

# Analysis of Clinical Trial Activity in Massachusetts

May 22, 2008

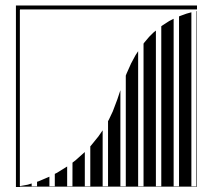
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FLETCHER SPAGHT, INC.

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Boston, MA

Established 1983



# Agenda

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## Introduction & Status

- Executive Summary

## Background Data

- Massachusetts clinical trials sites
- Phase detail
- Industry sponsored sites
- NIH funding

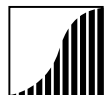
## Company Data

- Pharmas with large MA presence
- Top 10 US Pharmas

## Primary Research

- Interviews
- Interest in increasing trials
- Barriers to increasing trials
- Suggested areas of improvement

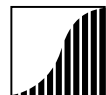
## Next Steps



# **Original Hypothesis: Increasing clinical trial activity in MA includes benefits for residents, companies and clinical sites**

There is a hypothesis that Massachusetts has the capacity to host a greater number of clinical trials and that increasing clinical trial activity is desirable

- It will increase economic activity in Massachusetts
  - more trials, more jobs
- Access to clinical trials improves patient care
  - Massachusetts will stay on the cutting edge of care if more trials are conducted there
- Clinical trials confer prestige on investigators and institutions
- Conducting more clinical trials in Massachusetts may be strategically attractive for companies
  - incentive for companies to move to Massachusetts
  - keep companies in Massachusetts



# Approach

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FSI obtained and analyzed data on clinical trials from two sources:

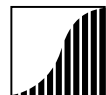
- Clinicaltrials.gov
  - listing of all clinical trials where there is intent to publish
  - analysis includes all trials from 2002-2007 that have at least 1 site in the US
    - 23,800 trials; 208,000 “experience points”
- FDA form 1572, Bioresearch Monitoring Information Systems (BMIS) file
  - IND submissions
  - original dataset from Paul Bleicher

FSI conducted 24 interviews

- 7 Academic medical centers (including 2 at Partners/MGH)
- 3 Community hospitals
- 5 Pharmaceutical companies (3 large, 2 small)
- 4 Device companies
- 2 CROs
- 3 Allied partners

Interim meeting held on 1/31/08 with task force chairs

Meeting to review results was held on 3/28/08 with full task force, and 5/8/08 with steering committee



## **Data indicate MA is doing well, especially with companies headquartered here; however there is room for growth**

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MA is among the top states for clinical trials, but there is capacity to grow

- Ranks 15<sup>th</sup> in the nation for with 833 “experience points”/million residents
- Ranks 11<sup>th</sup> in the nation with 4.58 patient care physicians/ “experience point”

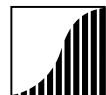
MA headquartered companies have just over 4% of their clinical trial sites in MA vs. only 2.5% for all companies

- Home state advantage implies more economic activity, greater spending kept in MA
- Interview contacts confirmed desirability of nearby clinical trial sites

MA is underrepresented in industry drug trials

- Only 57% of trials in MA are commercially sponsored compared to 63-83% in other top trial states
- MA has more phase I & II trial sites and fewer phase III trial sites compared to other top trial states

Note: data includes all clinical trials from 2002-2007 on [clinicaltrials.gov](http://clinicaltrials.gov)



## Industry representatives expressed an interest in more trials in Massachusetts, as long as certain criteria are met

Criteria	Importance	Massachusetts Rating
Good site performance (data quality/adherence to protocol)	High	Good
Rapid enrollment	High (esp. Phase III)	Poor
Opinion leaders	High	Good
Existing Infrastructure	High	Varies
Ease of relationship/low administrative burden	Medium	Fair
Cost	Low	Fair
Proximity (and awareness it exists)	High (Device)	Varies



## Staffing, enrollment, infrastructure limitations and the lack of an easy relationship are some issues for MA sites

Issue	Conditions Creating Issue
Availability of qualified trial staff (CRC/CRA)	<ul style="list-style-type: none"> <li>• Low compensation</li> <li>• “Stepping stone” position to post-graduate studies</li> <li>• Nurses are an option, but they are a more costly resource</li> </ul>
Limited enrollment	<ul style="list-style-type: none"> <li>• MA population is only 2.5% of the US population</li> <li>• Concentration of AMCs in Boston area can create enrollment competition</li> <li>• Boston population not “treatment naïve”</li> </ul>
Infrastructure limitations	<ul style="list-style-type: none"> <li>• Especially in community sites that want to increase trials, infrastructure to conduct clinical trials may be limited (staff, physical space, equipment)</li> </ul>
Ease of relationship is lacking	<ul style="list-style-type: none"> <li>• The “hassle” factor is important for sponsors</li> <li>• Informal 2005 survey showed Boston AMCs took 10.5 weeks for IRB approval, should be around 6 weeks to be competitive</li> <li>• Anecdotally, many interviewees mentioned IRB delays as a limiting factor to conducting trials in MA</li> <li>• Contracting also mentioned, though many agreed that a standard statewide contract could be difficult to create and adopt</li> </ul>



## Marketing/PR, creation of a directory and support for training were suggested as non-policy improvements

Improvement	Feasibility	Interest	Time to implement
Marketing/PR Campaigns <ul style="list-style-type: none"> <li>• Detail research opportunities in MA</li> <li>• Direct to patients to create awareness</li> </ul>	High	High	Short
Create a Statewide Directory <ul style="list-style-type: none"> <li>• List specific sites, investigators &amp; interests</li> </ul>	High	High	Short
Human Capital <ul style="list-style-type: none"> <li>• Support of training programs</li> <li>• Advancement of young investigators</li> </ul>	High	High	Medium
Facilitate Alliances <ul style="list-style-type: none"> <li>• Community hospital interested in increasing trials could work with AMCs</li> </ul>	High	Medium	Medium
Software to phenotype populations <ul style="list-style-type: none"> <li>• Helps investigators accurately predict enrollment which is attractive to sponsors</li> </ul>	Medium	Medium	Long



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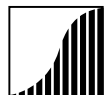
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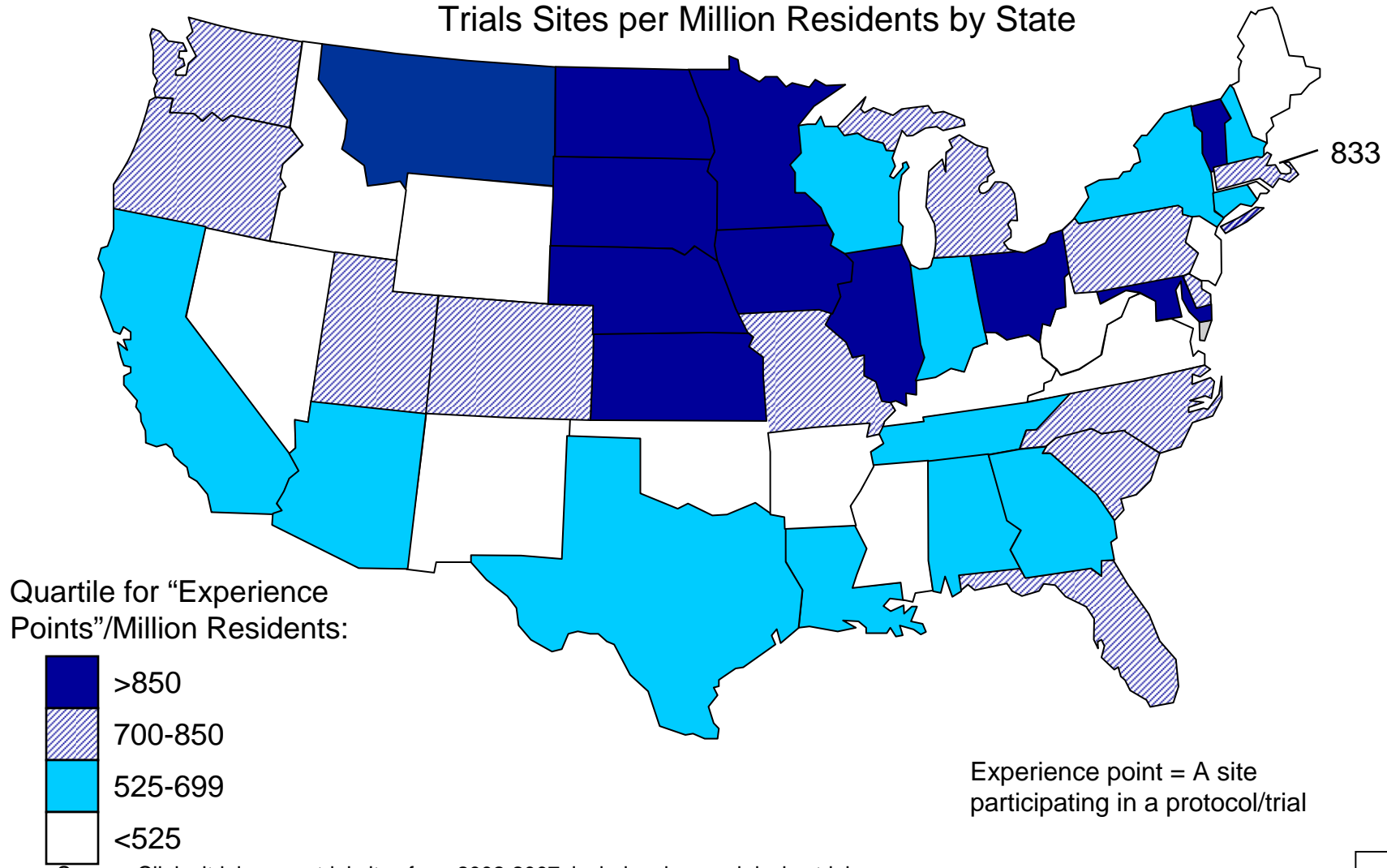
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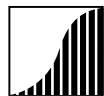


# MA ranks 15<sup>th</sup> in the nation with 833 trial sites (“experience points”) per million residents

Trials Sites per Million Residents by State

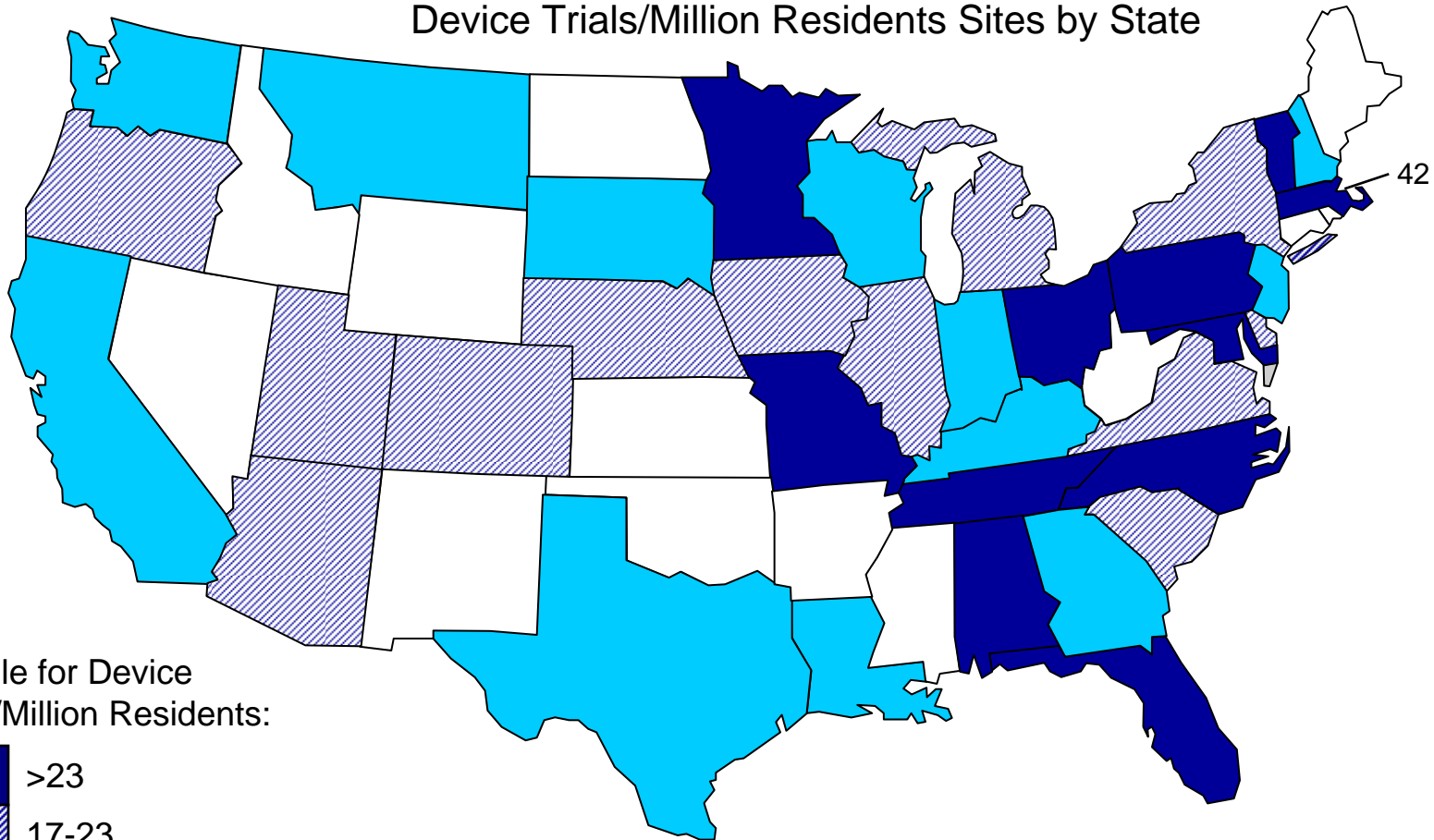


Source: Clinicaltrials.gov – trial sites from 2002-2007; includes drug and device trials

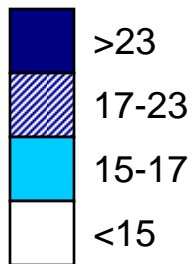


# Data limited, but MA ranks 1<sup>st</sup> in the US for device trials with 42 device trials/million residents

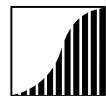
Device Trials/Million Residents Sites by State



Quartile for Device Trials/Million Residents:



Source: [clinicaltrials.gov](http://clinicaltrials.gov), device trials 2002-2007, FSI Analysis



## Over the past 5 years, Massachusetts has had a high ratio of MDs/trial and a low ratio of population/trial

State	# of Sites	% of Total US Sites	Pt Care MDs/Resident	Pt Care MDs/Trial	State Residents/Trial	Pop'n (M)	Pop'n (%)
CA	19,846	9.5%	232	4.25	1,837	36.5	12.2
FL	13,866	6.7%	220	2.87	1,304	18.1	6.0
TX	12,637	6.1%	188	3.51	1,860	23.5	7.8
OH	11,834	5.7%	234	2.27	970	11.5	3.8
NY	11,437	5.5%	338	5.71	1,688	19.3	6.4
IL	10,921	5.2%	243	2.85	1,175	12.8	4.3
PA	9,485	4.6%	258	3.38	1,312	12.4	4.4
MI	7,372	3.5%	216	2.96	1,369	10.1	3.4
NC	7,121	3.4%	223	2.78	1,244	8.9	3.0
MN	5,882	2.8%	255	2.24	878	5.2	1.8
MA	5,365	2.5%	382	4.58	1,199	6.4	2.1
US	208,032	100%	240	3.45	1,439	299.4	100.0

Note: Includes trials on clinicaltrials.gov, 2002-2007 receipt date, industry and non-industry; drug, device and other; no enrollment info  
 Source: clinicaltrials.gov, US Census, Physician characteristics and distribution in US, AMA, 2005



# Statistics indicate capacity based on physician availability, but patient enrollment could be limiting

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Massachusetts ranks 11<sup>th</sup> in the US in terms of clinical trial sites

- Over the past five years, Massachusetts has accounted for 2.5% of clinical trial sites in the US and houses 2.1% of the US population

Massachusetts has the highest ratio of patient care physicians per 100,000 residents versus all other states

- Could create enrollment issues since this indicates that each doctor sees fewer patients as compared to other states

Massachusetts has a very high ratio of patient care physicians per trial site (4.58) as compared to the US overall (3.45)

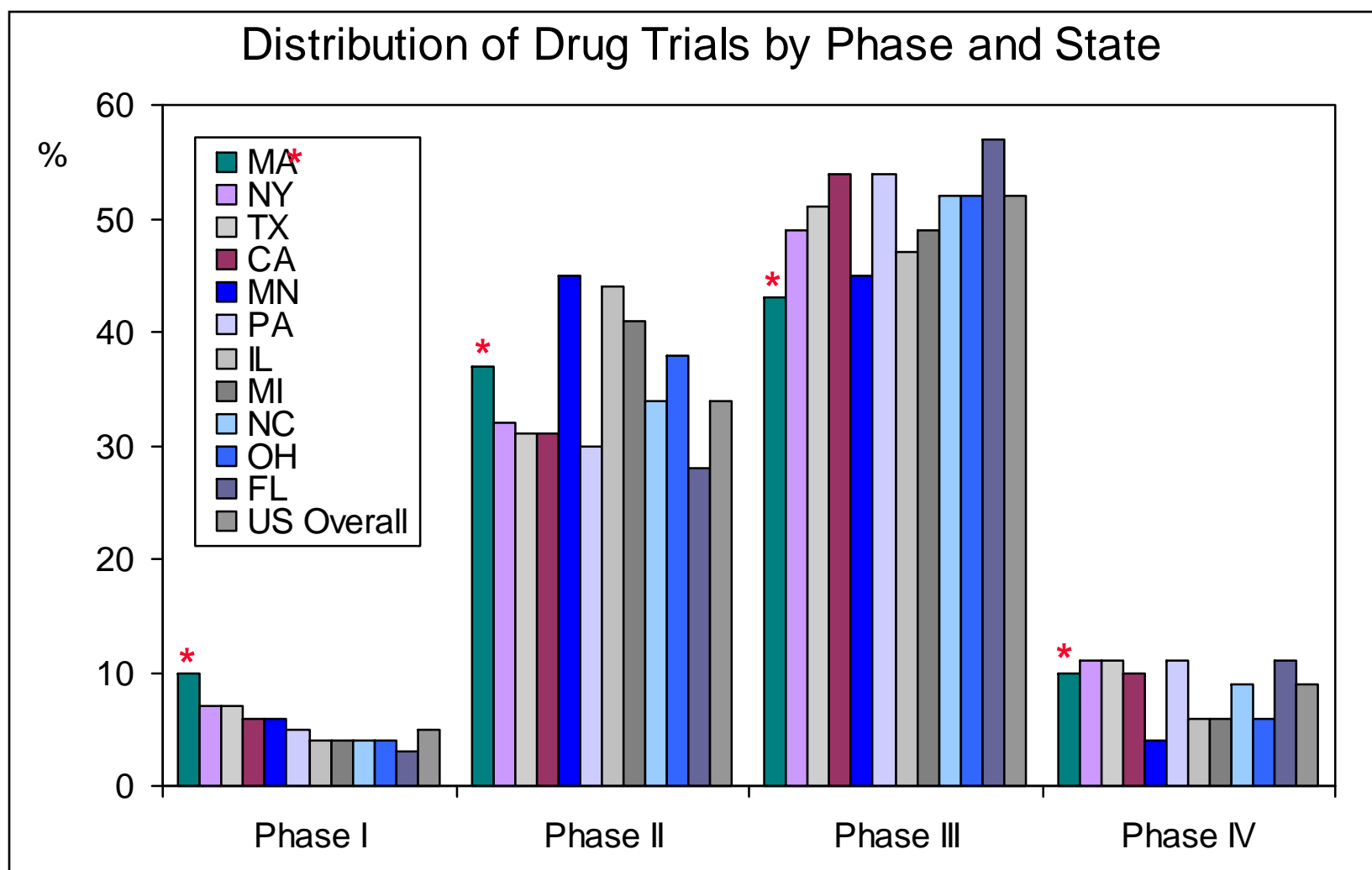
- Indicates capacity to do more trials based on physician availability

Massachusetts is on the lower end of the spectrum for the ratio of state residents per trial

- Indicates again that competition for patients could be a factor
- Especially important in phase III trials where patient enrollment is crucial



# As a % of drug trials within a state, MA has a high rate of phase I and II; lower rate of phase III compared to other states

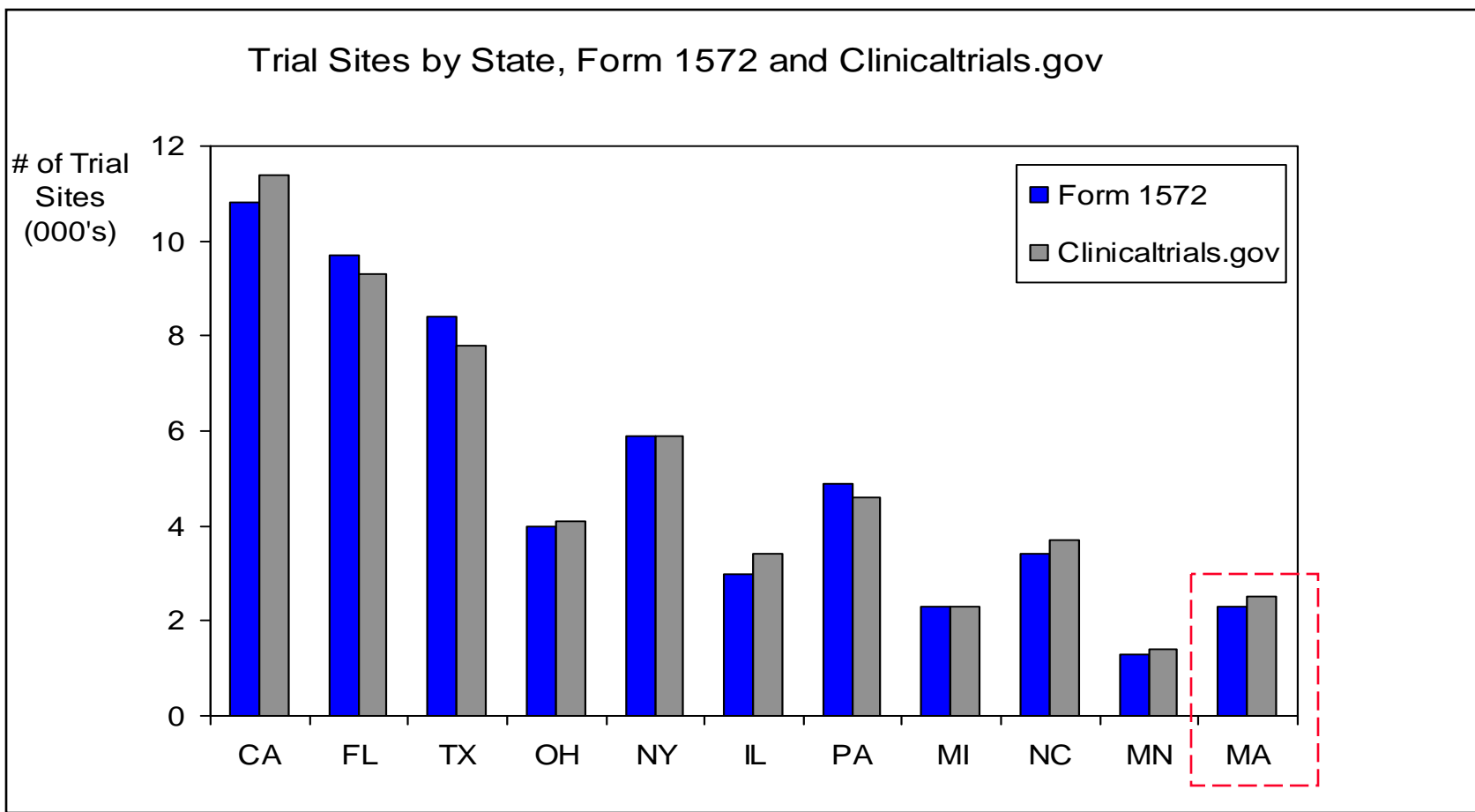


Note: Percentages calculated based only on trials where phase was reported (~89% of total)

Source: [clinicaltrials.gov](http://clinicaltrials.gov); FSI Analysis



# FDA data indicate that MA accounts for 2.5% of industry sponsored drug trial sites in the US

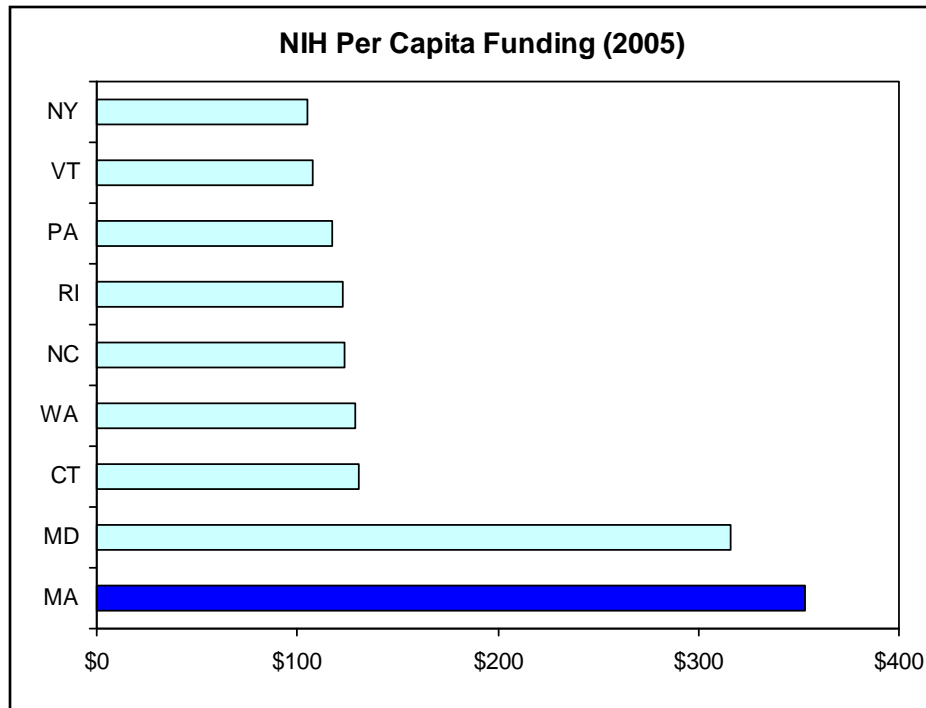


Form "1572" data is well correlated with clinicaltrials.gov data for drug trials

Source: BMIS FDA database (form 1572 data), 123k sites; clinicaltrials.gov commercial drug trials, 120k sites 2002-2007 US only



# Massachusetts leads the US in NIH funding per capita and is second only to California in total NIH funding



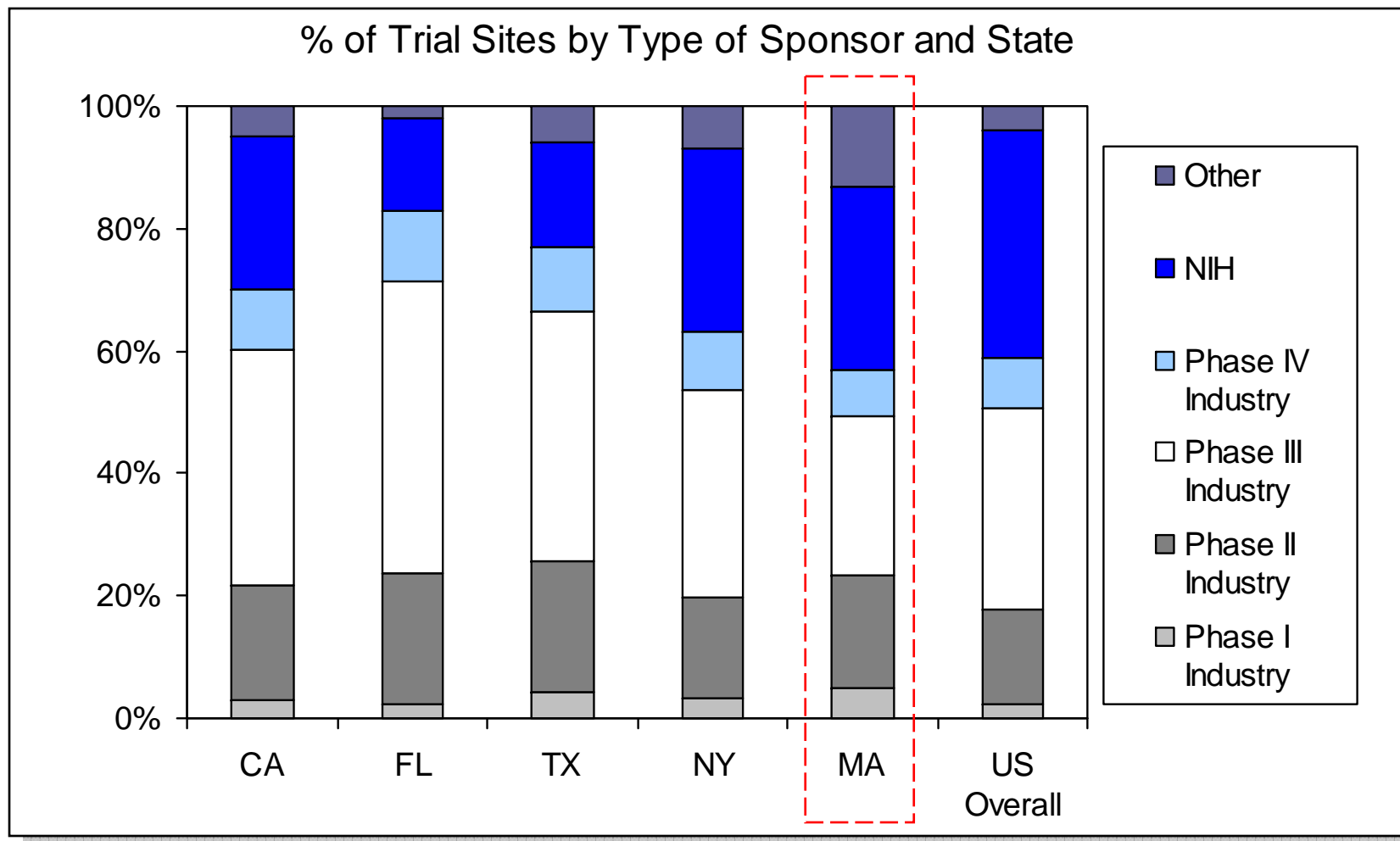
State	Total NIH Funding (\$M)
California	\$3,301
Massachusetts	\$2,273
New York	\$2,021
Maryland	\$1,764
Pennsylvania	\$1,452
Texas	\$1,150
North Carolina	\$1,078
Washington	\$813
Illinois	\$734
Ohio	\$717

MA receives the most NIH funding per capita (\$355 2006)

Source: Super Cluster; NEHI, MTC, PwC; NIH Office of Extramural Research



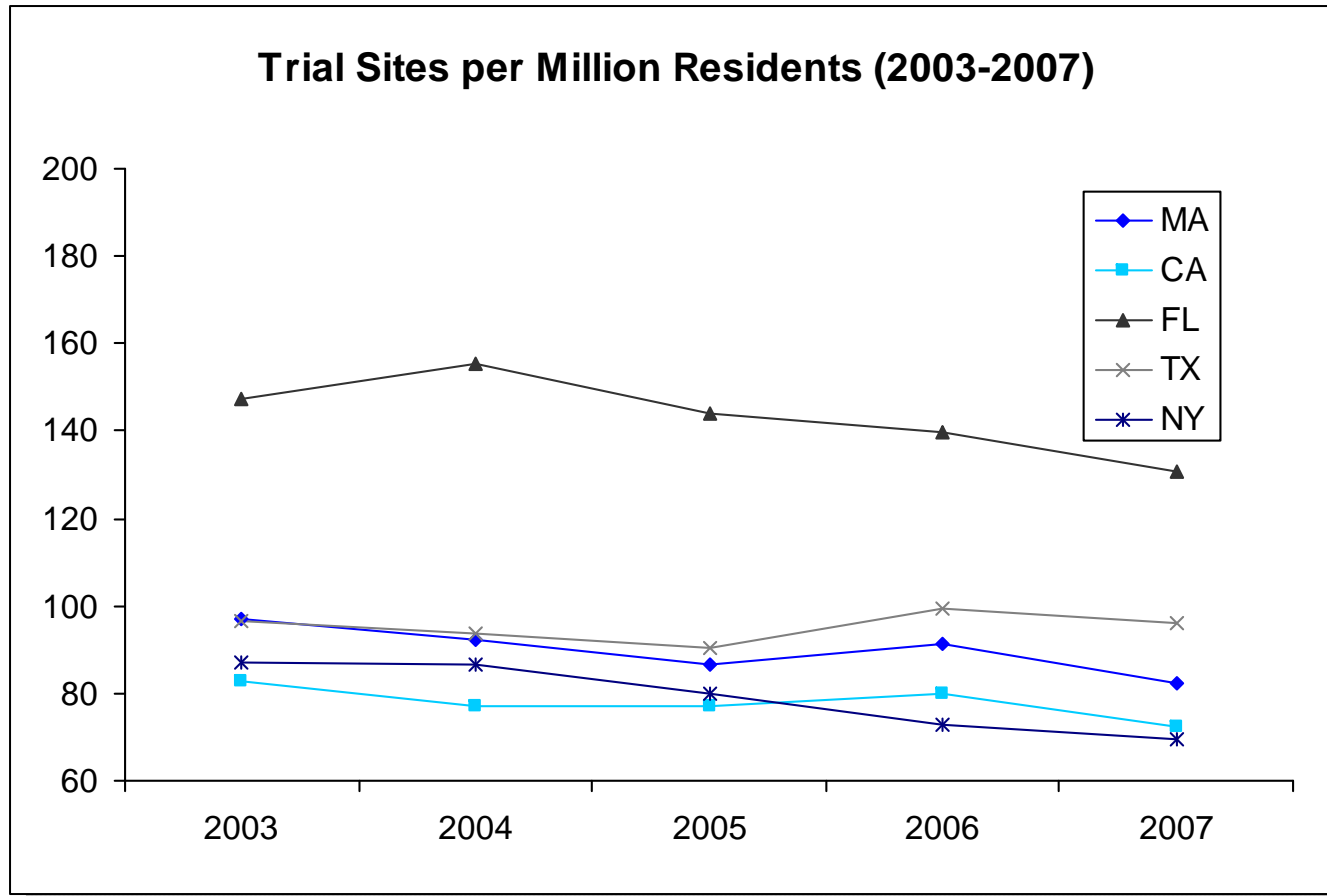
# MA has a smaller fraction of industry sponsored sites than other top states



Note: based on number of trials not \$  
 Source: clinicaltrials.gov, FSI Analysis

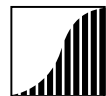


# MA industry trials sites per residents have decreased slightly over the past 5 years; pattern similar to other states



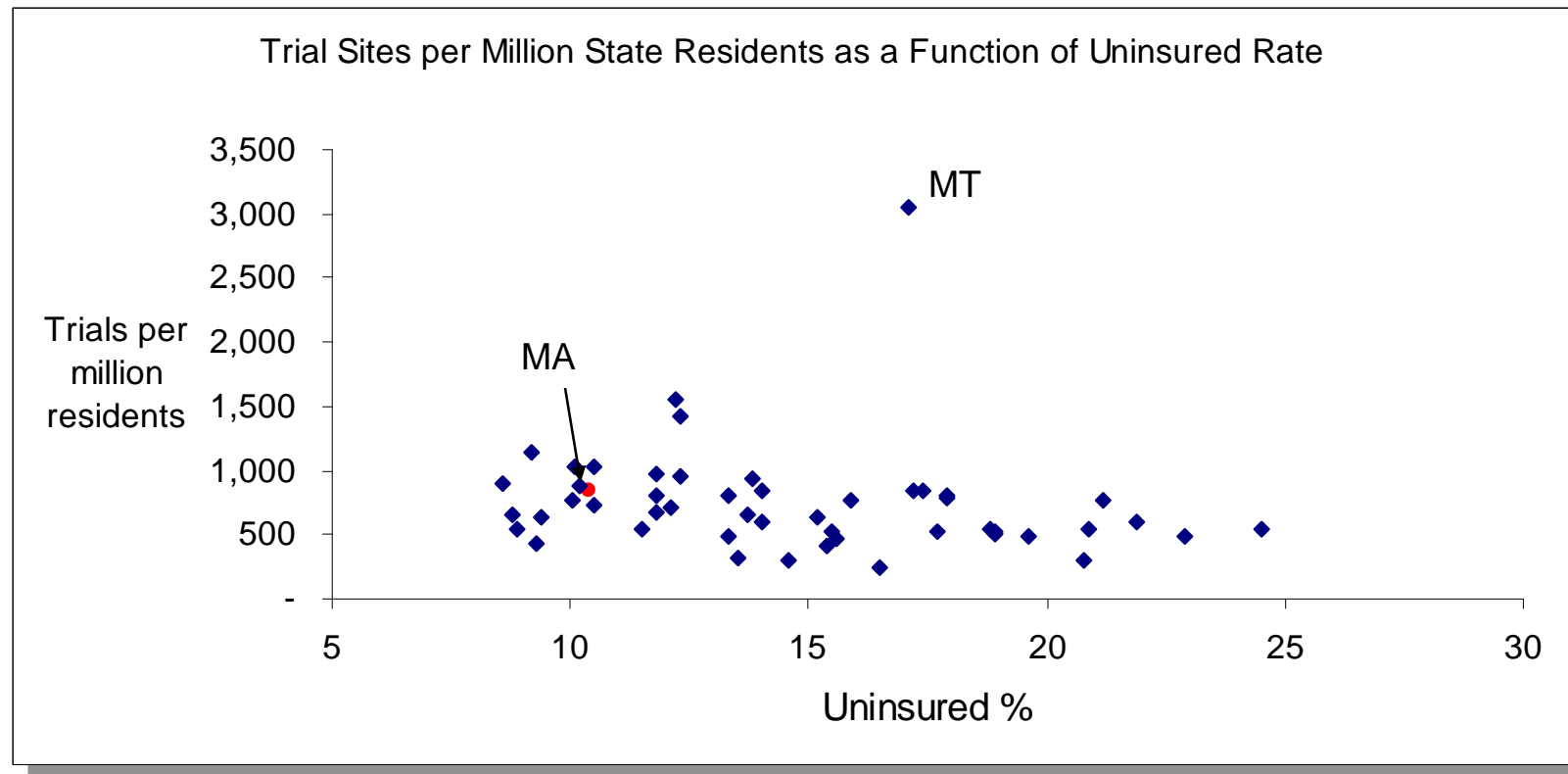
MA has a competitive number of industry trial sites per million residents

Source: FDA form 1572 dataset





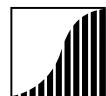
## However, there is little association between state uninsured rate and trial per population



There is a slight inverse correlation between the % uninsured in a state and the number of trials per 1M residents

- Larger states have higher rates of uninsured and this is where trials are sited

Source: clinicaltrials.gov all US trial sites, all sponsors, drug and device; % uninsured from US Census



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## For biotech companies with a large MA presence, 3.1% of trial sites are here, *vs.* the US average of 2.5%

% of trial sites by state, pharma/biotechnology

	MA EE's	CA	FL	TX	OH	NY	IL	PA	MI	NC	MN	MA
Genzyme*	3,671	8.7	6.9	9.2	4.4	6.4	4.3	4.6	1.9	3.9	2.3	4.6
Wyeth	2,800	12.8	11.7	5.8	4.7	5.5	3.5	6.0	2.3	2.0	0.8	2.6
Novartis	1,600	11.8	8.5	7.5	3.9	5.4	3.3	4.4	2.3	3.2	1.6	2.9
Biogen*	1,380	11.3	5.6	8.4	3.8	7.4	4.0	5.5	4.9	2.8	1.8	2.6
Millennium*	1,000	12.8	5.5	6.6	3.6	11.3	3.3	4.4	1.5	3.3	1.1	10.9
Vertex*	680	10.3	7.2	8.2	3.6	5.2	3.6	5.7	2.1	4.6	2.1	4.6
Sepracor*	504	14.4	7.4	7.1	3.3	3.6	1.7	4.4	1.3	4.9	0.6	2.4
Alkermes*	450	6.5	11.6	12.9	0.6	4.5	4.5	4.5	1.9	3.2	0.6	2.6
Serono	450	13.9	9.7	5.6	2.1	7.6	4.2	2.1	3.5	4.2	2.8	9.0
Shire	390	8.7	11.0	9.7	4.0	4.3	2.7	4.0	3.0	5.0	0.7	1.7
Average of above	N/A	11.8	9.0	7.3	4.1	5.7	3.4	4.9	2.4	3.4	1.4	3.1
Overall Industry	N/A	11.4	9.3	7.8	4.1	5.9	3.4	4.6	2.3	3.7	1.4	2.5

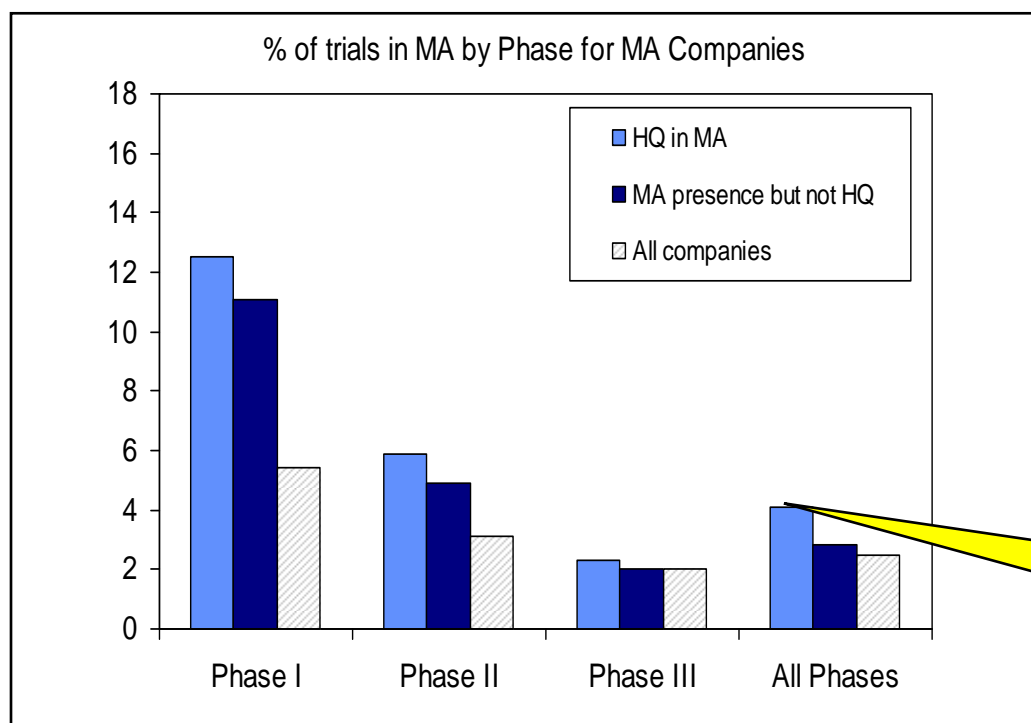
\* Indicates MA corporate HQ

Note: Companies selected from the 2007 Boston Business Journal Book of lists, by MA employee numbers

Source: Clinicaltrials.gov; FSI analysis



# Companies HQ'ed in MA have a higher percentage of trial sites here than other companies with a large presence



MA site count for all industry sponsored drug trials, 2002-2007 (n)

	I	II	III
HQ in MA	26	49	31
MA Presence not HQ	45	82	109
All Co's	263	1,016	1,397

60% more MA sites for MA HQ (4.1% vs. 2.5%)

Companies with headquarters in MA are more likely to do clinical trials here than those with a large presence (but not HQ)

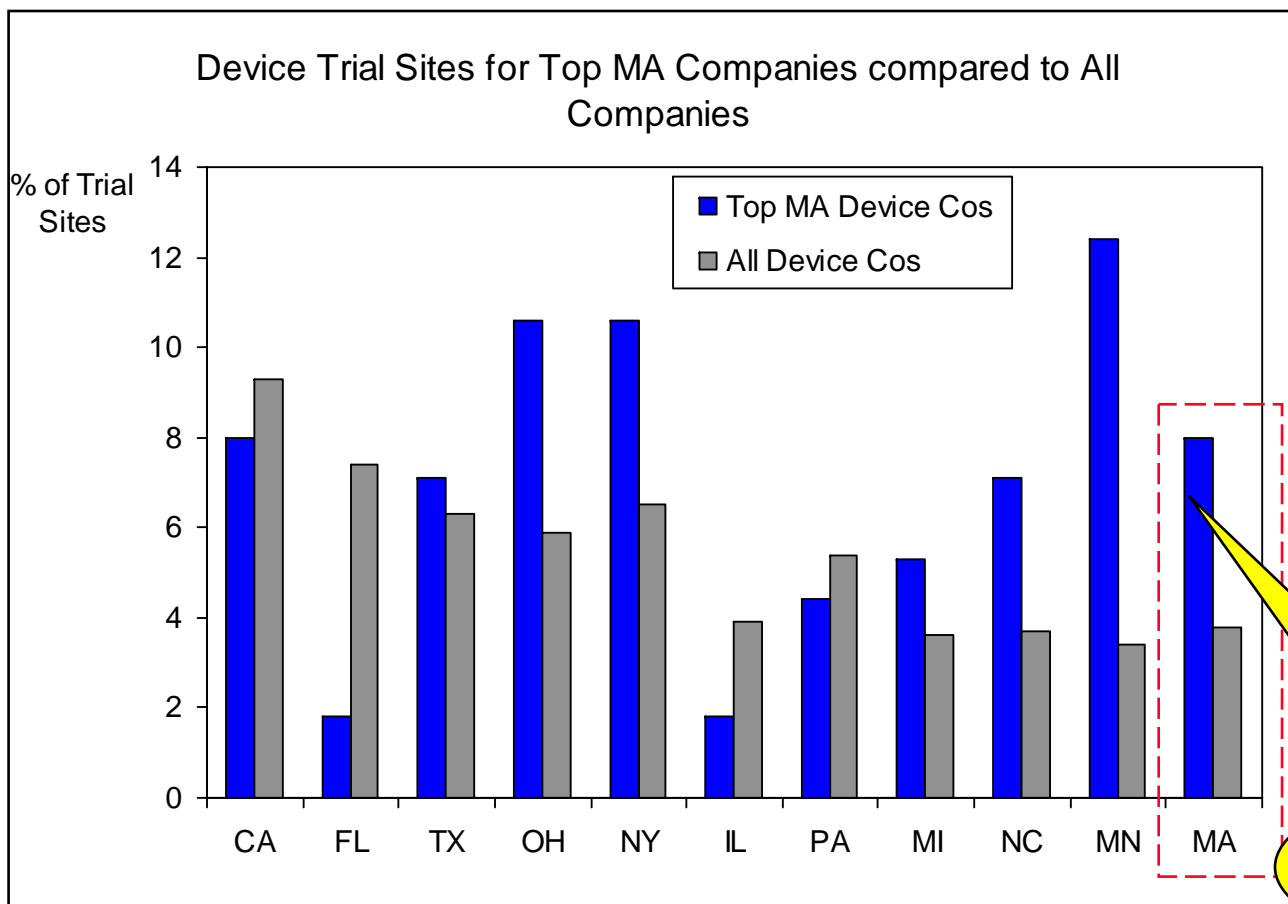
- Trend is most pronounced for Phase I & II studies

“There is a tendency to do more trials in a state where the company is located, but it isn't necessarily strategic for drug companies.” -CRO

Source: Clinicaltrials.gov; FSI Analysis



# Data sparse, but trend that MA HQ'ed device companies are twice as likely as others to site trials in MA



Company	MA EE's
Tyco Healthcare	2,200
Boston Scientific	2,251
Zoll Medical	1,000
Haemonetics	670
Abiomed	200
Candela	165
Aspect Medical	163
Inverness	88

~100% more MA sites for MA HQ (8% vs. 3.9%)

Note: data is sparse, there were only 113 trials over the past 5 years for these MA HQ'ed sites

Of the 113 sites of MA device companies, 9 were in MA

Source: Book of Lists, large MA device companies; clinicaltrials.gov commercial drug trials 2002-2007



## In the aggregate, MA economy benefits from increased clinical trials

Although trials are intended to be “break-even” for the site, they do bring additional revenue

- Sponsor’s perspective: spending does not vary within US
- Clinical site perspective: do not emphasize revenue benefit
  - smaller sites mentioned struggle to break-even
- MA perspective: larger slice of the pie if MA HQ’ed sponsor

**Hypothetical drug development program:**

	Non-MA Company	MA HQ Company
\$ to clin site per enrolled patient	\$10,000	\$10,000
Total patients*	4,500	4,500
% of Trials in MA	2.5	4.1
MA patients	112	185
\$ to MA sites	\$1.12M	\$1.85M

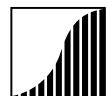
Delta spent by sponsor in MA: \$730k\*\*

Device companies HQ’ed in MA have a stronger preference for MA sites

- Resource limitations: key people interact more intensively with sites

\*Phase I: 30 patients/subjects, Phase II: 500 patients (2 protocols), Phase III: 4,000 patients (10 protocols)

\*\*Not entirely incremental



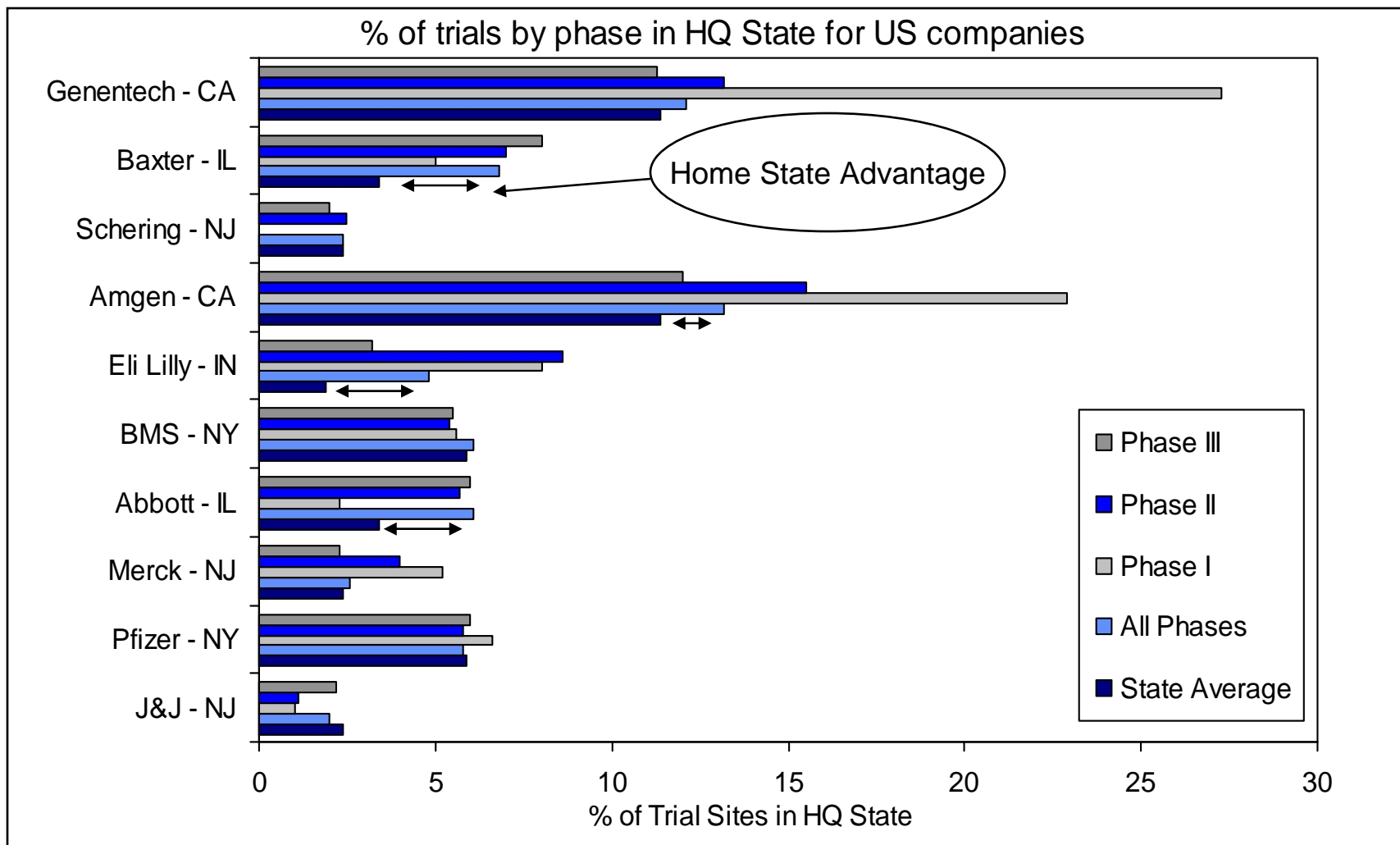
## Of the ten largest US pharmaceutical companies, sites in MA are similar to the national average of 2.5%

	CA	FL	TX	OH	NY	IL	PA	MI	NC	MN	MA
J&J	11.5	9.3	8.3	4.1	5.9	3.4	5.3	1.9	3.4	1.1	2.7
Pfizer	11.2	9.7	8.1	3.9	5.9	3.2	4.1	2.4	4.0	1.2	2.6
Merck	10.9	10.5	7.8	4.5	4.2	3.2	6.9	2.3	3.7	1.1	2.1
Abbott	8.4	9.2	5.5	5.1	6.2	6.1	4.9	2.0	4.5	1.3	2.8
BMS	10.9	9.9	8.3	4.0	6.1	3.0	5.0	1.9	4.4	1.2	2.5
Eli Lilly	10.5	8.4	7.5	3.7	5.3	3.6	4.4	2.4	3.3	1.4	2.6
Amgen	13.2	7.8	7.2	3.1	6.5	3.4	4.6	3.3	3.0	0.9	2.1
Schering Plough	10.1	7.9	9.5	3.3	7.3	2.6	5.4	1.6	4.2	2.1	3.6
Baxter	11.3	7.9	7.9	8.7	4.2	6.8	5.7	4.2	1.5	1.5	3.8
Genentech	12.1	7.7	7.6	4.4	5.4	3.7	3.6	2.6	3.7	1.3	3.5
<b>Top 10 Average</b>	<b>11.1</b>	<b>9.2</b>	<b>7.9</b>	<b>4.1</b>	<b>5.7</b>	<b>3.4</b>	<b>4.7</b>	<b>2.3</b>	<b>3.9</b>	<b>1.2</b>	<b>2.7</b>
<b>Overall Industry</b>	<b>11.4</b>	<b>9.3</b>	<b>7.8</b>	<b>4.1</b>	<b>5.9</b>	<b>3.4</b>	<b>4.6</b>	<b>2.3</b>	<b>3.7</b>	<b>1.4</b>	<b>2.5</b>

Note: J&J includes large subsidiaries: Ortho Biotech, McNeil, Janssen & Centocor; light shading indicates HQ state  
Source: Clinicaltrials.gov; FSI Analysis



# Most large US pharma companies have a larger share of trials in their HQ state as compared to the average



Source: Clinicaltrials.gov; FSI Analysis; state averages are a % of US commercially sponsored drug trial sites in each state



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- Barriers to increasing trials
- Suggested areas of improvement

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## FSI conducted interviews with diverse members of the clinical trial industry in Massachusetts

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Name	Title	Company	Category
Hal Jenson, MD	Chief Academic Officer	Baystate Health	AMC
Tom Moore, MD	Director, Office of Clinical Research	Boston University	AMC
Philip Kantoff, MD	Chief Clinical Research Officer, Division of Solid Tumor Oncology	Dana Farber Cancer Institute	AMC
Ranch Kimball	CEO & President	Joslin Diabetes Center	AMC
Chris Colecchi, MPH	VP, Research Ventures and Licensing	Partners Healthcare	AMC
William Crowley, MD	Director, Clinical Research	Partners/MGH	AMC
Sheila Noone, PhD	Director, Office of Clinical Research	UMass Medical School	AMC
John Sullivan, MD	Vice Chancellor for Research	UMass Medical School	AMC
Lynn Shields, RN, BSN, MBA	Director of Research Compliance	Cape Cod Healthcare	Community Hosp
Deborah Perry	Director, Research Administration	Lahey Clinic	Community Hosp
Arlan Fuller, MD	Gynecologic Oncologist	Winchester Hospital	Community Hosp
Leslie Rose	Director, Clinical Research	Haemonetics	Device
Andrew Levin, PhD	President & CEO	Immunetics, Inc.	Device
John Wlassich, PhD	VP Product Development	Nomir Medical	Device
Gary Freeman	VP Technology	Zoll Medical Corp.	Device



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Name	Title	Company	Category
Bob Anderson	Division Council	Abbott Labs	Pharma (Big)
Kathy Johnson	Attorney	Abbott Labs	Pharma (Big)
Mark Goldberg, MD	Senior VP, Clinical Research	Genzyme	Pharma (Big)
Andrew Denker, MD	Sr. Director of Clinical Pharmacology	Merck & Co.	Pharma (Big)
Robert Mulroy	President & CEO	Merrimack Pharmaceuticals, Inc.	Pharma (Small)
Ganesh Venkataraman, PhD	Founder & Senior VP, Research	Momenta Pharmaceuticals	Pharma (Small)
Mordecai Kramer	Director of Business Development	Harvard Clinical Research Institute	CRO
Joshua Schultz	VP, Clinical Research Services	PAREXEL	CRO
Bryan Pearce	Northeast Strategic Growth Markets Leader	Ernst & Young, LLP	Allied
Scott Sarazen	Global Biotechnology Markets Leader	Ernst & Young, LLP	Allied
Karen Nelson	Sr. VP Clinical Affairs	Massachusetts Hospital Association	Allied
Paul Bleicher, MD, PhD	Chairman and Founder	Phase Forward	Allied



# Interviews confirmed task force hypotheses regarding AMC/non-AMC motivations

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## AMCs

- Institutional imperative
- Investigator initiated
- Early stage/new science
- NIH trials
- Phase I (onc.) & II



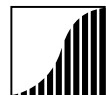
The right trials build reputation and confer prestige

## Non-AMCs

- Individually motivated
- Commercially sponsored
- Phase II & III, investigators have greater clinical responsibility and less time devoted to research
- Institutional/individual reputation

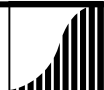


Improved patient care (not necessarily promotion/pay)




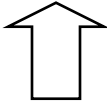

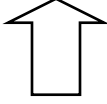
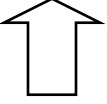
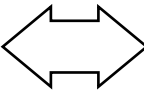
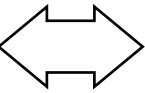
## Among AMCs there was unanimous interest in increasing clinical trials mainly in early phases

Institute	Phase I	Phase II	Phase III	Phase IV	Comments
Dana Farber Cancer Institute	↑				<ul style="list-style-type: none"> <li>• Pride ourselves on PI initiated</li> <li>• More “first in man” novel therapeutics</li> <li>• Phase I not healthy subjects for cancer</li> </ul>
Boston University		↑			<ul style="list-style-type: none"> <li>• Currently conduct a lot of phase III</li> <li>• Invest more in PI/trial design</li> <li>• Investigator initiated</li> </ul>
University of Massachusetts	↑	↑			<ul style="list-style-type: none"> <li>• Developing inpatient unit for phase I</li> <li>• Would also like to increase Phase II</li> <li>• Building a first class research enterprise</li> </ul>
Partners/MGH		↑			<ul style="list-style-type: none"> <li>• Specific interest in increasing phase IIA</li> <li>• Infrastructure can’t support later phases</li> <li>• More high prestige, important precedent</li> <li>• Collaboration on science &amp; protocols</li> <li>• High volume phase III not as interesting</li> <li>• Bridge between preclinical and clinical</li> </ul>
Baystate Health		↑	↑		<ul style="list-style-type: none"> <li>• Different from Boston hospitals; do a lot of phase III trials</li> <li>• 3-4 years building an outpatient facility</li> </ul>
Joslin Diabetes Center		↑			<ul style="list-style-type: none"> <li>• A lot of funding for phase II – the interesting work</li> </ul>



## Non-AMCs in MA also expressed interest in increasing clinical trials, with a focus on phase II & III

Though community hospitals expressed interest in clinical trials, it was very hard to locate the correct person to speak with at these institutions

Institute	Phase I	Phase II	Phase III	Phase IV	Comments
Lahey Clinic					<ul style="list-style-type: none"> <li>Industry focused, protocols already written which is good for MDs with patient load</li> <li>Trials seen as adding to patient care</li> </ul>
Winchester Hospital					<ul style="list-style-type: none"> <li>Alliance with AMC would be best for patients as well as trial enrollment</li> </ul>
Cape Cod Healthcare					<ul style="list-style-type: none"> <li>Content with the level of trials currently being conducted</li> </ul>

“It is definitely something we are looking at...here it is a physician initiated interest, with younger physicians coming on board, almost all of them are interested.”

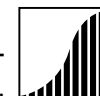
*-Community Hospital*

“I have recognized over time it was going to be exceedingly important to the care of patients to have clinical trials in the community setting.”

*-Community Hospital*

“Some of the smaller hospitals are hungrier and may push through faster {to trial initiation}.”

*-Small Pharma*



## Industry representatives expressed an interest in more trials in Massachusetts, as long as certain criteria are met

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Criteria	Importance	Massachusetts Rating
Good site performance (data quality/adherence to protocol)	High	Good
Rapid enrollment	High (esp. Phase III)	Poor
Opinion leaders	High	Good
Existing Infrastructure	High	Varies
Ease of relationship/low administrative burden	Medium	Fair
Cost	Low	Fair
Proximity (and awareness it exists)	High (Device)	Varies



# Site selection: Pharma - enrollment, CRC quality/ experience, KOLs; Devices - KOLs, proximity, enrollment

	Pharma Trials
Phase I (1-2 Sites)	<ul style="list-style-type: none"> <li>• Largely commercial facilities</li> <li>• Oncology – opinion leaders</li> </ul>
Phase II (5-20 Sites)	<ul style="list-style-type: none"> <li>• Site performance (Protocol and CRC/CRA exp &amp; quality)</li> <li>• Opinion leaders</li> <li>• Enrollment</li> </ul>
Phase III (50-100 Sites)	<ul style="list-style-type: none"> <li>• Enrollment</li> <li>• Enrollment</li> <li>• Enrollment</li> <li>• Site performance (Protocol and CRC/CRA exp &amp; quality)</li> <li>• Opinion leaders</li> </ul>

	Device Trials
Feasibility/ Pilot (1-2 Sites)	<ul style="list-style-type: none"> <li>• Opinion leaders</li> <li>• Relationships</li> <li>• Proximity</li> </ul>
Pivotal (Up to 40-60 Sites for PMA)	<ul style="list-style-type: none"> <li>• Opinion leaders</li> <li>• Enrollment</li> <li>•</li> <li>•</li> <li>• Proximity</li> </ul>

85-90%

10-15%

“10-20% of phase III sites will be large AMCs more or less due to marketing reasons.”

– *Pharma Company*

“Typically speaking, 20-30% of investigators will enroll 80% of your subjects, 50% will enroll 20% and 20-30% will enroll no one. This is consistent across phase II and III and therapeutic areas.”

- *CRO*



## Site performance including the quality and experience of CRA/CRCs could be improved to make MA more attractive

The quality of research sites needs to be proven in order to attract sponsors

- Investigators and staff should be well trained to follow protocol
  - firm understanding of inclusions/exclusion, data integrity/collection
  - results are reliable

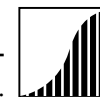
Training and clinical trial experience for both CRCs and investigators were the chief factors

“In the past, choosing investigator sites was more of an ad hoc process than it should be...if I used someone in the past, then I’d use them again. We’re more and more data driven now. Past performance correlates with future performance.” *CRO*

The Collaborative could help improve site quality in MA in several ways

- Support continuing education and training programs for CRA/CRCs and first time investigators
  - especially at sites that don’t have the bandwidth to do this on their own
  - came up in early interview, many later seconded and emphasized
- Tax breaks to professionals who are interested in pursuing research careers
  - growth in investigators is only 5%, patient population growth is 10-15%

“The average community based program needs personnel to understand how the trials are done, how data is recorded and IT to support it all. **The LSC could help with educational processes.**”  
*Community Hospital*



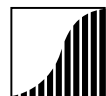
# The LSC could support continuing education to ensure MA sites maintain a quality workforce

CRC model differs between AMC and community hospitals

AMC Model	Community Hospital Model
<p>Pre-MD/PhD</p> <ul style="list-style-type: none"> <li>• Low cost</li> <li>• High turnover</li> <li>• Motivated</li> </ul> <p>Not replicable in community setting</p>	<p>Nurses or administrative</p> <ul style="list-style-type: none"> <li>• Certificate/training</li> <li>• Lower turnover</li> <li>• Research is an interesting job enhancement</li> </ul> <p>Nurses are a costly resource</p>



- Community college certificate programs
- Commercial education/seminars
- Outreach/cooperative programs from AMCs



# Rapid enrollment is an important selection factor in drug trial sites; especially for phase III

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Enrolling the appropriate patients rapidly is crucial to the success of trials

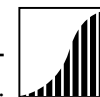
- Large number of subjects is critical in phase III studies
- Rapid enrollment shortens time to market

Many factors influence enrollment

- Population/patient flow
  - “We look at a clinical site’s ability to execute as well as how many patients they can enroll per month; population in MA isn’t as large as that of California” *Pharma Company*
- Type of patients
  - treatment naïve vs. refractory patients for 1<sup>st</sup> line treatments
  - competition for patients at AMCs
- CRC skill/experience at recruitment/persuasion of patients
- Knowledge of patient base and ability to “exploit”/proactive outreach

There are several approaches the Collaborative could take to help MA sites with enrollment

- Build public awareness: PR around trials and website “opportunities”
- Mining the patient base: Support efforts of practices and institutions to “phenotype” and reach out to patient base
  - “One of the biggest factors is knowing who your patients are...**support at a governmental level to build these databases would help**...More often than not, people are glad someone is looking out for them.” *CRO*
- Facilitate alliances between AMCs and community sites



## Opinion/thought leaders are very important for the success of a clinical trial; especially in early phases

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Inclusion of opinion leaders who are well respected in their field are an important factor in site selection

- Especially important in early stage drug trials and device trials

MA is known for having an abundance of opinion leaders

- Many well respected AMCs
- Community hospitals have affiliations with larger research institutions – or could

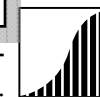
Opinion leaders often only want to do cutting edge trials

“I’ve found that with the Boston hospitals, there is minimal interest in doing {our} kind of study. We just want FDA {510k} approval, they are more interested in patient outcome and drug studies.” *Device company*

Academic Opinion leaders appear to have little trouble in attracting clinical research

“Massachusetts has a lot of thought leaders which is a good ‘hook’ for companies looking to site trials here” *Pharma company*

Away from the “bleeding edge” institutions and companies could benefit from greater awareness/PR about capabilities



## **Sites with existing infrastructure are attractive to sponsors because there would likely be less logistic hassle in set up**

Overall, sponsors have a desire to work with experienced sites and do not want to “reinvent the wheel”

- Space to accommodate additional appointments
  - Refrigerator, storage, specimen handling awareness
  - Experienced staff and administrators
- } As well as higher level of infrastructure to support IRB, contracts, *etc.*

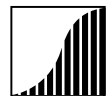
Factors that influence infrastructure include

- Physical space limitations
  - “We need space – especially an outpatient center which could be shared by multiple investigators, because subjects enrolled in trials tend to have more visits than those not enrolled.”  
*AMC*
- Prior trial experience
  - Once the infrastructure is created, it will be there for the next trial

The Collaborative could support improvements in infrastructure by

- Financially supporting (through tax breaks *etc.*) the “start-up” costs for trial sites to procure the necessary infrastructure to perform research
- Support the training of CRA/CRCs

The LSC could support infrastructure initiatives and training for trial administrators



# Sponsors look to work with sites with whom they can have a partnership; ease of this relationship is crucial

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The “hassle factor” is an important one for sponsors when choosing sites for their trials

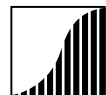
- IRB process
  - 2005 informal survey shows Boston AMCs took about 10.5 weeks to IRB approval; should be at 6 weeks to be competitive
  - Boston tends to have a “red pen” culture
- Contract process
  - many master agreements exist between sites and sponsors
  - statewide standard agreement likely not possible
  - those who indicated that they could benefit from a standard agreements don’t really need them
  - budgeting/indemnification/publishing

“The single biggest issue around picking an AMC and the reason private practice has taken a larger share...the hassle factor in working with them is the multiple rounds of discussion you need to have with the investigator, grant office, legal, *etc.*... local IRBs which don’t meet very often, higher overhead, issues around indemnification & publication. IRBs with local IRBs take 30 weeks to initiate vs. 18 weeks for private practice with a central IRB.”

*CRO*

“I have desperately been trying to get a trial started in Boston for 6 months....there is difficulty with contracting, competition and a lot of investigators trying to balance a lot.”

*Pharma company*



# IRB delays were mentioned most frequently as the most rate limiting step in clinical trial set up

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AMCs noted IRB approval process at their institutions can be slow

“Historically, IRB approval has taken so long that the study is fully enrolled elsewhere by the time we got approval.”  
*AMC*

“We may not always have the capacity to do more studies as there are always issues ‘clogging’ the {IRB} system.”  
*AMC*

“Harvard is the only IRB that has a ‘red pen’ culture, they actually change the protocols. Johns Hopkins and Stanford either approve or don’t approve.”  
*AMC*

*AMC*

Industry sponsors agreed that the IRB process is extremely rate limiting, especially at large teaching hospitals

“We tried to do a trial with {Boston AMC}, but we kept being bumped off the IRB agenda, so after 8 months, we went elsewhere.”  
*Device company*

“Sometimes by the time industry gets trials opened and started up at a Harvard teaching hospital the study is already fully enrolled because IRB approval takes a long time.”  
*Pharma company*

*Pharma company*

Contacts did not advocate strongly putting efforts into IRB changes

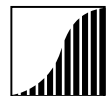
- AMCs unlikely to change
- Not a big issue elsewhere (outside or centralized IRBs already accepted)



## **Contracts were mentioned as problematic, but not necessarily as a place to focus the Collaborative's energy**

Many interviewees commented on contract issues when prompted

- Agreed with hypothesis that contracts can be rate limiting
  - budgeting
  - IP
  - indemnification
  - publishing
- Sense from sponsors that contracting is a greater issue at AMCs
  - most contacts did not believe that AMCs would be willing to move to a standard agreement
- Most contacts in both industry and hospitals had access to contract templates
- Master agreements are helpful and common
  - do vary from one pair of entities to another
- Even within AMCs there is not consensus on important contract terms



# Lack of actual consensus among AMCs may limit standardization of contracts

A survey<sup>1</sup> of 107 AMCs showed incomplete consensus among institutions on restrictive contract provisions, illustrating the difficulty of creating a standard contract

## Substantial Consensus (Acceptable to $\geq 80\%$ )

- Sponsor may review manuscripts before pub\*
- Sponsor may not forbid publication
- No sponsor revisions of manuscripts (other than IP protection)
- Sponsor may delay pub while patent app filed
- No restrictions on investigator's other funding sources
- Sponsors may not prohibit independent site pub
- Sponsor will own data

## Intermediate Consensus (Acceptable to 60-79%)

- Investigators may not alter protocol
- No outside discussion of research results before complete
- Sponsor may not limit outside discussion after complete
- Sponsor may alter study design after agreement
- No mandatory arbitration
- Terms of agreement are confidential

\*agreement in principle, but time threshold varied greatly

## Little Consensus (Acceptable to ~50-60%)

- Sponsor may not include their own statistical analyses in pub
- Sponsor may prohibit sharing of raw data with outsiders
- Sponsor will write manuscript for review by investigator
- Sponsor will store data and release portions to investigators

FSI rephrased for categorization

<sup>1</sup>Mello *et al.* (2005). "Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry." *N Engl J Med.* (352):21



## While contracts can be rate limiting, few contacts felt we should focus there

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Several contacts felt contracts were under control and were not enthusiastic about that focus

“We have one contracting office for all Harvard Institutions and use a standard template. This is something we’ve largely figured out.” *AMC*

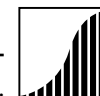
“Two attorneys work on contracts – they are savvy; we don’t get many complaints.” *AMC*

Issues around contracts were mentioned, but most felt this could not be addressed easily

“We have a lot of master agreements, however, there are challenges with these as well because divisions don’t always talk to each other and new lawyers and managers want to review terms anyway.” *AMC*

“There was an effort a few years ago from 8-9 AMCs where they drafted a standard contract and when they brought it back to their home institutions, none of them would adopt it. There are substantive issues that people legitimately don’t agree on....lawyers work from a worst case scenario....there is a jobs program aspect to this.” *AMC*

“We have started to develop standing contracts with the sites frequently used – protocols are attachments and reference the original agreement. This has likely shaved a significant amount of time in man hours off getting trials started.” *Device company*



## Proximity to a site is important, especially for device trials where more “engineering” is involved

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MA location is strategic for sponsors when new science, preclinical

- Technology originated in MA research institutions and spun out
- Close collaboration on new science (Partners/Genzyme)

For most MA companies, having trial sites in MA is convenient but not strategic

- Device companies, small start-ups have stronger preference for MA sites

“{Having trial sites in Massachusetts} is less of an issue for big companies...for smaller companies who have limited resources in terms of time and money, having far-flung sites is a difficult drain.”  
*Device Company*

- Some companies may choose to have their trials close, as long as other criteria are met

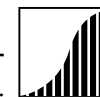
“There are plusses to having trials in Boston...it is easier to move samples around and to have meetings with people who are local – just send people in a car.”  
*Pharma company*

The Collaborative could help encourage using local sites

- “Match-making” for companies and less well-known sites who have an interest in trials
- “Road-show” to introduce less well known sites to sponsors

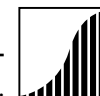
PR needs to be salient to site selection criteria

- Highlight clinical trial expertise, trained CRCs
- Patient base
- Not: “Cape Cod and lobsters” (other states’ efforts considered ineffectual)



## CE support for CRCs and investigators and marketing of sites – ideas that floated to the top

Suggested Improvement	Details
Human Capital	<ul style="list-style-type: none"> <li>• State funding to support continuing education and certification for CRCs, investigators and IRB panelists</li> <li>• Support advancement of young investigators</li> <li>• Creates an attractive MA workforce</li> <li>• Tax breaks for those interested in pursuing a research career</li> </ul>
Increase Marketing/PR	<ul style="list-style-type: none"> <li>• Marketing to pharma/device companies detailing clinical research opportunities in MA</li> <li>• Direct marketing to patients regarding importance as well as increasing awareness of existing trials</li> </ul>
Software to phenotype patient populations	<ul style="list-style-type: none"> <li>• Investigators to accurately predict how many eligible patients they may have for a study</li> <li>• Support outreach and enrollment</li> </ul>
Speed up IRB Approval Process	<ul style="list-style-type: none"> <li>• Outsource IRB (BU – Western)</li> <li>• Implement more frequent IRB meetings (DFCI, Baystate)</li> <li>• Establish reciprocal IRB agreements</li> <li>• Pay IRB members so that it becomes a priority</li> </ul>



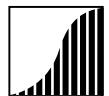
## Additional targets for improvement for task force efforts

Suggested Improvement	Details
Create a statewide IRB	<ul style="list-style-type: none"> <li>• Cover all trials performed in the state</li> <li>• Attract companies to have trial sites in MA due to ease of use [note: MA usually a minority of total sites]</li> </ul>
Statewide Directory “Match Making”	<ul style="list-style-type: none"> <li>• List of sites, investigators and interests in MA</li> <li>• Ensure all interested investigators are known to pharma/CROs</li> <li>• Needs to be specific</li> </ul>
“Rethink how trials are done”	<ul style="list-style-type: none"> <li>• Eliminate age old linear phase I, II, III structure</li> <li>• Genotype &amp; phenotype information</li> <li>• FDA wants change but cannot do it in response to industry pressure</li> <li>• Represents an opportunity for MA to lead</li> </ul>
Facilitate alliances	<ul style="list-style-type: none"> <li>• Community hospitals are interested in doing clinical trials, help make alliances easier with AMCs</li> <li>• 80% of trials used to be done at AMCs, now only 30%; industry is moving to community hospitals &amp; overseas</li> </ul>
Regulatory Changes	<ul style="list-style-type: none"> <li>• Outlaw insurance discrimination based on genetic information; would increase enrollment</li> <li>• Represents opportunity for MA to lead (more states to effect change)</li> </ul>



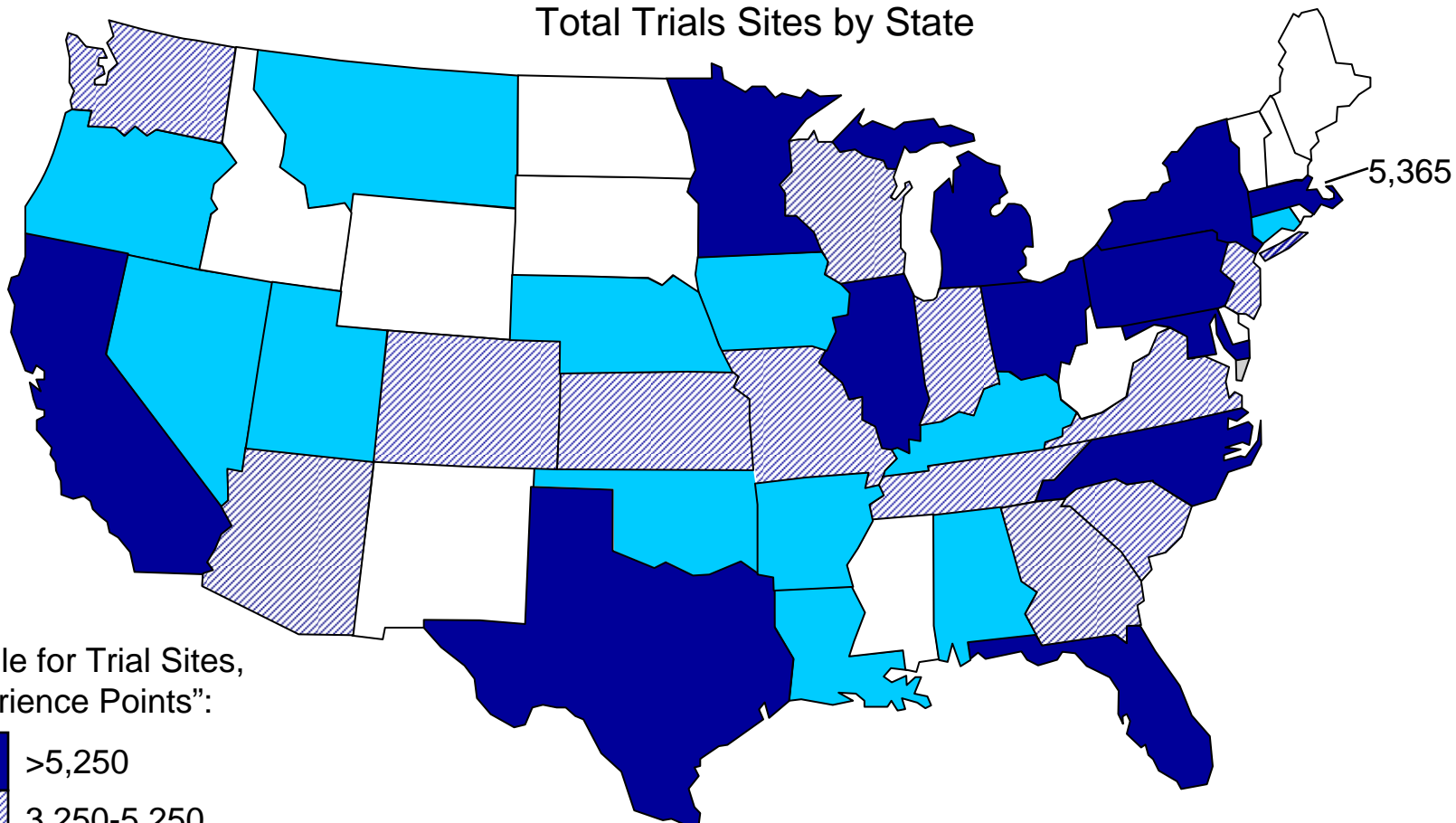
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# Appendix

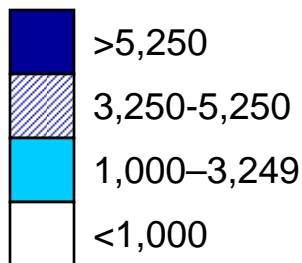


# Massachusetts ranks 11<sup>th</sup> in the nation for total number of clinical trial “experience points” from 2002-2007

Total Trials Sites by State

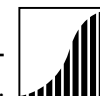


Quartile for Trial Sites, "Experience Points":

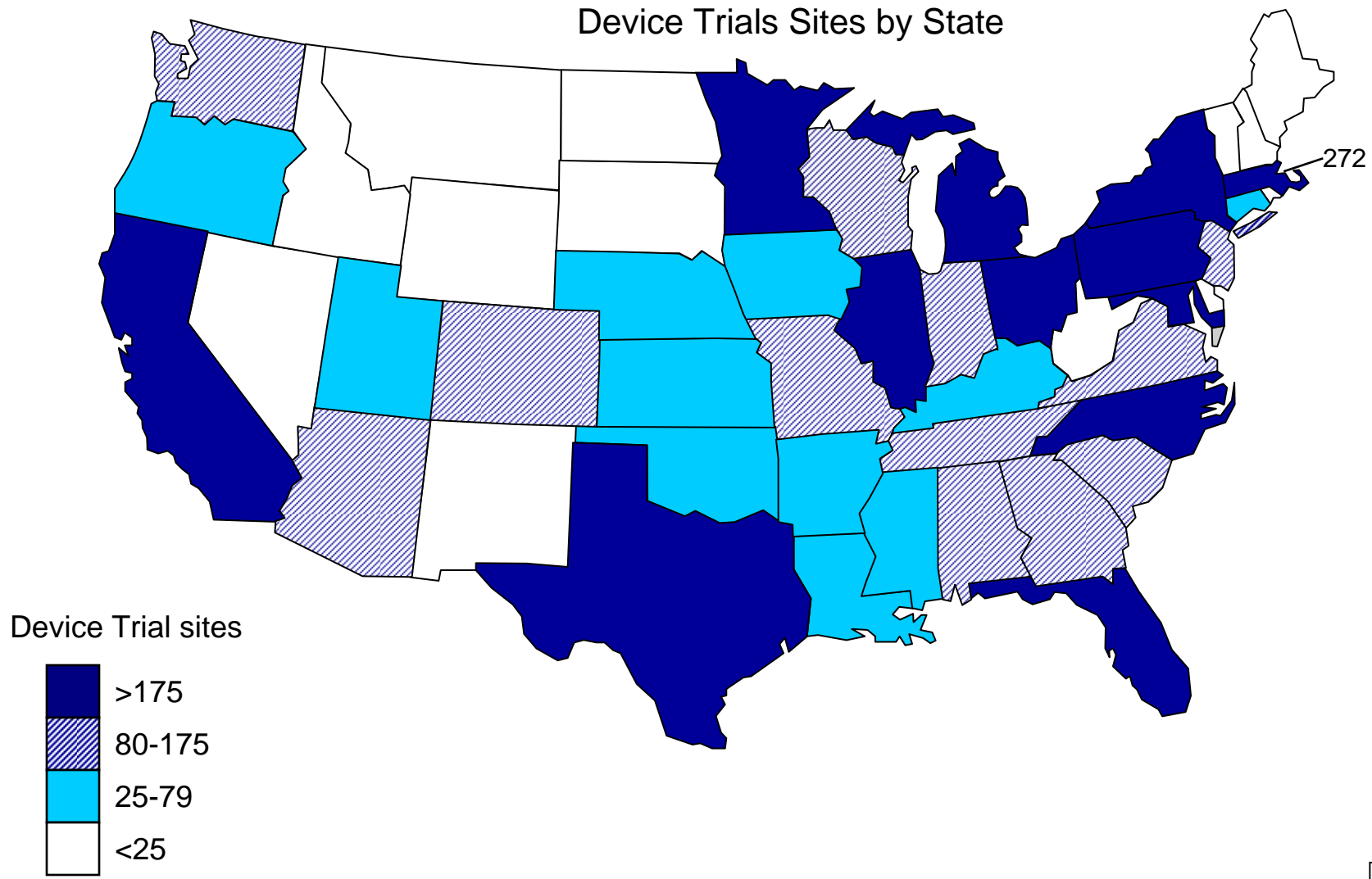


Experience point = A site participating in a protocol/trial

Source: Clinicaltrials.gov – trial sites from 2002-2007; includes drug and device trials



# Data limited, but MA ranks 7<sup>th</sup> in the US for device trials



Source: [clinicaltrials.gov](http://clinicaltrials.gov), device trials 2002-2007, FSI Analysis

