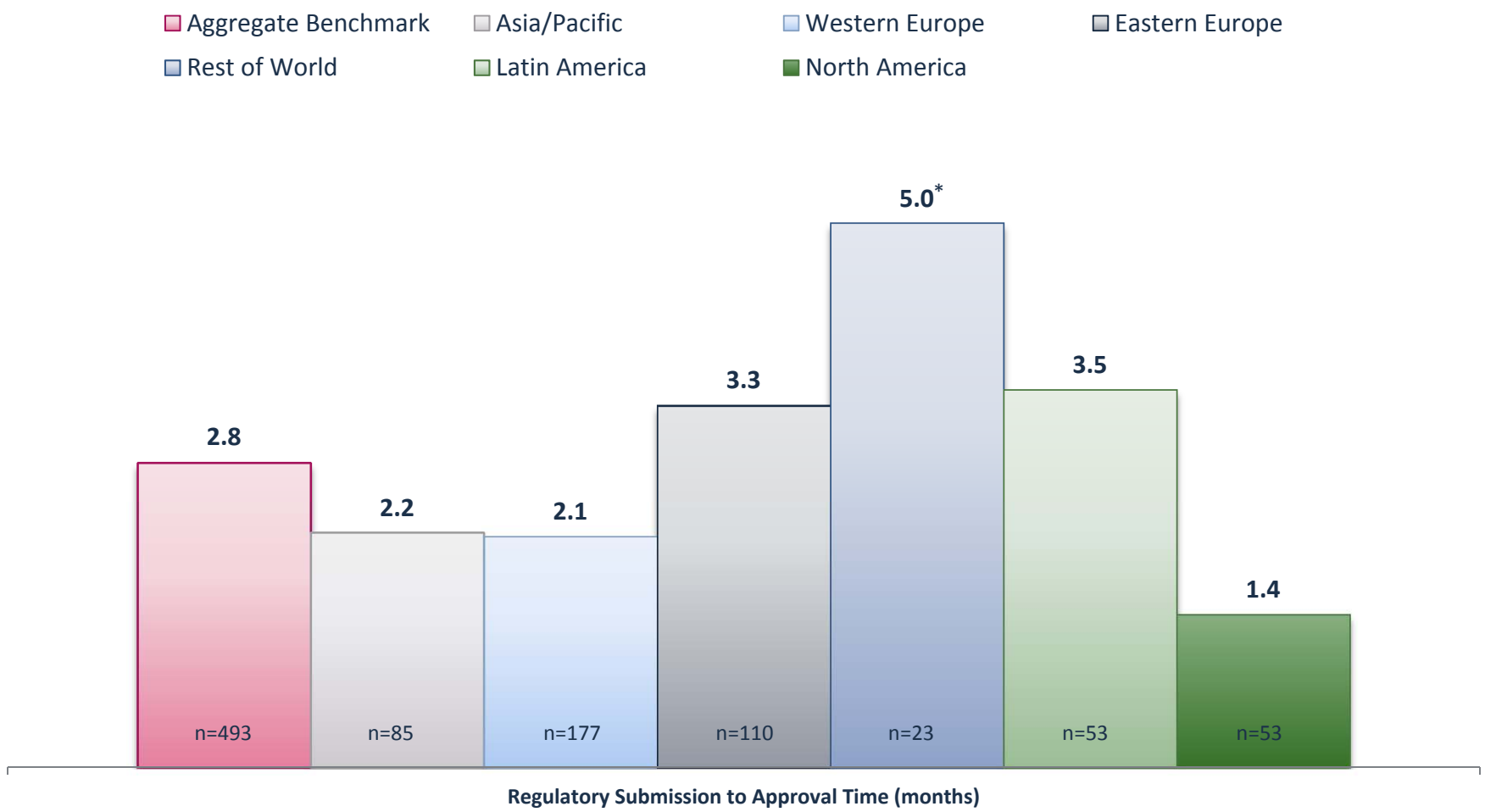


NOTE: Aggregate benchmark excludes Phase 1

* Interpret with caution due to low number of data points

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Regulatory Approval by Region



NOTE: Aggregate benchmark excludes Phase 1

* Interpret with caution due to low number of data points

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Thank You!

Adam Mathias, Research Analyst

Adam.Mathias@tufts.edu

Mary Jo Lamberti, Senior Project Manager

Mary_Jo.Lamberti@tufts.edu

Ken Getz, Senior Research Fellow, Assistant Professor

Kenneth.Getz@tufts.edu

Tufts CSDD, Tufts Medical School

APPENDIX

Background and Context

- **Little to no data benchmarking study initiation practices**
- **Dramatic changes in operating environment**
  - Rising volume of global clinical trial activity
  - More sites enrolling patients
  - Competition for patients
  - Logistical complexity
  - Regulatory pressures
  - Company consolidation and downsizing

Working Group Model

- **Working group format is used to target scholarly study of the most valued and relevant topical issues to aid management decision-making**
- **Working Group Participants:**
  - Collaborated with Tufts CSDD on the development of a data collection tool
  - Provided company data based on study sampling frame
  - Provided ongoing feedback and input during the study
  - Participate in a roundtable discussion to review preliminary analysis

Project Objectives

MEANINGFUL, USEFUL DATA

- To gather detailed quantitative metrics
- To capture baseline data benchmarking sponsor and CRO practices
- To identify and quantify trends in study initiation process
- To compare custom company data with working group benchmarks
- To communicate and share high level findings with the industry
- To stimulate additional study

Participating Companies

Amgen	AstraZeneca	Bayer	Biogen Idec	BMS
Covance	Genentech /Roche	Sanofi/ Genzyme	GSK	INC
J&J	Merck	Millennium	Otsuka	Paragon
PRA	RPS	Shire	Vertex	

Data Characteristics

- **Missing company data**
  - Organizational Structure
  - Overall perceptions
- **Incomplete data**
  - Number of studies very limited for some therapeutic areas:
    - Hematology
    - Dermatology
    - Gastrointestinal
    - Immunology
    - Transplant

Data Characteristics

- **Most Complete:**
  - Study phase
  - Age of study patients
  - TA
  - Molecule type
  - Route of administration
  - Eligibility criteria
  - Treatment procedures
  - Visit frequency
  - Enrollment timeline
  - Enrollment rates
  - Date of protocol approval
  - Date site is initiated

Data Characteristics

- **Least Complete:**
  - Number of sites by region
  - Type of site initiated
  - Date of site selection
  - Date of pre-study visit
  - Date either contract or budget sent to site
  - Date of contract execution
  - Date of regulatory authority submission
  - Date of regulatory authority approval

Working Group Companies and Study Start-Up Teams

Company Type	n
Pharma/biotech	8
CRO	2

Company Size	n
Large (Revenues $4B to $50B)	7
Mid-Sized ($100M to $4B)	3
Small	0

Dedicated Start-Up Team	n
Yes	3
No	7

Working Group Companies and Study Start-Up Teams

Team/Department Reports to:	n
Clinical Operations or Clinical Development	2
Site or Trial Operations	1

Team/Department Characteristics	Mean
Age (years)	1.3
Size (FTE)	6.5

If NO dedicated team, handled by:	n
Clinical Operations	2
Study Teams	4
Both Study Teams and Clinical Operations	2

Overall Perceptions

Study initiation cycle times can be…	n
Greatly Shortened	2
Somewhat shortened	6
Minimally shortened	0
Not at all shortened	0

Importance of shorter study initiation cycle times…	n
Very Important	7
Somewhat important	1
Not very important	0
Not at all important	0

Companies and their Study Start-Up Groups

Organization implemented any initiatives to improve study initiation?	n
Yes	8
No	0

# of Studies Initiated per Year	(n =7)
Mean	87.6
Median	40.0

Site Initiation Timeline Variance

	Protocol Approval to 25%			25 to 50% Approved Sites			50 to 100% Approved Sites		
BENCHMARK	Avg.	Range	CoVar.	Avg.	Range	CoVar.	Avg.	Range	CoVar.
Phase I	3.5	0 - 8.9	1.1	1.5	0 - 11.2	1.7	4.9	0 - 20.8	1.3
Phase II/III	6.1	2.1- 21.3	0.7	2.4	0 - 11.5	1.0	8.2	0 - 36.1	0.1

“First Patient-In” Cycle Time Variance

	Pre-Study Visit to Contract/Budget Sent to Site			Contract/Budget Sent to Execution		
BENCHMARK	Avg.	Range	CoVar.	Avg.	Range	CoVar.
Phase I	2.52	0.2 - 8.4	1.1	1.42	0.1 - 6.8	1.1
Phase II/III/IV	2.97	0 - 17.4	1.1	3.16	0 - 21.5	1.0

	Execution to Initiation			Initiation to First Patient In		
BENCHMARK	Avg.	Range	CoVar.	Avg.	Range	CoVar.
Phase I	0.98	0 – 4.3	1.2	1.61	0 - 13.6	1.3
Phase II/III/IV	1.81	0 - 21.4	1.2	2.46	0 - 30.8	1.3