Informed Consent to Study Purpose in Randomized Clinical Trials of Antibiotics, 1991 Through 2011

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IMPORTANCE Potential research participants may assume that randomized trials comparing new interventions with older interventions always hypothesize greater efficacy for the new intervention, as in superiority trials. However, antibiotic trials frequently use “noninferiority” hypotheses allowing a degree of inferior efficacy deemed “clinically acceptable” compared with an older effective drug, in exchange for nonefficacy benefits (eg, decreased adverse effects). Considering these different benefit-harm trade-offs, proper informed consent necessitates supplying different information on the purposes of superiority and noninferiority trials.

OBJECTIVE To determine the degree to which the study purpose is explained to potential participants in randomized clinical trials of antibiotics and the degree to which study protocols justify their selection of noninferiority hypotheses and amount of “clinically acceptable” inferiority.

DESIGN AND SETTING Cross-sectional analysis of study protocols, statistical analysis plans (SAPs), and informed consent forms (ICFs) from clinical study reports submitted to the European Medicines Agency. The ICFs were read by both methodologists and patient investigators.

MAIN OUTCOMES AND MEASURES Protocols and SAPs were used as the reference standard to determine prespecified primary hypothesis and record rationale for selection of noninferiority hypotheses and noninferiority margins. This information was cross-referenced against ICFs to determine whether ICFs explained the study purpose.

RESULTS We obtained trial documents from 78 randomized trials with prespecified efficacy hypotheses (6 superiority, 72 noninferiority) for 17 antibiotics conducted between 1991 and 2011 that enrolled 39 407 patients. Fifty were included in the ICF analysis. All ICFs contained sections describing study purpose; however, none consistently conveyed study hypothesis to both methodologists and patient investigators. Methodologists found that 1 of 50 conveyed a study purpose. Patient investigators found that 11 of 50 conveyed a study purpose, 7 accurately and 4 inaccurately compared with the reference standard. Seventy-one of 72 noninferiority trial protocols or SAPs provided no rationale for selection of noninferiority hypothesis. None provided a clinical rationale for the chosen amount of decreased efficacy.

CONCLUSIONS AND RELEVANCE Patients were not accurately informed of study purpose, which raises questions regarding the ethics of informed consent in antibiotic trials. Noninferiority and superiority trials entail different benefit-harm trade-offs that must be conveyed for ethical informed consent.

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Ethical clinical research is based on a respect for persons. The importance of obtaining informed consent from potential research participants is an unquestioned aspect of research involving humans. The Declaration of Helsinki, Belmont Report, and Common Rule all agree that a key element necessary to convey to participants is the purposes of research involving humans. The Declaration of Helsinki, Belmont Report, and Common Rule all agree that a key element necessary to convey to participants is the purposes of research involving humans.

Randomized clinical trials with active controls, sometimes called “head-to-head” studies, can evaluate “superiority” or “noninferiority” hypotheses of an experimental intervention compared with best standard of care. In superiority trials, the primary hypothesis is to evaluate improved efficacy of new interventions by ruling out any amount of inferior efficacy of experimental interventions compared with existing best standard of care. Noninferiority hypotheses allow an amount of “clinically acceptable” inferior efficacy of new interventions compared with older effective interventions, in exchange for potential nonefficacy benefits of new interventions, such as being “less toxic, less invasive, less costly, require fewer doses, improve quality of life, or have some other value to patients.” Noninferiority is determined by ruling out an amount of inferior efficacy chosen prior to the trial, called the “noninferiority margin.” Between 2002 and 2009, one-quarter of new drug approvals included evidence from noninferiority trials, with the majority being antimicrobial studies.

To our knowledge, there has been no systematic evaluation of information provided to potential research participants and whether it is sufficient to distinguish the differing study purposes of superiority and noninferiority trials. If potential research participants assume that they are enrolled in superiority trials that actually noninferiority trials or vice versa, they may incorrectly assess the balance of benefits and harms to which they may be exposed based on the study’s intended purpose.

Using informed consent forms (ICFs) obtained from regulatory filings for antibiotics, we evaluated (1) how often study purpose was conveyed to potential trial participants. We also assessed study protocols and statistical analysis plans (SAPs) of noninferiority trials to determine the rationale provided for choice of (2) noninferiority hypothesis and (3) noninferiority margin.

### Methods

Institutional review board approval was not sought for this study as this was non-human subjects research based on publicly available data. There was no need for anonymization because we did not evaluate patient-level data.

### Data Sources

In 2013 through 2014, we made a freedom of information request to the European Medicines Agency (EMA) for ICFs, study synopses, protocols, and SAPs (including any amendments) for all antibiotic trials in the EMA’s holdings. After an initial denial, our appeal was successful. The EMA reported that of 17 authorized antibiotics, it held study documents for 13 (retapamulin, inhaled aztreonam, inhaled colistin, dapto-

### Key Points

- **Question**: How often is the study purpose explained to potential participants in randomized clinical trials of antibiotics?
- **Findings**: In this cross-sectional analysis of trial documents submitted to regulators, no informed consent forms consistently conveyed the primary hypothesis of the study.
- **Meaning**: Patients enrolling in antibiotic clinical trials are not accurately informed of study purpose, raising fundamental questions of the ethics of consent in antibiotic drug trials.

### Selection Criteria

We included all antibiotic randomized clinical trials that had a prespecified efficacy hypothesis. We had no exclusion criteria at the study level.

Study documents for some trials did not include ICFs. For other studies, we received multiple ICF versions. For the latter, we selected the most recent ICF dated prior to the start of patient enrollment. If identically dated ICFs existed for differently aged populations, we chose the form used with the oldest population. When multiple ICFs met these criteria, for example, multiple ICFs for different study sites, we chose the first form that appeared in the documents.

### Study Outcomes

Our primary outcome measure was the proportion of ICFs that accurately conveyed sufficient detail to explain the primary hypothesis (superiority or noninferiority) using the protocols or SAPs as the reference standard. For noninferiority studies, we recorded any reasons given in trial documents for the selection of noninferiority hypotheses and noninferiority margins. We also recorded the noninferiority margin.

### Informed Consent Form Review

Five raters (2 methodologists with expertise in clinical trial design [T.J., D.I.M.] and 3 patient investigators [P.A.S., A.W., K.A.J]) judged whether ICFs explained the study purpose to potential participants, and if so, assigned the study purpose as...
superiority or noninferiority. Raters were provided with ICFs only and no other study documents. We aimed to increase raters’ comprehension by highlighting the following words that could be relevant to judging study purpose and statistical hypothesis wherever they appeared in consent forms: purpose, aim, goal, objective, hypothesis, evaluate, demonstrate, determine, compare, intend, intention, plan, similar, superior, inferior, better, worse, effective, less, effective, less, safe, tolerate, tolerable, justification. We did this because relevant information is not necessarily always located in the section of ICFs where study purpose is described (eg, sometimes labeled “Purpose” or “Why is this research study being done?”). Highlighting was automated with Adobe Acrobat Professional XI.

Patient investigators (P.A.S., A.W., K.A.) were selected by convenience and given a $500 honorarium. As we expected them to be unfamiliar with the terms “noninferiority” and “superiority,” we designed a questionnaire that enabled us to gauge their determination of study hypothesis without using explicit terms. No training was provided other than requesting their participation in a pilot of 2 trials selected on the basis of being the only 2 trials that named the study design in the study title printed on the ICF.

Patient investigators were provided with ICFs and asked to answer the following question: “Is the primary purpose of this trial to see whether the NEW DRUG is more effective than the CONTROL DRUG or is the primary purpose to see whether the NEW DRUG is not substantially worse than the CONTROL DRUG? Or can you not tell?” For the purpose of comparing patient investigator responses to methodologist responses, an answer of “more effective” was taken to indicate a superiority study and “not substantially worse” a noninferiority study.

Disagreements among rater pairs were reported descriptively and with \( k \) statistics. Subsequently, to compare methodologist and patient investigator judgments, we obtained a consensus methodologist and consensus patient investigator judgment for use in final data analysis by following Cochrane methods for reaching consensus.

Methodologists were asked whether the ICF described study purpose sufficiently to distinguish between superiority and noninferiority design, and if so, to judge the design.

One author (P.D.) also searched ICFs for keywords describing study purpose (keywords: purpose, aim, goal, objective, justification) and whether this was phrased to evaluate superiority (superior, better, more effective), similarity (similar), or inferiority (inferior, worse, less effective). Searching was automated with Adobe Acrobat Professional XI and hand reviewed.

### Data Analysis

We classified all included trials as superiority or noninferiority hypotheses based on the primary efficacy hypothesis as stated in the synopsis, protocol, or SAP. We classified trials called “equivalence” in reports as “noninferiority” trials, in line with international guidance defining noninferiority trials. Many active clinical trials called “equivalence” are noninferiority studies, as they specify only an amount of acceptable inferiority. None described an upper bound on greater efficacy as in equivalence trials. Studies were also categorized as studying a “serious” or “nonserious” disease based on whether the FDA has granted Qualified Infectious Disease Product (QIDP) status under the Generating Antibiotic Incentives Now (GAIN) Act in relation to the indication under investigation. The QIDP designation requires serious or life-threatening disease and a qualified pathogen.

Final judgments by methodologist and patient raters were compared with those based on the reference standard of study reports (study synopsis, protocol, or SAP). We present our analyses stratified by statistical hypothesis of the trial’s primary objective (superiority or noninferiority).

We tested 2 hypotheses using the Fisher exact test: first, that the proportion of ICFs that convey their study purpose clearly was equal for superiority and noninferiority trials, stratified by methodologists and patient investigators; second, that ICFs convey their study purpose equally clearly to both methodologists and patient investigators (as assessed by the proportion of correct ratings). We used \( P < .05 \) to indicate statistical significance and 2-sided testing.

### Results

The EMA provided study documents for 107 trials of 17 antibiotics, of which 78 trials (for 17 drugs) met inclusion criteria (6 superiority trials, 72 noninferiority trials). Of these, 26 trials were excluded from the ICF analysis, primarily because the EMA did not possess ICFs. We also excluded from the ICF analysis 2 trials used in our pilot to develop our methods, leaving a total of 50 trials included in ICF analysis. Details of trials included and excluded, with reasons, are provided in the eFigure in the Supplement and our dataset.13

A total of 39,407 patients were enrolled in 78 trials. Patients enrolled in the 52 trials for which we had ICFs totaled 28,548. Approximately one-half of the included trials (38 of 78) started between 1991 and 2000, and half (36 of 78) commenced between 2001 and 2011.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Superiority Trials (n = 6)</th>
<th>Noninferiority Trials (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial enrollment start date, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1991-1995</td>
<td>0</td>
<td>22 (31)</td>
</tr>
<tr>
<td>1996-2000</td>
<td>0</td>
<td>16 (22)</td>
</tr>
<tr>
<td>2001-2005</td>
<td>2 (33)</td>
<td>23 (32)</td>
</tr>
<tr>
<td>2006-2010</td>
<td>1 (17)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>2011</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Study date unknown</td>
<td>3 (50)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Severity of disease under study, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonserious</td>
<td>1 (17)</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Serious</td>
<td>5 (83)</td>
<td>53 (74)</td>
</tr>
<tr>
<td>Noninferiority margin, median (IQR), %</td>
<td>NA (−10 to −10)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; NA, not applicable.
6) studied serious diseases. Three-quarters of noninferiority trials (53 of 72) studied serious diseases (Table 1).

Automated keyword searching showed that all ICFs included a study purpose section. Five ICFs included words such as “better” or “superior,” 4 of which were noninferiority trials (eTable in the Supplement). For example, 1 ICF informed patients that, “The study doctor will give PAR-101 to some people in this study to see if it is safe and tolerable, and can help them with their CDAD [Clostridium difficile-associated diarrhea]. Another purpose of this study is to find out if taking PAR-101 is better than taking vancomycin.” However, the SAP defined the primary hypothesis as noninferiority. See the eBox in the Supplement for other examples.

In the ICF analysis, prior to consensus the 2 methodologist raters’ independent judgments on study hypothesis were concordant (mostly “cannot tell”) in 42 of 50 (84% agreement; unweighted $\kappa < 0$) trials. After consensus, they judged 49 of 50 ICFs as containing insufficient information to judge study hypothesis. For the 3 patient investigator raters, agreement was 12 of 50 (24%; unweighted $\kappa = 0.07$), 16 of 50 (32%; unweighted $\kappa = 0.23$), and 31 of 50 (62%; unweighted $\kappa = 0.18$). After consensus, patient investigator raters judged 38 of 50 (76%) ICFs as containing insufficient information to judge study hypothesis.

None of the ICFs consistently conveyed study purpose simultaneously to both methodologist and patient investigator raters. For the methodologist raters, 1 of 50 (2%) ICFs conveyed study purpose. This ICF was rated as a superiority trial whereas the protocol or SAP defined the primary hypothesis as noninferiority. This was the aforementioned trial in which the ICF included wording stating, “the purpose of this study is to find out if taking PAR-101 is better than taking vancomycin.” For patient investigators, 7 of 50 (14%) ICFs conveyed study purpose accurately (5 noninferiority and 2 superiority trials) and 4 (8%) conveyed the incorrect hypothesis (all 4 were noninferiority trials judged as superiority trials) compared with the protocols or SAPs. The remaining 38 (76%) trials’ ICFs did not convey a study purpose (Table 2).

Because none of the ICFs rated by methodologists consistently conveyed study purpose accurately, we could not reject the hypothesis that ICFs from superiority and noninferiority trials convey study purpose equally clearly. For patient advocate raters, ICFs from superiority trials conveyed study purpose accurately more commonly than noninferiority trials (50% vs 11%; $P = .09$). Finally, we rejected the null hypothesis that ICFs convey their study purpose equally clearly to both methodologists and patient investigators (0% vs 14%; $P = .01$) (Table 3).

In protocols or SAPs, we could not locate a rationale for selection of noninferiority hypotheses in 71 of 72 (99%) noninferiority trials. The single trial that provided a justification explained that a placebo-controlled trial would be unethical given the type of disease (severe acute bacterial skin and skin structure infections with large lesions and systemic signs of infection) and an active-controlled superiority trial would be unethical “because highly effective antibiotic treatment exists” (Table 4).

We located a written explanation of the choice of noninferiority margin in 51 of 72 (71%) trials, whereas 21 (29%) trials did not include a justification for the noninferiority margin choice. Thirty-seven (51%) trial documents indicated that the noninferiority margin was chosen in accordance with a guidance from the FDA, commonly citing 2 specific FDA documents (Table 4). Six (8%) trials referenced the effect of the control drug from previous placebo-controlled trials, as delineated in FDA regulation and international guidance. No trials provided a clinical rationale explaining why the chosen amount of inferiority should be considered “clinically acceptable.”

Among noninferiority studies, the median noninferiority margin was −10% (interquartile range, −15% to −10%) (Table 1).

### Discussion

Our analysis of 50 antibiotic trials submitted to regulatory agencies for marketing approval over 2 decades found that potential participants were not accurately informed of study purpose in ICFs. Neither patient investigators nor experienced methodologists could determine the purpose for the majority of trials. These results raise questions about the ethics of antibiotic development. Clarity on study purpose is central to the ethical principles of respect for persons, as well as minimizing risk; it is also crucial to understanding alternative treatments noted in foundational documents regarding experimentation involving humans, and a requirement for proper informed consent in the Common Rule.

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Table 4. Rationale for Selection of Noninferiority Study Design and Margin

<table>
<thead>
<tr>
<th>Rationale</th>
<th>No. (%) of Studies (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For study design</td>
<td></td>
</tr>
<tr>
<td>Alternative treatment for antibiotic resistance</td>
<td>0</td>
</tr>
<tr>
<td>Decreased adverse events</td>
<td>0</td>
</tr>
<tr>
<td>Dosing convenience</td>
<td>0</td>
</tr>
<tr>
<td>Guidance from FDA</td>
<td>0</td>
</tr>
<tr>
<td>Placebo-controlled superiority study unethical</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Highly effective therapy already exists</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other rationale</td>
<td>0</td>
</tr>
<tr>
<td>No rationale given</td>
<td>71 (99)</td>
</tr>
<tr>
<td>For margin</td>
<td></td>
</tr>
<tr>
<td>Reference to previous placebo-controlled trial(s)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Reference to previous active-controlled trial(s)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Reference to previous noninferiority trial(s)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Reference to previous surveillance study</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Patient input was sought</td>
<td>0</td>
</tr>
<tr>
<td>Guidance from FDA</td>
<td>37 (51)</td>
</tr>
<tr>
<td>Prior drug approval</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other rationale</td>
<td>4 (6)</td>
</tr>
<tr>
<td>No rationale given</td>
<td>21 (29)</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, Food and Drug Administration.

Others have noted that informed consent should differ between superiority and noninferiority trials, given differences in trade-offs between efficacy and harm. In superiority trials, investigators hypothesize increased efficacy compared with best standard of care. In noninferiority trials, investigators hypothesize that some decreased effectiveness compared with effective best standard of care would be acceptable to potential research participants in exchange for potential nonefficacy benefits such as decreased adverse effects or improved convenience.

Whereas all ICFs included a study purpose section (usually labeled “Purpose”), none consistently conveyed the primary hypothesis of noninferiority or superiority. One reason may be historical: when randomized trials became the standard, few effective therapies existed and placebo controls were common. The important ethical documents were drafted when superiority hypotheses were the norm. The term “noninferiority” did not exist until the 1980s.21

Today, nearly one-third of premarking trials have active controls.22 For antibiotics, the proportion is higher and noninferiority trials are common.9,23 Living ethical guidance documents need updating to reflect this changing landscape. Investigators need guidance on how to ensure that ICFs convey study purpose. We are unaware of ICF model language for noninferiority trials, although some have offered sample language for “equivalence” trials.24 However, investigators should avoid wording that implies that a noninferiority trial evaluates equality of interventions because noninferiority trials cannot show that 2 interventions are not different by any amount (as in superiority trials). To aid efforts to develop model language, investigators, sponsors, and institutional review boards could prospectively publish ICFs and study protocols in trial registries. The recent US Department of Health and Human Services Final Rule (effective January 2017) indicates that ClinicalTrials.gov will accommodate optional posting of ICFs and requires posting of protocols and SAPs.25 In the Box, we offer sample language for ICFs for noninferiority trials.

We found that 99% of protocols or SAPs lacked a rationale for the selection of noninferiority hypotheses. One reason may be that investigators believe that “noninferior” means “equal to” or “as effective as,” thus assuming that they are not exposing participants to increased risk of harm. Ruling out no loss of effectiveness at all necessitates superiority trials.

In the single trial that offered a rationale, investigators stated that a placebo-controlled superiority trial would be unethical in severe skin infections and that an active-controlled superiority trial would be unethical “because highly effective antibiotic treatment exists.” However, the reason placebo-controlled trials are considered unethical is that they may
expose patients who have effective options to increased harm from a less effective intervention (placebo). The primary hypothesis in noninferiority trials also allows for lesser effectiveness with a new drug in patients who have effective options (the control drug). Therefore, noninferiority trials raise the same ethical issues as placebo-controlled trials. Challenges in demonstrating added benefits with new antibiotics do not make superiority trials “unethical” but highlight either a lack of unmet medical need for improved efficacy in patients for whom the effectiveness of an old therapy is already reasonable or the need to focus on nonantibiotic interventions that might improve outcomes.26

Clarity of study purpose is particularly important in serious and/or life-threatening diseases. More than 90% of analyzed trials used noninferiority hypotheses, with deaths in 64% of them, and recent antibiotic approvals via noninferiority have increased morbidity and mortality.27–29 In life-threatening disease, potential research participants may accept increased adverse effects for potentially prolonged and/or improved life investigated in superiority trials. However, potential participants may not find noninferiority trials acceptable if they are not willing to give up any amount of efficacy, even in exchange for fewer adverse effects or improved convenience, particularly in acute life-threatening infections where decreased efficacy implies increased morbidity or mortality compared with the active control. The EMA has noted, “Where the treatment under consideration is used for the prevention of death or irreversible morbidity...it can be very difficult to justify a noninferiority margin of any size.”30 The FDA has stated that “it is essential for public health protection that a new therapy be as effective as alternatives that are already approved for marketing when...the disease to be treated is life-threatening or...the disease to be treated is a contagious illness.”31,32 This indicates that noninferiority is not an appropriate study design for serious diseases because there is no “clinically acceptable” inferior efficacy in such cases.3

Noninferiority trials may be acceptable in non-life-threatening diseases in which research participants might accept some amount of lesser effectiveness not resulting in death or irreversible harm in exchange for superiority on fewer adverse effects, with the amounts determined by valid patient surveys.33

We found that 71% of noninferiority studies provided a rationale for selection of noninferiority margins. Many provided this rationale in the discussion of sample size derivation. Half mentioned FDA guidance,15,16 but none provided clinical reasoning or involvement from patients in selecting the amount of decreased effectiveness considered “acceptable.” Noninferiority margins that allow for absolute decreases in effectiveness of −15% to −10% mean that as many as 1 in 6 to 10 patients may receive less effective new interventions compared with older effective therapy. This suggests that major trial decisions are driven by convention, sample size considerations, or following regulatory suggestions, leaving unclear what, if any, consideration is given to patient perspectives. The patient perspective is important because noninferiority margins are a central factor to determining whether a trial ultimately meets its primary objective, but also because the margin reflects subjective judgments regarding the amount of decreased efficacy that patients would find acceptable, as well as the type and amount of nonefficacy benefits that constitute an acceptable trade-off.

Limitations
Our study has limitations. Because we only assessed ICFs, we do not know what other information was provided to participants, how well they understood the ICF, or whether they read it. We also cannot generalize our findings beyond antibiotic trials. Finally, we included study documents irrespective of their date stamp. The degree that study hypotheses might have changed over time and were not reflected consistently across documents may have caused misclassification.

Conclusions
Patients enrolling in clinical trials of antibiotics are not accurately informed of study purpose. Because noninferiority trials do not intend to demonstrate superior efficacy of new interventions and entail trade-offs of lesser efficacy for other benefits, this study raises fundamental questions of the ethics of consent in antibiotic trials.
REFERENCES


30. Committee for Medicinal Products for Human Use; Efficacy Working Party; Committee for Release for Consultation. Committee for Medicinal Products
A noninferiority trial is a study in which a new treatment is compared with an existing, already available treatment, but in which the statistical analysis does not evaluate the possible superiority of the new treatment. Rather, it tests whether the new treatment is not worse than the existing treatment, using a prespecified threshold for the evaluation (the “noninferiority margin”). In this issue of JAMA Internal Medicine, Doshi et al1 explore both what patients are being told, and what they should be told, about the purpose of the research when being asked to participate in a noninferiority trial designed to test the comparative efficacy and safety of antibiotics.

Doshi et al2 analyze patient informed consent forms used in noninferiority trials and show that they are rarely clear enough to let a patient know that the trial is a noninferiority trial, in contrast to a superiority trial. They conclude that this is a substantial ethical problem. But by exploring why certain types of disclosures are ethically required, we can perhaps instead conclude that, consistent with the deeper concerns raised by Doshi et al,1 the real issue here is not about disclosing study purposes, but rather about being sure that potential participants have received an appropriate explanation of a study’s risks.

Why is there a requirement to disclose information about a study’s purpose to potential participants? Certain types of information about a study’s purpose would be important to many people in making a decision about whether to participate. People who have certain religious views might, for example, not want to participate in a study about new forms of contraceptives. Or someone might decline to participate in a study about new forms of antibiotics, simply because they are being tested for efficacy.”2(p49) They would also disclose that the new drug might be less effective than the standard treatment.2(p49) They would also disclose that the new drug might be less effective than the standard treatment.

On the other hand, it is not obvious that knowing that a trial’s purpose is to demonstrate noninferiority, as opposed to superiority, should in a similar way be relevant to prospective participants. Doshi et al2 propose specific language that the consent form should contain, which would highlight that the study is taking place to “determine whether the new (drug) is no more than X% (eg, 10%) less effective than the standard treatment.” They would also disclose that the new drug might be better for certain patients (due to having, for example, fewer adverse effects). Nonetheless, many patients reading such a proposed disclosure could come to the conclusion that this new drug is, for the most part, not as good as the comparison drug. Or that perhaps they should not be volunteering their time and effort, let alone risking their health, to support this seemingly marginally useful endeavor.

Would this be an accurate conclusion for why these trials are allowed to take place with an explicit goal to test for noninferiority of a treatment? Probably not, and thus their proposed disclosure might actually misinform potential study participants. In fact, the leading justification for noninferiority trials is that they serve an important purpose in correcting for a type of study bias, and thus allowing the approval of certain types of drugs—in particular, antibiotics that can be effective against drug-resistant bacteria. Here, for example, is a discussion of 1 aspect of these trials from a paper by the Antimicrobial Availability Task Force of the Infectious Diseases Society of America that was included in a US Food and Drug Administration briefing document that Doshi et al3 themselves cite: “Ironically, while resistance decreases the efficacy of available antimicrobial agents, it paradoxically increases the difficulty of superiority testing of new antimicrobial agents because patients infected with bacteria resistant to the approved comparator drug used in a clinical trial are excluded from enrollment in that trial. Since these excluded patients are the very patients for whom a new antimicrobial agent is likely to be superior to the approved comparator drug, antimicrobial trials are inherently biased against finding superiority of the new agent. Therefore noninferiority (NI) trials have become the standard method by which investigational antimicrobial agents are tested for efficacy.”2(p49)

Given the growing problem of antibiotic resistance, there is an urgent need to be approving more antibiotics. And the findings of Doshi et al3 themselves demonstrate that noninferiority studies seem to be the accepted mechanism for obtaining such approvals: of the 78 trials for which they obtained data, 72 (92%) were noninferiority trials.

The bottom line is that the usual justification for this type of trial rests on fairly complicated and technical study design issues relating to how our society chooses to allow particular products to be approved for marketing. Regardless of whether one fully agrees with the existing rules allowing the conduct of such trials (such as whether using a noninferiority analysis is the right way to correct for study bias), it does not seem reasonable to ask a participant to try to understand the complicated debate in the research community about whether these trials should even be allowed.