Why are there not more Bayesian Clinical Trials? Results from a Survey of Clinicians in the Clinical Trial Community.

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BSWG KOL Lecture

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Disclaimer

This presentation reflects the views of the BSWG medical outreach team and should not be construed to represent the views or policies of the FDA or other associations.

BSWG Medical Outreach

- Bayesian Scientific Working Group, Medical Outreach team
  - Objective: enhance understanding of Bayesian methods with the vision to ensure that Bayesian methods are well-understood and utilized where appropriate for design and analysis throughout the medical product development process

- Diverse group of individuals from academia, industry, and regulatory authorities.

Bayesian Survey

- Audience: Medical Researchers (non-statisticians)

- Survey objectives included determining:
  - Biggest perceived barriers to implementing Bayesian methods
  - Preferences for increased comfort in using Bayesian methods
  - Audience interpretation of frequentist results
  - Audience interpretation of Bayesian results

TIRS Special Section on Bayesian Clinical Trials

- Results and recommendations written in in two articles
  - Perceived Barriers and Preferences for increased comfort with Bayesian methods
  - Interpretation of classical and Bayesian statistics among medical researchers

- Survey results were published as part of a special Bayesian series
  - May 2023 edition of the *Therapeutic Innovation & Regulatory Science* journal

- Collection of six articles
  - Tutorial, regulatory articles, and rare diseases

Materials and Methods

- 22 question survey of medical researchers involved in clinical trials
  - Academia
  - Pharmaceutical companies
  - Clinical research organizations
  - Regulatory institutions
- Captured demographics, education background, perceived barriers and preferences for Bayesian methods, interpretation of classical and Bayesian analysis results
- 323 respondents (~1600 recipients)
- Limitation: Administered in Nov-Dec 2019, pre-COVID 19 restrictions

Demographics

	Overall (N=323)
Highest Degree	
Bachelors	2 (0.6%)
Masters	35 (10.8%)
MD, DO, MD/PhD	216 (66.9%)
PharmD	7 (2.2%)
PhD	62 (19.2%)
Missing	1 (0.3%)
Number of Years since degree completion	
Under 5 yrs	33 (10.2%)
5 to 10 yrs	58 (18.0%)
10 to 20 yrs	106 (32.8%)
20+ yrs	124 (38.4%)
Missing	2 (0.6%)
Organization	
Academic	38 (11.8%)
Clinical Research Org	96 (29.7%)
Medical Practice	19 (5.9%)
Pharma/HTA Development	108 (33.4%)
Regulatory	60 (18.6%)
Missing	2 (0.6%)
Work Role	
Academic	16 (5.0%)
Clinical Research Physician/Scientist	108 (33.4%)
Management	22 (6.8%)
Medical Monitor/Study Lead	98 (30.3%)
Medical Practice	15 (4.6%)
Regulatory Reviewer	54 (16.7%)
Other: Regulatory Manager	3 (0.9%)
Other	4 (1.2%)
Missing	3 (0.9%)
Has Previous Bayesian Training	
No training	137 (42.4%)
Has some training	186 (57.6%)
Comfortable Interpreting Bayes	
Comfortable Interpreting	27 (8.4%)
Little/No Comfort	183 (56.7%)
Some, but not interpreting	110 (34.1%)
Missing	3 (0.9%)

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Rank biggest barriers to your organization's accepting and implementing a Bayesian design or analysis as the primary approach to a clinical trial

1st The Bayesian approach is not applicable, and my organization sees no benefit

2nd Insufficient knowledge of Bayesian approaches

3rd Lack of clarity/guidance from regulators

4th Reluctance from my internal regulatory team

5th Reluctance from my internal statistical team

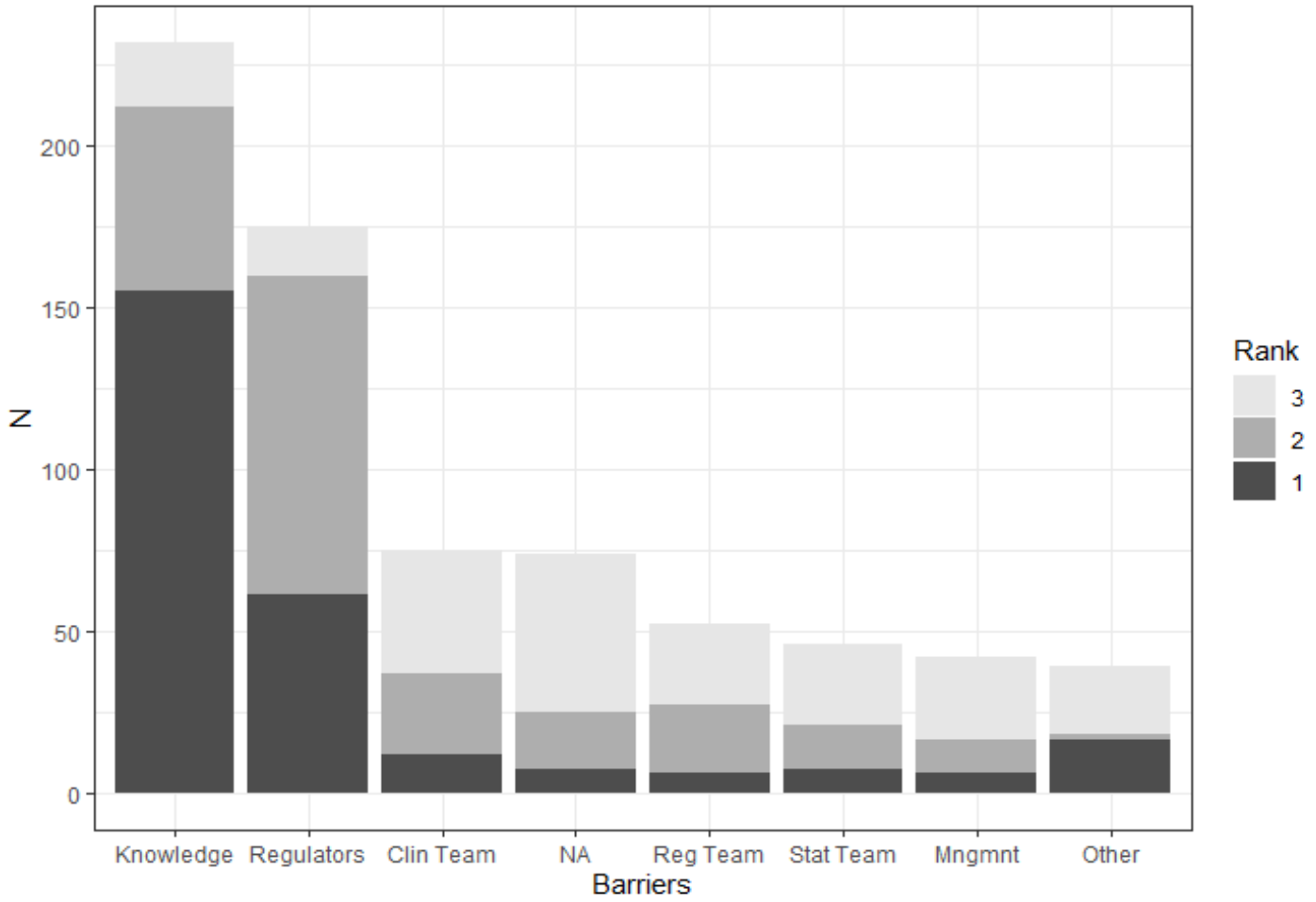
6th Reluctance from my internal clinical team

7th Reluctance from upper management

8th Other

Perceived Barriers (1)

1. **Knowledge**: Insufficient knowledge of Bayesian approaches
2. **Regulators**: Lack of clarity/guidance from regulators
3. **Clinical Team**: Reluctance from my internal clinical team
4. **NA**: The Bayesian approach is not applicable, and my organization sees no benefit
5. **Reg Team**: Reluctance from my internal regulatory team
6. **Stat Team**: Reluctance from my internal statistical team
7. **Mngmnt**: Reluctance from upper management
8. **Other**

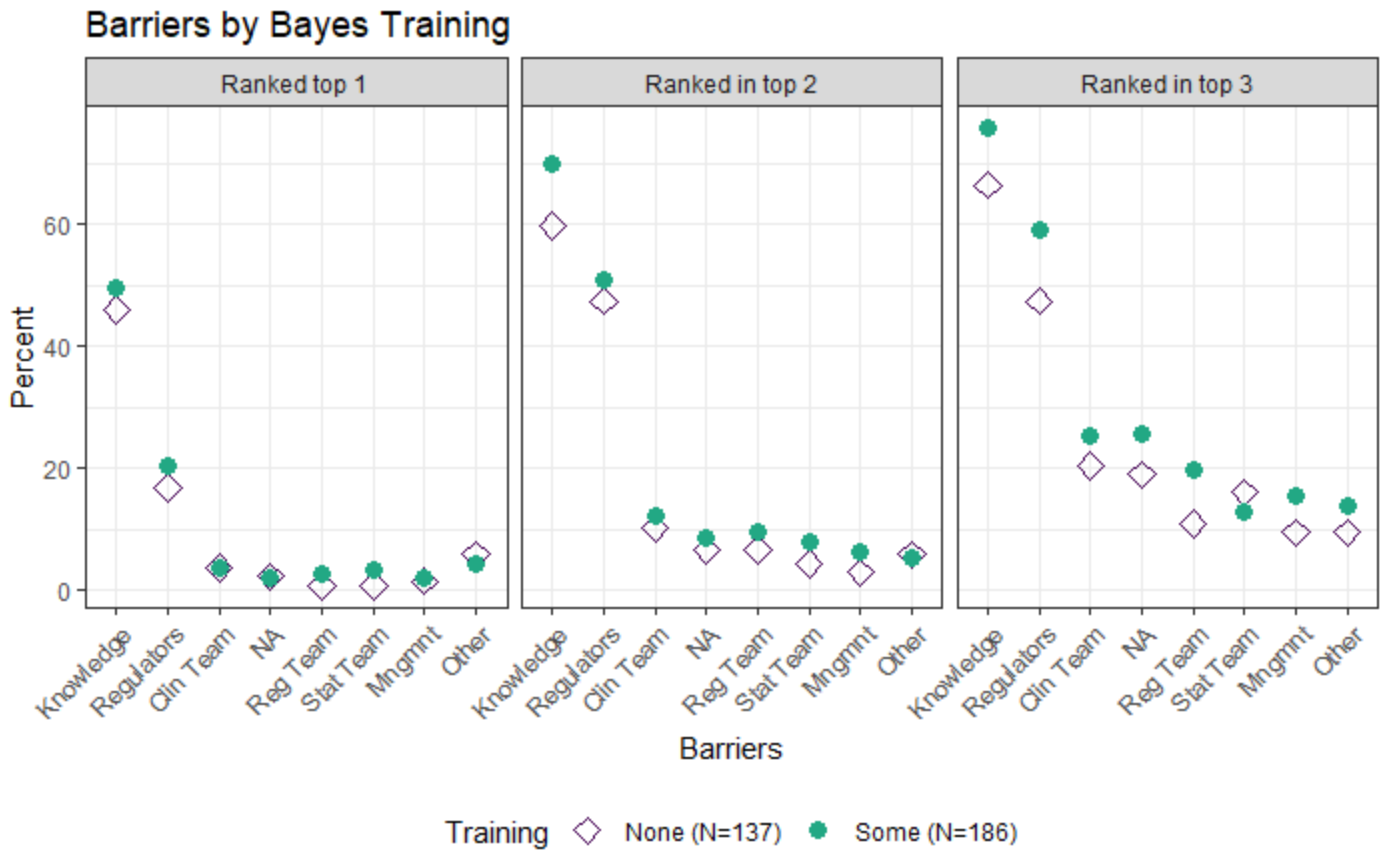


Perceived Barriers (2)

- Insufficient knowledge of Bayesian approaches for clinical trials was considered the top barrier
- A lack of regulatory guidance was a clear second
- Having previous Bayesian training made little difference in these perceived barriers
  - Could be indicative of insufficient Bayesian training currently available for medical researchers

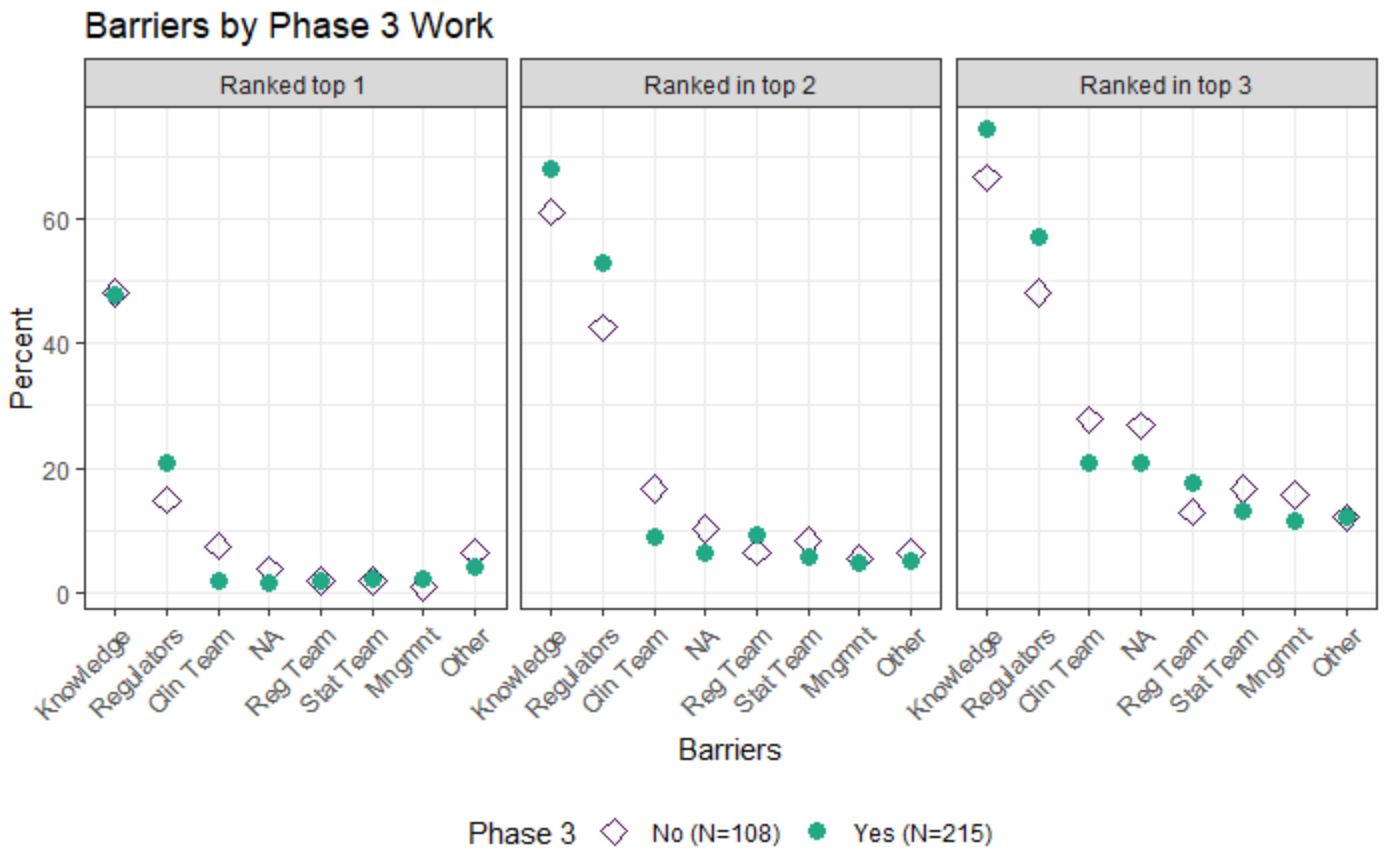
Perceived Barriers by Previous Bayesian Training

- Little difference in top-ranked perceived barriers
  - Those with no training were more likely to not rank the barriers
- Perceived lack of knowledge seemed less important amongst those with a graduate course in Bayesian methods



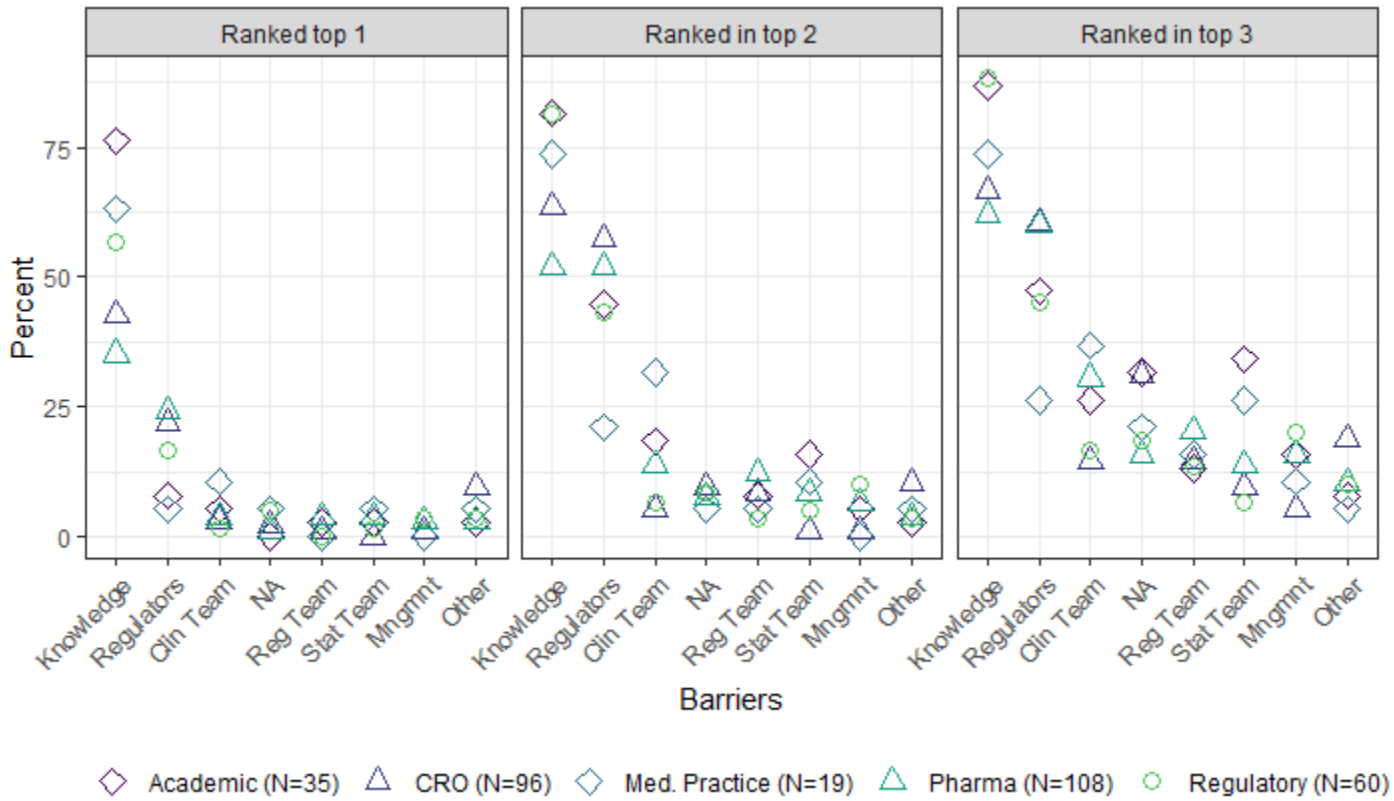
Perceived Barriers by Phase 3 Work

- Similar top ranked categories
- Those in Phase 3 have a slightly stronger perception of a regulatory barrier



Perceived Barriers by Work Organization

- Lack of knowledge top ranked for all organizations



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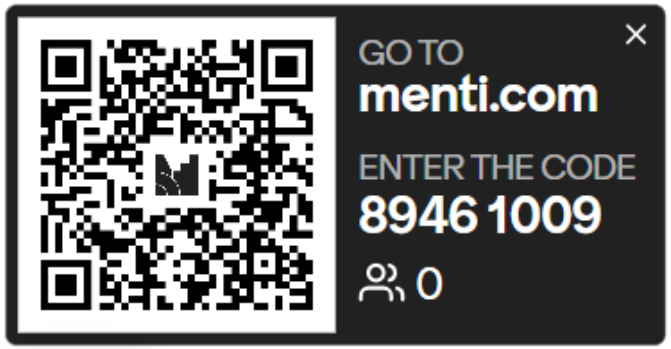
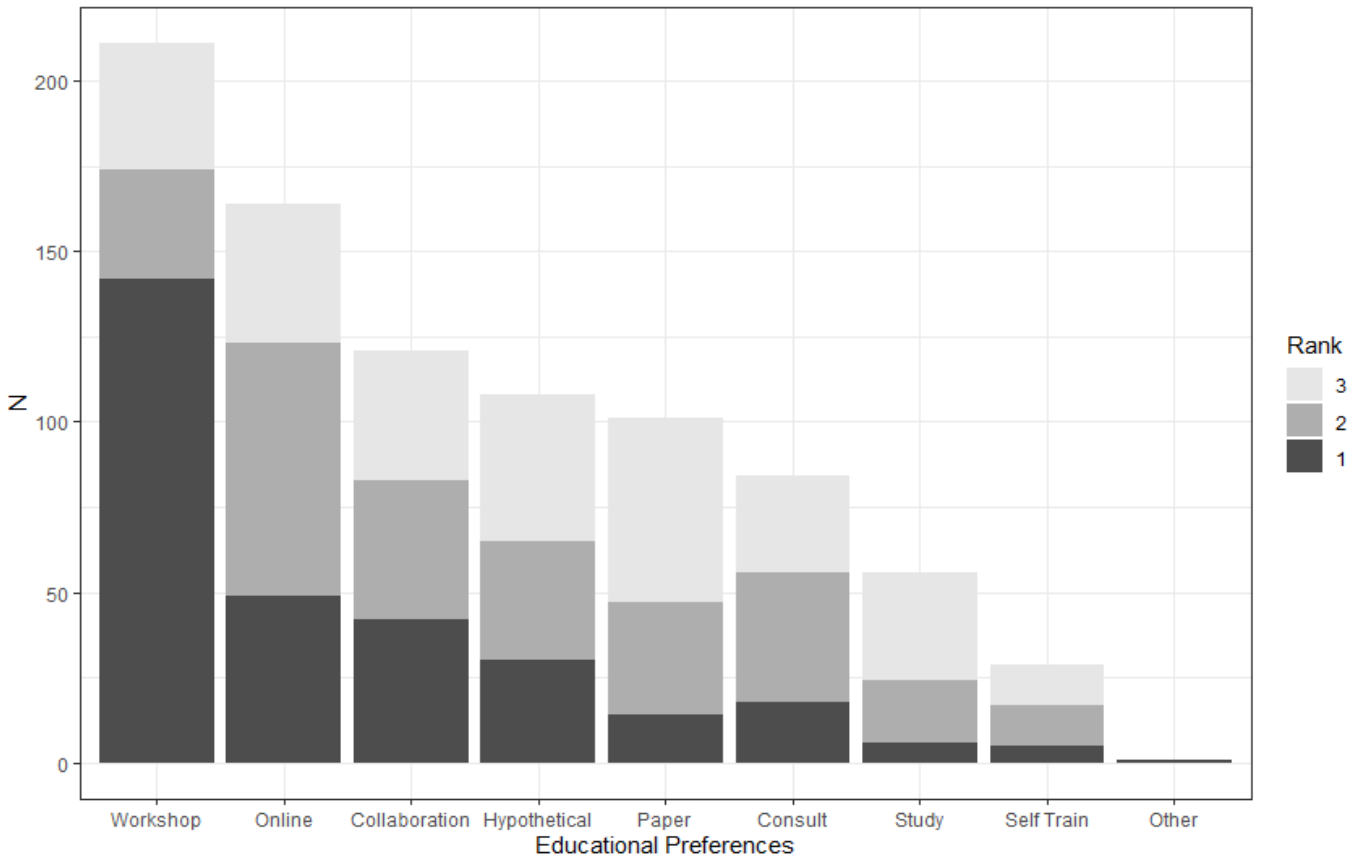
What would make you more comfortable using a Bayesian design and analysis on a primary objective in a clinical trial?



Increased Comfort with Bayesian Methods (1)

1. **Workshop**: In-person training at a workshop, conference or internal to my organization.
2. **Online**: Online training with Q&A (e.g., live webinar, online course), with slides and recording available
3. **Collaboration**: Close collaboration between the clinical statisticians and medical teams for a project
4. **Hypothetical**: Participating in the creating of a hypothetical study in which the primary analysis is Bayesian with guidance from an instructor
5. **Paper**: A white paper written for clinicians to better understand Bayesian methods
6. **Consult**: 1-1 consultation with Bayesian expert(s)
7. **Study**: Written case studies
8. **Self-Train**: Self-training via books/journals, etc
9. **Other**: write-in responses for this were generally along the lines of “regulatory acceptance”

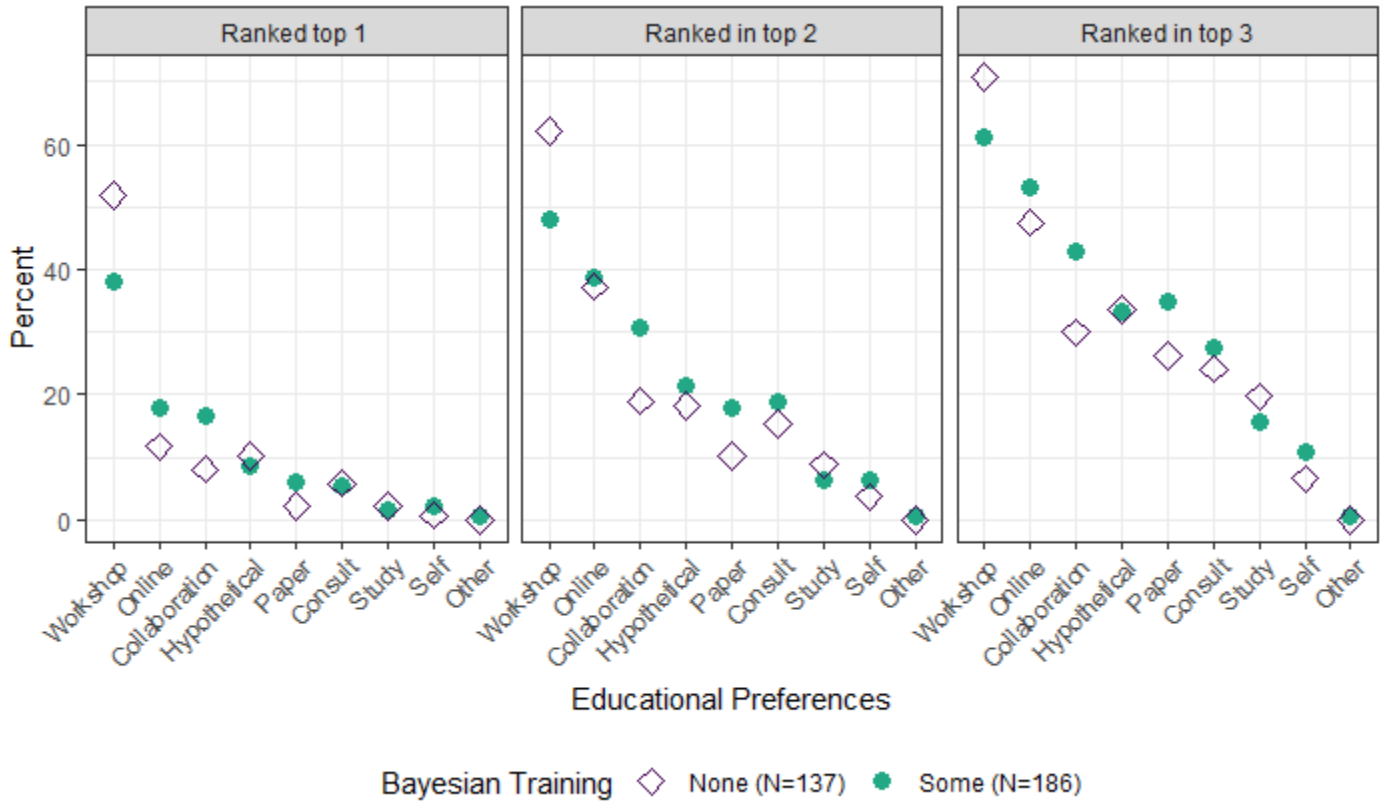


Increased Comfort with Bayesian Methods (2)

- In person training was the clear top choice
- Online training was the second preference
- Stronger preference for in-person workshops amongst those with no previous training
- Pre-COVID 19 → in-person preferences likely changed for some
  - In-person training was almost 3x higher than the next highest

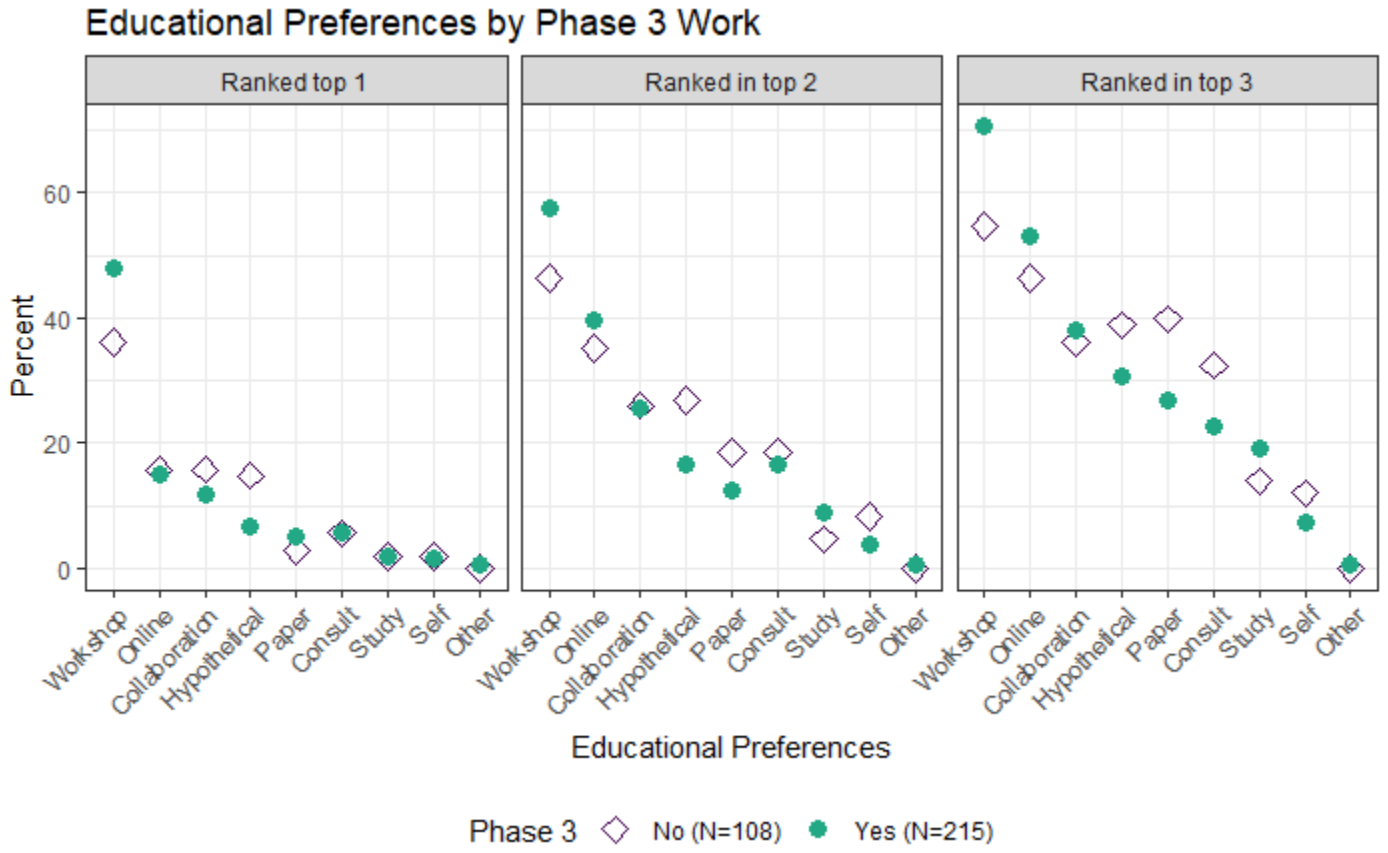
Educational Preferences by Previous Bayesian Training

- Preferences relatively unchanged by previous training
- Stronger preference for in-person workshops amongst those with no previous Bayesian training



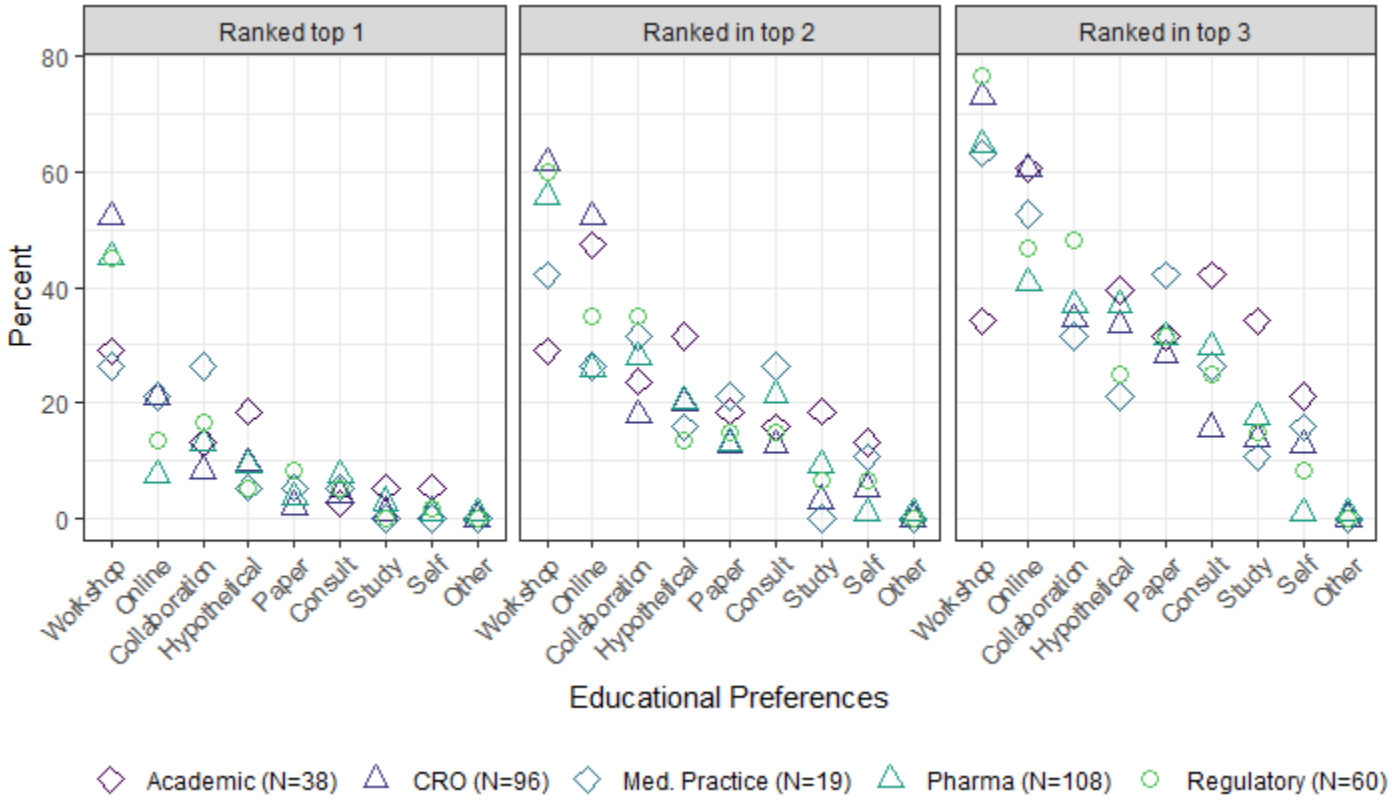
Educational Preferences by Phase 3 Work

- Preferences unchanged by Phase 3 work



Educational Preferences by Work Organization

- CROs, pharma, and regulatory had stronger preferences for workshops



Recommendations

- Need for education on Bayesian methods with guidance from competent authorities
- Introductory training for medical researchers presented through an in-person workshop that could also be broadcast online with live Q&A for those who prefer not to meet in person
- Stronger preferences for online training or a collaborative project among those with previous Bayesian training
  - Useful for higher level training that may assume some baseline understanding

Part 2: Interpretation and Preferences

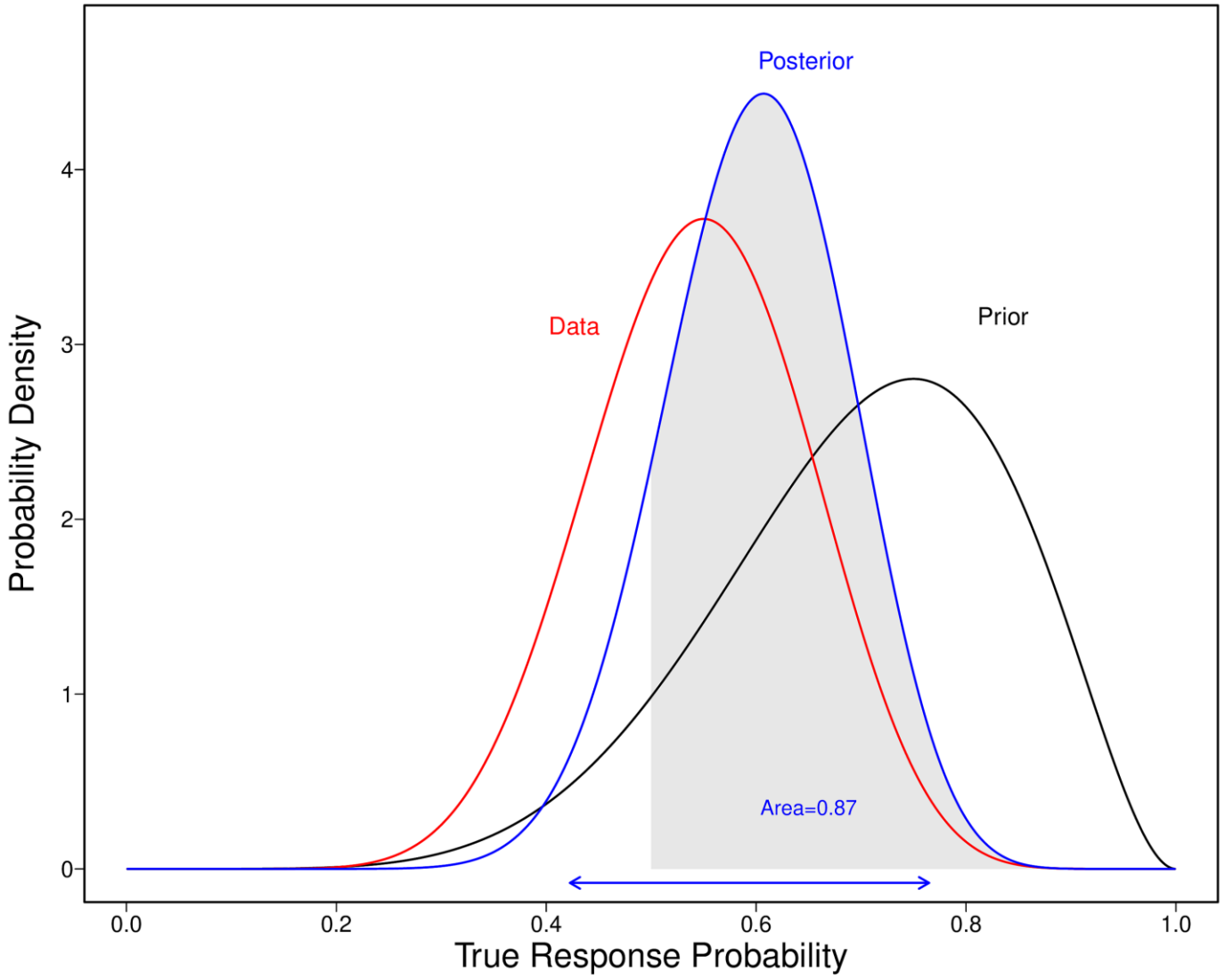
Statistical Interpretation and Preferences
Short Scenario

- Presentation of an example proof-of-concept (POC) clinical trial were presented along with the results of a prior single arm pilot study
  - Single Arm Study
    - 7 of 10 patients responded to treatment
  - POC Study
    - Sample size of 20 patients
    - Null Hypothesis: The response rate of the drug is ≤ 50%
    - 11 of 20 (55%) patients responded resulting in:
      - P-value = 0.41
      - Confidence Interval = (0.35, 1)

Statistical Interpretation and Preferences

Short Scenario

- Using the single arm study as the prior distribution, and the POC study as the new data produces the posterior distribution (all 3 distributions seen to the right)
- From the posterior we can get:
  - Area under the posterior curve > 0.5 = 0.87 (posterior probability)
  - 95% posterior credible interval for the response rate = (0.42, 0.76)



Statistical Interpretation and Preferences
Interpretation Questions

P-value
A. The probability that your drug has a response rate greater than 50% is 0.41
B. The probability that your drug has a response rate of 50% or less is 0.41
C. If the null is true, the probability of incorrectly rejecting the null is 0.41
D. **If the null is true and we repeat the study, the probability is 0.41 that at least 11 patients will respond**

Confidence Interval
A. 95% of the population will have a response rate between 0.35 and 1
B. There is a 95% probability that the true response rate is between 0.35 and 1
C. **If we repeated the study many times, the true proportion of responders would be contained in 95% of the confidence intervals produced**
D. In repeating the study, there's a 95% probability the sample response rate will be between 0.35 and 1

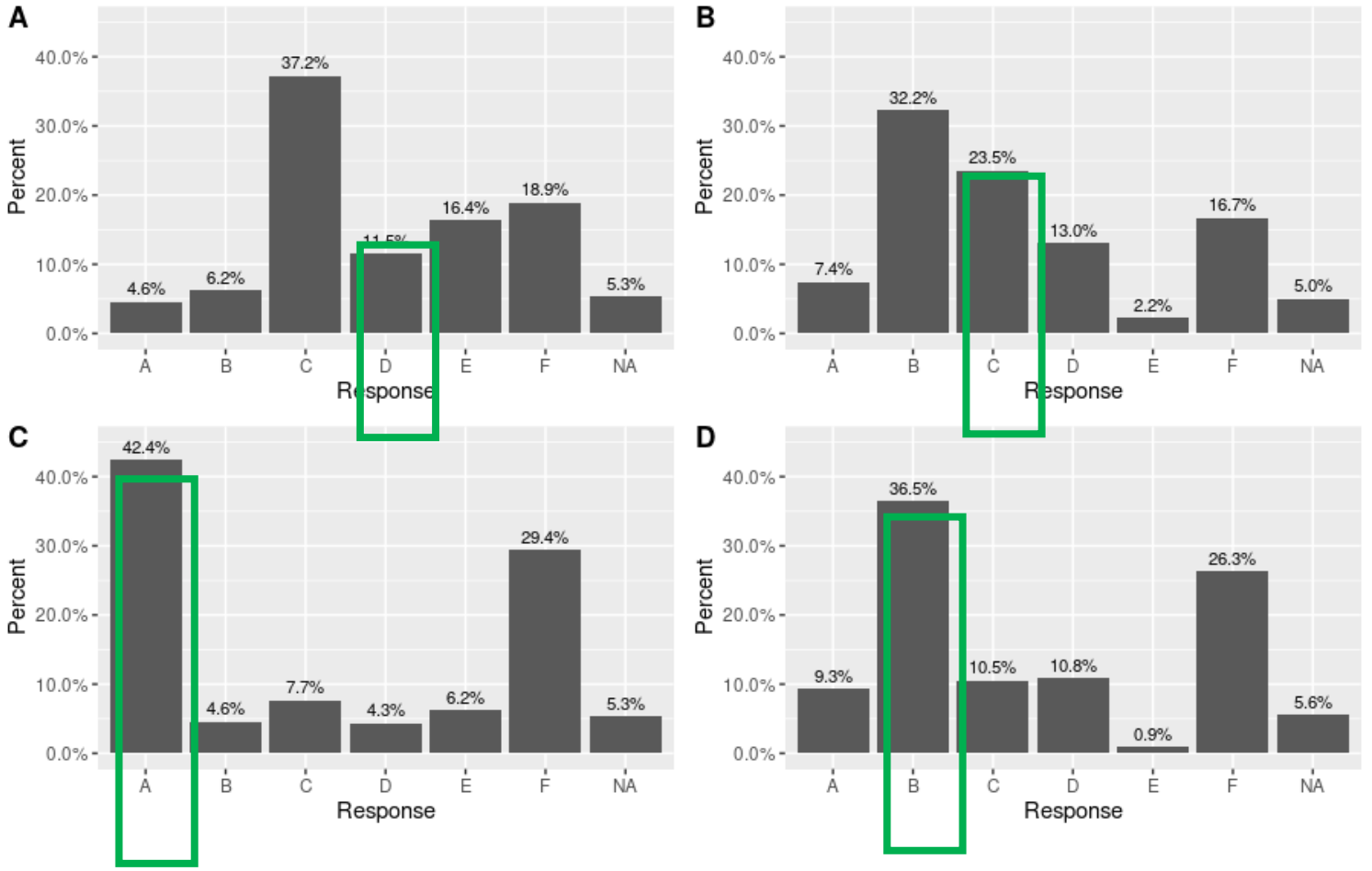
Posterior probability
A. **The probability that your drug has a response rate greater than 50% is 0.87**
B. The probability that your drug has a response rate of 50% or less is 0.87
C. If the null is true, the probability of incorrectly rejecting the null is 0.87
D. If the null is true and we repeat the study, the probability is 0.87 that at least 11 patients will respond

Credible Interval
A. 95% of the population will have a response rate between 0.42 and 0.76
B. **There is a 95% probability that the true response rate is between 0.42 and 0.76**
C. The true proportion of responders would be contained in 95% of the credible intervals produced in repeating the study
D. In repeating the study, there's a 95% probability the sample response rate will be between 0.42 and 0.76

The correct response is displayed in bold. For all questions, additional available responses are – E = None of the above; F = Choose not to answer; NA = Did not answer the question

Statistical Interpretation and Preferences

Interpretation Questions

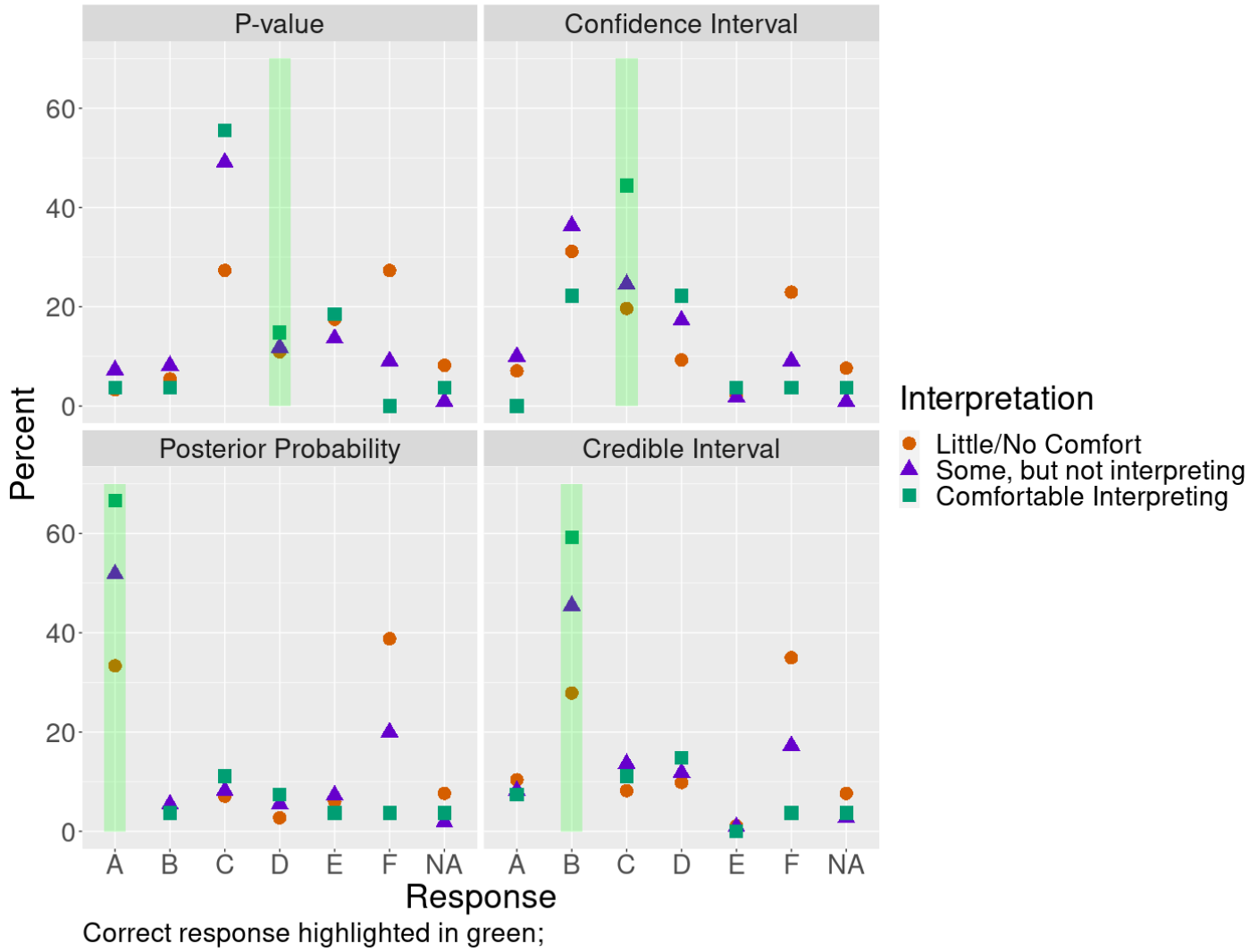


For all plots responses:
E = None of the Above
and
F = Choose not to answer

Plots - A = p-value; B = confidence interval; C = posterior probability; D = credible interval;

Statistical Interpretation and Preferences

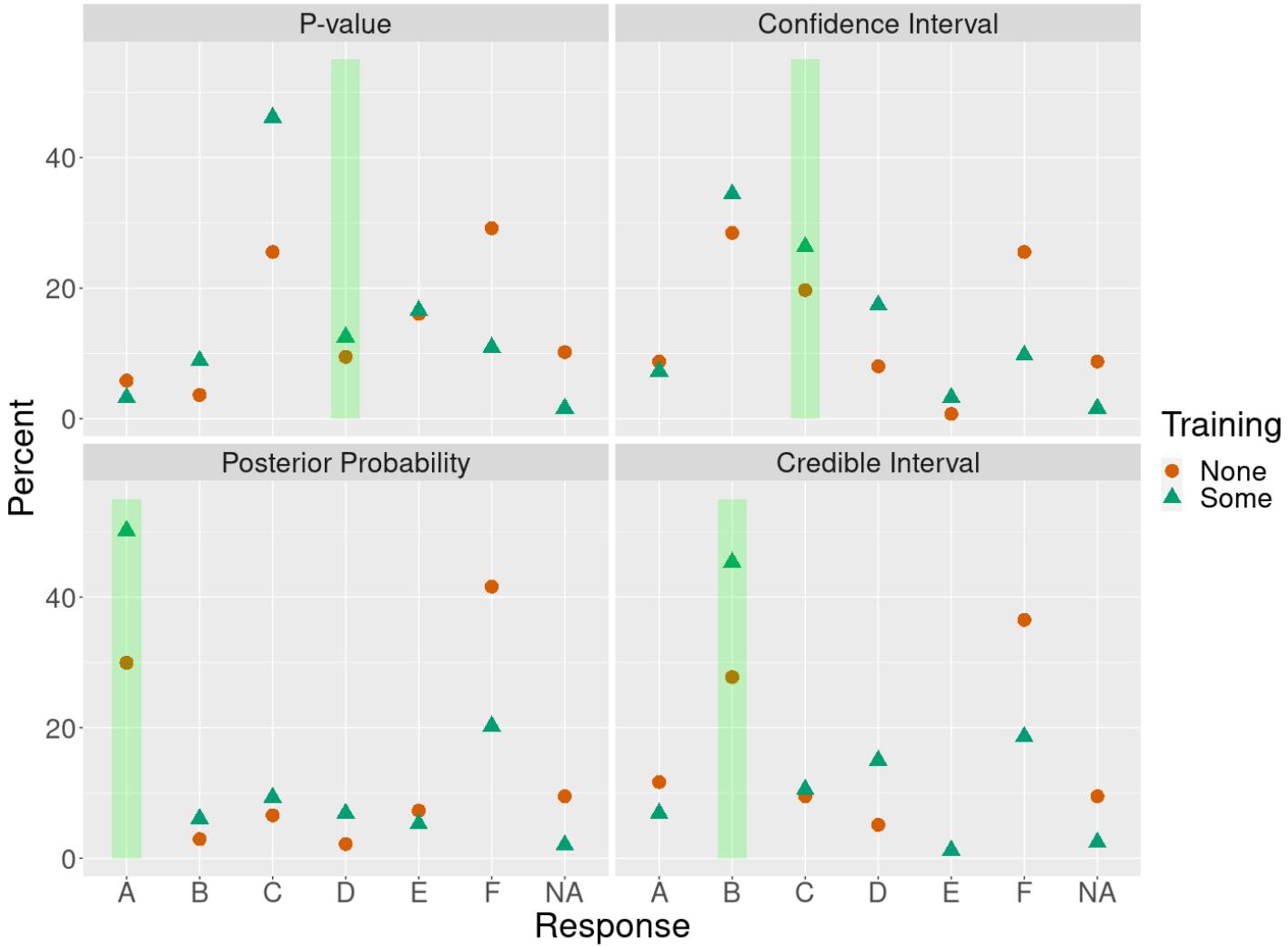
Responses to each question by the subgroup of comfort level interpreting Bayesian analyses



Correct response highlighted in green;

Statistical Interpretation and Preferences

Responses to each question by the subgroup of previous Bayesian training



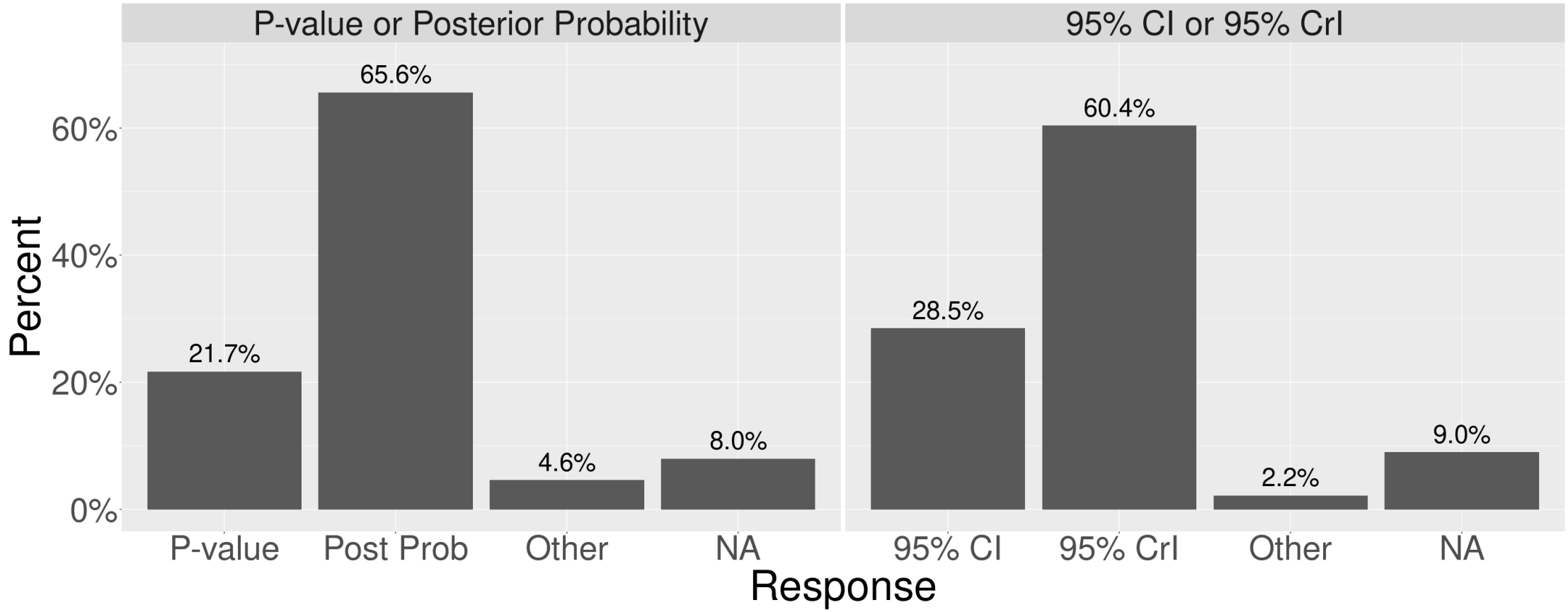
Correct response highlighted in green;

Statistical Interpretation and Preferences
Usefulness Questions

- After the interpretation questions respondents were shown the correct interpretation for each statistic
- Respondents were then asked which statistic they felt was more useful for decision making:
  - The p-value vs posterior probability
  - The confidence interval or credible interval

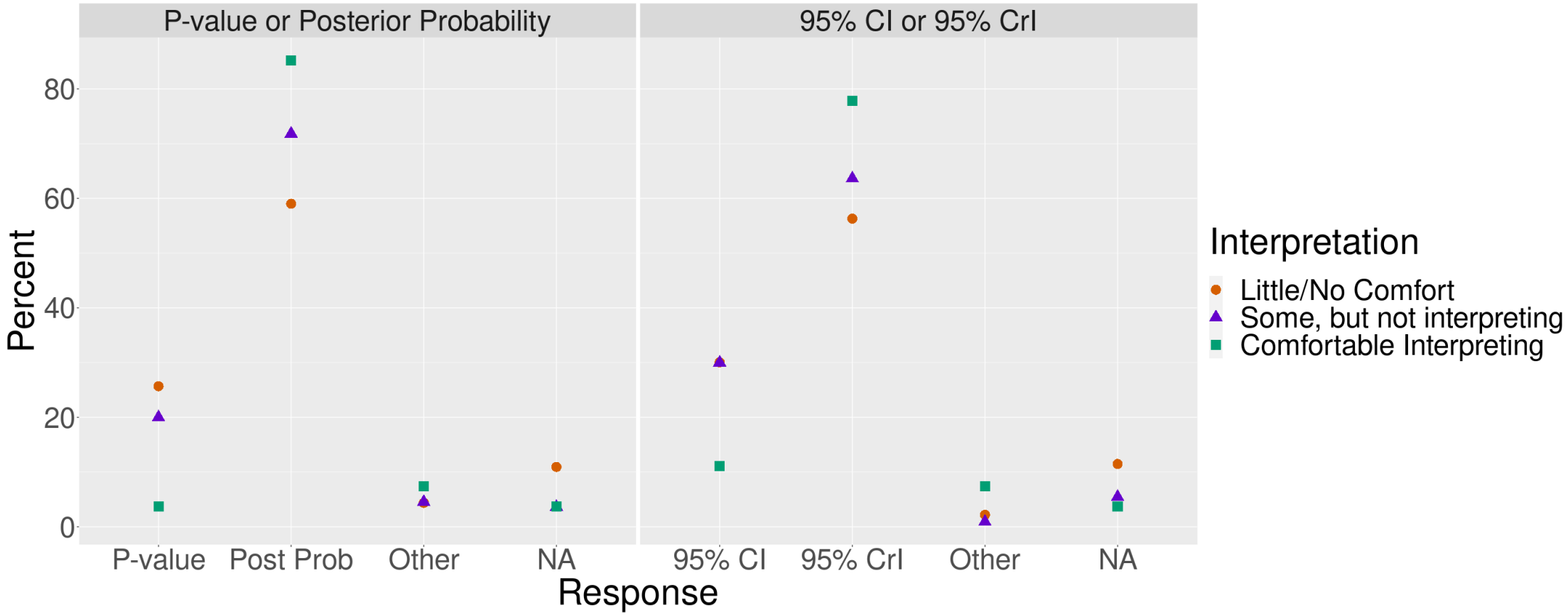
Statistical Interpretation and Preferences

Usefulness Questions



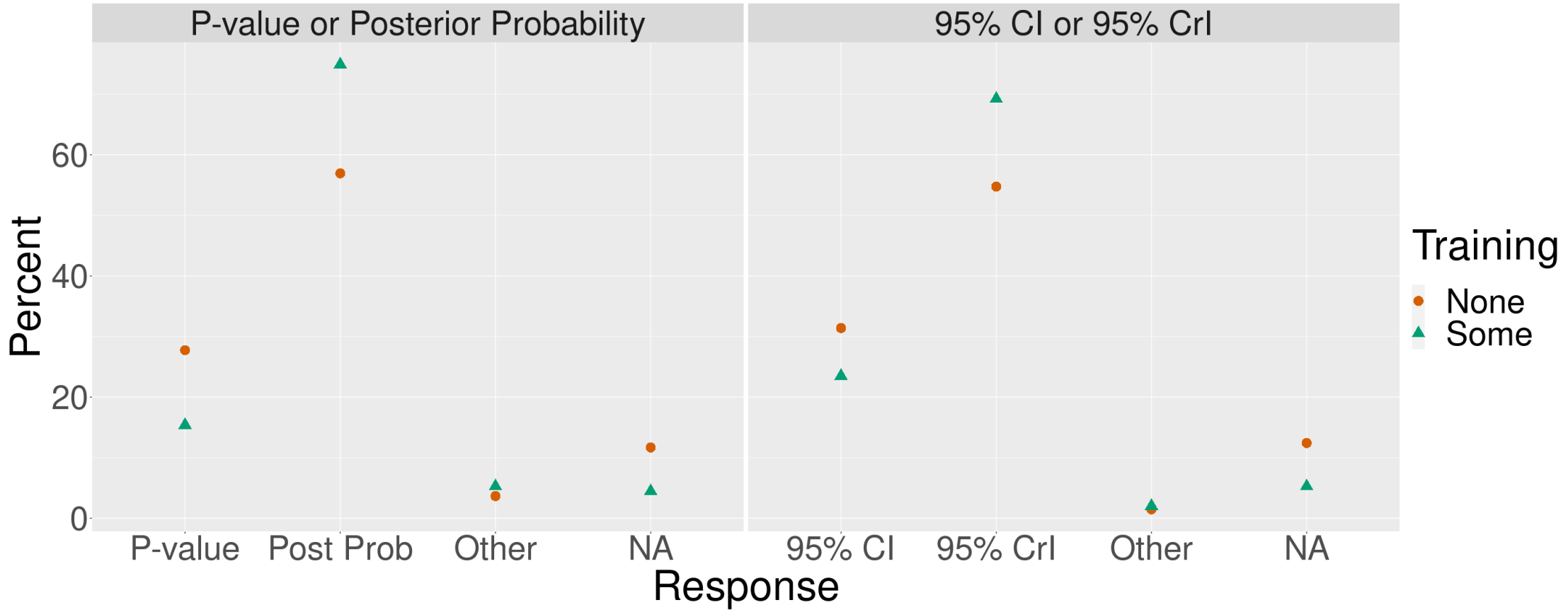
Statistical Interpretation and Preferences

Usefulness Questions



Statistical Interpretation and Preferences

Usefulness Questions



Limitations

- Response rate <20%
  - Interpretation limited to medical researchers who were motivated to respond
  - Most responders were not Bayesian enthusiasts
  - Many had little to no comfort with this methodology
- No set standards for what constitutes substantial evidence of effectiveness with these methods
- Implementation requires specific statistical and computational expertise to ensure sound results
- Limited context to the interpretation scenario since the comparison was only on clinicians interpretations of final statistical outputs.
  - They may have other objections to using Bayesian methods such as the proper choice of a prior.

Discussion

- Only 11.5% (p-value) and 23.5% (CI) of researchers interpreted the conventional statistics correctly
  - This aligns with prior publications showing confusion surrounding significance testing.
  - Nearly 25% of respondents either skipped these two interpretation questions or selected “choose not to answer” indicating significant uncertainty interpreting results.
- For Bayesian statistics, 42.4% (posterior probability) and 36.5% (credible interval) of respondents answered correctly
  - While this could indicate a better understanding of Bayesian interpretation, other factors may have influenced the results.
  - Higher percent of respondents (>30%) either did not respond or selected “choose not to answer”

Conclusions

- More educational opportunities in the use of both conventional and Bayesian statistics would be valuable for the non-statistical community
  - This will aid in the movement to reduce the use of p-values and promote the use of effect sizes and differences

- The usefulness questions confirmed our expectation that Bayesian statistics are easier to interpret than conventional statistics.

Ongoing and Future Work

- The medical outreach group contributed to an educational session on Bayesian Statistics at the DIA annual meetings in June
- We are currently contributing to the creation of a Bayesian education course at the University of California at San Francisco, led by Steve Ruberg
- There is new leadership in the medical outreach team and we will be discussing some options on which direction to take in providing additional educational opportunities.
  - If anyone is interested in participating, please contact the co-leads Natalia Muhlemann (natalia.muhlemann@cytel.com) or Purvi Prajapati (prajapati_purvi@lilly.com)

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