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European Federation of Statisticians in the Pharmaceutical Industry  
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# ICH E9(R1) Implementation Experiences

**Chrissie Fletcher, VP Biostatistics, GSK**

**On behalf of the EFPIA/EFSPi Estimand Implementation Working Group (EIWG)**

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# Disclaimer

The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of GSK.

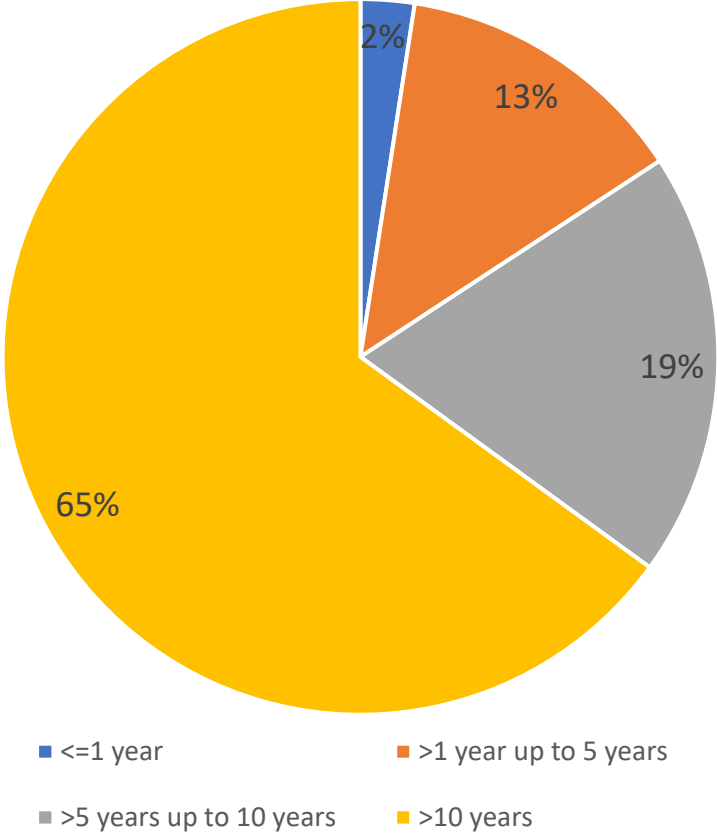
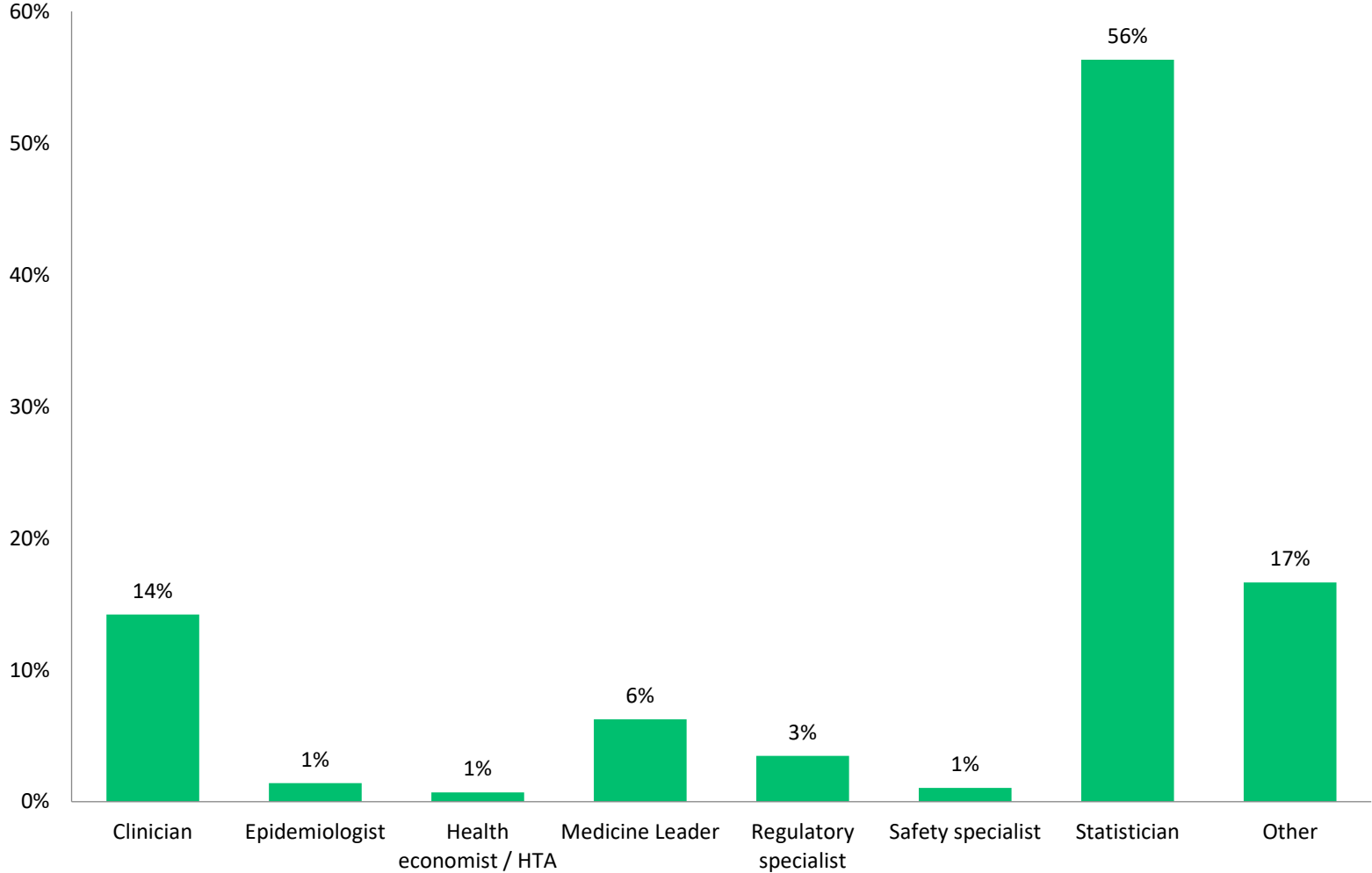
# Agenda

- Results of ICH E9(R1) implementation survey led by Industry (EFPIA/EFSPI) in 2021
- Key recommendations from 2-years of a new thinking in clinical trials
- EIWG Estimand Academy
- Conclusions

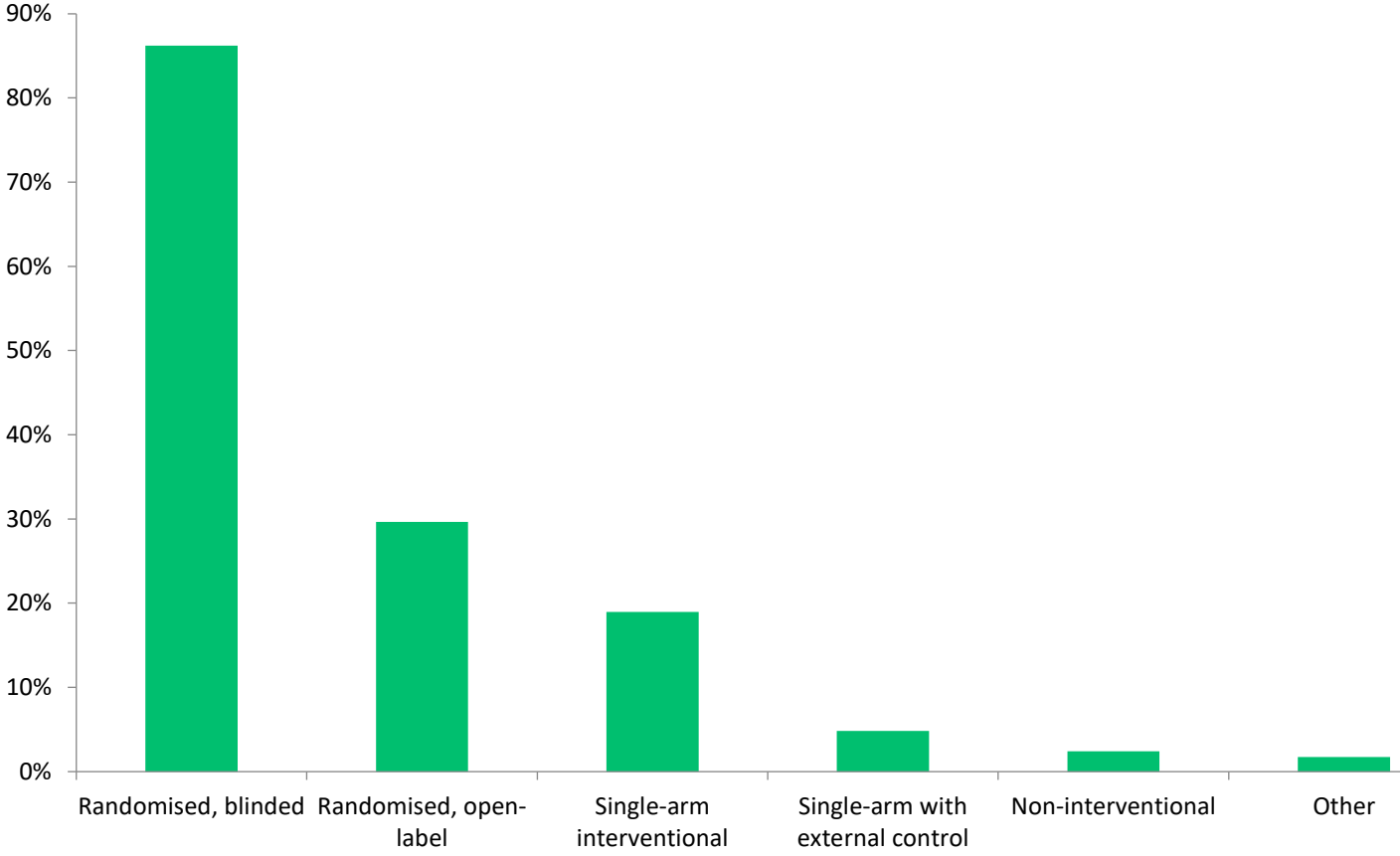
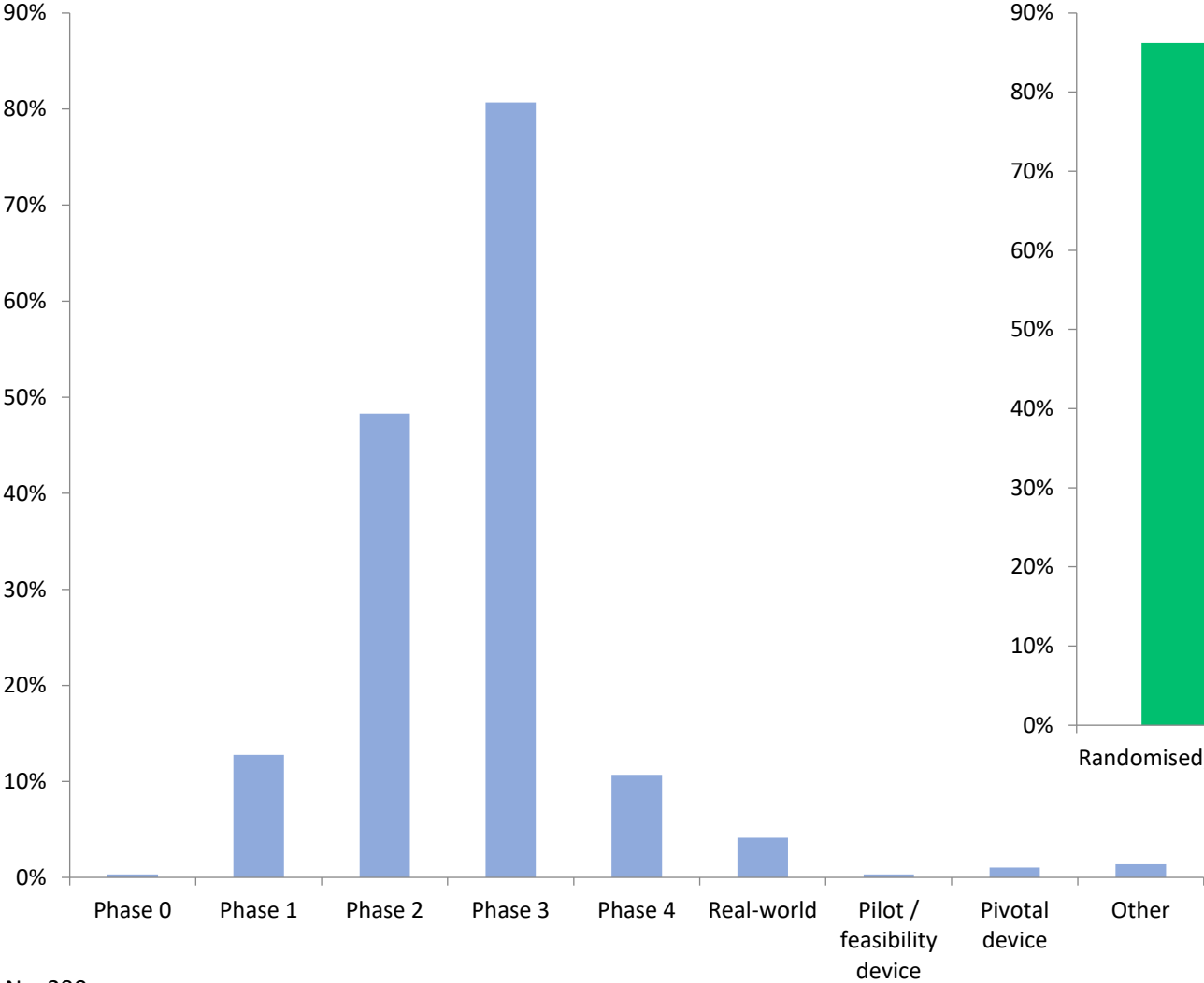
# Aim of EFPIA/EFSPI ICH E9(R1) implementation survey

- Solicit status of implementation in Pharma companies including levels of awareness, training and applications of ICH E9(R1) in clinical research
- Survey conducted in March-April 2021, 577 respondents
- Those with experience of ICH E9(R1): further questions asked:
  - Types and phases of clinical studies
  - How framework has been implemented
  - Who has been involved in using framework
  - Interactions with regulatory agencies
  - Rating experiences
  - Where additional information could be helpful
  - View on value of defining estimands
  - Feedback on concerns or potential issues in applying framework
- All respondents could provide general comments

# Majority of respondents were statisticians, and with $\geq 10$ years clinical research experience



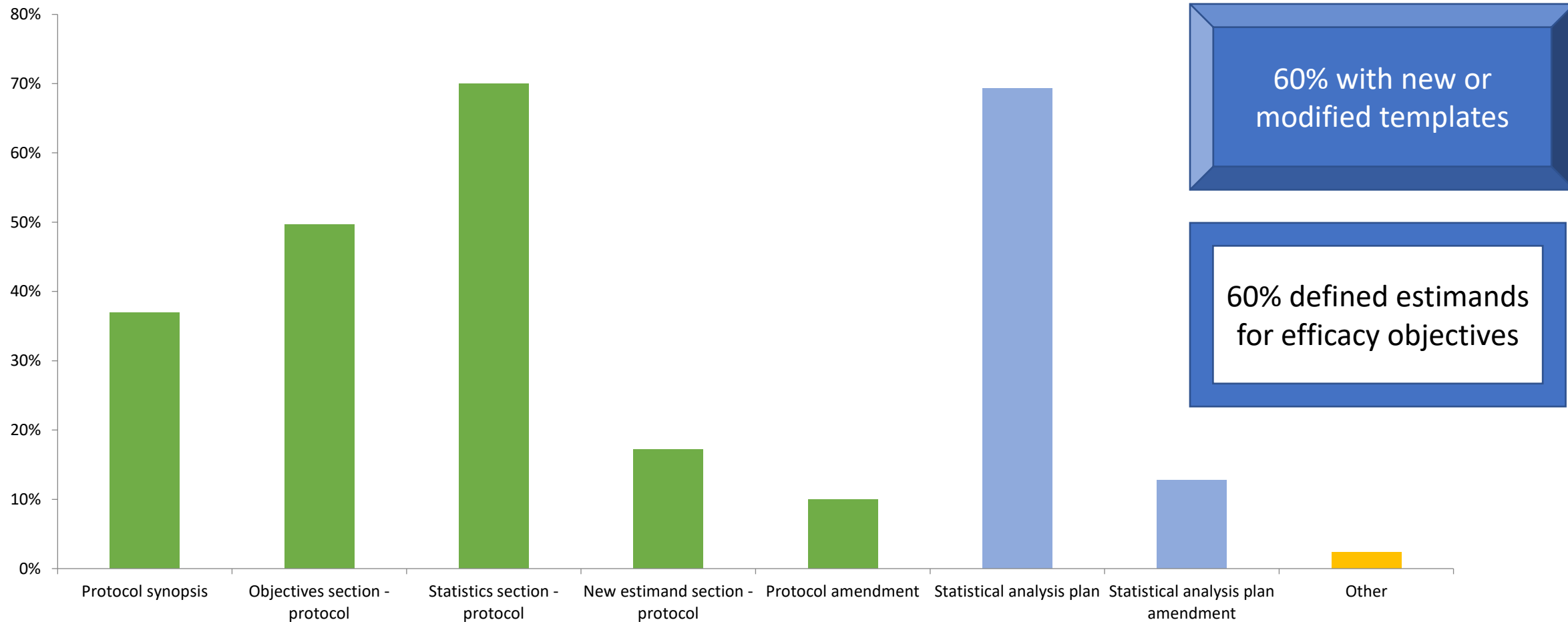
# Experience of framework highest in phase 3 and phase 2 and in randomised studies



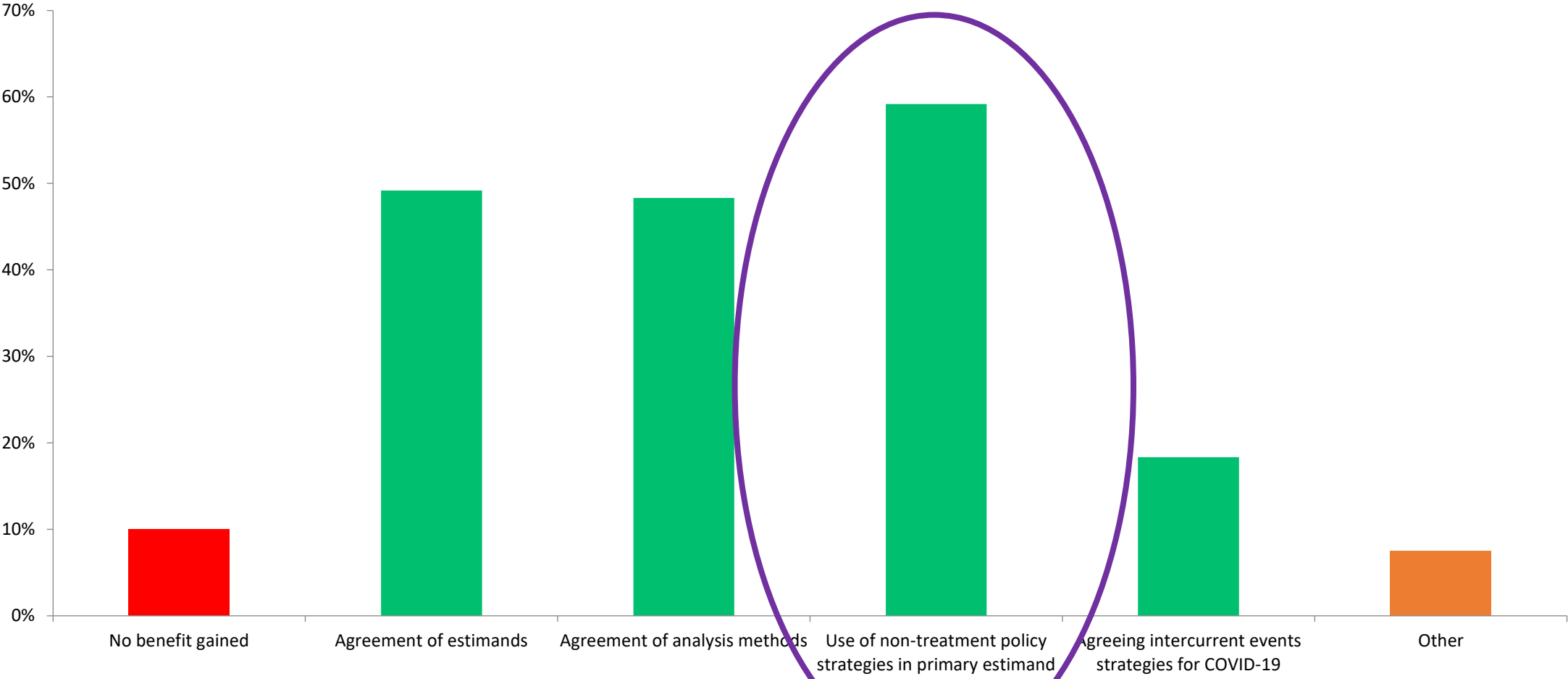
N = 290

N = 290

# Estimands being described in protocols and statistical analysis plans

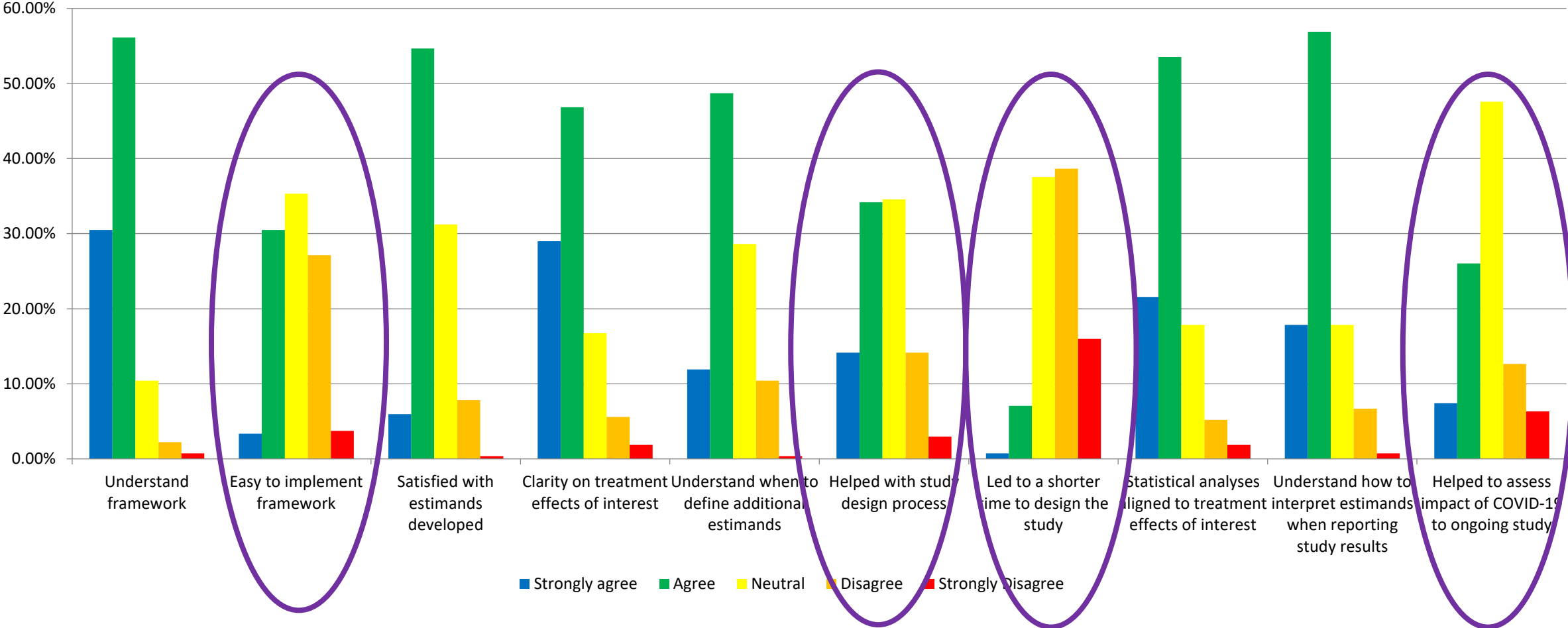


# Half of respondents noted engaging with regulatory agencies resulted with agreement in estimands and analysis methods

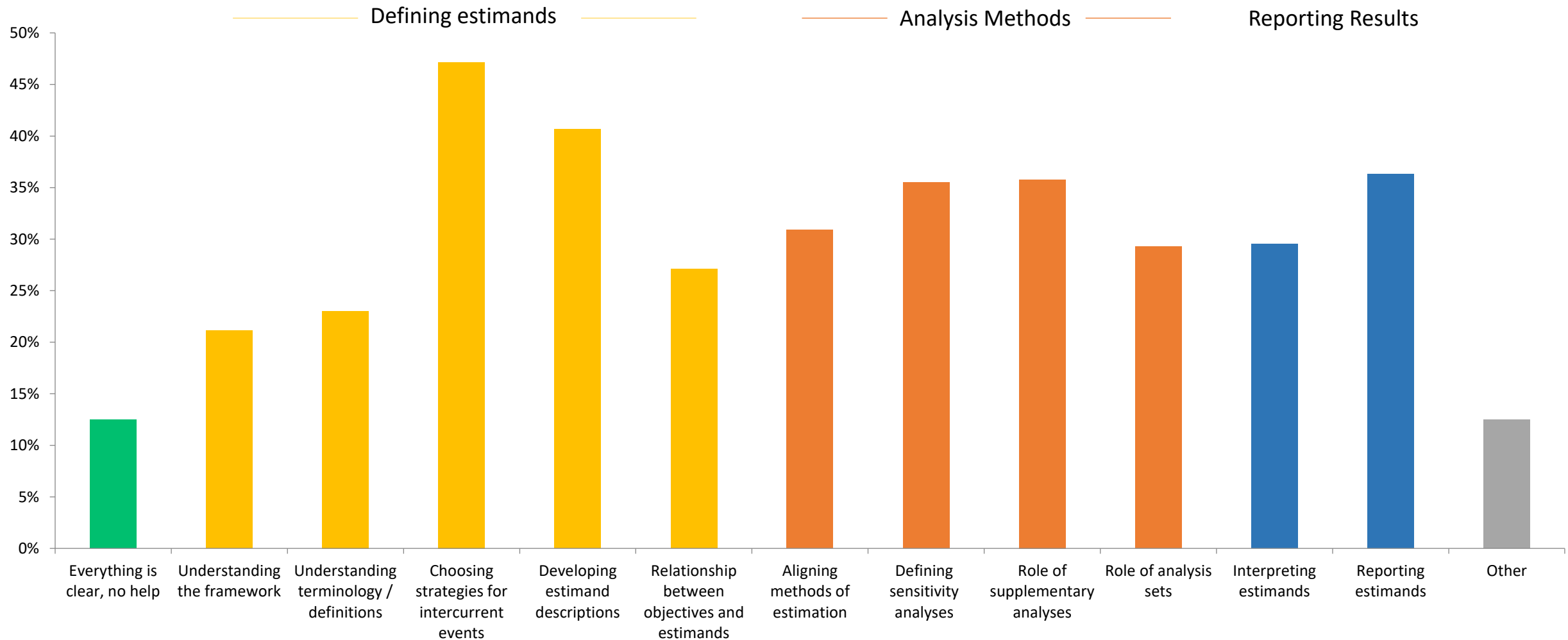




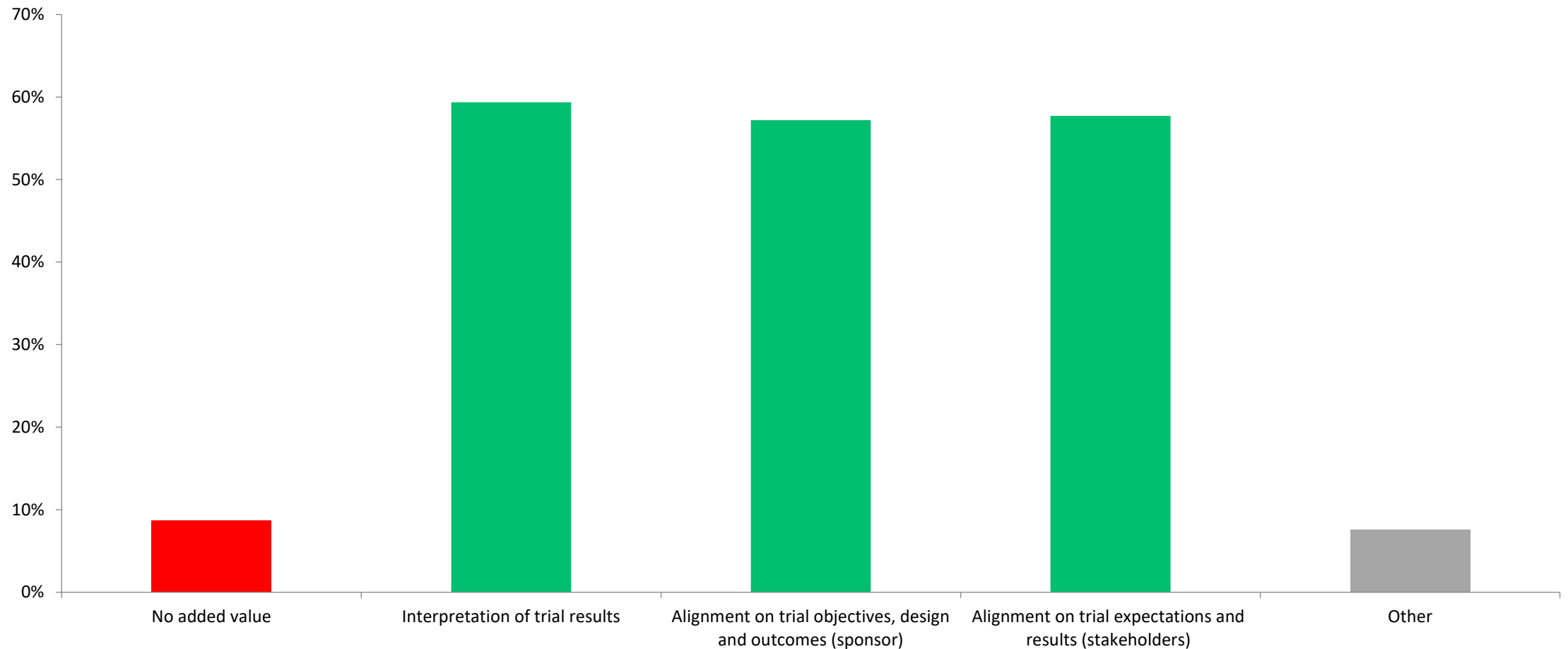
# Rating experiences indicates majority understand framework but not easy to implement and study design took longer



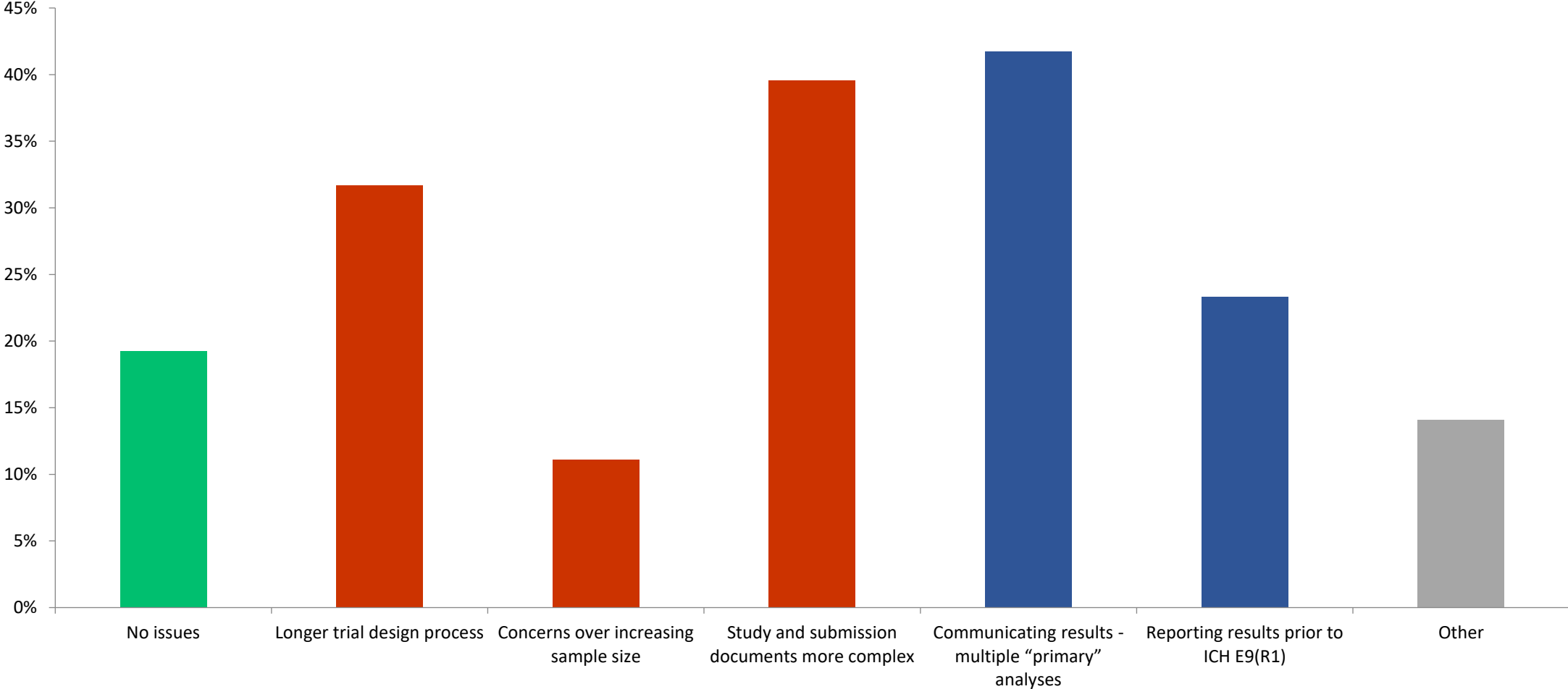
# More information would be useful in defining estimands, analysis methods & reporting results



# Half of respondents noted defining estimands adds value



# Concerns the framework increases trial design, more complex documents and communicating multiple 'primary' results




# Survey key conclusions

- Implementation of ICH E9(R1) is a journey and will take time
- Training continues to be an area of focus – ideally with case studies
- The estimand framework is leading to more alignment between sponsors and regulators on study objectives and treatment effects
- Further information on the estimand framework is needed to increase ease of implementation
- Concerns remain if framework will increase complexity in clinical trials processes and how best to report and interpret results



# Marking 2-Years of New Thinking in Clinical Trials: The Estimand Journey

C. Fletcher<sup>1</sup>  · N. Hefting<sup>2</sup> · M. Wright<sup>3</sup> · J. Bell<sup>4</sup> · J. Anzures-Cabrera<sup>5</sup> · D. Wright<sup>6</sup> · H. Lynggaard<sup>7</sup> · A. Schueler<sup>8</sup>

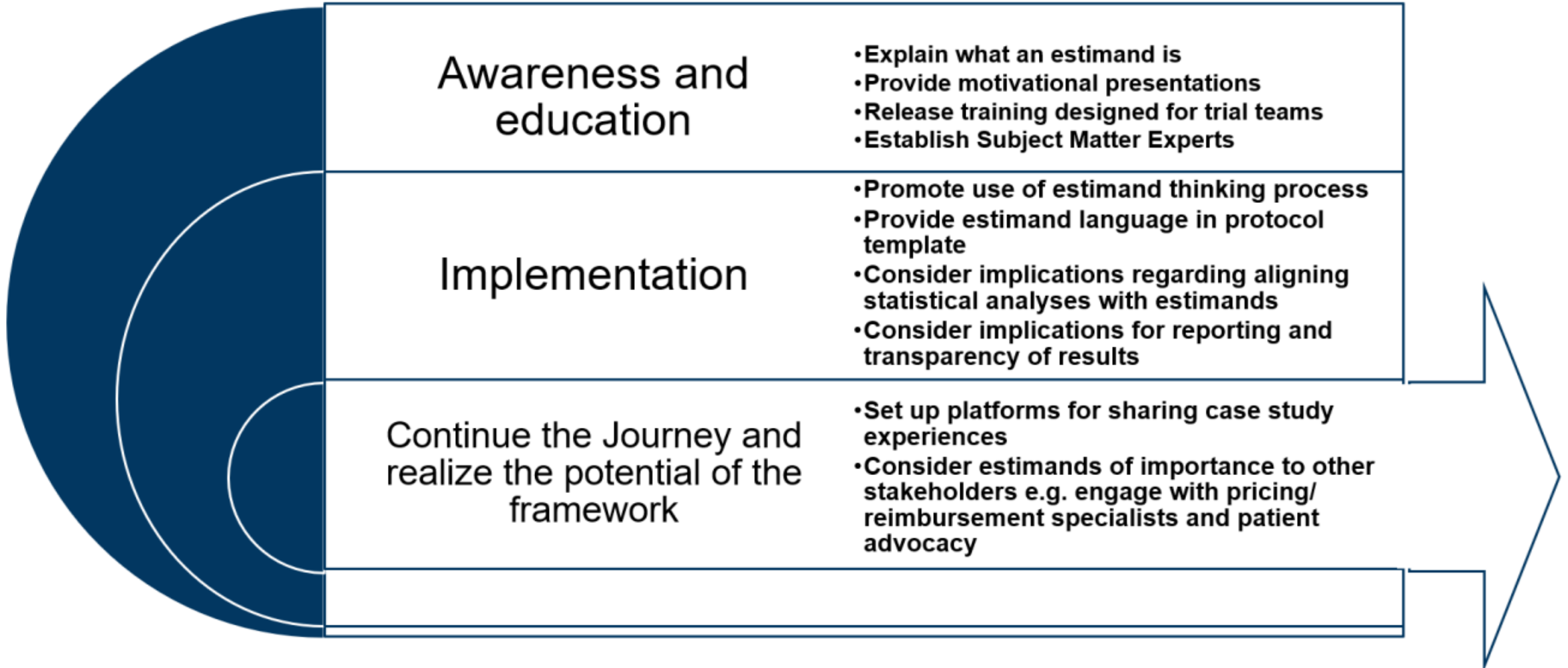
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## Abstract

The ICH E9(R1) addendum on *Estimands and Sensitivity Analyses in Clinical Trials* has introduced a new estimand framework for the design, conduct, analysis, and interpretation of clinical trials. We share Pharmaceutical Industry experiences of implementing the estimand framework in the first two years since the final guidance became available with key lessons learned and highlight what else needs to be done to continue the journey in embedding the estimand framework in clinical trials. Emerging best practices and points to consider on strategies for implementing a new estimand thinking process are provided. Whilst much of the focus of implementing ICH E9(R1) to date has been on defining estimands, we highlight some of the important aspects relating to the choice of statistical analysis methods and sensitivity analyses to ensure estimands can be estimated robustly with minimal bias. In particular, we discuss the implications if complete follow-up is not possible when the treatment policy strategy is being used to handle intercurrent events. ICH E9(R1) was introduced just before the start of the COVID-19 pandemic, but a positive outcome from the pandemic has been an acceleration in the adoption of the

# Typical approach to implementing estimands



# Recommendations for implementing estimands framework

1. Promote the use of the **estimand thinking process as a tool** to establish clear links between trial objectives, estimands (treatment effects), choice of trial design, trial conduct and statistical analysis.
2. Where possible **use non-technical language** to encourage cross-functional collaboration and discussion about estimands and make estimand thinking a routine part of clinical development.
3. Ensure **clinical trial teams, investigators and patients are aware of the need to collect all data** which are essential to evaluate the primary (and key secondary estimands) in order for missing data to be minimized.
4. Focus on **the data that will form the basis for the analysis of each estimand** that reflects both the patients and the observations to be included.
5. **Share case studies** illustrating how to incorporate estimands in clinical trial protocols and statistical analysis plans, and how to communicate estimands and results in clinical study reports and publications.
6. Offer **drop-in consultation sessions** allowing teams to access timely advice from experts.
7. **Obtain feedback from regulatory agencies and other key stakeholders** on proposed estimand and estimation strategies, including justifications, as early as possible. Share this feedback across teams.
8. **Provide trainings and host seminars** including diverse and cross-functional facilitators to promote discussions about estimands in the broader scientific community.



# EIWG Estimand Academy

## Aim: Sharing case studies

- 1. [PIONEERing estimands in clinical research](#)
- 2. [Estimands in oncology](#)
- 3. [Estimands from trial planning to publications in medical journals: the ETHOS trial](#)

Future webinars planned:

Webinar	Date	Responsible
1. Impact of estimands	30 June / 1st July	EIWG Training subteam
2. Case study in neuroscience	TBC (target Sep)	Estimands in Neuroscience group
3. Estimands in early development	Oct/Nov 2022	EIWG early development subgroup

# Examples of other EIWG activities

- Variety of sub-teams focussing on:
  - Incorporating estimands into clinical trial protocols (publication under review 'Trials')
  - Estimands in early phase studies
  - Estimands in non-inferiority studies
  - Estimands in non-interventional studies
  - Reporting and communicating estimands
  - Estimation methods
  - EIWG central resource for all materials
- Developing publications, white papers and discussing other publications emerging
- Reviewing guidelines e.g. ICH M11 and new protocol template, EUnetHTA methodology guidelines
- Discussing with NIH how to incorporate estimands in CT.GOV
- Discussing with authors of CONSORT/SPIRIT how estimands are incorporated

# Conclusions

- Estimand framework has shifted focus from ITT analysis to clearly defining treatment effects of interest
- Requires cross-functional input and alignment and is not purely a statistical analysis problem to solve
- New definition of sensitivity analysis ensures analyses are now aligned to each estimand
- Case studies, training and awareness sessions have helped to illustrate key concepts but the language and new terminology introduced has been challenging
- Most attention on defining estimands, now increasing focus on analysis methods and reporting estimands
- The estimands journey continues and there is more work to do to support broader implementation