

The background of the slide features a blurred array of orange, round pills in the upper left corner, and a single, sharp orange pill in the lower right corner. The pills are set against a white background.

Summary of Results of Perspectives On LSTs Survey

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Why We Need to Encourage Trials Intended to Inform and Shape Practice Patterns



Potential Applications to Transplantation

- Clarify role of induction immunosuppression (i.e., none vs. blocking agents vs. lytic agents)
 - Trials have typically evaluated short-term outcomes like rejection rates and complication rates.
- Determine best practices for prophylaxis versus preemptive strategies for the prevention of CMV
 - Trials have typically evaluated incidence of CMV disease.
- Optimize maintenance immunosuppression regimens
 - Trials have typically evaluated rejection rates as a primary outcome. Patient and graft survival have been underpowered secondary outcomes.

But statistically significant data on patient and graft survival are what patients and practitioners really want!!

Why aren't streamlined trials conducted to provide meaningful answers these fundamental questions?



Data

Home > Donation & Transplantation > Data

- >> History
- >> Awareness & Promotion
- >> Organ Allocation
- >> Living Donation
- >> Organ Procurement and Transplantation Network
- >> Membership Network
 - How to Apply
- >> Policy Management

UNOS developed an online database system, called UNet, to collect, store, analyze and publish all OPTN data that pertains to the patient waiting list, organ matching, and transplants.

Launched on October 25, 1999, this system contains data regarding every organ donation and transplant event occurring in the United States since 1986. UNet is a fail-safe, 24/7, secure Internet-based transplant information database. It enables the nation's organ transplant institutions to:

- register patients for transplants
- match donated organs to waiting patients
- manage the time-sensitive, life-critical data of all patients, before and after their transplants

Could randomized trials conceivably use these databases or other simple designs to collect outcome data for the types of endpoints that matter most?

Parallel examples exist across a variety of therapeutic areas (e.g., dialysis, diabetes, obesity). Yet, sponsors rarely choose LSTs or other streamlined approaches to support their investigations.

Why is there a disconnect between the data that patients and practitioners want and the science that sponsors support?

CTTI LST Project

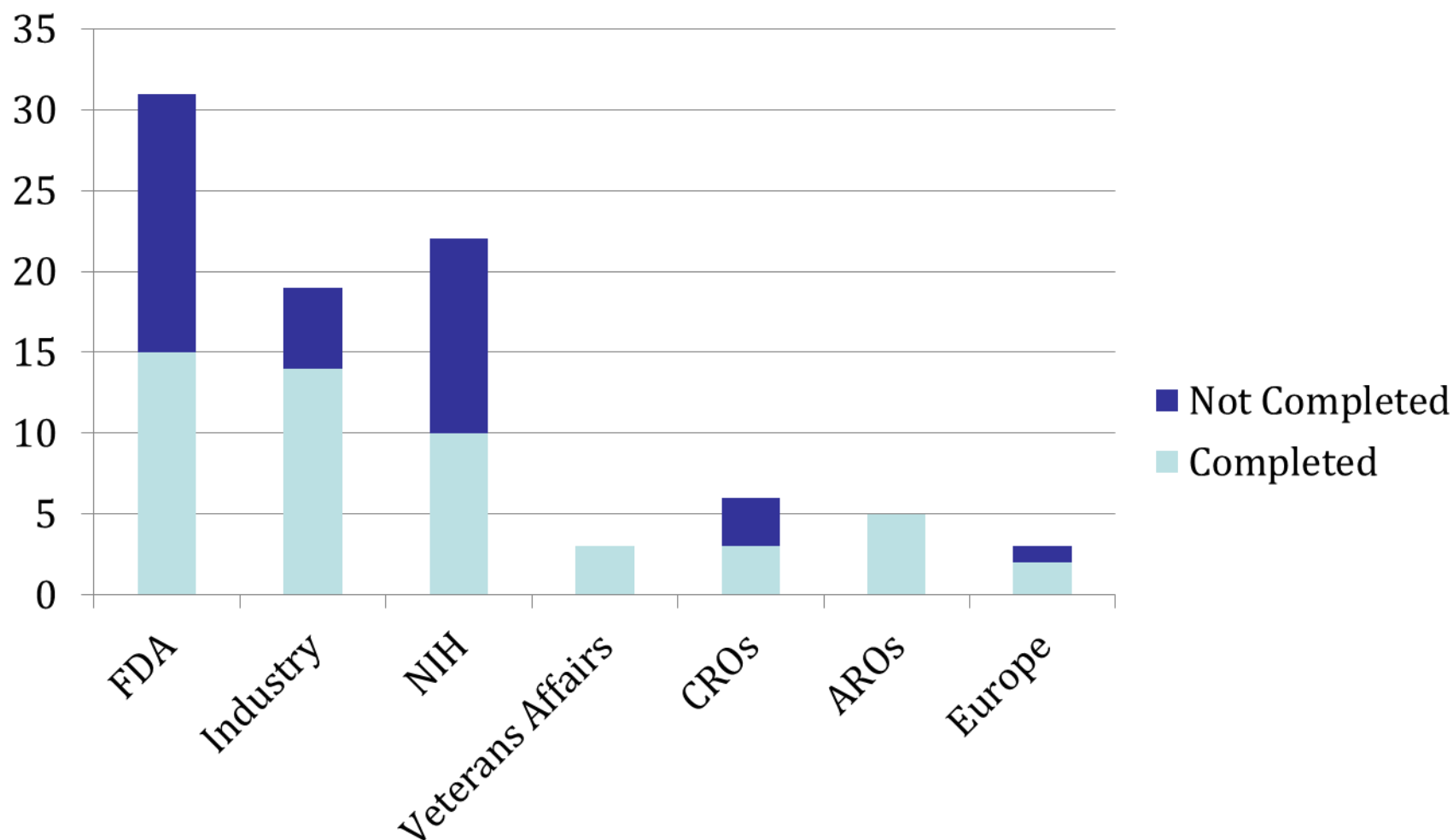
Goal: To develop recommendations to facilitate and promote the adoption of LST designs for regulatory and other purposes

First step of project was to survey the various stakeholders in the clinical trial enterprise who influence the selection of trial designs to better understand the real and perceived barriers to using LSTs

Survey on Stakeholder Perspectives on LSTs

- Web-based survey with modules of questions appropriate to different sectors of the clinical trials enterprise
- Different stakeholder groups completed parallel, but non-identical, surveys to provide complementary information about the role of LSTs in supporting regulatory action
- CTTI targeted a total of 89 respondents and received 53 completed surveys. The results of one survey were discarded as the respondent incorrectly self-identified as a member of FDA
- More detailed data were provided in the background materials than is possible to review in this session!!

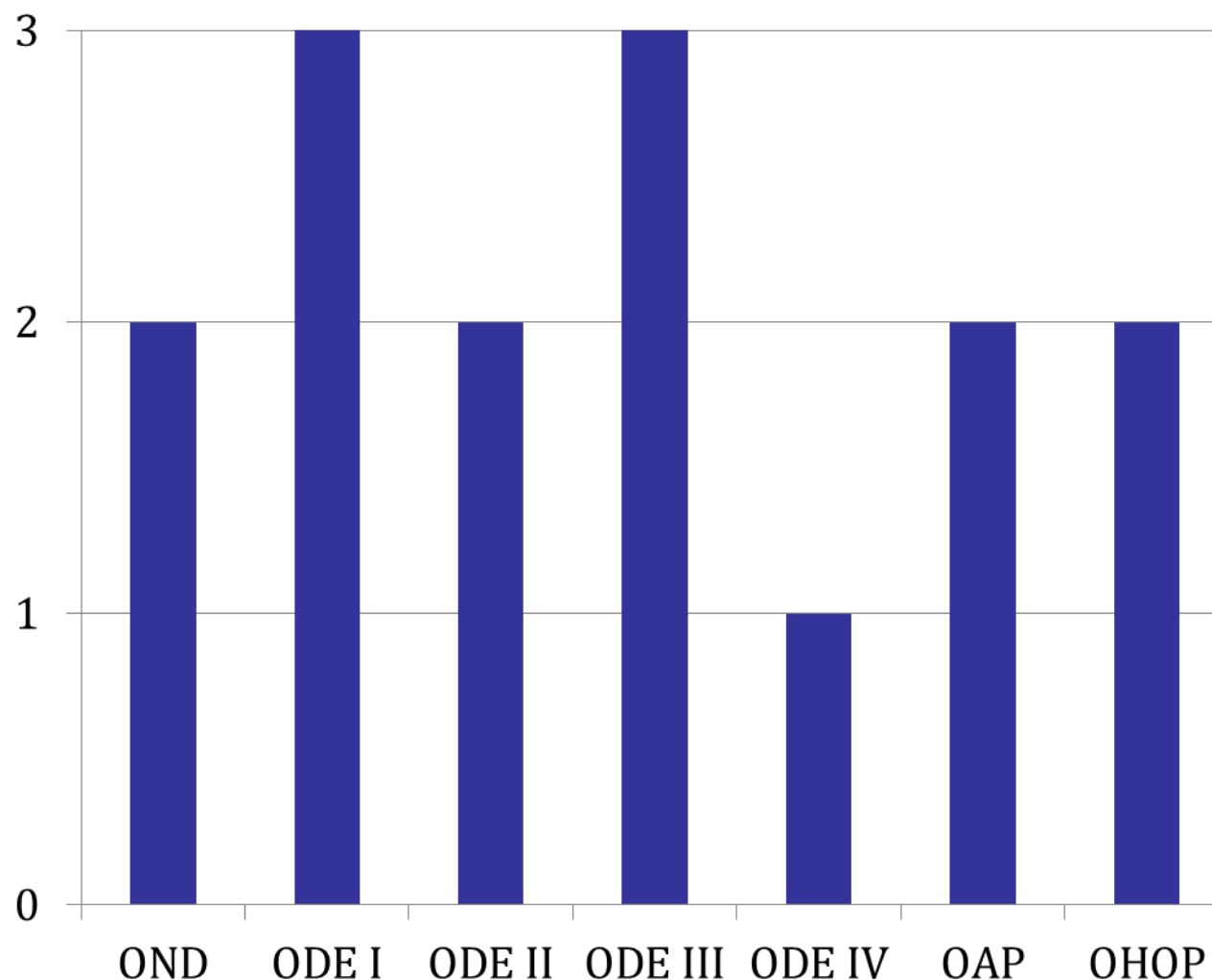
Status of Surveys Sent to Targeted Respondents





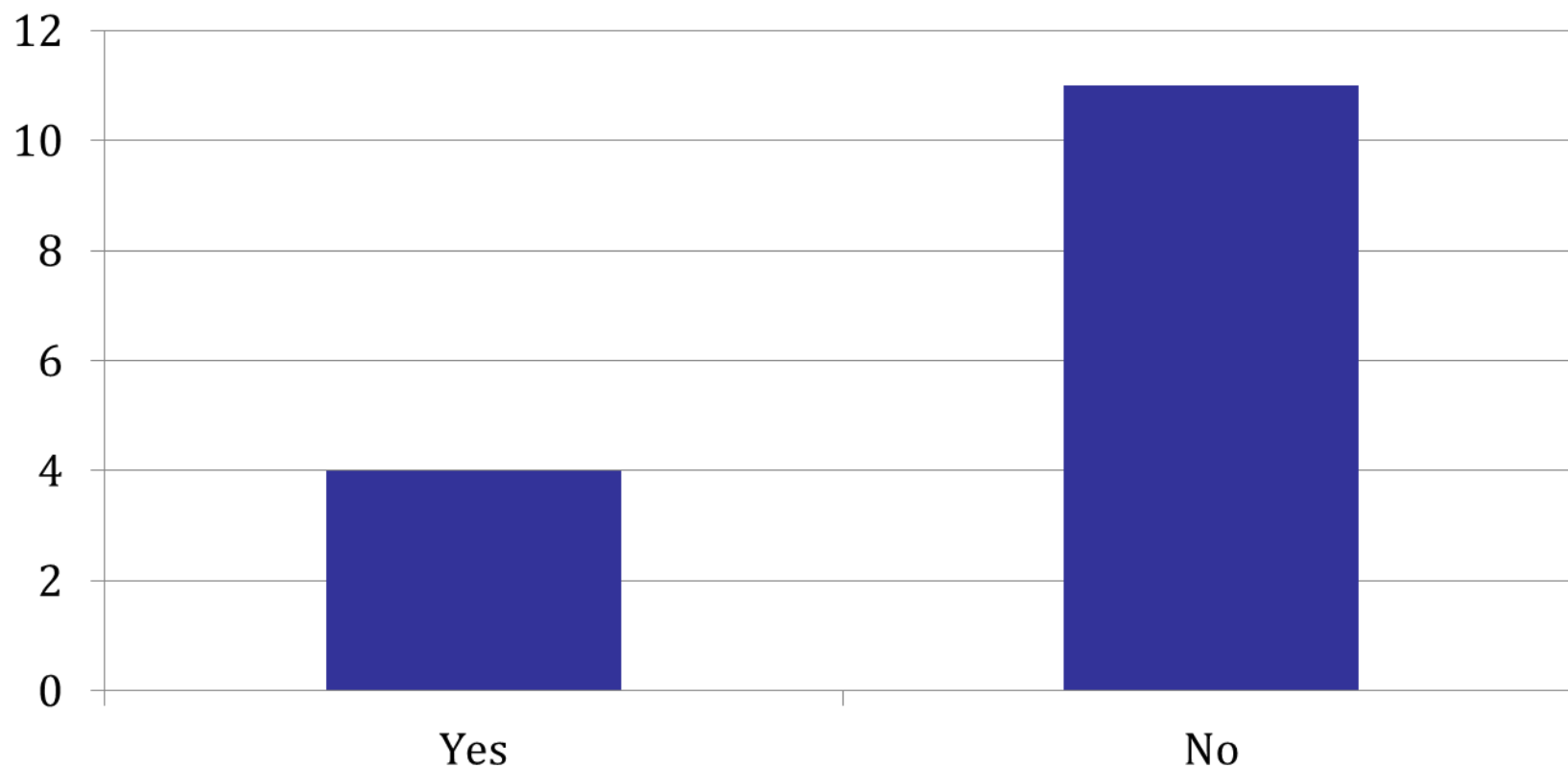
SELECTED DATA FROM FDA RESPONSES TO SURVEY

Demographics of FDA Respondents

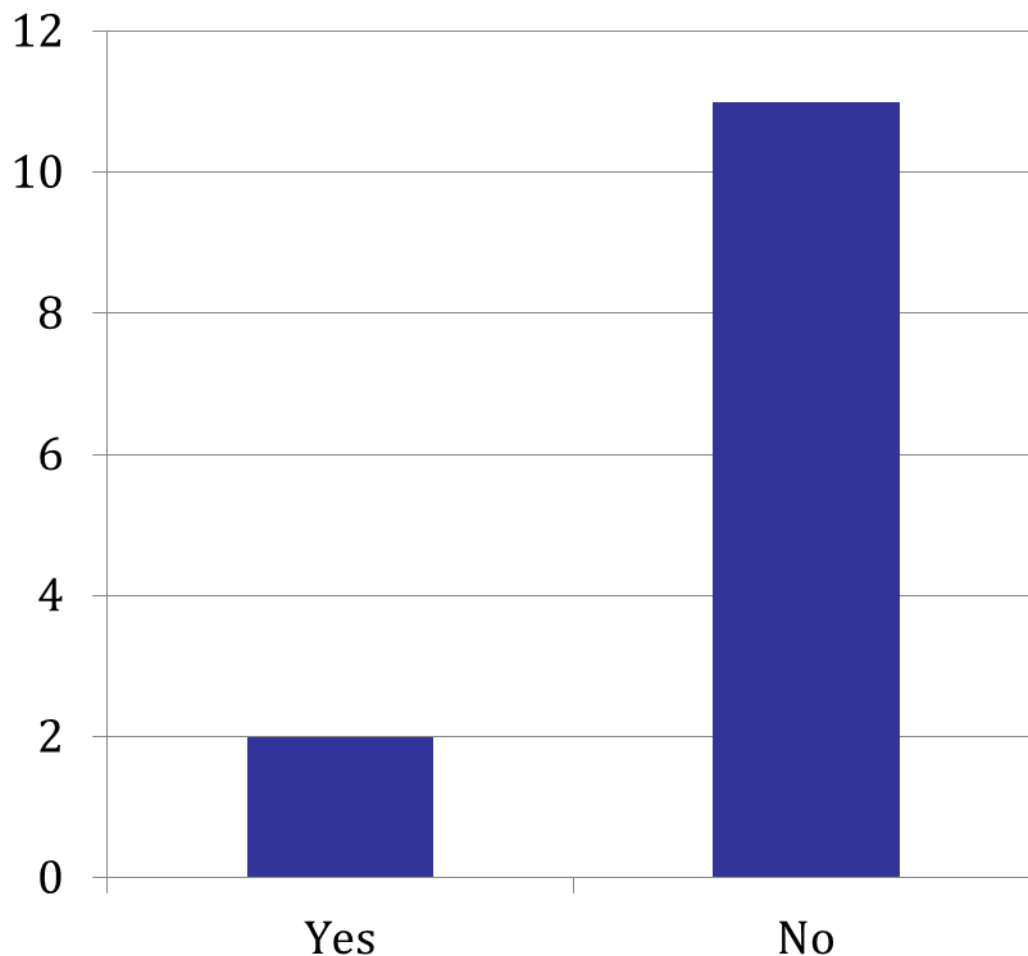


The survey captured data from approximately 50% of the individuals with signatory authority in CDER's Office of New Drugs. The respondents were fairly evenly distributed across the OND Offices.

Does your division ever receive NDA submissions that are primarily supported by LSTs?

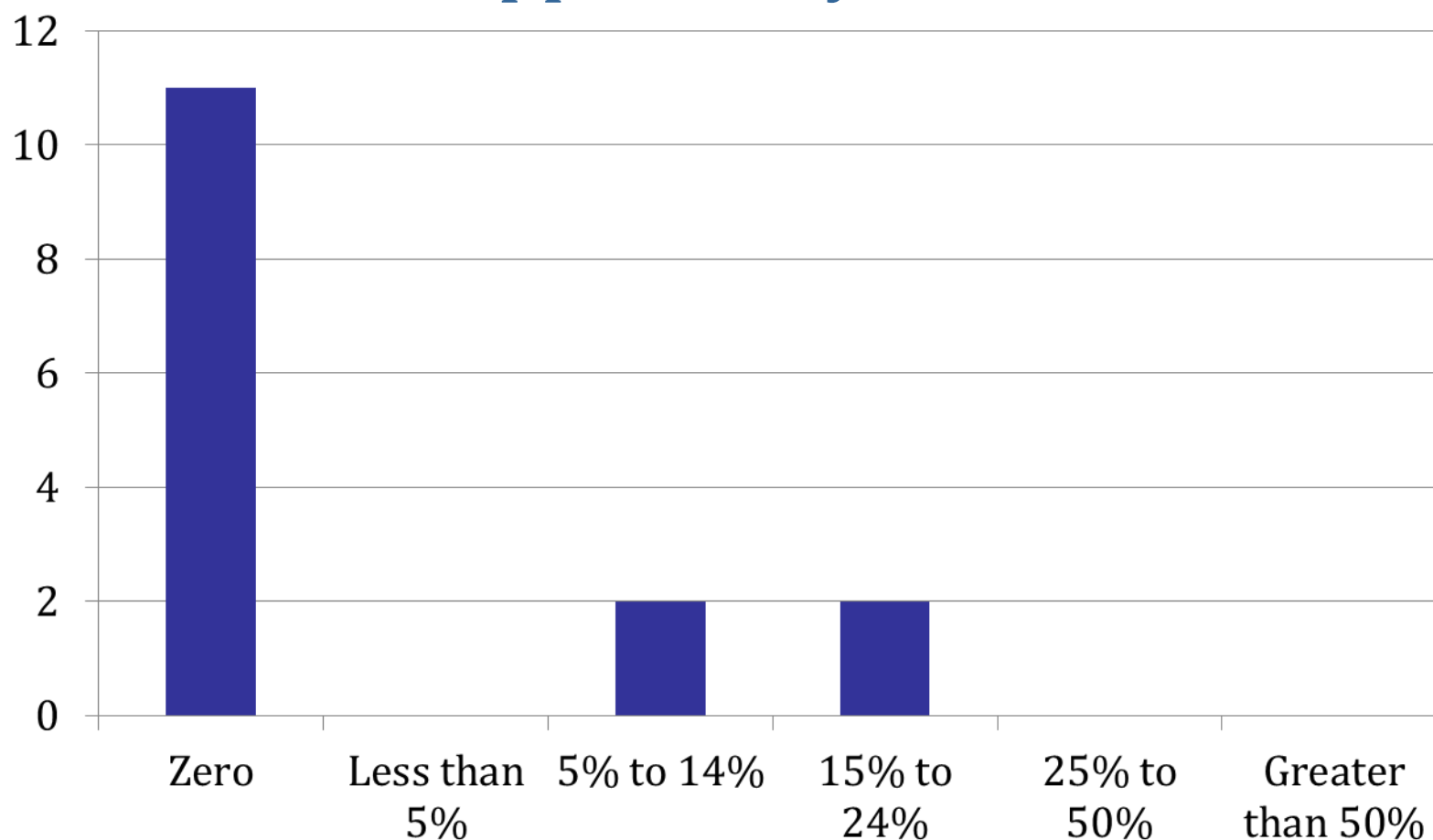


Have you recommended sponsors not use LST designs?



Note: This questions was posed only to those who responded that their divisions never received NDA submissions primarily supported by LSTs.

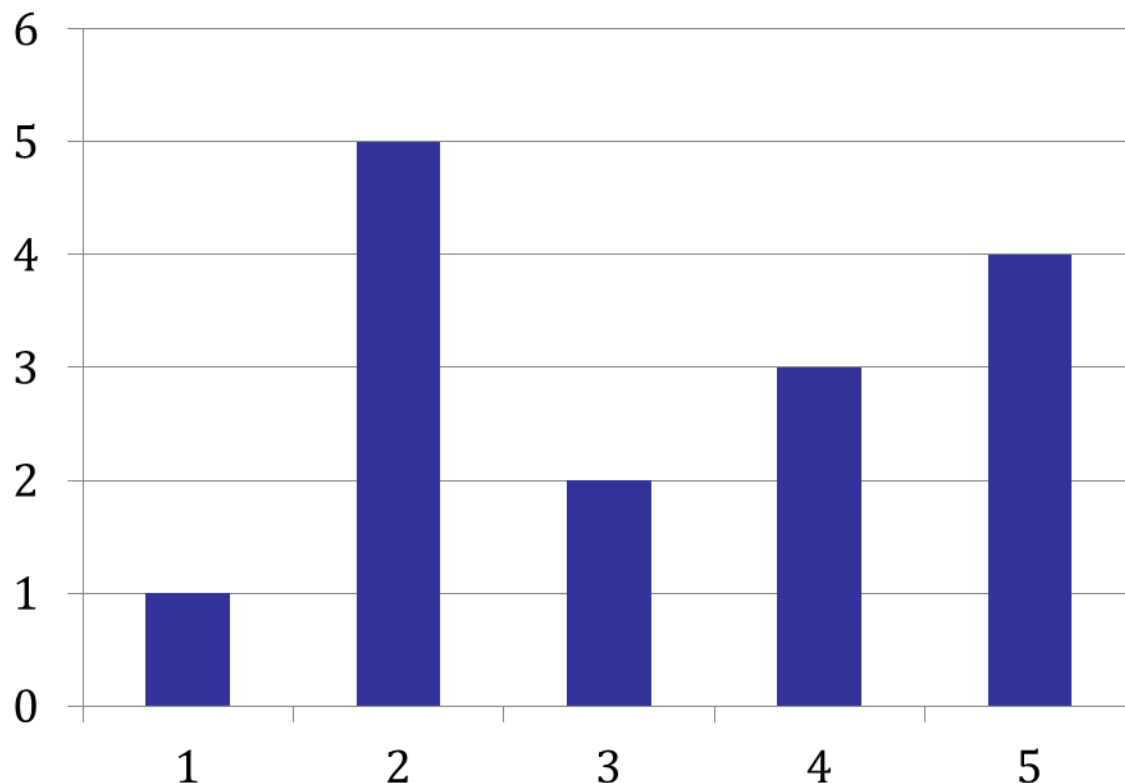
What percent of NDA submissions to your division are supported by LSTs?



Original NDA/BLA application where the safety profile had been established in Phase 1 and Phase 2

Receptiveness

(1 = not receptive; 5 = very receptive)

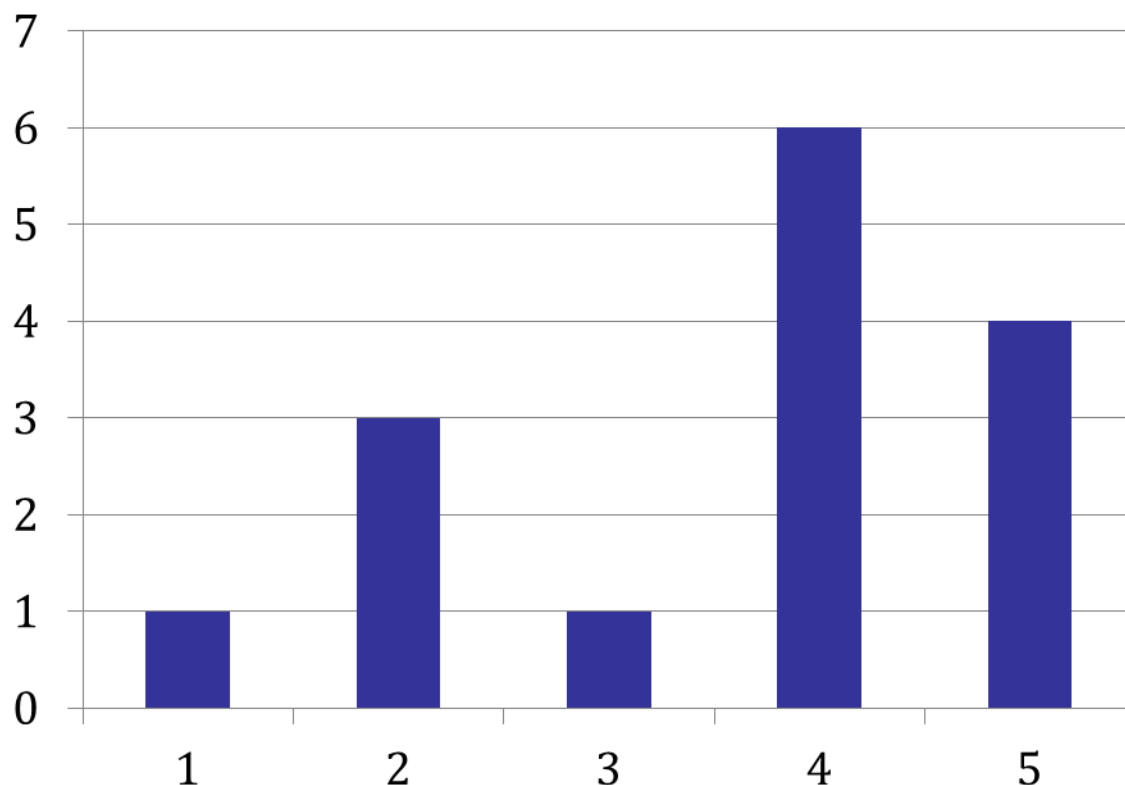


The responses indicate a heterogeneity of opinions across review divisions

Supplemental NDA/BLA application for a new indication of a previously marketed product

Receptiveness

(1 = not receptive; 5 = very receptive)

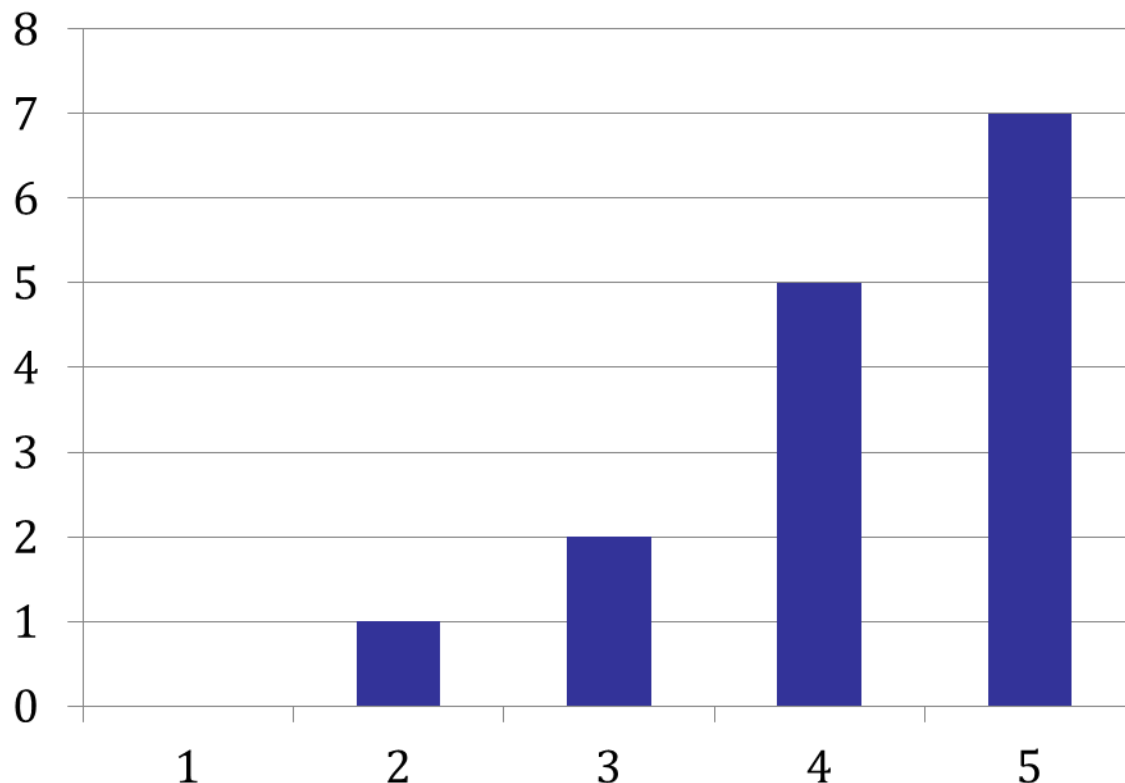


Some heterogeneity of opinions across review divisions persists in this context

Supplemental NDA/BLA application in support of a change in labeling other than a new indication

Receptiveness

(1 = not receptive; 5 = very receptive)

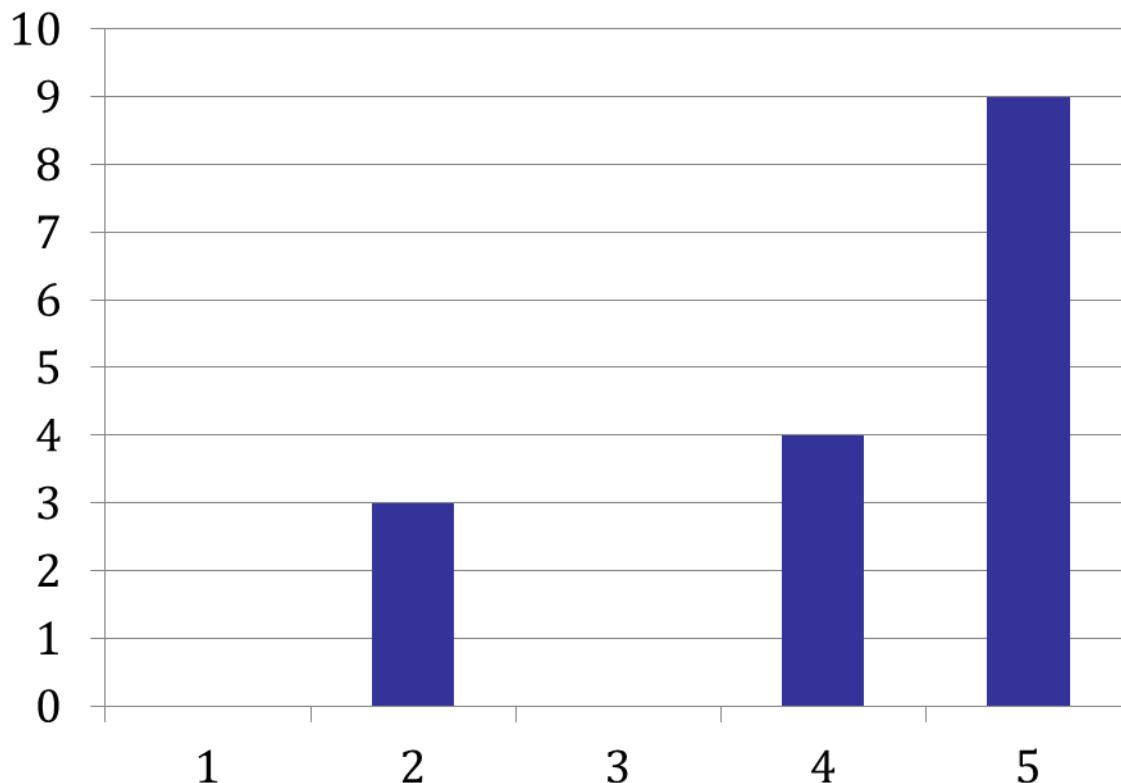


Majority of divisions indicate favorable view in this context

In response to a post-marketing requirement

Receptiveness

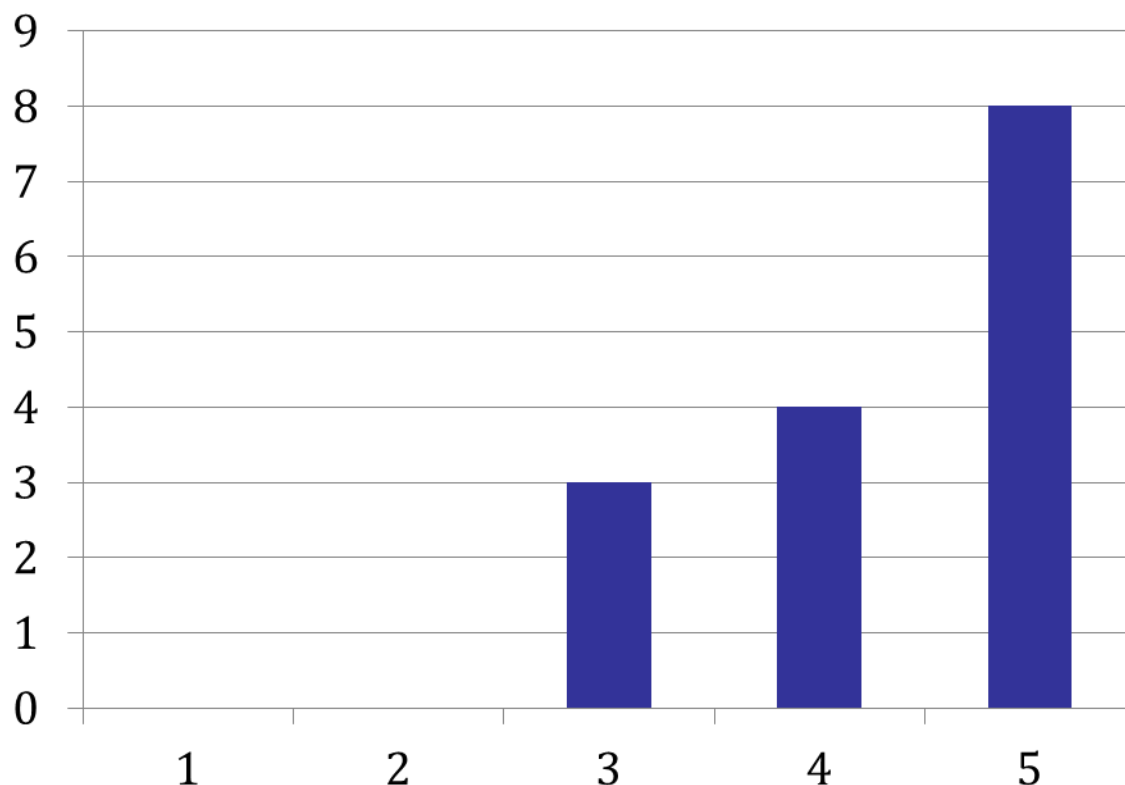
(1 = not receptive; 5 = very receptive)



Clear majority indicate favorable view in this context

To address an outstanding safety concern, not required by regulatory agency

Receptiveness
(1 = not receptive; 5 = very receptive)



Clear majority indicate favorable view in this context

Major Concerns of FDA Respondents Regarding Use of LSTs in Support of NDAs

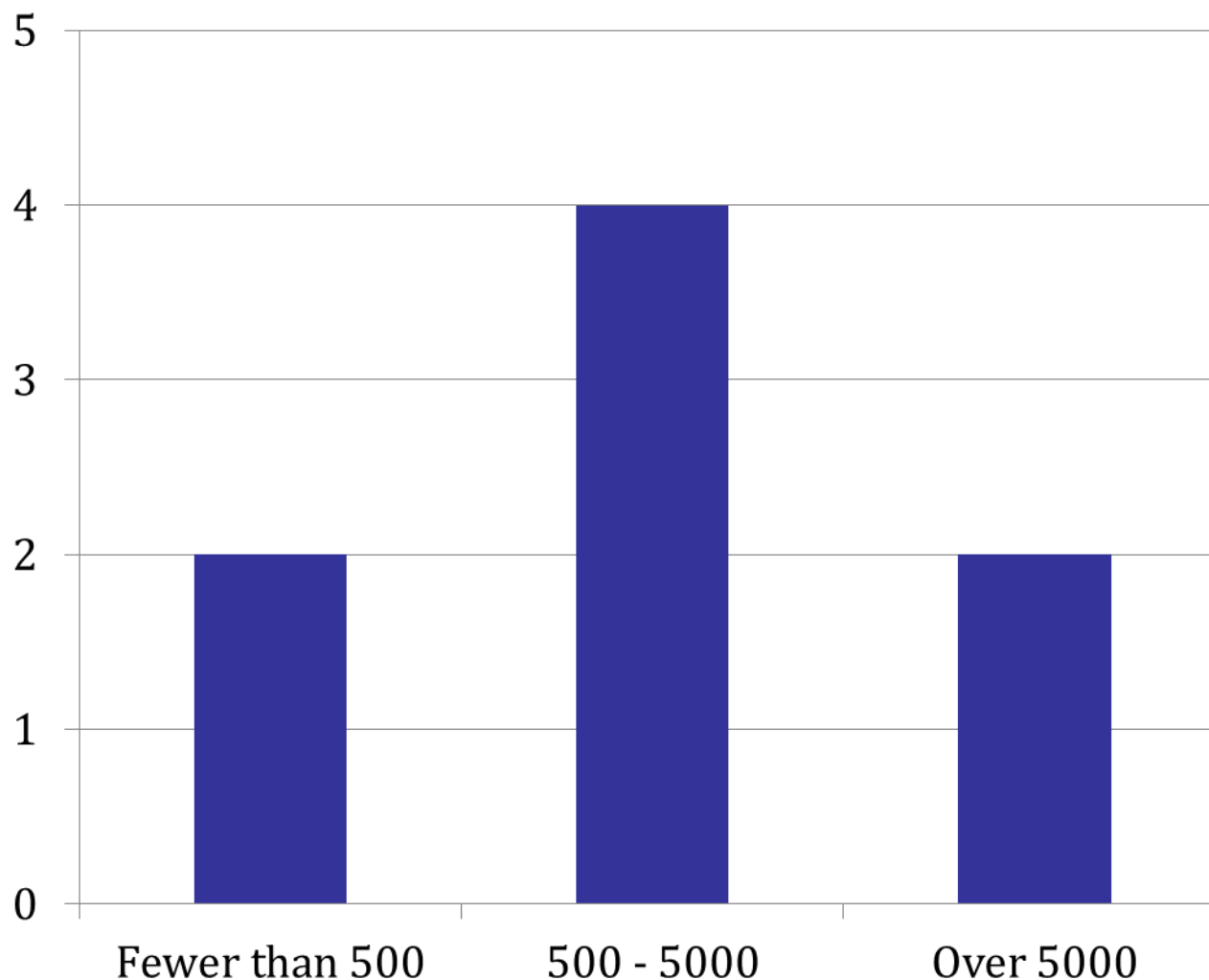
- 1) Possible need of more granular data to assess unanticipated safety signals
- 2) Continued need for granular data to further assess overall safety profile of the product
- 3) Feasibility of recruiting sufficient numbers of patients/investigators/sites in given therapeutic area

Policy Barriers to Use of LSTs in Support of NDA Applications Cited by FDA Respondents

- 10 of 15 indicated no policy barriers exist
- Two concrete examples of potential barriers provided by respondents included:
 1. Need to consider the possibility of an audit by the Office of Scientific Investigation during the design phase of an LST
 2. Concerns of individual reviewer/team

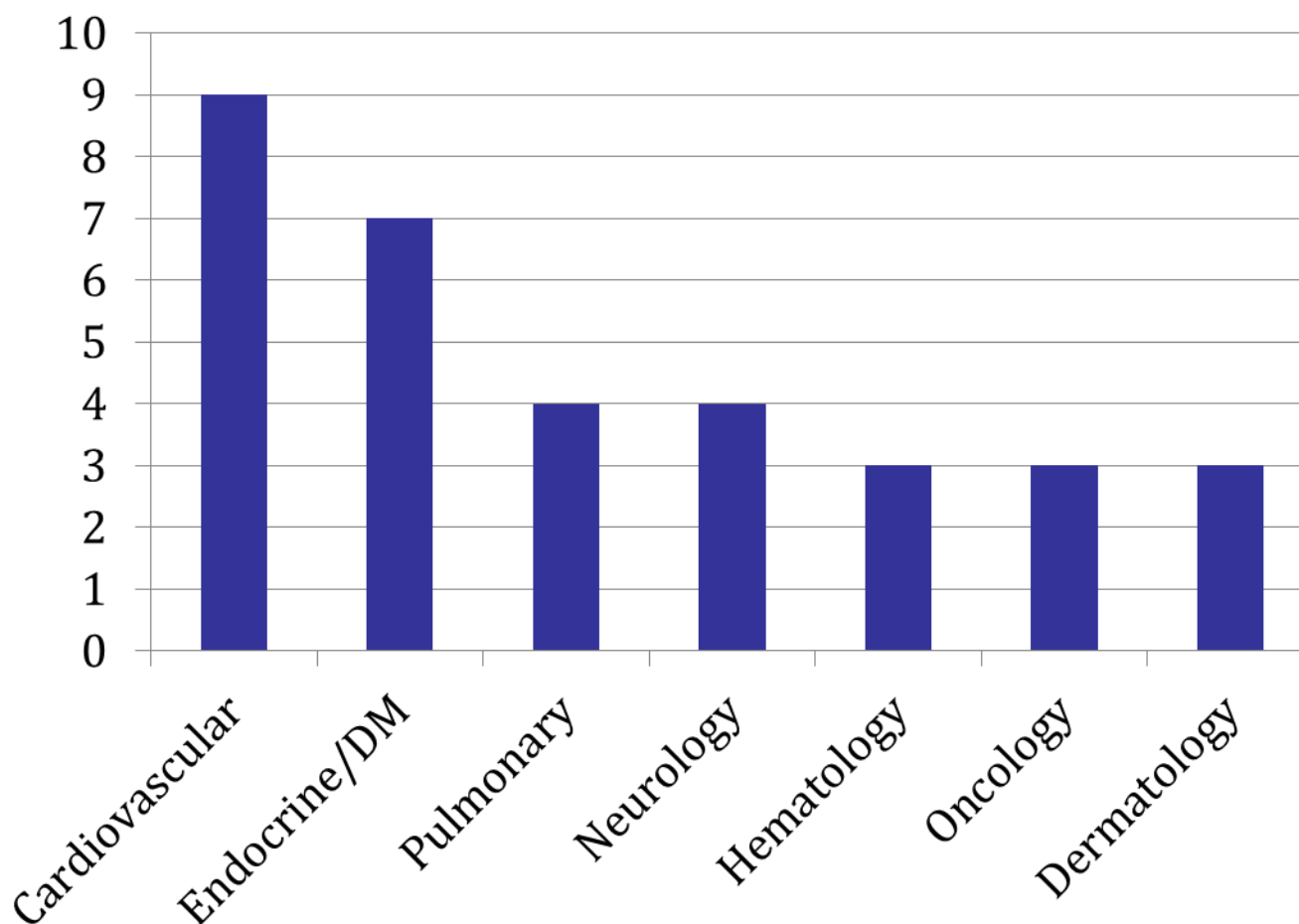
SELECTED DATA FROM INDUSTRY RESPONSES TO SURVEY

Demographics of Industry Respondents



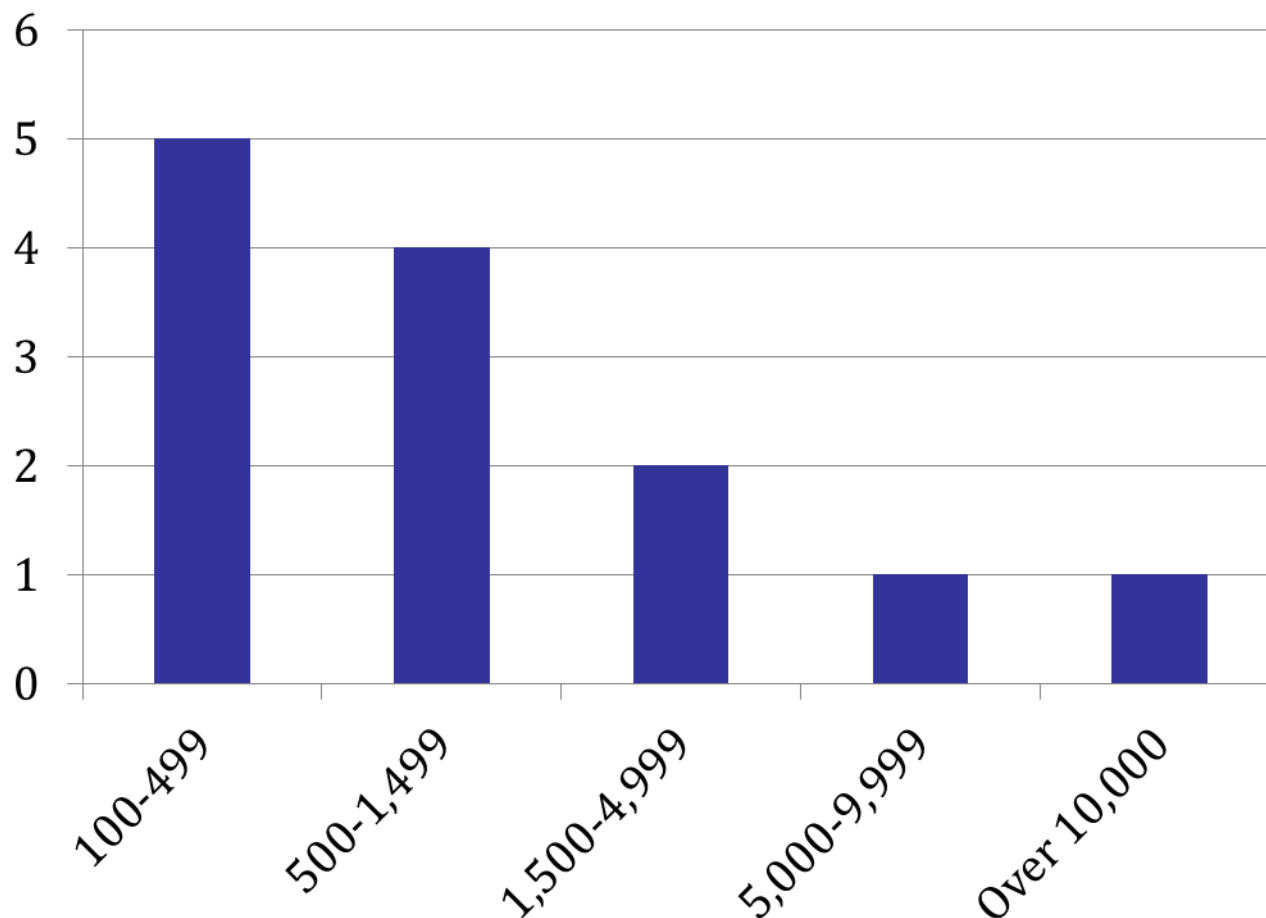
The survey captured data from 14 industry respondents, representing a range of small, mid-sized, and large pharmaceutical and biotech companies.

Therapeutic Areas Where Respondents Are Using or Developing LSTs



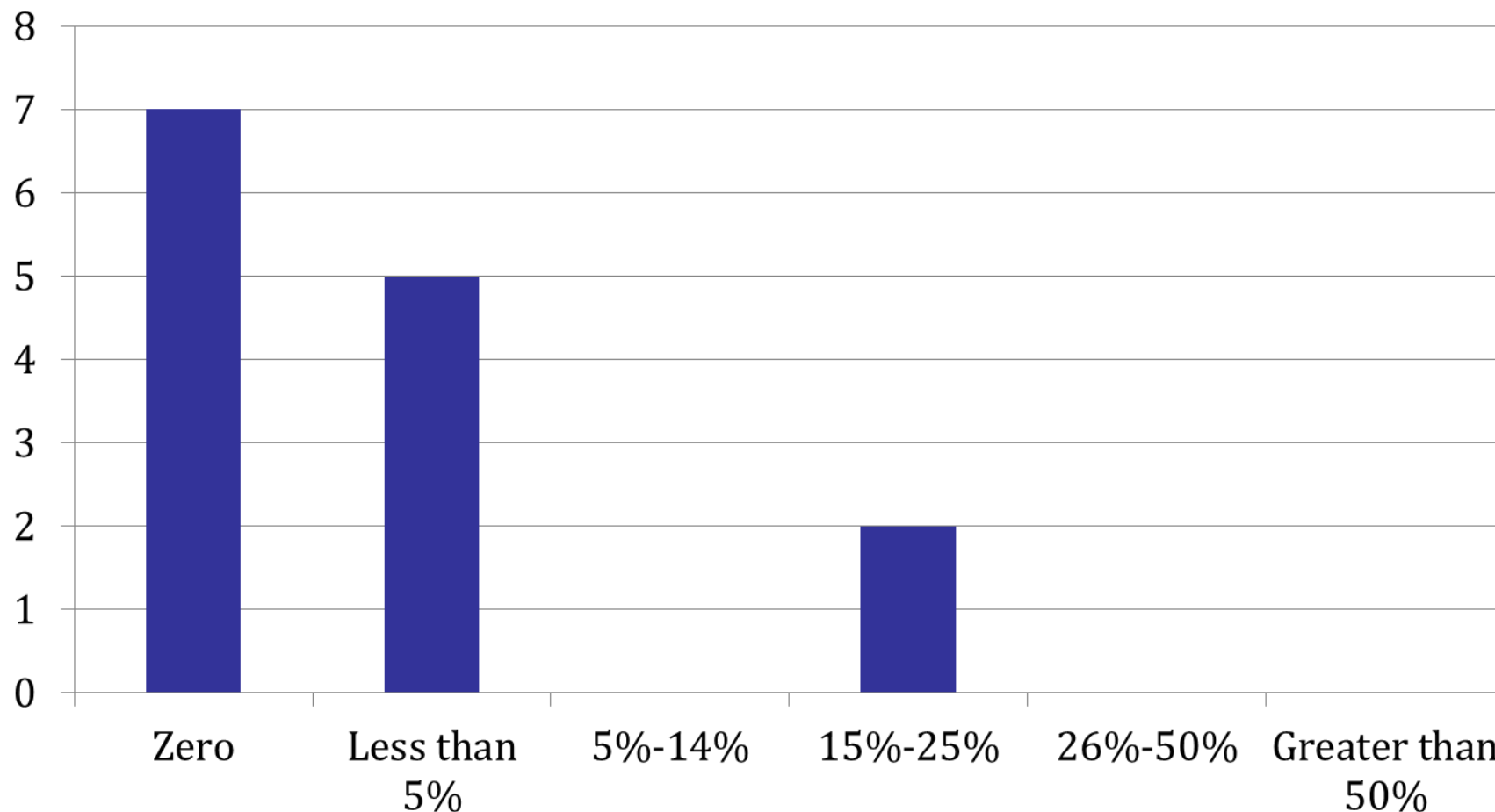
Several other therapeutic areas had two or fewer respondents reporting activity.

How many subjects does your typical trial enroll?

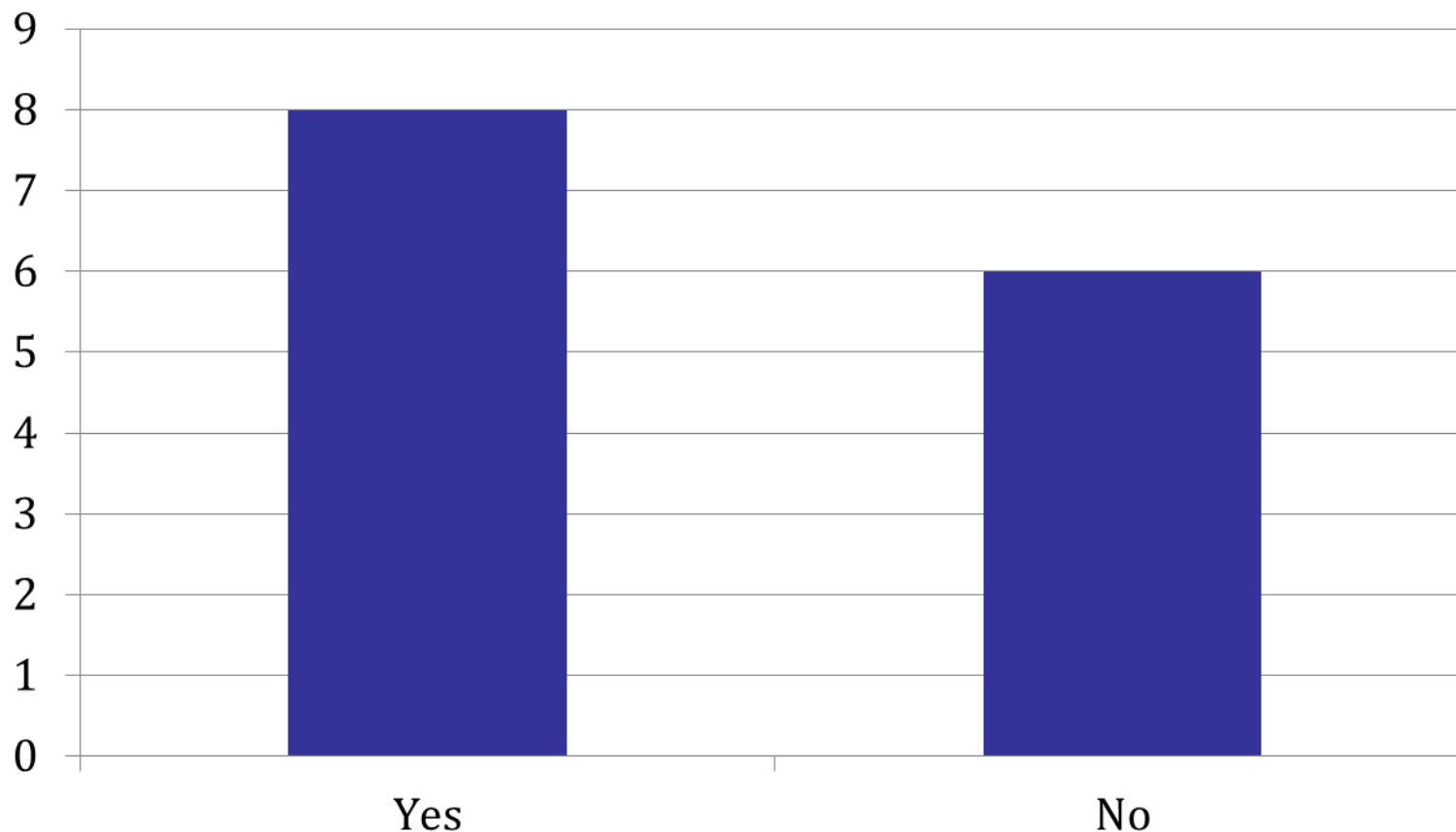


Although the respondents indicated that they primarily conducted Phase III pivotal trials, most also reported that the size of their typical trial was under 1,500 subjects.

What percentage of your organization's trials follow an LST design?



Have you ever started with an LST design and ended up with a large complex trial?



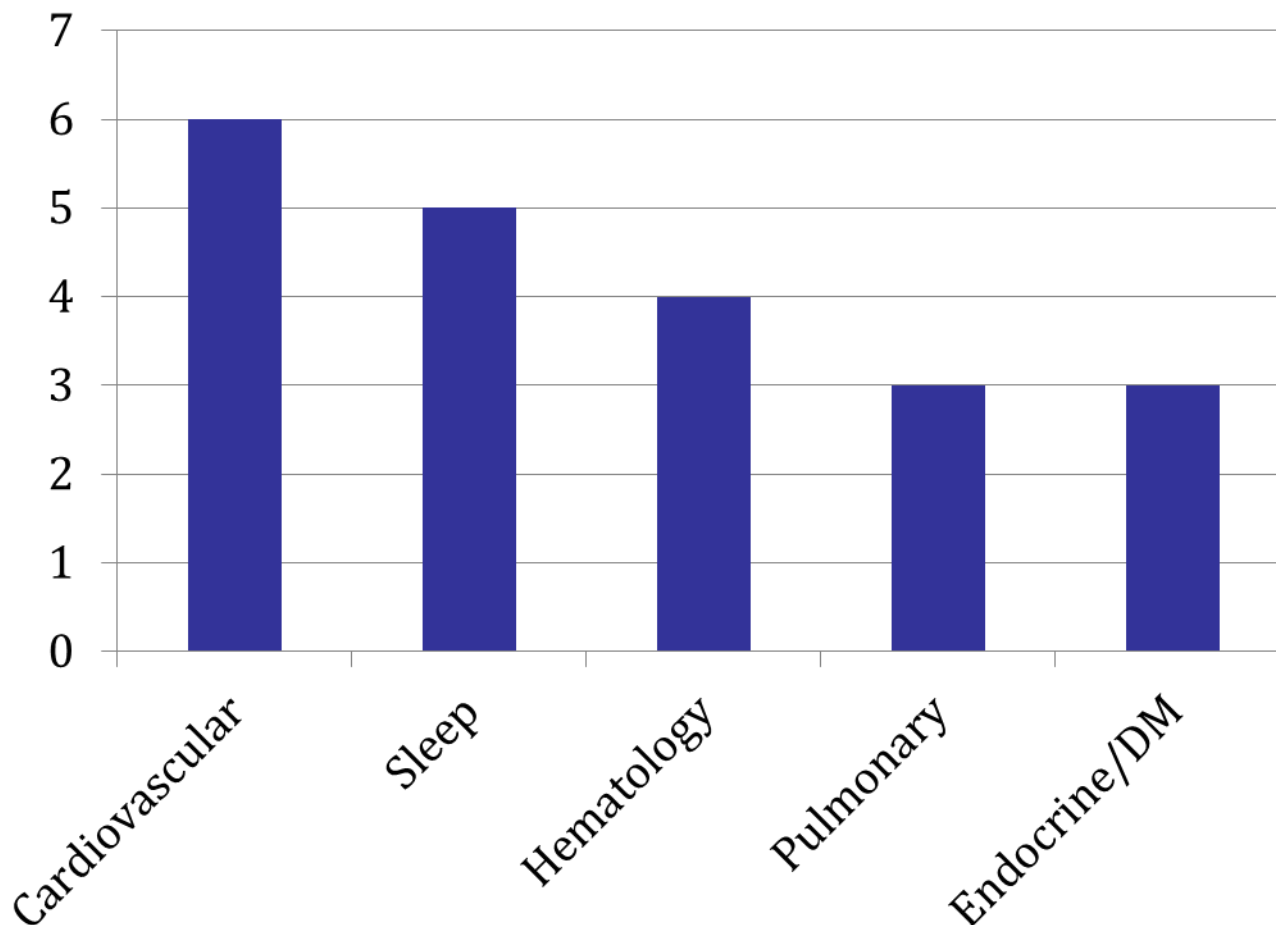
Summary of Industry Views and Concerns

- 13/14 Industry respondents reported that the regulatory goal of the trial was the most important criterion determining the design of a given trial.
- Most commonly reported drivers of complexity were fear that regulators would ask for more granular data after completion of trial and fear of negative audit findings
- Other barriers cited to conducting LSTs included 1) a lack of experience and 2) a belief that current regulations and guidances prohibit [e.g., “need to intensely monitor and report all adverse events (even if minor and understood)”]

Responses imply that views and actions of regulators impact significantly on willingness to perform LSTs

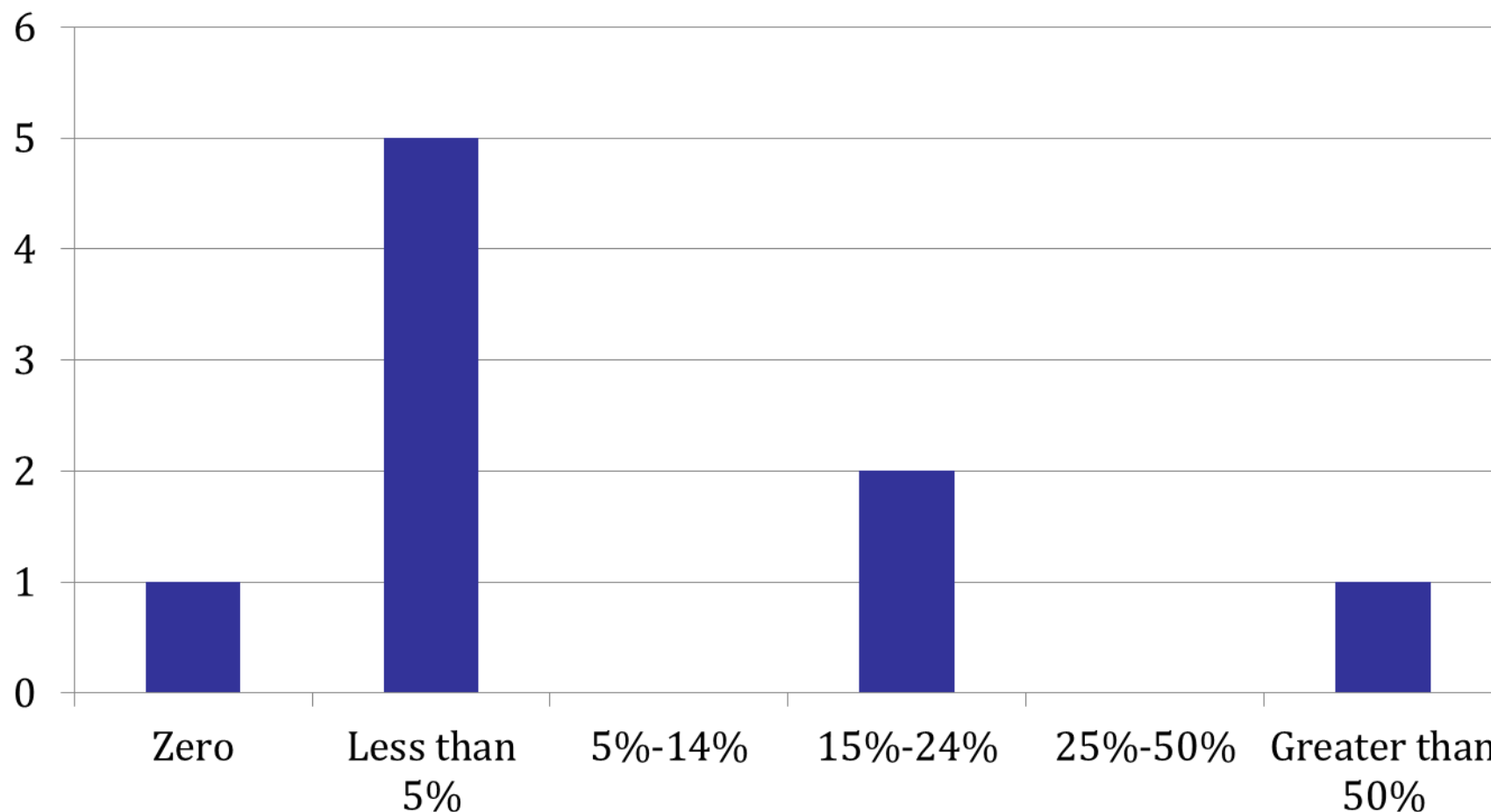
SELECTED DATA FROM NIH RESPONSES TO SURVEY

Therapeutic Areas Where NIH Respondents Are Using or Developing LSTs

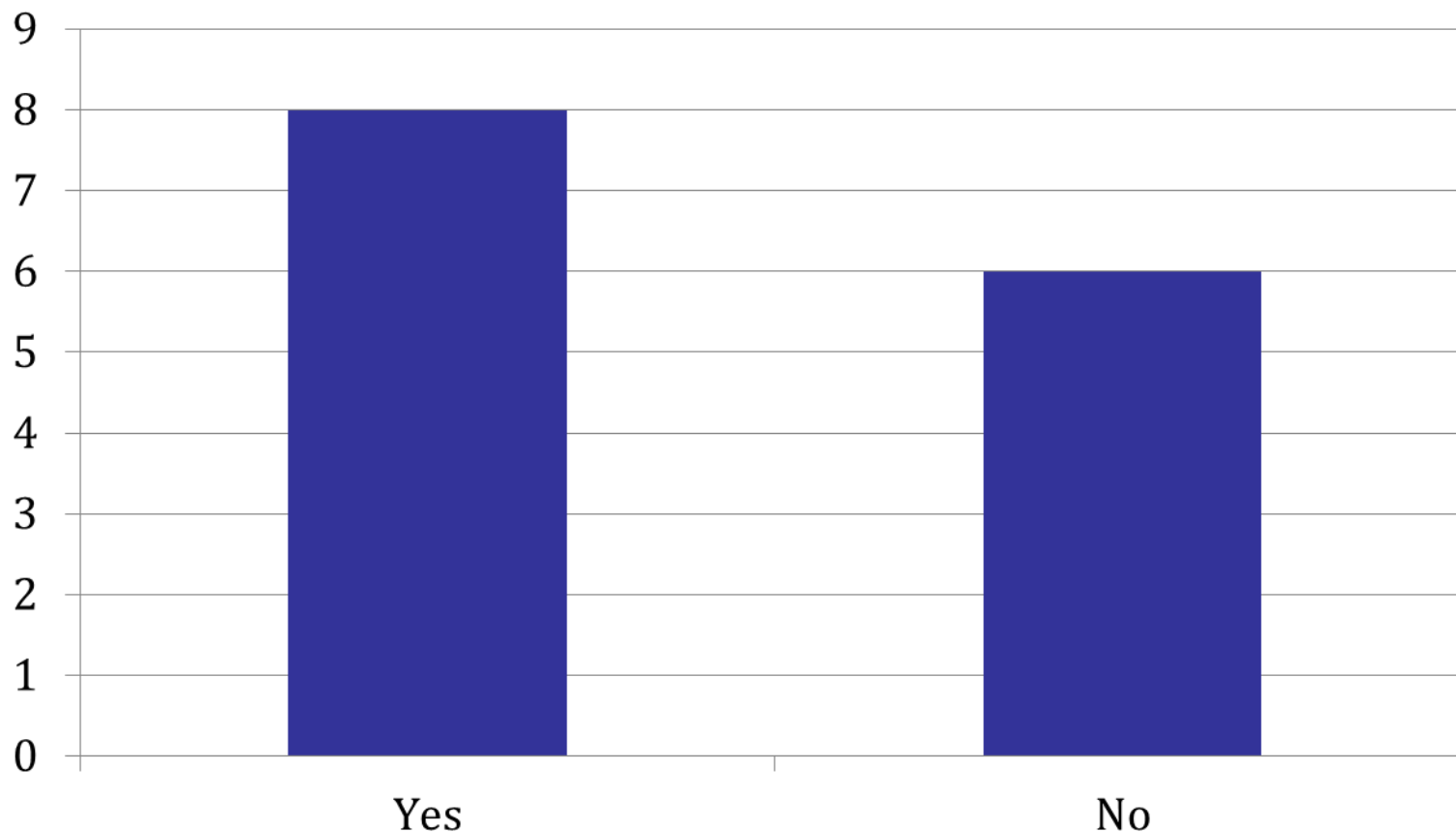


Several other therapeutic areas had two or fewer respondents reporting activity.

What percentage of your organization's trials follow an LST design?



Have you ever started with an LST design and ended up with a large complex trial?

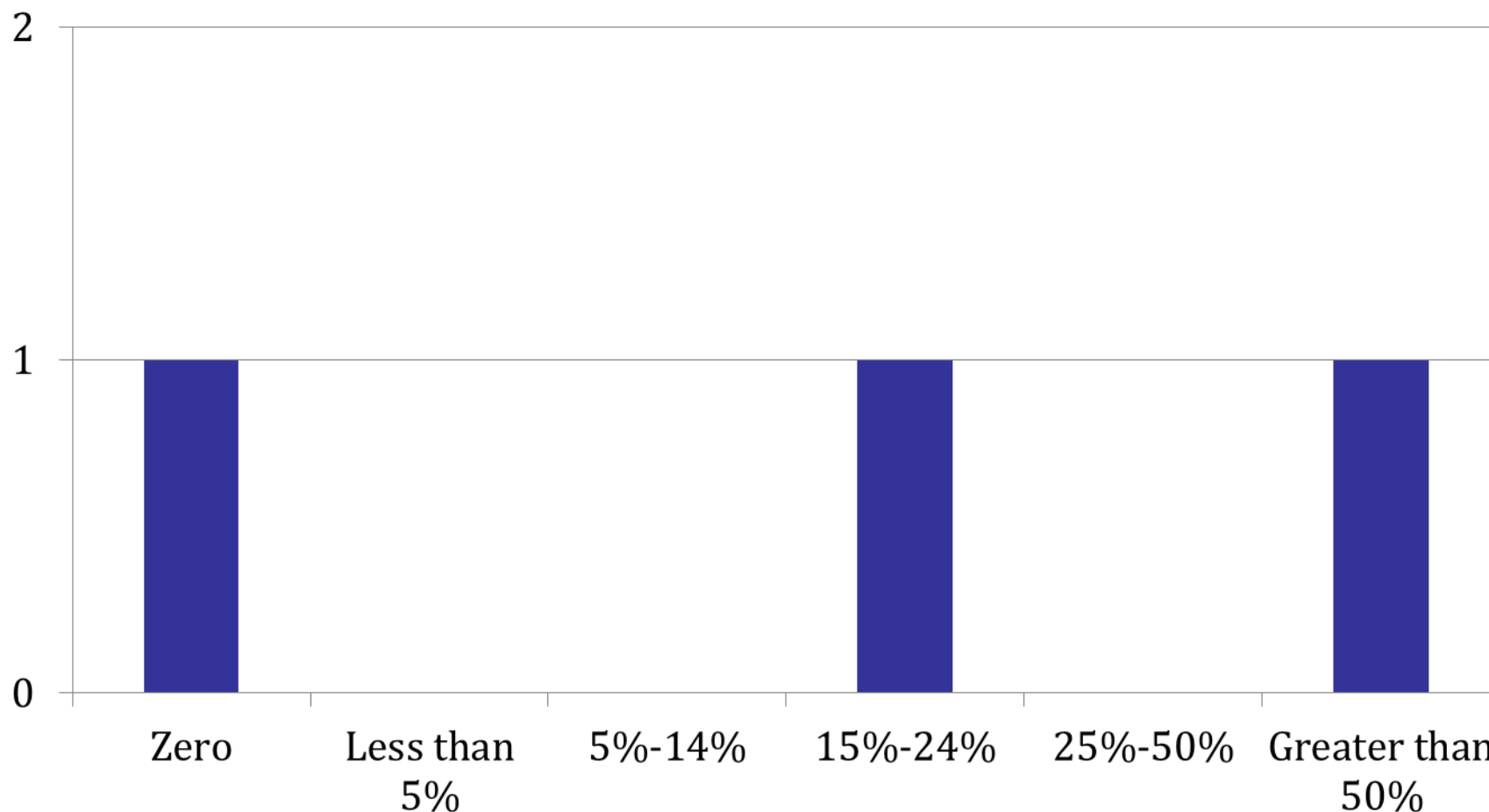


Summary of NIH Views and Concerns

- NIH respondents reported that money was the most important criterion determining the design of a given trial.
- Most commonly reported drivers of complexity were the demands of key opinion leaders. Regulatory concerns did not appear to have significant impact on this issue.
- The survey responses consistently cite NIH culture as the primary barrier to its funding of LSTs: NIH favors studies that generate mechanistic data and support the development of many new hypotheses/papers. The sense that the mission of NIH may have more to do with advancing basic science than addressing public health may limit the support of funding for LST designs.

SELECTED DATA FROM VA RESPONSES TO SURVEY

What percentage of your organization's trials follow an LST design?

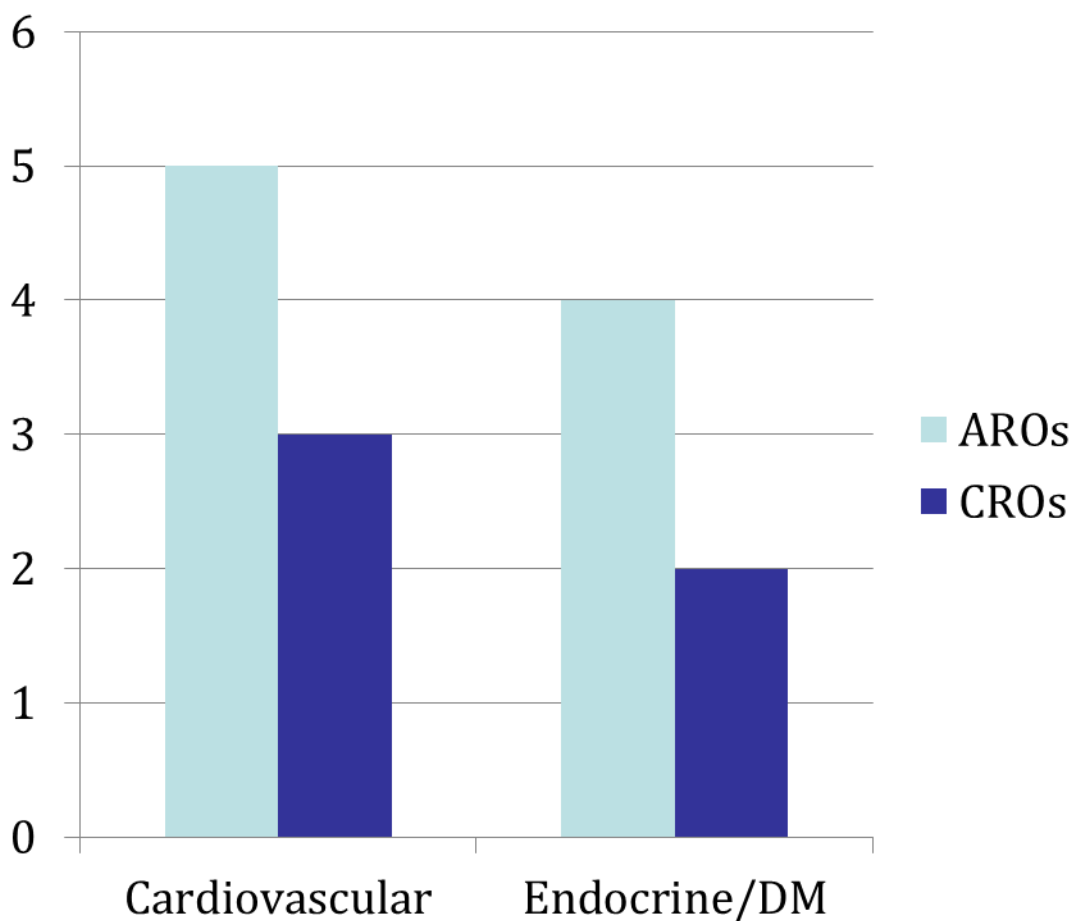


Summary of VA Views and Concerns

- VA respondents reported unanimously that money was the most important criterion determining the design of a given trial.
- Unanimously they indicated that VA performs LSTs as practice-based studies to inform practicing clinicians
- Regulatory concerns did not appear to impact significantly on decisions regarding study design

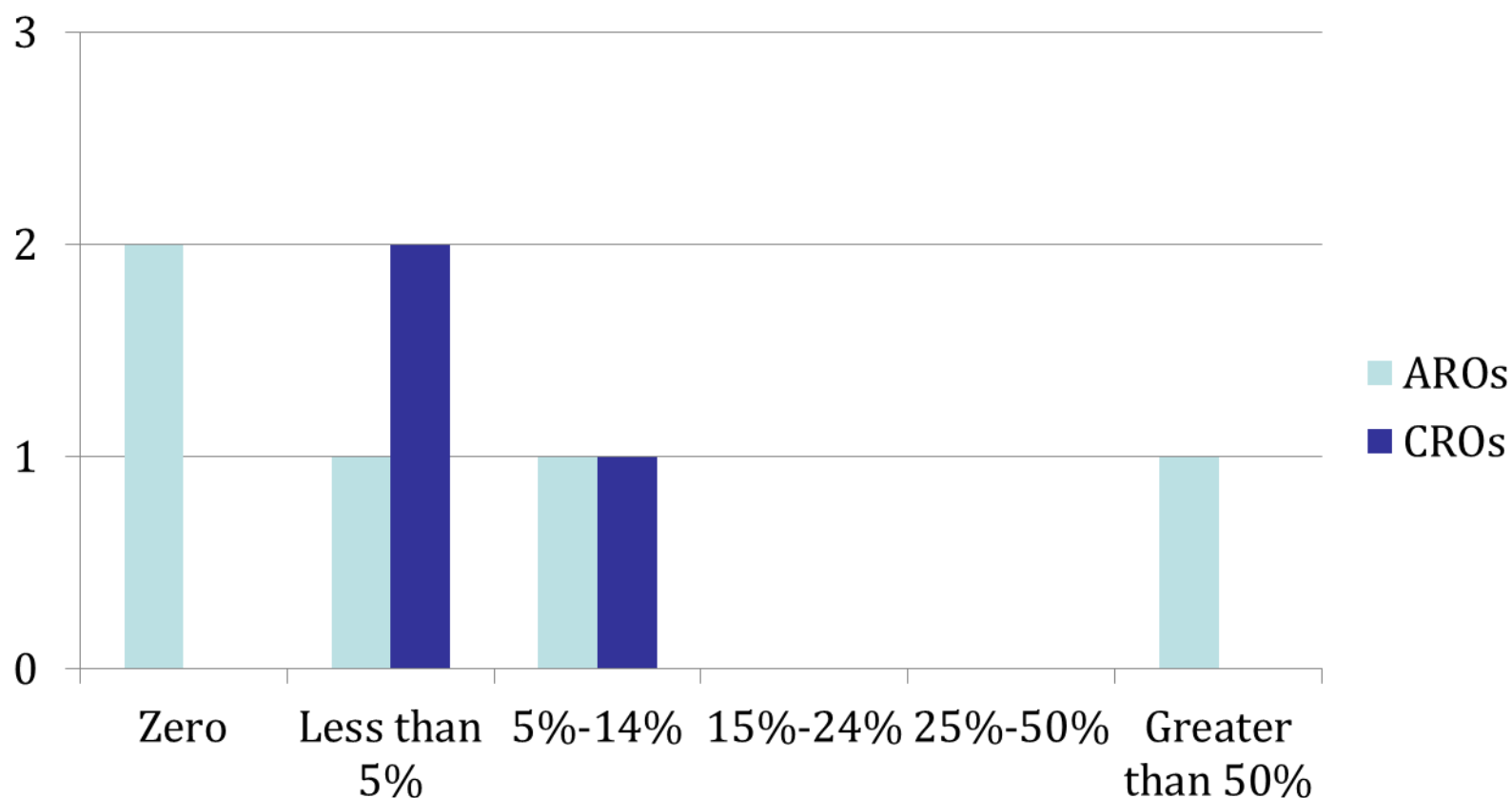
SELECTED DATA FROM ACADEMIC AND CONTRACT RESEARCH ORGANIZATION RESPONSES TO SURVEY

Therapeutic Areas Where AROs and CROs Respondents Are Using or Developing LSTs



Several other therapeutic areas had two or fewer respondents reporting activity.

What percentage of your organization's trials follow and LST design?



Overall Summary of Findings from Survey

- At present, neither industry nor government sponsors are dedicating a large percentage of available research resources to conduct LSTs
- Heterogeneous views exist within OND with regards to usefulness of data from LSTs for supporting applications for original approvals or new indications, though most divisions believed such data could support other new labeling and address safety concerns (including PMRs).
- FDA and industry share the concern that LSTs have a risk of regulators wanting more granular data after a trial is completed.

Overall Summary of Findings from Survey (2)

- Industry appears willing to support those trial designs that will allow them to achieve their regulatory goals
- NIH has historically had a preference for funding research that generate lots of mechanistic data rather than research intended to answer a focused question
- Particularly with regards to research conducted by NIH and AROs, key opinion leaders can represent an additional important driver of complexity
- Cardiovascular and Endocrine/DM are commonly selected therapeutic areas for LSTs. Unclear whether this reflects a particular suitability or whether this is a cultural artifact.

What are the opportunities to facilitate the research that patients and practitioners want?

- While the missions of NIH, industry, and FDA are not perfectly aligned with that of a learning healthcare system, are there any action items that could facilitate the conduct of patient-focused research?
- Do the guidances described by Dr Kweder address any of the important barriers? Could guidances addressing any other issues help?
- Can NIH accommodate both basic science and practice-focused research?
- What is the role of PCORI?

