State of Clinical Trials:
An Analysis of Clinical.Trials.Gov

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Agenda

1. **Overview**
2. **Data**
3. **Conclusions**
4. **Lively Discussion**

First, what do you think?

How are clinical trials doing?

(NIH merit scale -1 = best; 9 = worst)

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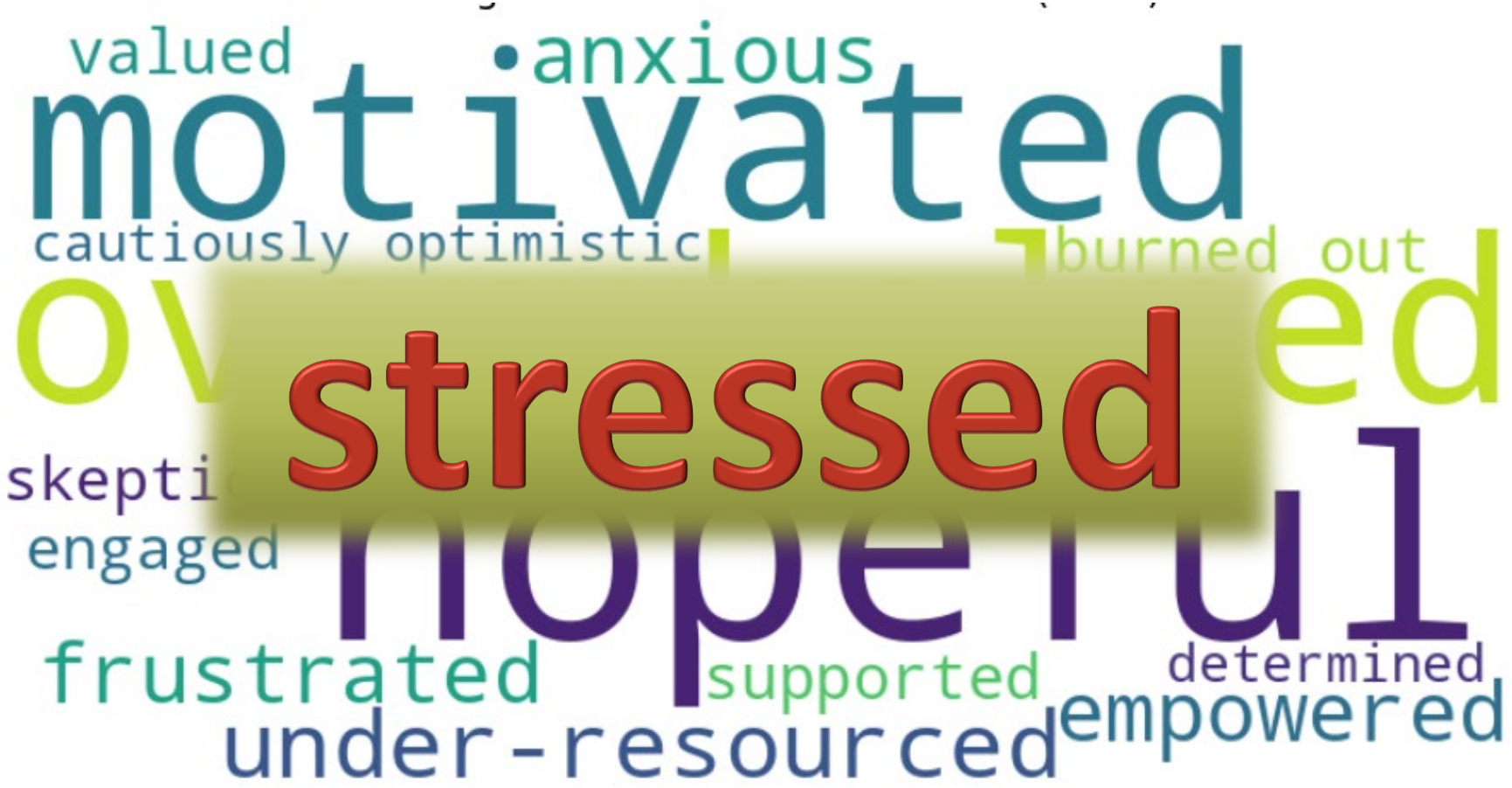
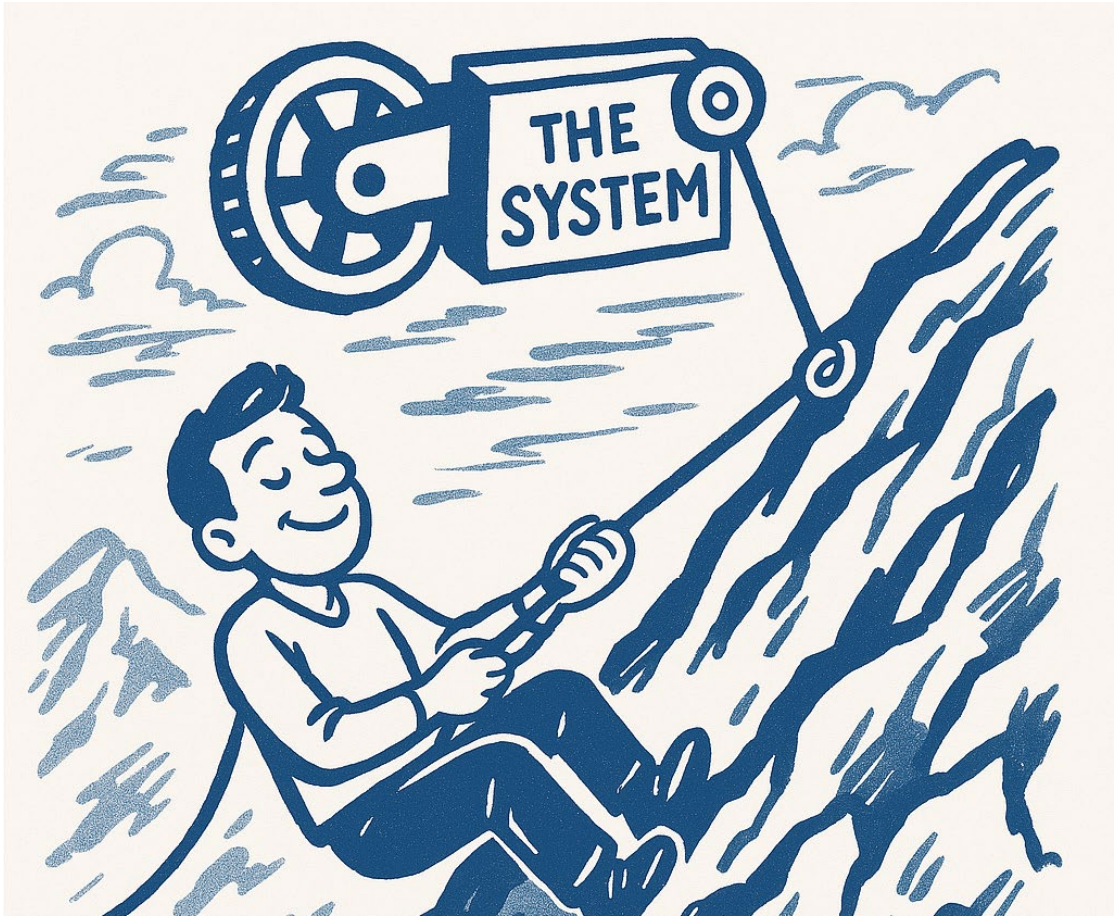
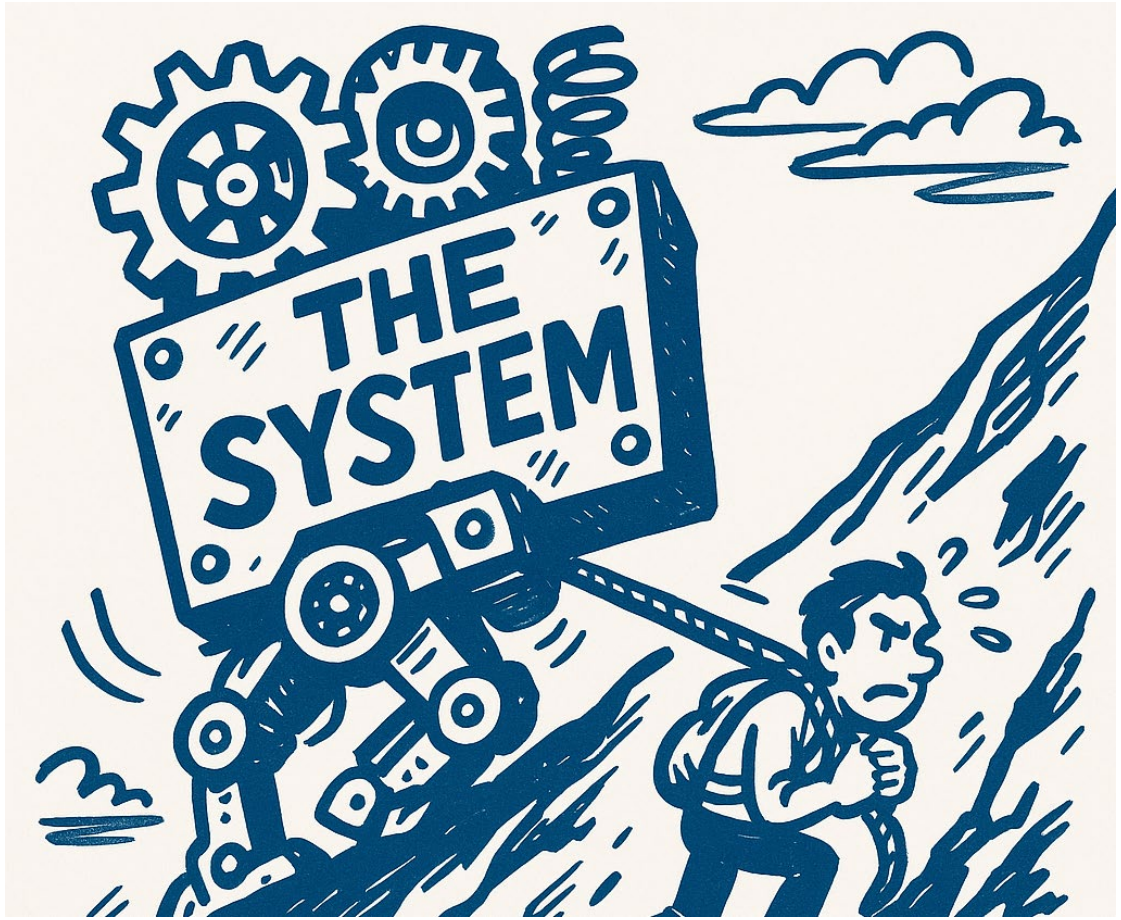
AI’s Answer on the State of Clinical Trials



Which perspective do various players have?





Many challenges…

JAMA Network™

Patient Enrollment for Cardiovascular Clinical Trials in the United States

Research Letter

February 12, 2025

Patient Enrollment for Cardiovascular Clinical Trials in the United States

Muhammad Shahzeb Khan, MD, MSc[1,2,3]; Adeena Jamil, MBBS[4]; Muteia Shakoor, MBBS[4]; et al

» Author Affiliations | Article Information

JAMA Cardiol. 2025;10(3):298-300. doi:10.1001/jamacardio.2024.5537

Table 2. Site-Specific Enrollment Characteristics for Trials Reporting Patient-per-Site Data

	Patients enrolled			No. (%)		
					Sites enrolling <10 patients	
Trial	Total No.	US, No. (%)	Total sites, No.	US sites	Overall	US[a]
Total	89 172	17 705 (19.9)	4388	1133 (25.8)	2014 (45.8)	659 (58.1)
ISCHEMIA-CKD	777	159 (20.5)	118	36 (30.5)	95 (80.5)	31 (86.1)
COP-AF	3209	355 (11.1)	45	8 (17.8)	12 (26.7)	3 (37.5)
THEMIS	19 220	2266 (11.8)	1297	307 (23.7)	668 (51.5)	228 (74.3)
ILUMIEN IV: OPTIMAL PCI	2487	909 (36.6)	80	35 (43.8)	23 (28.7)	14 (40.0)
PARADISE-MI	5702	454 (8.0)	494	82 (16.6)	284 (57.5)	73 (89.0)
REPRIEVE	7769	3787 (48.7)	145	100 (69.0)	23 (15.9)	18 (18.0)
SELECT	17 604	3652 (20.7)	804	201 (25.0)	220 (27.4)	58 (28.9)
ISCHEMIA	5179	853 (16.5)	319	109 (34.2)	207 (64.9)	88 (80.7)
AEGIS-II	18 219	1993 (10.9)	899	196 (21.8)	450 (50.1)	138 (70.4)
TWILIGHT	9006	3277 (36.4)	187	59 (31.6)	32 (17.1)	8 (13.6)

Clinical Trial Humility

- North America:
  - Most sites: 1377 sites [31.4%]
  - Lowest median enrollment (8.0 patients/site)
- South America,
  - Fewest sites: 329 sites [7.5%]
  - Highest patients per site (24.8 patients/site)
- Eastern Europe
  - Highest median per-site enrollment (16.0 patients/site)

- Author's Conclusion:
- … Notably, the United States had the **most sites** but enrolled **significantly fewer patients**.

- These trends suggest **underlying legal, regulatory, and cost-related barriers**, highlighting the need for improved clinical trial infrastructure.

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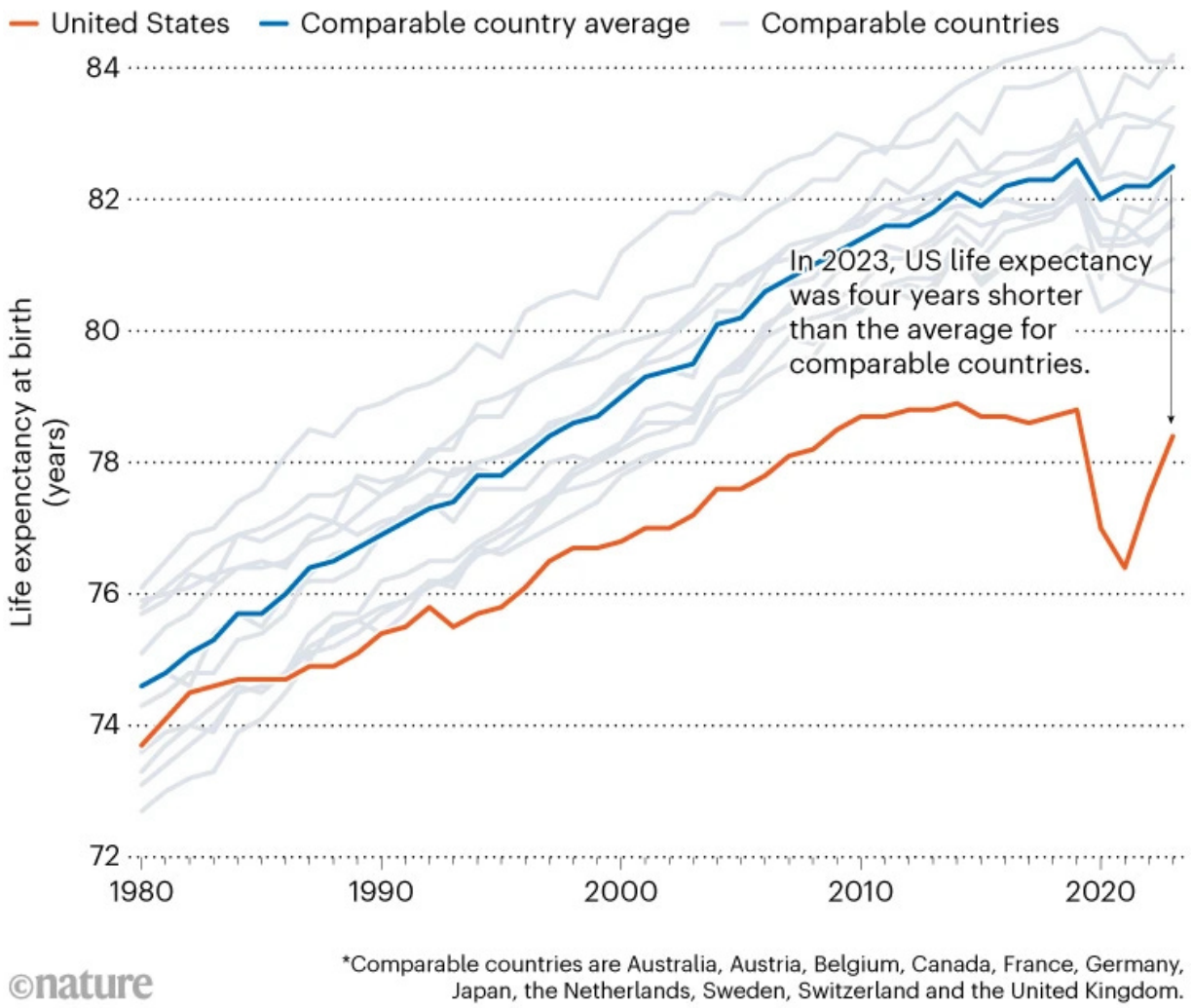
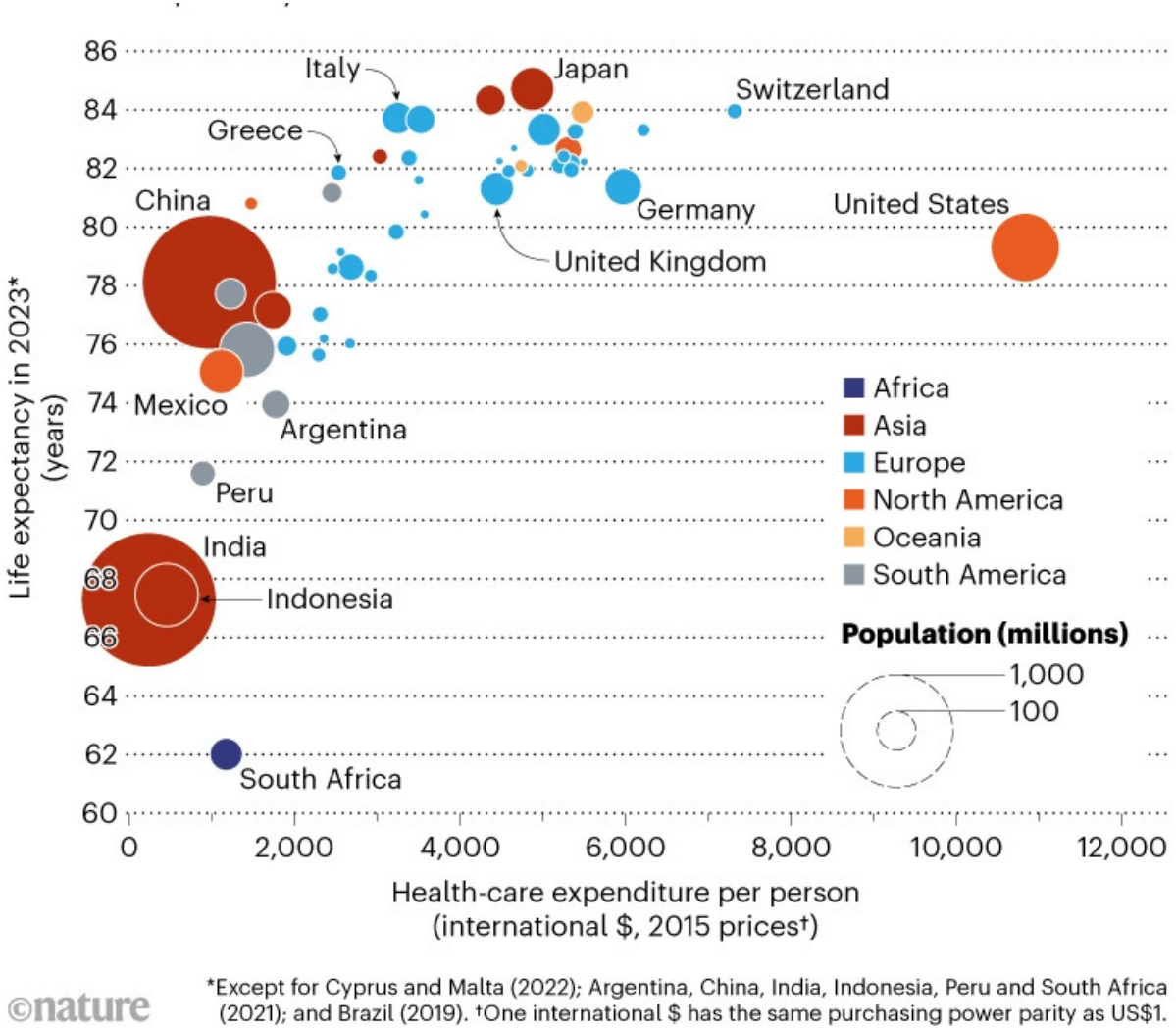
Bending the Health Curve: Life and Value





https://robcaliff272993.substack.com/p/taking-the-highway-to-better-health

The Good News.

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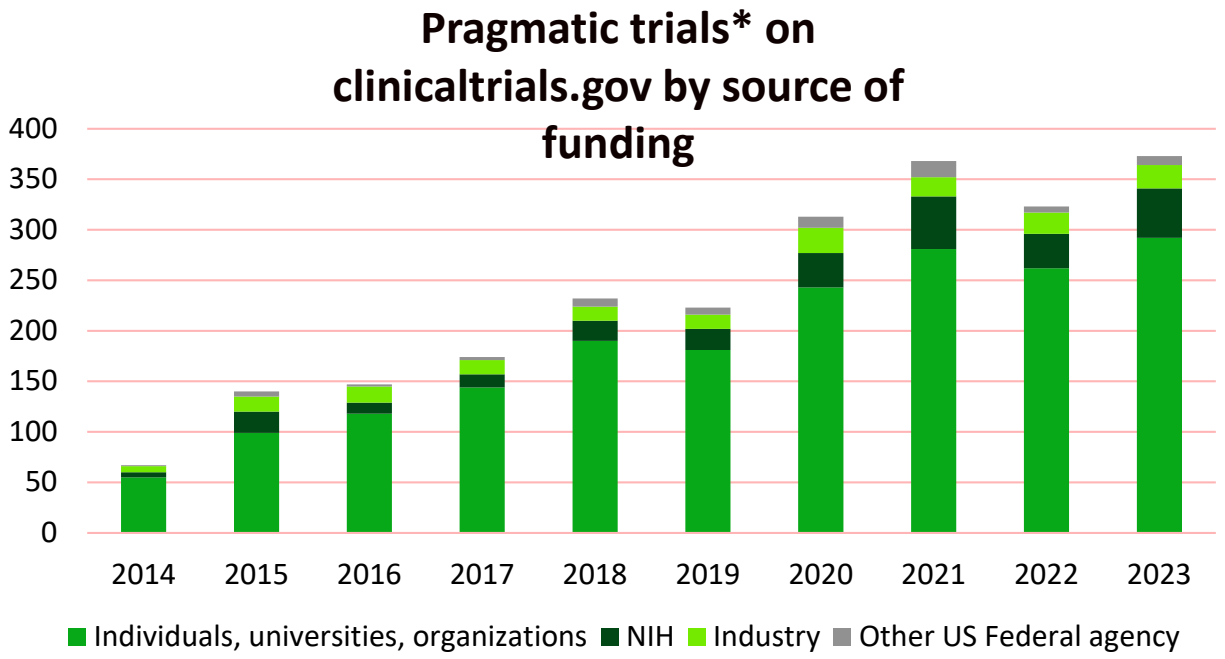
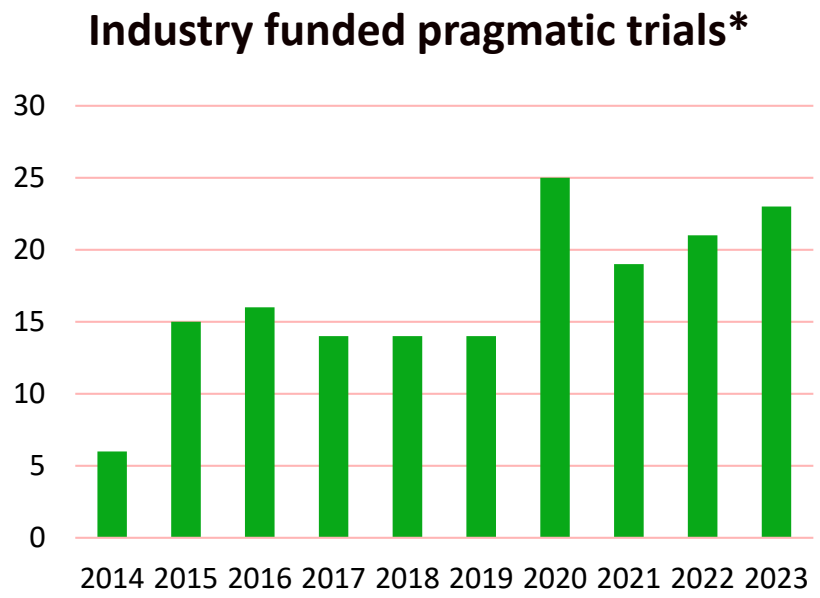
“Pragmatic Clinical Trials” Over the Last 10 Years





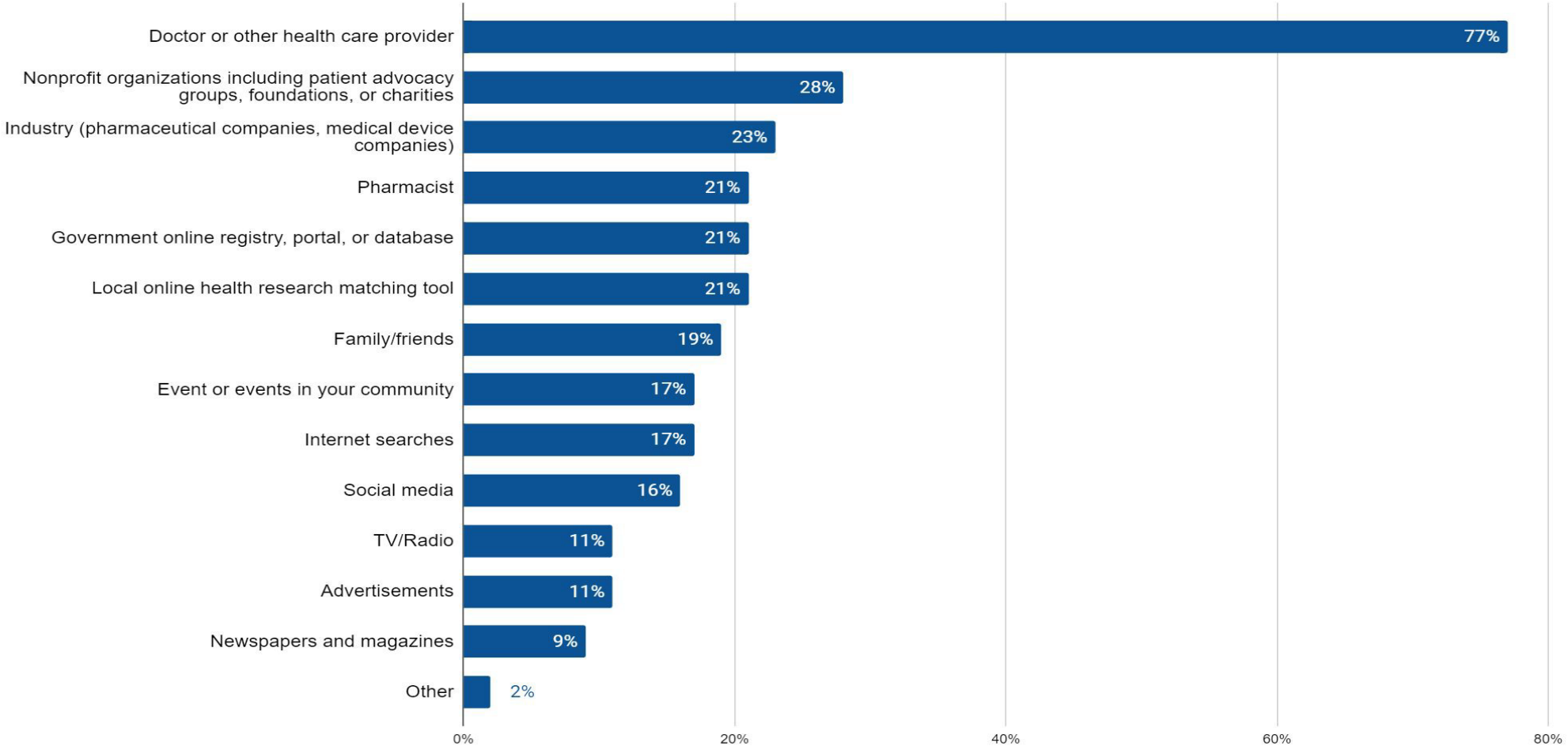
*Used the clinicaltrials.gov search engine under “other terms” using the search term ‘pragmatic’ to identify PCTs with a start date in the specified year.

Main sponsors: universities, individuals (e.g., academics), research institutes, medical centers/clinics, pharma, digital therapeutics/AI health technology companies, non-profits.

Main collaborators: NIH Institutes, pharma, private medical centers/clinics, engineering/manufacturing companies, national government bodies (MoH).

Doctors/health care providers are by far the top choice for information on clinical trials

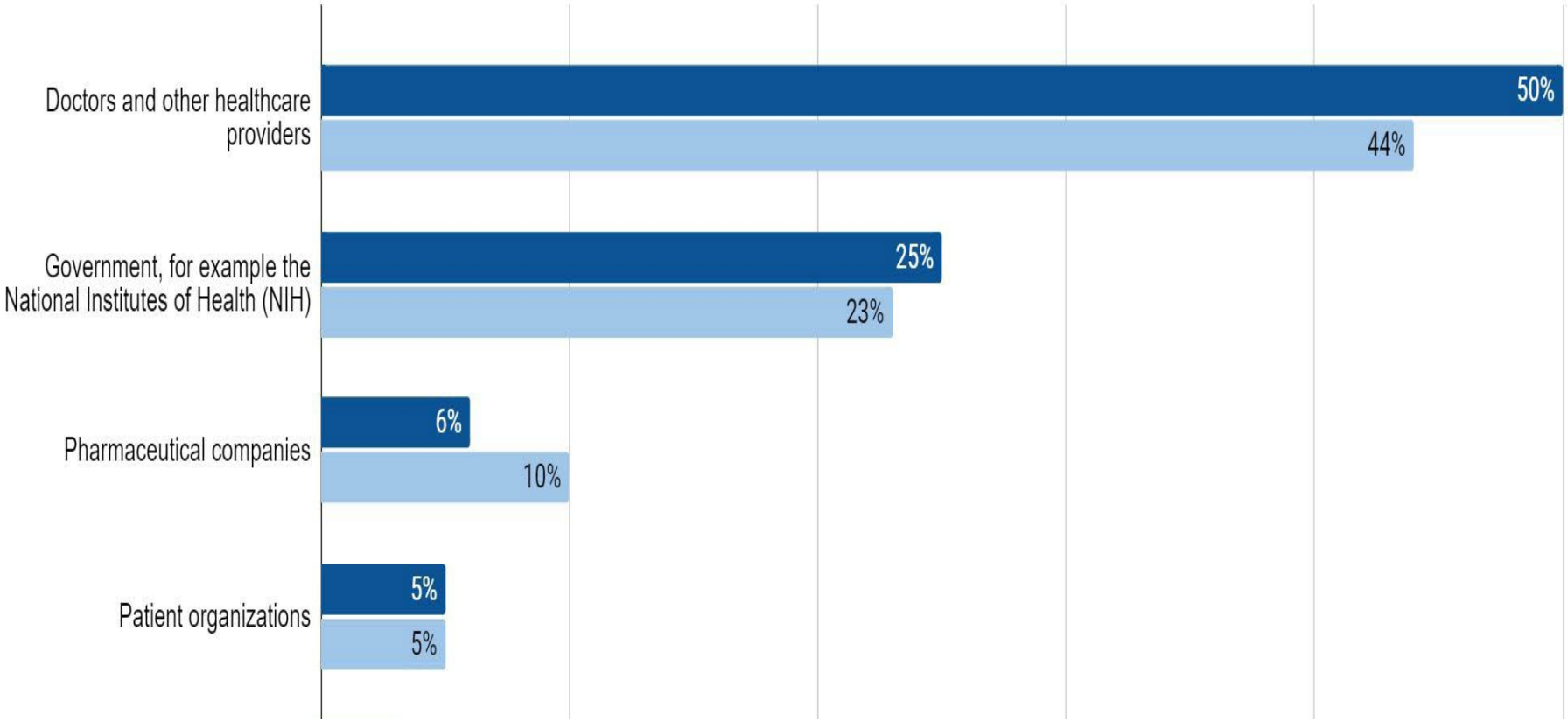
Where would you prefer to get information about participating in a clinical trial? (Check all that apply)



Source: A Research!America survey of U.S. adults conducted in October 2023.

Americans feel doctors and healthcare providers have the most responsibility for clinical trial education

Which organizations listed below would you say have the greatest responsibility in educating the public about clinical trials?



▲ Up from 44% in 2017 to 50% in 2023.

Source: A Research!America survey of U.S. adults in October 2023.

High Regulatory Interest:
CDER's Center for Clinical Trial Innovation

- **CDER Center for Clinical Trial Innovation (C3TI)**
- **Key Initiatives:**

1. **Point-of-Care or Pragmatic Trials**: Integrating clinical trials into routine clinical practice to generate real-world evidence.
2. **Bayesian Analyses**: Utilizing advanced statistical methods to enhance trial design and data interpretation.
3. **Selective Safety Data Collection**: Focusing on collecting essential safety data to streamline trial processes.

We can do what was once imaginary.

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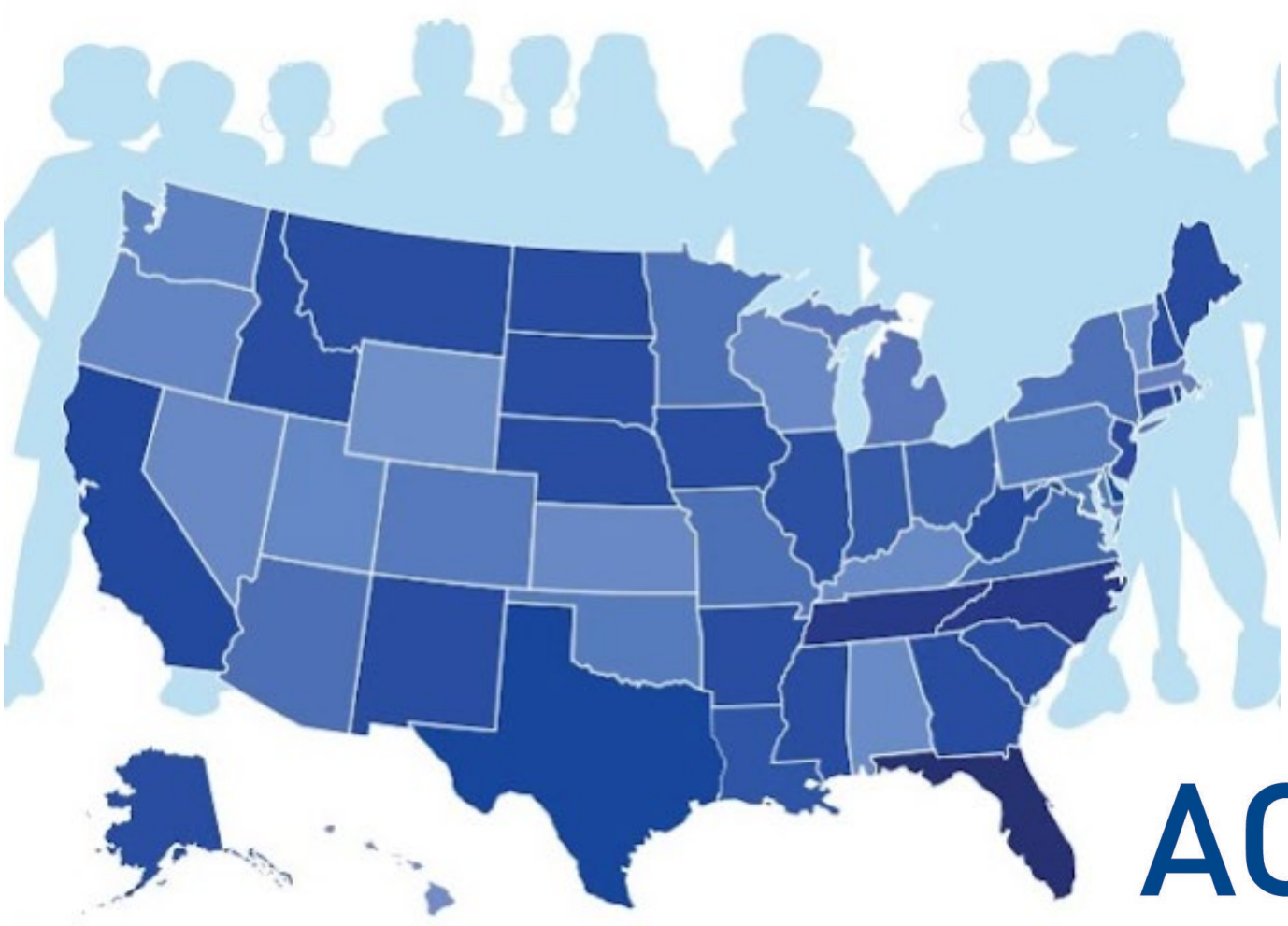
Clinical Trial Options Everywhere for Everyone



ACTIV-6

What was the state of clinical trials 15 years ago?

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State of Clinical Trials: 2007-2010

Original Contribution

May 2, 2012

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD; Deborah A. Zarin, MD; Judith M. Kramer, MD, MS; et al

» Author Affiliations | Article Information

JAMA. 2012;307(17):1838-1847. doi:10.1001/jama.2012.3424

Conclusion: Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

Explanatory hypotheses?

Small, crappy trials (SCTs)

OR

Too many great ideas

‘system’

Suggested solutions:
Prioritize, Fix the System, Larger Trials/System (e.g. platforms)

And now, how are doing?

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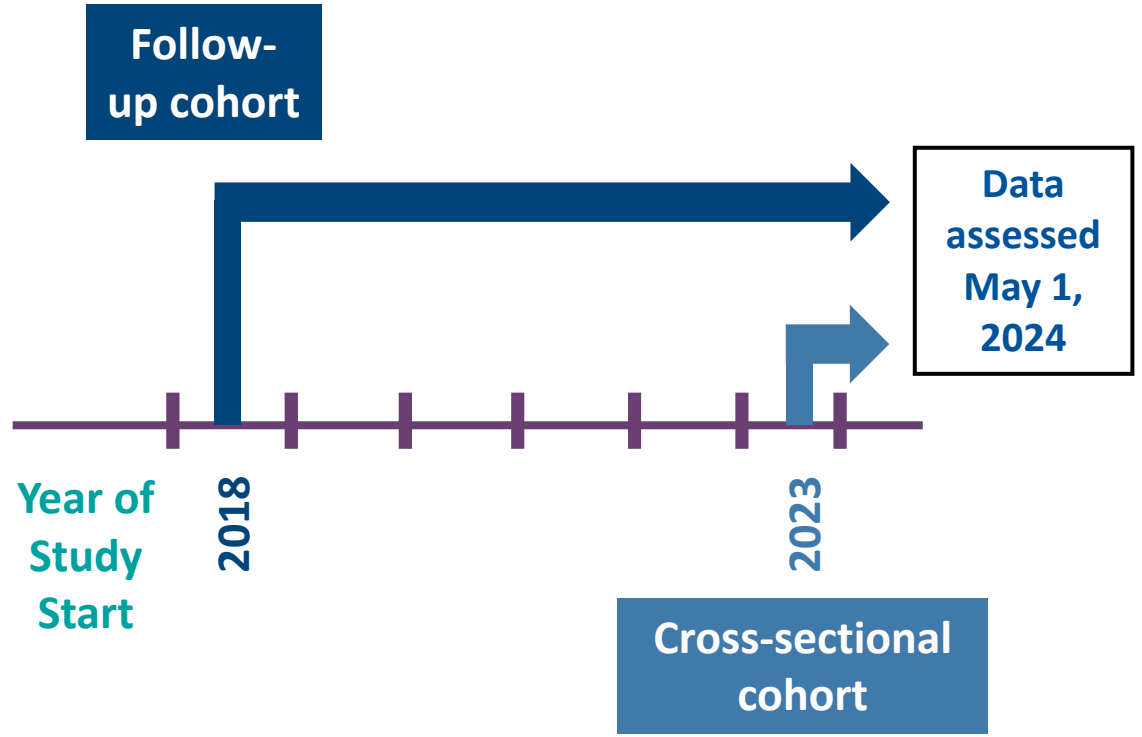
Objective

To provide an updated characterization of interventional clinical trials in the U.S. to inform national policy discussions on optimizing the evidence-generation system

Methods

Retrospective analyses using the database for Aggregate Analysis of ClinicalTrials.gov (AACT)[1,2]

- Interventional clinical trials
- Registered in ClinicalTrials.gov as of 05/01/2024
- At least one U.S. site

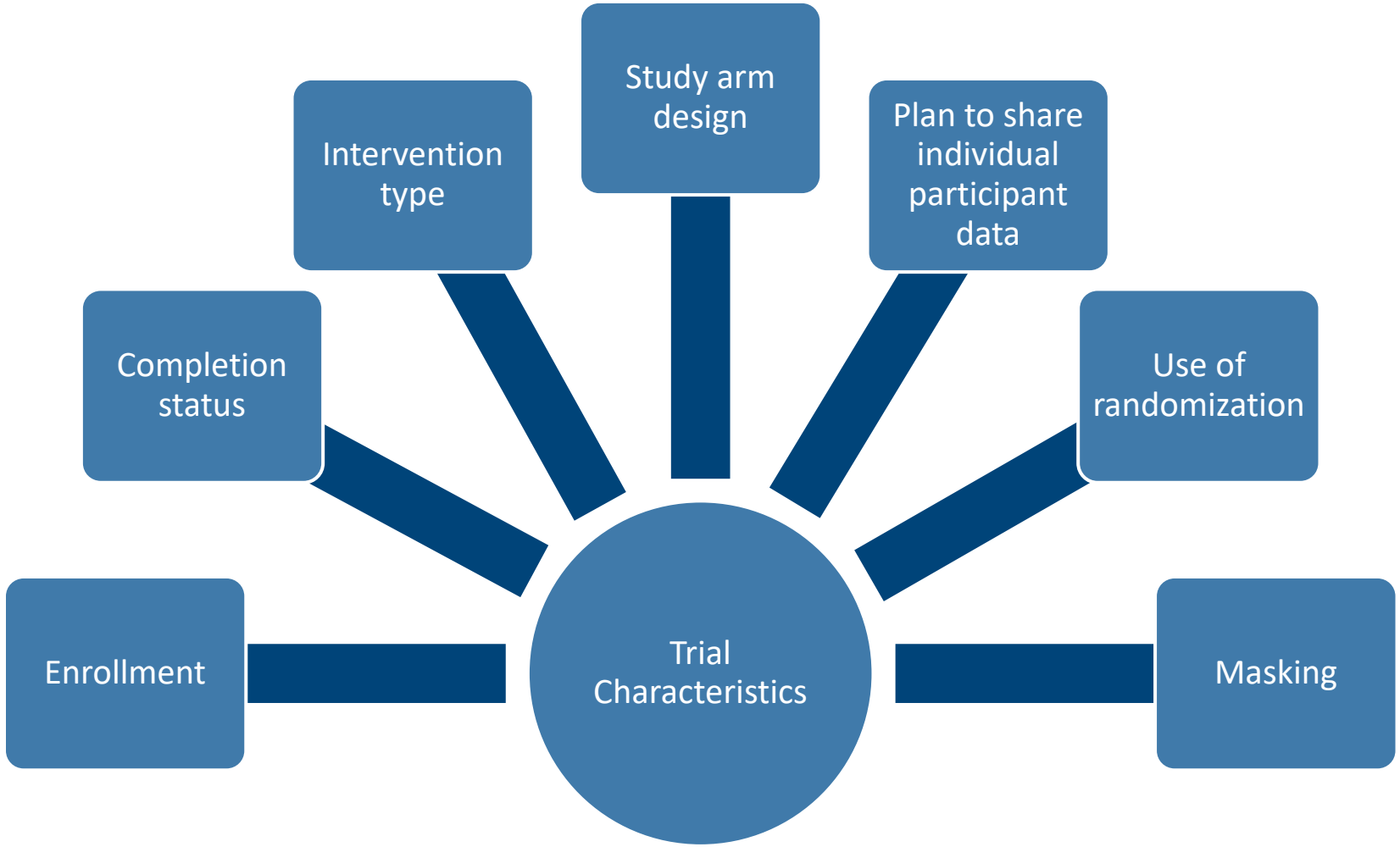


1. National Library of Medicine. ClinicalTrials.gov. https://clinicaltrials.gov/
2. Clinical Trials Transformation Initiative (CTTI). AACT Database. Available at: https://aact.ctti-clinicaltrials.org/

Methods

Exposures

- Primary Funding Source (industry, NIH, other federal, other)
- Therapeutic Area (cancer, cardiovascular, mental health)



Results

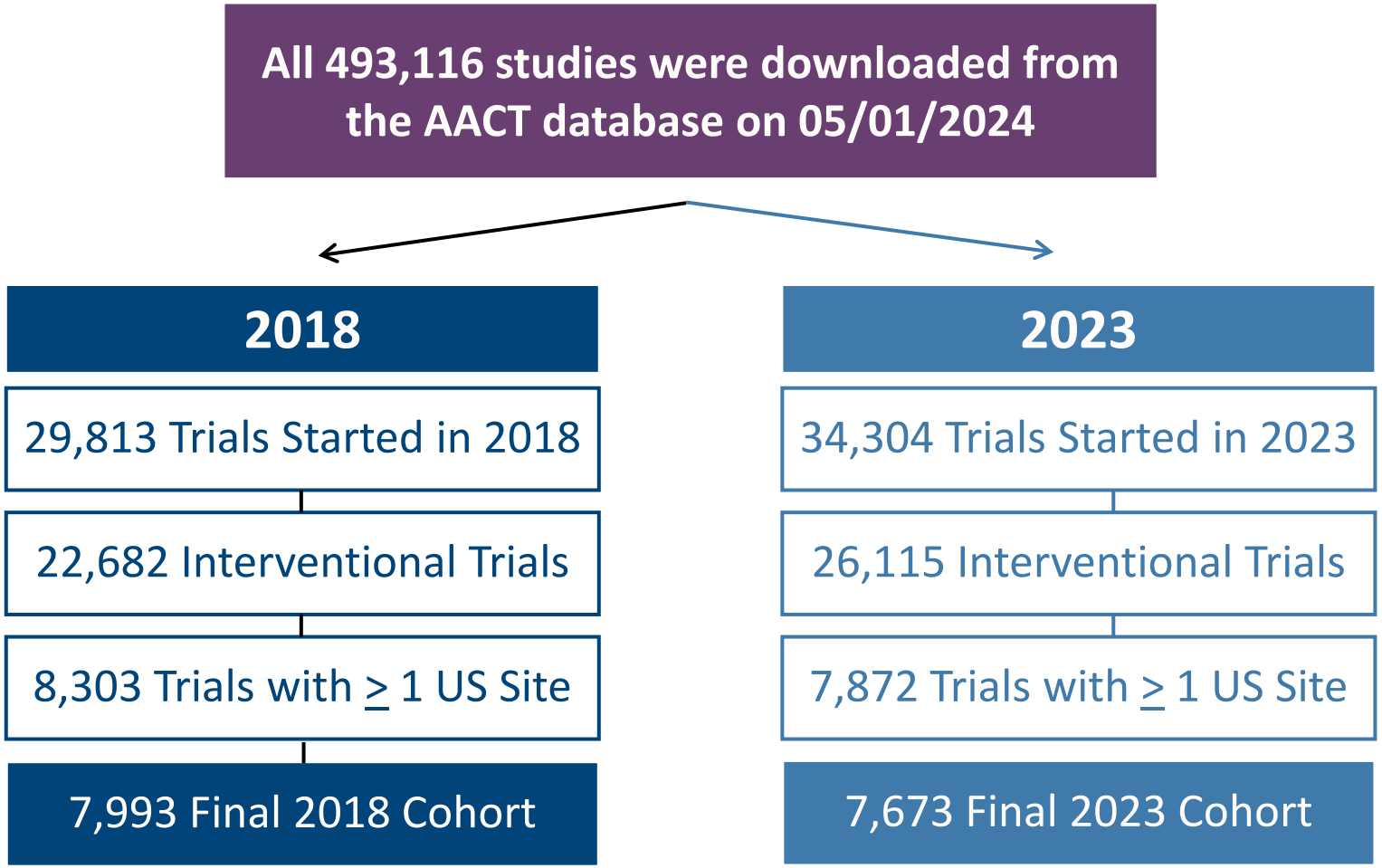
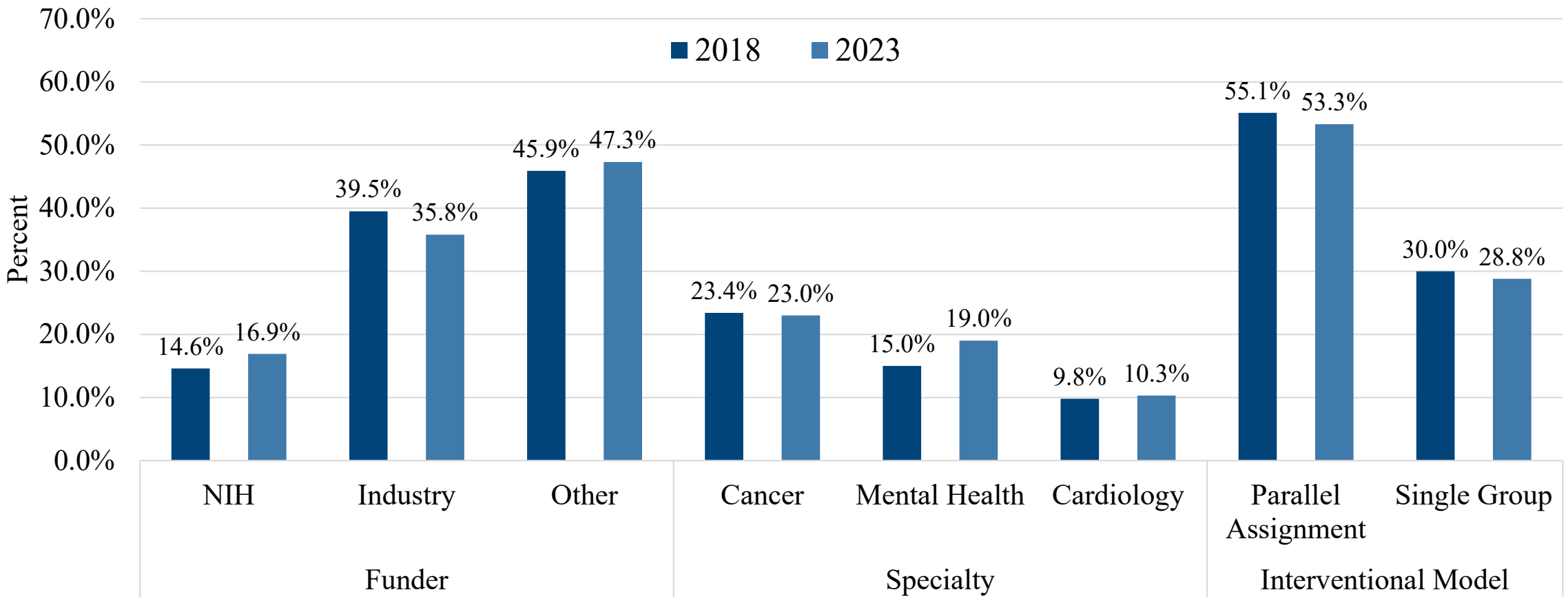

All 493,116 studies were downloaded from the AACT database on 05/01/2024
2018
29,813 Trials Started in 2018
22,682 Interventional Trials
8,303 Trials with ≥ 1 US Site
7,993 Final 2018 Cohort
2023
34,304 Trials Started in 2023
26,115 Interventional Trials
7,872 Trials with ≥ 1 US Site
7,673 Final 2023 Cohort

Figure 1: Select Characteristics by Start Year



Results by Start Year

2018 (N=7,993)

- Enrollment*:
  - ≤ 100 (68.4 %)
  - ≤ 1,000 (96.9%)
- Drug (44.7%), Behavioral (19.4%)
- Of studies with more than one arm, 83.2% were randomized
- Of the randomized studies, 64.7% used some form of masking

2023 (N=7673)

- Enrollment*:
  - ≤ 100 (63.5 %)
  - ≤ 1,000 (95.7%)
- Drug (39.2%), Behavioral (25.8%)
- Of studies with more than one arm, 85.0% were randomized
- Of the randomized studies, 63.5% used some form of masking

* Enrollment in the 2018 and 2023 trials should not be directly compared. 81.9% of the 2018 trials reported actual vs anticipated enrollment, whereas 13.7% of the 2023 trials reported actual enrollment.

Results by Therapeutic Area: Started in 2023

	All Trials	Cancer (23.0%)	Cardiovascular (10.3%)	Mental Health (19.4%)
Median Enrollment	65 (30, 180)	60 (30, 150)	70 (30, 210)	75 (40, 200)
Single Group Design	28.8%	41.7%	29.9%	23.2%
Drug Intervention	39.2%	61.0%	30.3%	19.4%
Behavioral Intervention	25.8%	13.2%	23.4%	55.2%

Figure 2: Percent of Interventional Clinical Trials Started in 2018 Completed within Five Years by Funder

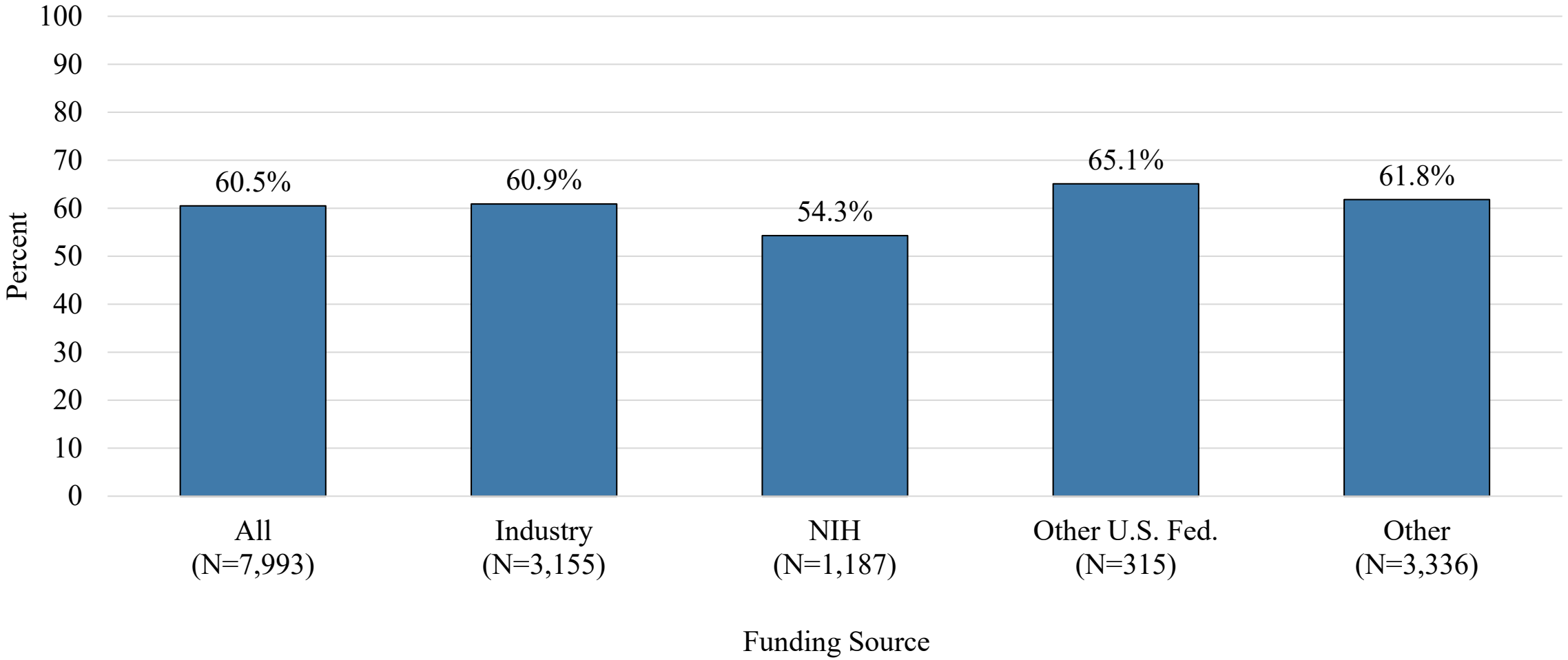


Figure 3: Median (25th – 75th Percentiles) Enrollment for Interventional Clinical Trials Started in 2023 by Funder

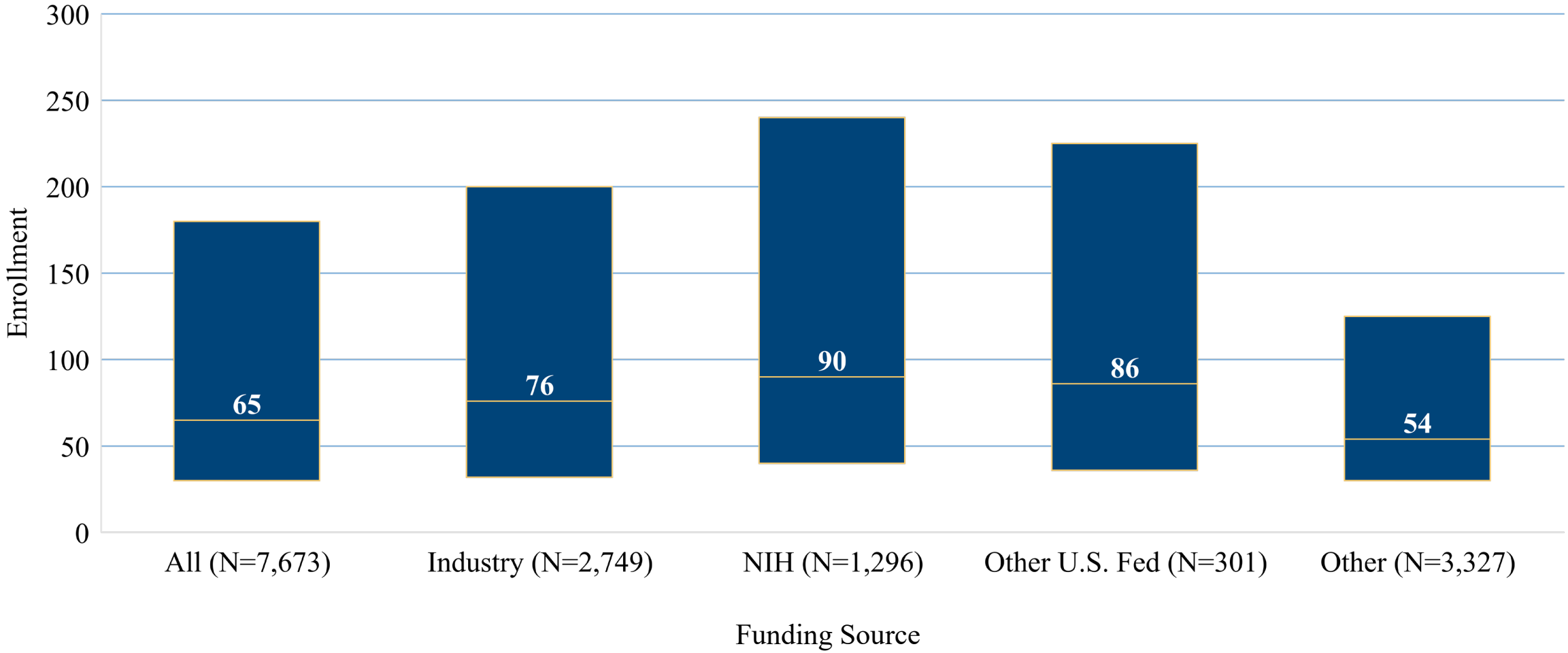
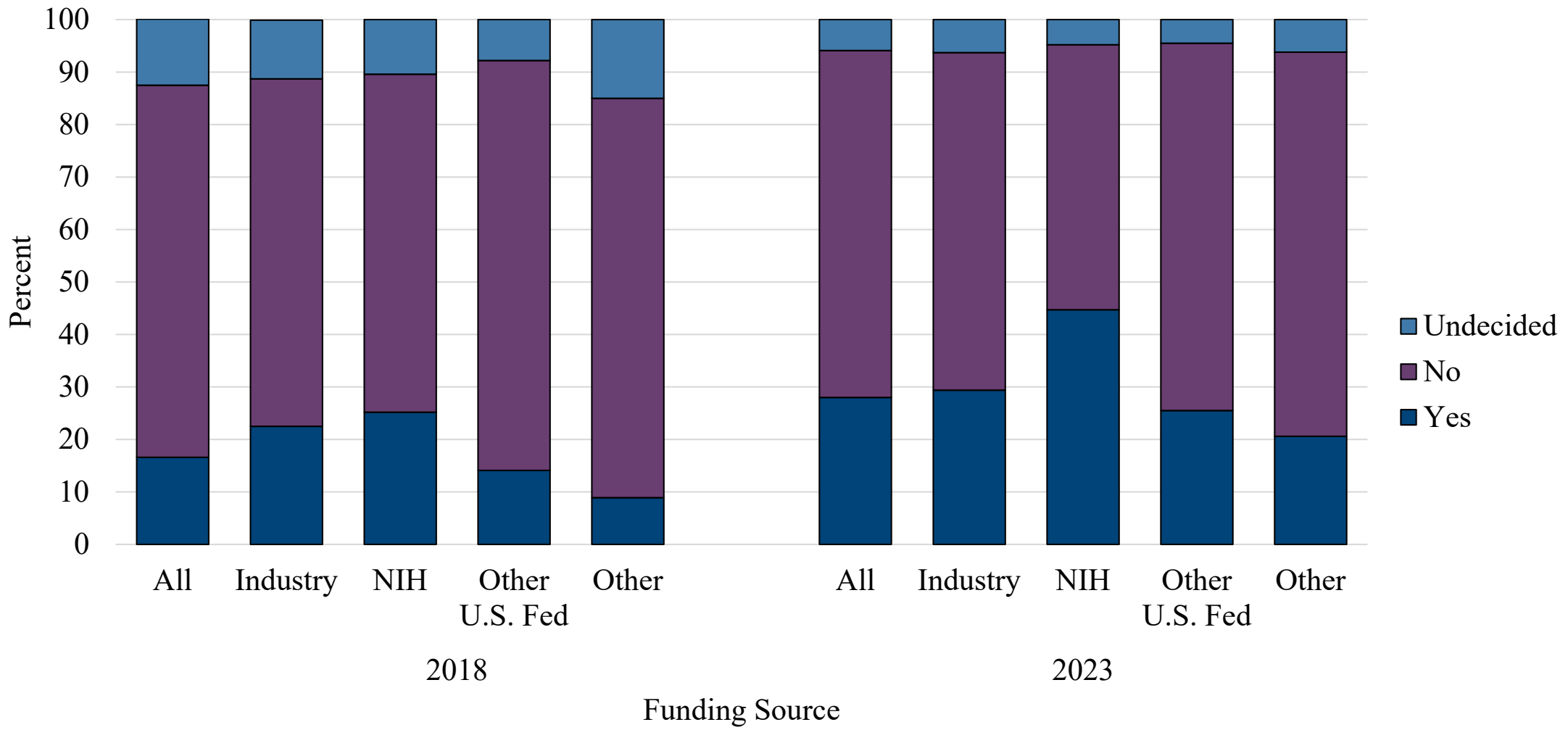


Figure 4: Plan to Share Individual Participant Data (IPD) Among Interventional Clinical Trials Started in 2018 and 2023 by Funder



Limitations

- ClinicalTrials.gov does not include all clinical trials in the U.S.
- The 2012 analysis of interventional trials registered in ClinicalTrials.gov included all trials, whereas our analysis was restricted to interventional trials with at least one U.S. site
- Policies since 2012 have increased the scope of trials required to be registered in ClinicalTrials.gov and improved reporting requirements

Conclusions

- Many trials remain small, lack a control group, and are incomplete after five years
- Although small clinical trials without controls may be appropriate or necessary in specific contexts, such trials are also less likely to produce actionable data
- National policies prioritizing a more rapid, rigorous evidence generation system will likely be necessary to create a clinical trial ecosystem best equipped to advance public health

Policy Approaches

- Streamline trial start-up processes, institutional review board (IRB) approvals, and contracting
- Enable scalable technologies to support greater trial participation
- Invest in modern clinical trial design strategies, including adaptive designs, master protocols, and platform trials
- Require public reporting of key performance indicators and pay-for-performance results
- Create stronger data sharing requirements and accountability rules

Thank you

- Robert M. Clare, MS
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- Lesley H. Curtis, PhD
- Brad G. Hammill, DrPH
- Martin J. Landray, PhD
- Chris J. Lindsell, PhD
- Scott M. Palmer, MD, MHS
- Sara Bristol Calvert, PharmD

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Panel

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