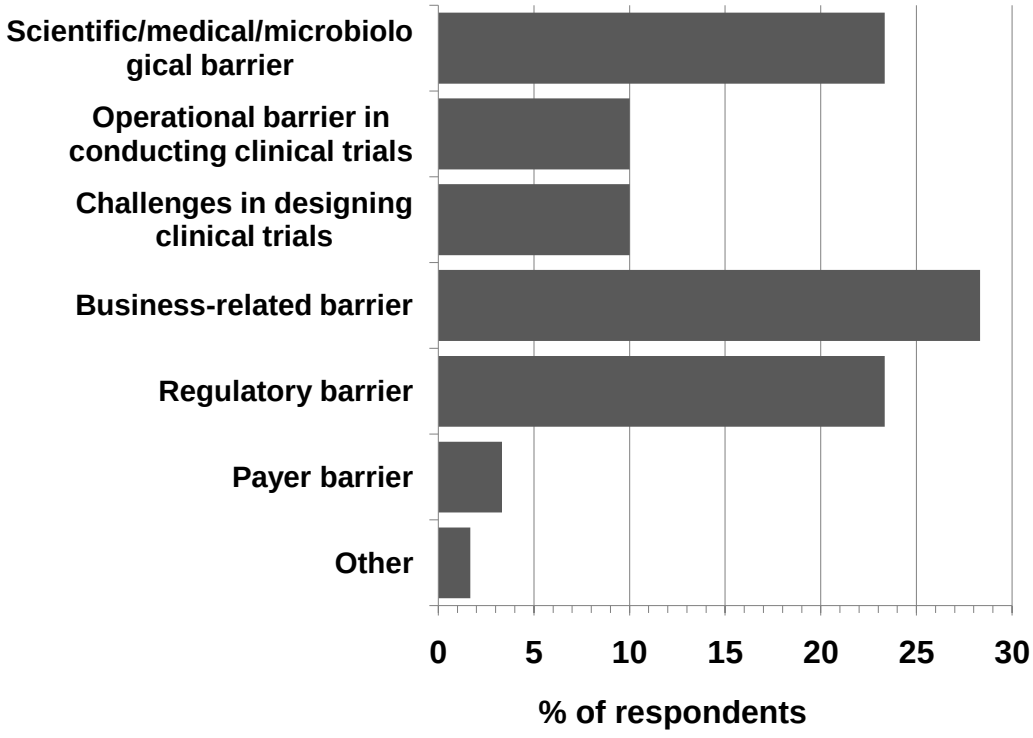
Material and methods

An online anonymous survey was designed using LimeSurvey® (http://www.limesurvey.org/). A user acceptance test was performed by six volunteers on a first version. Questions were then edited based on test users' feedback. The final online survey included a total of 16 questions. The types of questions were single and multiple choice questions, as well as rating scales. Questions were grouped in topics as follows: respondents' characteristics (3 questions); general issues in clinical development of antibacterials (3 questions); large non-inferiority phase 3 randomized controlled trials (RCT; 2 questions); dose-finding (2 questions); regulatory changes (2 questions); and development of new antibacterial agents for MDRO infections (4 questions). The need for specific information was balanced against the time required by responders to complete the survey. As some questions were not mandatory, number of responder per question varies between 60 and 40 over the course of the survey.

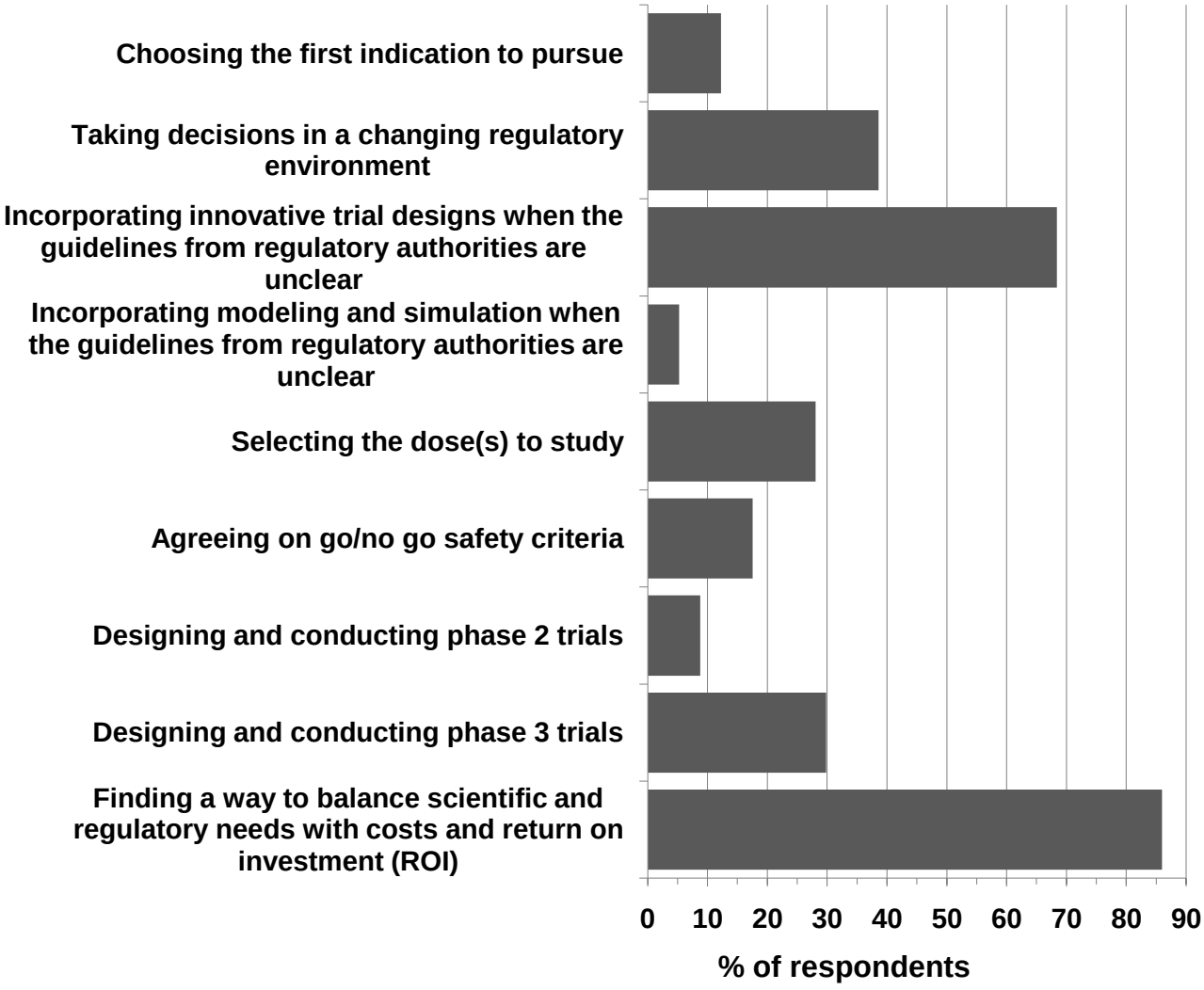
A link to the final 16-question survey was sent between August and November 2013 by email to primary contacts within 28 small, medium or large pharmaceutical companies and 7 consultants active in antibacterial clinical development in the US and EU. Companies with antibacterial compounds only at the early research or preclinical stages were not included. Contacted pharmaceutical and consulting companies included in alphabetical order: Achaogen; Actelion Pharmaceuticals; Anacor; Anti-Infectives Consulting; AstraZeneca; Basilea Pharmaceutica; Bayer; Cantab Biopharmaceuticals; CEFAIA; Cempra; Cubist; DaVolterra; Durata Therapeutics; Eumedica Pharmaceuticals; Cerexa; Furiex Pharmaceuticals; GlaxoSmithKline; Granzer Regulatory Consulting & Services; Infectious Disease Drug Development Consulting; Janssen Pharmaceuticals; Boyd Consultants; Chemical Biology Ventures; Melinta Therapeutics; Merck & Company; Nabriva Therapeutics; Novartis; Paratek Pharmaceuticals; Pfizer; Polyphor; Rempex Pharmaceuticals; Roger Echols; Sanofi Aventis; Sergio Lociuro; Tetraphase Pharmaceuticals; The Medicines Company; Theravance Biopharma; THOT Consulting.

Primary contacts within companies were identified through personal networks, company websites, and LinkedIn®. These contacts included chief executive or medical officers/head of clinical development or group leaders/program heads/medical directors for the antibacterial area. Primary contacts were asked to complete the survey themselves as well as forward the survey link to other colleagues working on clinical development of new antibacterial agents. All respondents agreed that their responses would be saved, analyzed anonymously, and made publically available through a peer reviewed publication. For the analysis, a respondent was defined as a participant who answered the three respondent characteristics' questions and at least the first question on general issues in clinical development of antibacterials (Supplementary Figure 1). Results were summarized descriptively.



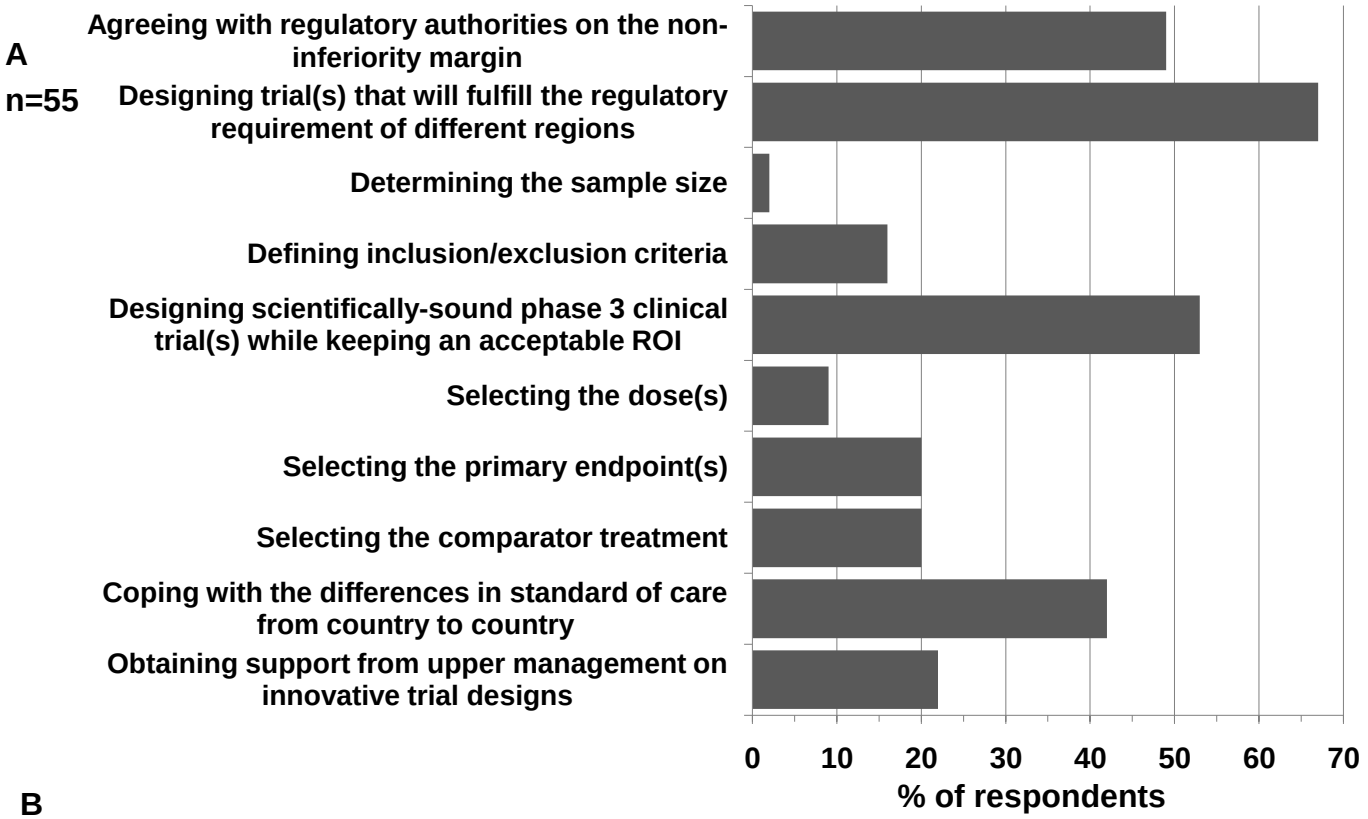
Supplementary figure 1 What is the most challenging barrier to successfully develop and bring to patients new antibacterial agents?

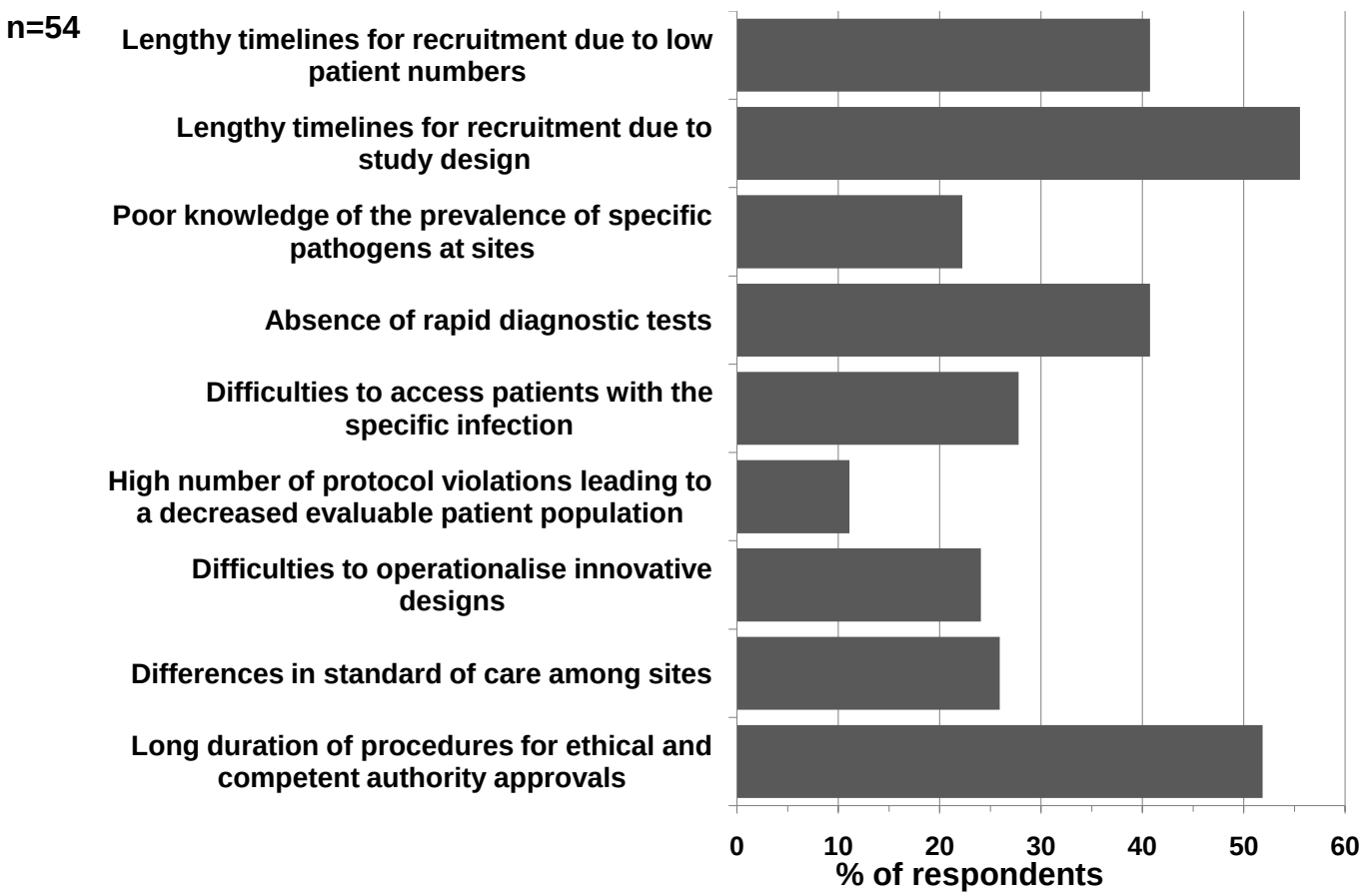
N=60. Other: Transition from phase 2a to phase 3.



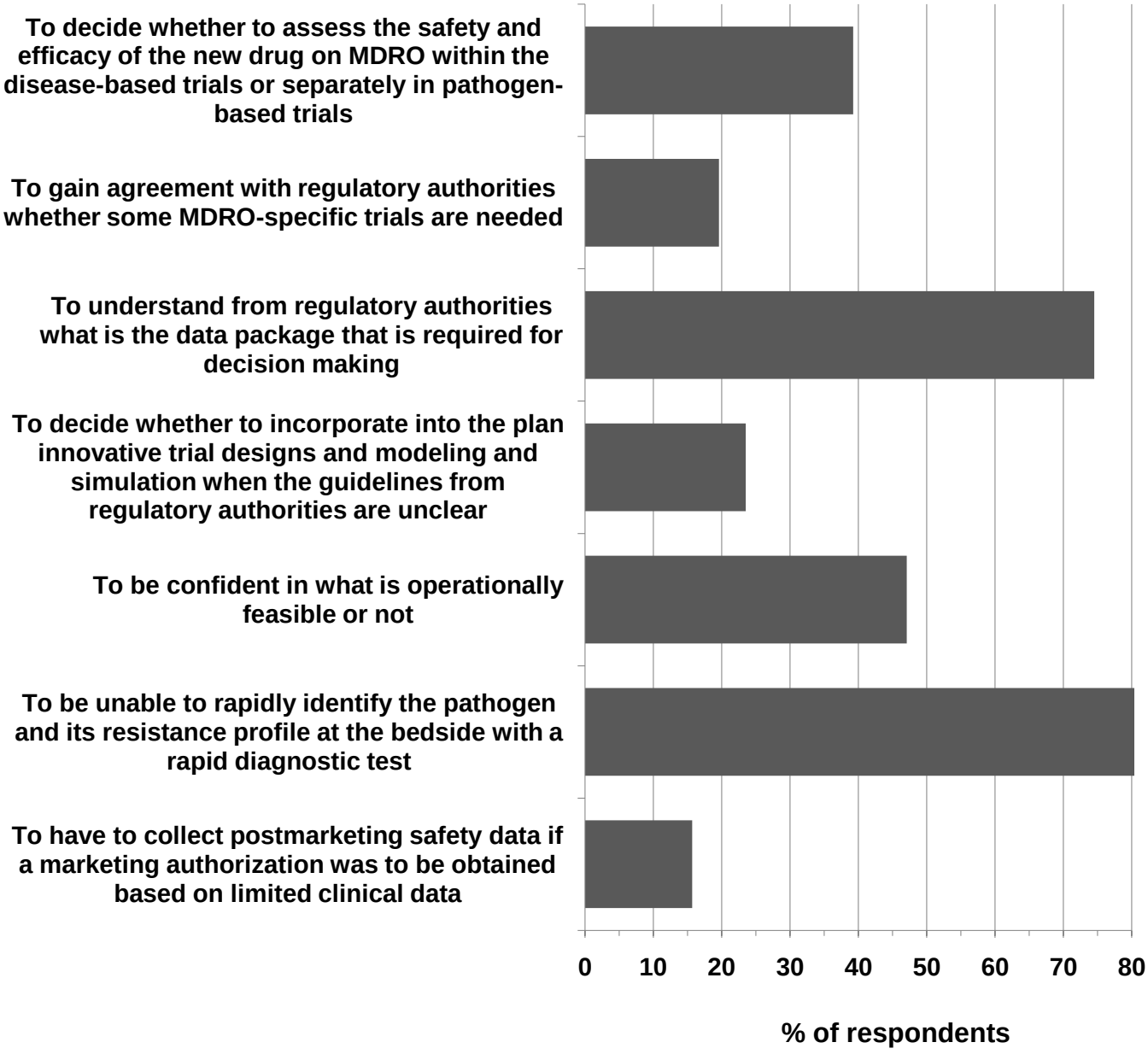
Supplementary figure 2 Which are the 3 most challenging issues to agree upon in a clinical development plan for a new broad-spectrum antibacterial agent within a multidisciplinary R&D team?

n=57.



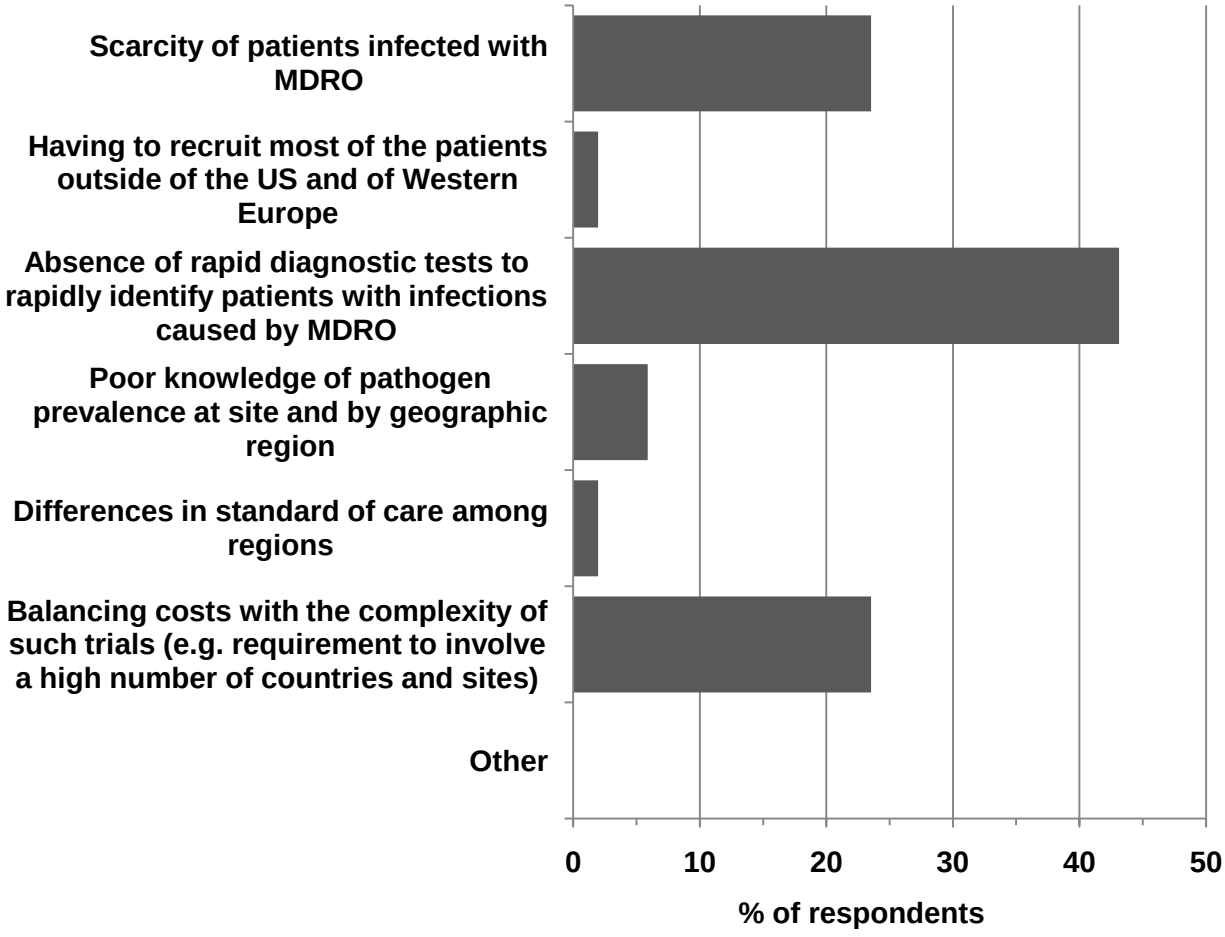


Supplementary figure 3 When designing (A) or setting up and conducting (B) large non-inferiority phase 3 randomized controlled trials for new broad-spectrum antibacterial agents, which are the 3 most difficult points to decide upon?



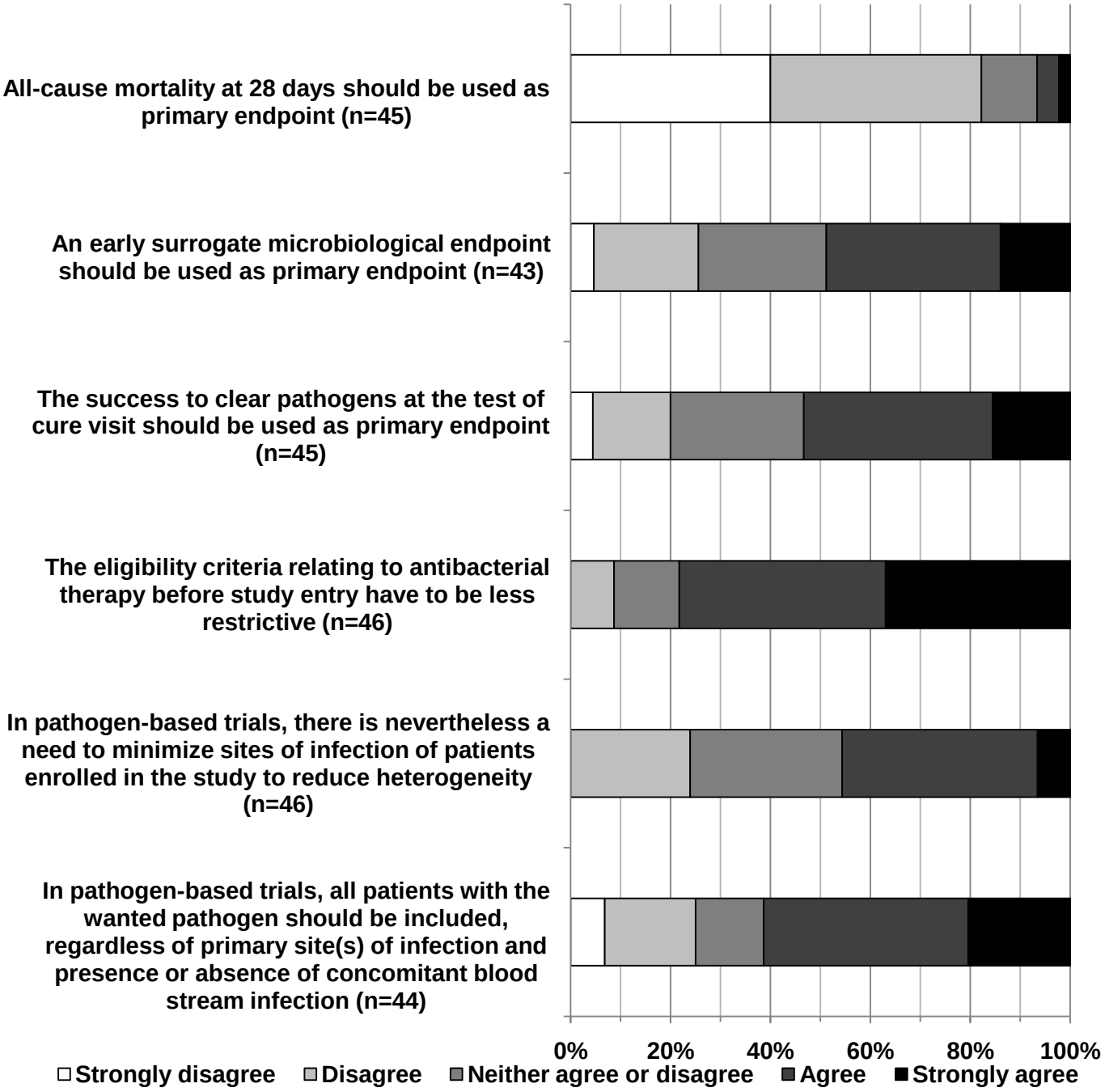
Supplementary figure 4 What are the 3 most challenging issues to assess efficacy and safety of a new antibacterial agent against multi-drug resistant organisms (MDRO)?

n=51.

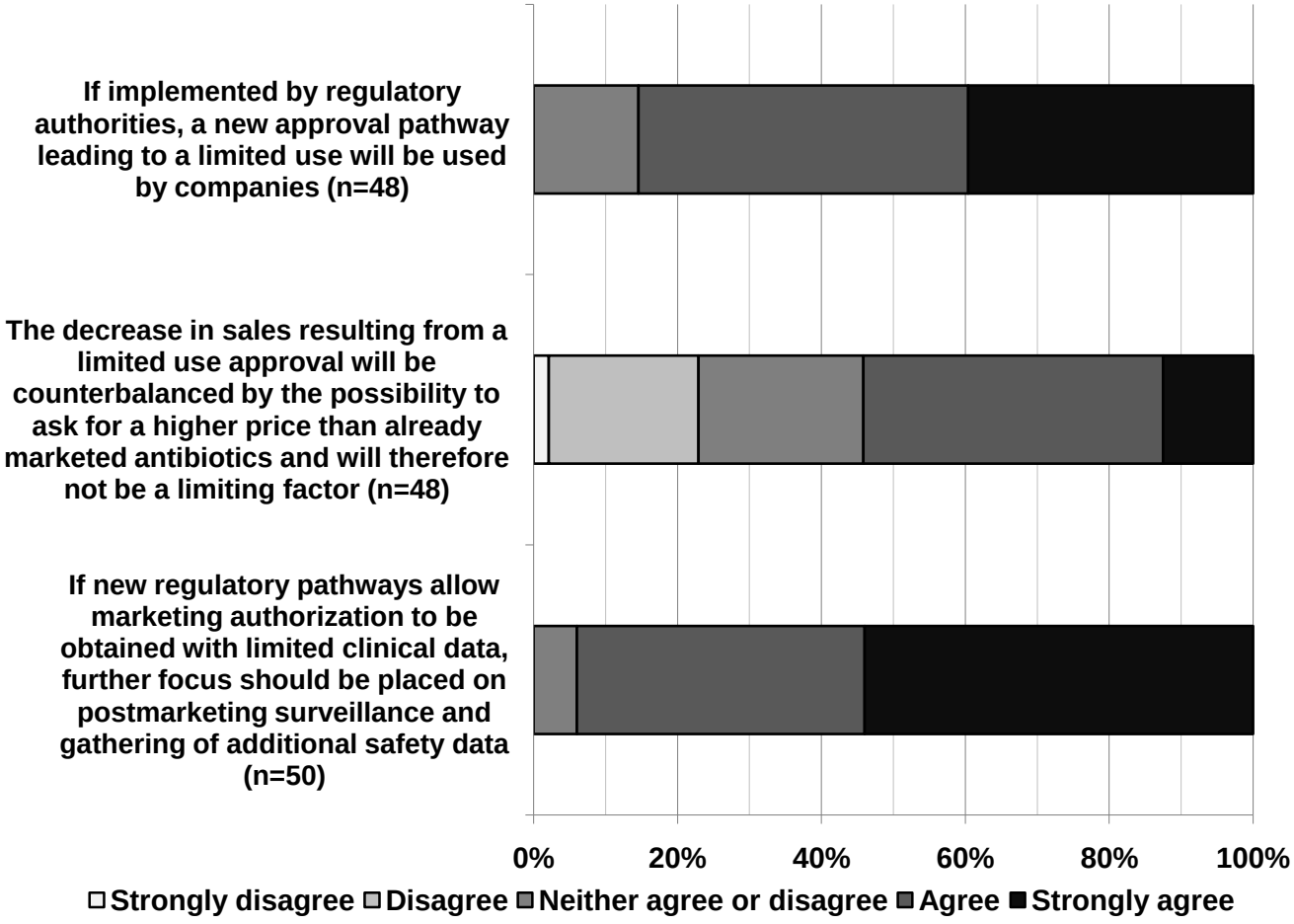


Supplementary figure 5 What is the most challenging issue encountered when conducting trials in which inclusion is restricted to patients with infections caused by multi-drug resistant organisms (MDRO)?

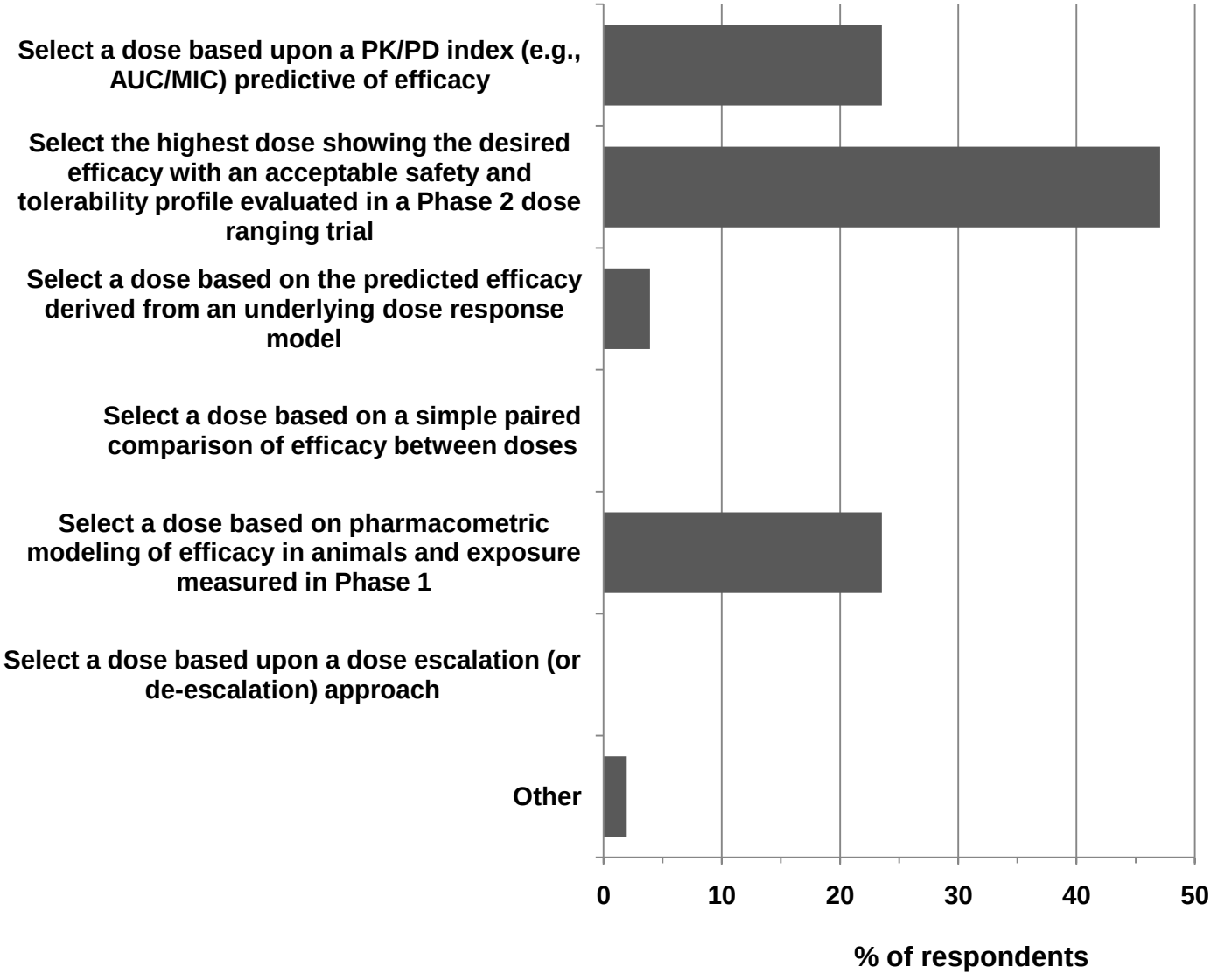
n=51.



Supplementary figure 6 Opinion on primary endpoint(s) and inclusion/exclusion criteria for pathogen-based trials assessing safety and efficacy of new antibacterial agents on infections caused by multi-drug resistant organisms (MDRO).

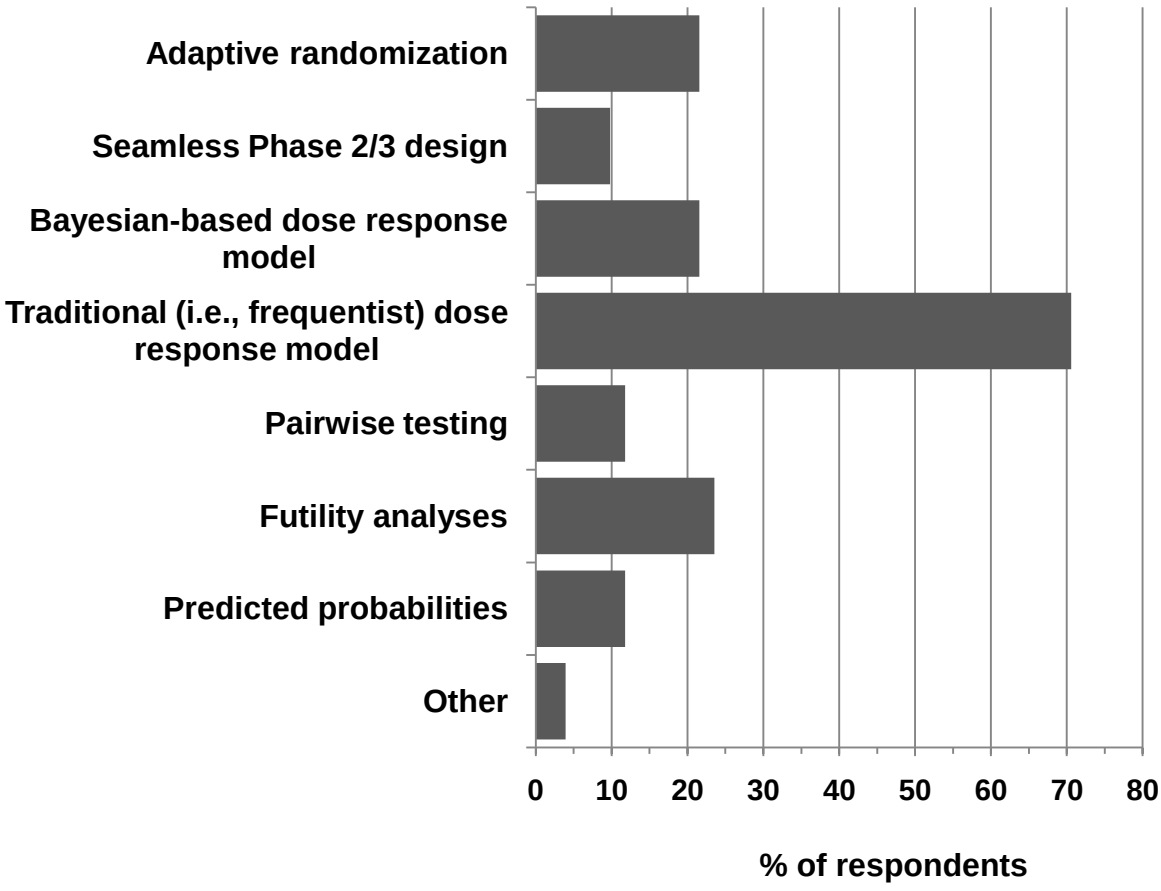


Supplementary figure 7 Opinion on new regulatory pathways and guidance.



Supplementary figure 8 Which of the following procedures is most commonly used to select a dose to investigate in phase 3 trials evaluating the safety and efficacy of new antibacterial agents?

n=51. Other (n=1): Dose selected based on PK/PD and simple paired comparison based on healthy volunteer safety data. PK/PD = Pharmacokinetic/Pharmacodynamic; AUC/MIC = Area under the concentration-time curve/Minimum inhibitory concentration.



Supplementary figure 9 Which of the following trial design features are commonly incorporated in phase 2 dose findings trials (choose all that apply)?

n=51. Other (n=2): Pharmacometric analyses; progress directly from phase 1 to phase 3.