CLINICAL INVESTIGATION

Design of clinical trials of antibacterial agents for community-acquired bacterial pneumonia

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Standards for the conduct of clinical trials of antibacterial agents for community-acquired bacterial pneumonia (CABP) have changed dramatically in recent years. A draft guidance from the US FDA on the conduct of such trials was issued in March 2009. However, the guidance has already faced substantial criticism during the open public comment period, resulting in uncertainty regarding the appropriate design of such studies from a regulatory perspective. Controversies regarding the magnitude of the treatment effect associated with antibacterial therapy versus placebo/no therapy, the appropriate timing, nature and noninferiority margin for the primary efficacy end point, and other clinical and statistical issues have complicated efforts to reach consensus on appropriate trial design of antibacterial therapy for CABP. It is critical that studies of new drugs for CABP are designed to ensure that they are feasible to conduct and that their results are scientifically valid, statistically rigorous and clinically meaningful. Based on 3 years of active dialog between clinical, statistical, and regulatory experts, this article proposes an approach to enable a balance of clinical trial feasibility with appropriate scientific, statistical and clinical rigor.

Keywords: clinical trial • community-acquired bacterial pneumonia • composite end point • justification of noninferiority margin • noninferiority study

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Clinical trials of new antibacterial agents for the treatment of community-acquired bacterial pneumonia (CABP) typically test the hypothesis that the new drugs are not inferior to an unacceptable degree relative to established antibacterial agents (i.e., using a noninferiority clinical trial design). The US FDA has recently re-evaluated the appropriateness of the noninferiority trial design for CABP, as it has for many other diseases. This re-evaluation of the regulatory standards for CABP trials is the result of both a greater understanding of the statistical complexities underpinning the interpretation of results from noninferiority trials [1–4,101,102], as well as intense public scrutiny in the aftermath of highly publicized post-approval drug failures, such as that of telithromycin [5–7], for which questions of safety and appropriateness of noninferiority trial conduct were raised.

As discussed in the International Conference on Harmonization (ICH) E9 and E10 guidances [103,104], experimental drugs should be approved based on noninferiority clinical trials only when the comparator drug can be confidently known to be superior in efficacy to placebo for the disease under study. Unfortunately, antibacterial agents were among the first effective drugs, and their use preceded by two decades the widespread conduct of randomized, controlled studies [8,9]. Hence, for most serious or life-threatening infections, including CABP caused by typical bacteria, no placebo-controlled studies have ever been conducted. Unfortunately, the absence of previous placebo-controlled trials complicates the statistical justification of modern noninferiority clinical trials for CABP.

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The resulting regulatory uncertainty regarding acceptable trial design for the evaluation of antibacterial agents for the treatment of CABP has contributed to limited investment in the already fragile antibiotic research and development pipeline [10]. Meanwhile, the need for new antibacterial agents is becoming more urgent. This article summarizes 3 years of active dialogue between clinical, statistical and regulatory experts regarding challenges in the design, conduct, and interpretation of clinical trials of antibacterial agents for the treatment of CABP. We suggest a path forward that balances the critical public health need to ensure that: antibacterial agents that are approved are safe and effective for the disease in question; clinical trials used to evaluate promising agents are ethical; and, the development of critically needed new antibacterial agents is feasible.

■ Are placebo-controlled trials of antibacterial agents for CABP appropriate?

In 2007, the lack of a widely accepted, defined treatment effect size for antibacterial agents for CABP led to considerations of the need to perform placebo-controlled studies to define the benefit of antibacterial therapy for this disease. As a result, in January 2008 the Infectious Diseases Society of America (IDSA) and FDA held a workshop examining clinical trial design for CABP [11]. On the first day of the workshop, the possibility of performing placebo-controlled trials to define the magnitude of efficacy of antibacterial agents for CABP was mentioned more than two dozen times, including repeated mention by advocates of this approach [105]. That a requirement for placebo-controlled trials was being considered seriously is underscored by the fact that 3 months after the workshop, the FDA specifically asked its Anti-Infective Drug Advisory Committee to vote on whether such studies could or should be conducted [106]. These discussions regarding the potential conduct of placebo-controlled studies of CABP occurred despite the fact that CABP was a leading killer of Americans at the beginning of the 20th Century, causing Osler to refer to the disease as "the Captain of the men of death" [12]. Furthermore, it has since been established that delays in instituting antibiotic treatment are associated with worse survival and clinical outcome of CABP [13–15], making the use of rescue therapy as a way to mitigate the risk of a placebo arm untenable.

In 2008, the IDSA published a position paper on trial design for antibiotic treatment of CABP in which the conduct of placebo-controlled trials was explicitly rejected as being unethical [16]. The position paper emphasized that CABP caused by 'typical' pyogenic bacteria (e.g., *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Staphylococcus aureus* and *Klebsiella pneumoniae*), as well as by *Legionella*, has an unacceptable fatality rate without treatment. Ethically, placebo cannot be administered to patients with such infections given the existence of alternative therapies universally accepted as efficacious and life-saving. By contrast, pneumonia caused by *Mycoplasma pneumoniae* is typically mild and not life-threatening. Nevertheless, two randomized, placebo-controlled trials and three prospective nonrandomized studies have already demonstrated significant, clinically meaningful benefit of active versus inactive antibacterial agents or placebo for this disease [17–21], making future such studies unethical to conduct. After the IDSA presented its position at the FDA Anti-Infectives Drug Advisory Committee in April 2008, the Committee [107] and the FDA itself [108] agreed that placebo-controlled trials of antibacterial agents for the treatment of CABP were unethical and should not be conducted.

■ Can active-controlled superiority studies be conducted of antibacterial agents for the treatment of CABP?

New antibacterial agents are clearly needed to treat bacteria that have become resistant to currently available treatment options. However, it is unethical to knowingly withhold alternative active therapy from a patient with a serious or life-threatening bacterial infection. Therefore, enrollment criteria and comparator antibacterial agents for clinical trials are selected to ensure that all or almost all patients enrolled receive therapy to which the etiologic bacteria are susceptible; patients infected with bacteria resistant to the comparator antibacterial agent are excluded from clinical trials. As antibacterial agents are very effective when used to treat infections caused by susceptible bacteria, demonstration of superiority of a new drug against an active comparator in this setting is unlikely. Indeed, a remarkable consistency of treatment effect has been seen across all recent CABP trials, independent of the particular drug under study, with a ~90 ±5% clinical response rate in both experimental and comparator arms [22] (as compared with a ~40% clinical response rate in the pre-antibiotic era [16,23]). Hence, while ethical, active-controlled superiority studies are impractical to conduct for CABP.

Since active-controlled superiority trials are impractical and placebo-controlled superiority trials are unethical, noninferiority studies for CABP are necessary, reasonable and the only scientifically valid approach to enable future approval of new antibacterial agents for the treatment of CABP.

Noninferiority trial design parameters

■ What should the primary efficacy end point & noninferiority margin be?

Data quantifying the mortality benefit of antibacterial agents

Despite the lack of randomized, placebo-controlled trials, more than a dozen clinical studies using historical or concurrent controls have unanimously demonstrated a substantial mortality benefit of antibacterial agents for the treatment of CABP in both children and adults [16,24,25]. In historically controlled studies of patients with confirmed *S. pneumoniae* CABP, mortality rates in the pre- versus immediate post-antibiotic era were 38% versus 12%, respectively, for a 26% (95% CI: 24–28%) absolute reduction in mortality with antibacterial treatment (number needed to treat (NNT) to save a life of ~4) [16]. In concurrent-controlled studies of patients with lobar pneumonia (many of whom did not have microbiological confirmation of bacterial etiology of disease), the mortality rates without versus with antibacterial therapy were 23% versus 7%, for a 16% (95% CI: 10–22%) absolute reduction in death with antibacterial therapy (NNT to save a life of ~6) [16]. Antibacterial agents substantially reduced death across all age and disease severity strata, although a substantially greater absolute mortality reduction was seen in older patients. Specifically, for patients aged less than 30, 30–59 or 60 years or older, the absolute reduction in mortality associated with antibiotic use was 11% (95% CI: 8–13%), 27% (25–30%) and 45% (39–54%), respectively [16]. Despite initial doubt expressed by some during the January 2008 workshop [109], the existence and validity of data demonstrating that antibacterial agents are effective for patients with CABP, across all ages and disease severity, are compelling and no longer in dispute [110].

The limitations of mortality as an end point

After consensus developed that there was a substantial mortality benefit of antibacterial agents for CABP, and that placebo-controlled studies would be unethical, it was suggested that mortality was the only valid end point for clinical trials in CABP [111]. However, mortality rates observed in modern, noninferiority clinical trials in CABP have been approximately 2%. Even if a population with a mortality rate of 5% could be enrolled, a noninferiority study based on mortality would require more than 5,000 patients to be enrolled (assuming 90% power, 25% microbiological confirmation of infection and noninferiority odds ratio margin of 1.6). Two such noninferiority studies likely would be required for approval of the new drug, meaning that 10,000 patients would have to be enrolled, at a likely cost of more than US$500 million. Such studies are unlikely to be feasible and the predicted cost would represent a tremendous disincentive for investment by industry in antibacterial development. However, using a composite primary end point of survival or clinical response may allow such studies to be conducted practically and rigorously.

Composite end point: alive and resolution of signs and symptoms of infection

The IDSA and FDA have summarized the substantial evidence of improvement in clinical response mediated by antibacterial agents for the treatment of CABP [16,24,112]. Clinical benefit was seen across all disease severity strata, from the least sick, healthy, young military recruits with atypical pneumonia to the sickest patients with bacteremic, *S. pneumoniae* pneumonia. At the December 2009 Anti-Infective Drug Advisory Committee meeting, Mary Singer from the FDA presented data on the clinical response of patients with CABP treated with sulfonamide drugs or background therapy (Figure 1A) [112]. In the historical literature, clinical response was defined by the achievement of the 'crisis' of CABP, after which the fever broke, heart rate and respiratory rate slowed, and the patient became markedly more comfortable [23,26]. The maximal separation of the clinical response rates between patients treated with sulfonamides versus background medical therapy occurred at day 3–4, with approximately 90% absolute difference in point estimates of clinical resolution (Figure 1).

Consternation has been expressed by some that the magnitude of this difference narrowed over the subsequent several days, such that by day 7, close to 40% of patients who did not get treated with antibacterial agents had spontaneously resolved their pneumonia. The fact that difference in rates of resolution of infection between treated and untreated patients was maximal at day 3 to 4 has led some to suggest that the primary efficacy analysis for a CABP clinical trial should occur at day 3 rather than at end of therapy or test of cure. This approach is clinically inadequate and does not reflect the standard expectation that modern antibacterial therapy results in durable cure of infection, not merely improvement at an earlier time point. Patients and physicians appropriately expect antibacterial therapy that cures infections, and a primary efficacy analysis focused on an early time point cannot answer this question. Therefore, an early time point is clinically unacceptable as the primary efficacy outcome measure.

It is also statistically unnecessary to use an early time point for a primary efficacy analysis for CABP clinical trials. Despite the fact that patients treated without antibacterial agents had a detectable rate of spontaneous

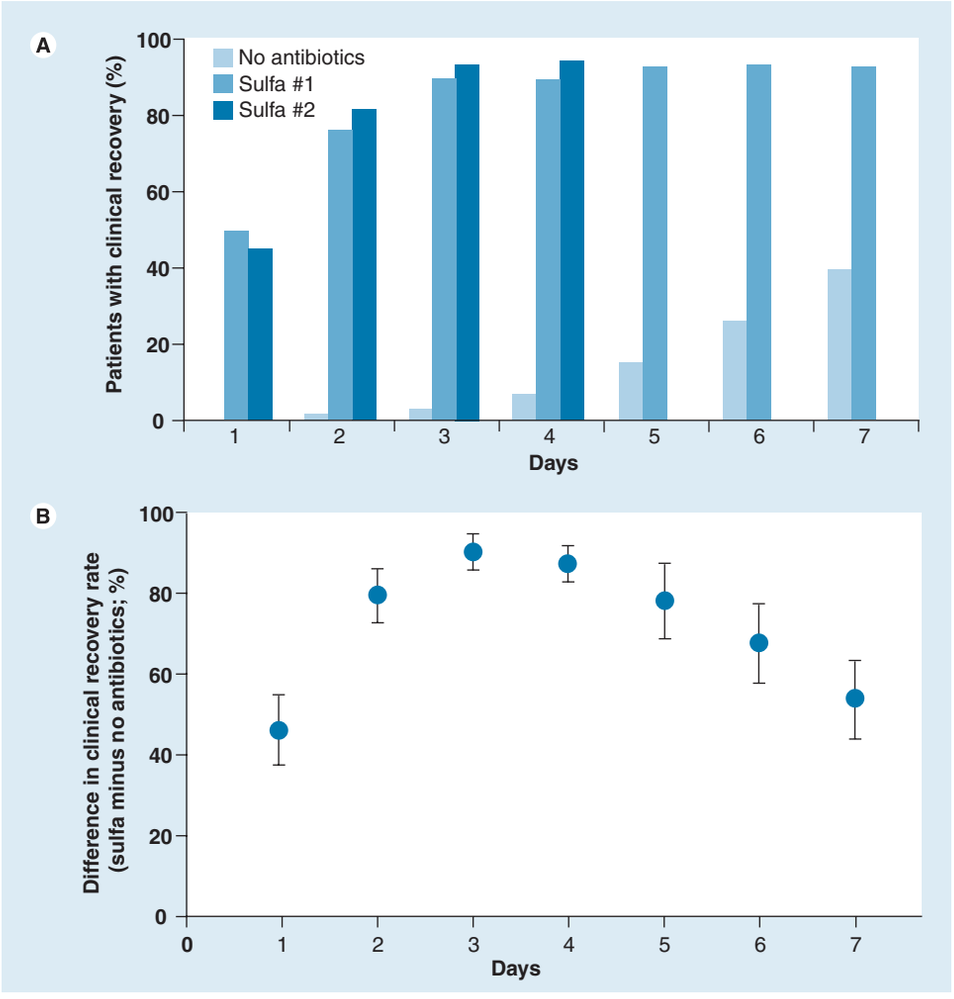

Figure 1. Improvement in clinical response in patients with community-acquired bacterial pneumonia treated with sulfonamide antibacterial agents versus standard background medical therapy without antibacterial agents. (A) Percent of clinically responding patients by day post-presentation to the hospital in three cohort studies, including one from 1937 (no antibacterial agents) [23] and two from 1939 (sulfapyridine #1 and 2) [28,29]. The pre-antibiotic study did not include dead patients in the analysis; by contrast both sulfonamide cohorts incorporated dead patients into the analysis. **(B)** Point estimates (open circle) and 95% CI (error bars) of the difference in clinical response rates between patients treated with sulfonamide (average of both studies through day 4, and then sulfapyridine #1 alone from day 5–7) versus no antibacterial therapy.

resolution of pneumonia by day 7 in historical studies, the lower bound of the 95% CI of the difference in the cure rates between the antibacterial and background therapy groups remained greater than 40% (absolute) at day 7 (Figure 1B).

Furthermore, the control curve for this analysis is taken from a cohort of 662 patients with *S. pneumoniae* pneumonia treated without antibacterial agents, "all of whom recovered without observed purulent complications" [23]. Therefore, the clinical response of the control group is artificially high, because those who died or who had purulent complications (e.g., empyema, endocarditis, pericarditis, meningitis, septic joints and glomerulonephritis) of CABP were explicitly excluded from this analysis cohort [23]. By contrast, deaths were not excluded from the studies of sulfonamide antibacterial therapy for CABP [27,28]. Thus the difference between clinical cure rates in patients treated with and without antibacterial agents as expressed is artificially low, and even more so at later times, as more dead patients in the control group are cumulatively excluded from the analysis. Furthermore, this estimate of antibacterial efficacy is based on comparison of sulfonamide antibacterial therapy, not penicillin therapy, to background medical care [23,27,28]. Yet penicillin therapy is substantially more effective than sulfonamide therapy for the treatment of CABP [16,29–32]. Therefore comparison of sulfonamide therapy versus no antibacterial therapy clearly results in a substantial underestimate of modern antibacterial effectiveness.

When evaluating the historical mortality and the clinical response data and formulating a composite end point, it is necessary to account for the fact that the control (no antibiotic) cohorts either provide only mortality data (summarized in [16]) without clinical failure data and or only clinical failure data without mortality data [23]. By contrast, both sulfonamide studies that report clinical failure data also report deaths (1/30 and 4/100 [27,28]). Of these two studies, only the smaller study reports clinical failure rates out to day 7 [27]. Thus, only its mortality data can be included in the composite analysis relevant to a modern study, in which the end point analysis is conducted at the end of therapy.

Several estimates of the antibacterial treatment effect size for a composite end point of survival and clinical response can be generated depending on the imputed mortality rates (Table 1). Based on data from concurrent controlled studies, the lower bound of the 95% CI of the difference in mortality of patients (of all ages) with CABP treated with antibacterial agents versus with no

Table 1. Estimated effect size of sulfonamide antibacterial agents versus background medical therapy for a composite end point of alive and clinical resolution at day 7.

Estimate	Mortality (%)		No sulfa imputed deaths for composite end point[†]	Clinical resolution (%)		Difference in composite outcome (%) (95% CI)[‡]
	Sulfa	No sulfa		Sulfa	No sulfa	
Base	3 [23] (1/30)	13[§]	99	93 [27] (28/30)	39 [23] (261/662)	64 (53–75)
Sensitivity #1	3	3[¶]	20			53 (42–64)
Sensitivity #2	7 [16] (21/308)	23 [16] (58/254)	198			71 (59–83)

[†]Number of deaths not included in the control (no antibacterial) dataset for clinical cure since that cohort of 662 patients excluded all patients who died [23], calculated as: [662 / (1 – mortality rate)] – 662. Deaths were not excluded from original sulfa dataset and hence did not need to be imputed.

[‡]Difference in proportion of Composite Success (alive and clinically resolved at day 7); Composite Success = (N (including imputed deaths) – total failures)/N. Total failures = imputed deaths + clinical failures at day 7.

[§]Estimate generated by adding the lower bound estimate of the difference in mortality with and without antibacterial agents from a previous systematic review [16] to the mortality rate in the only sulfonamide clinical trial that reported clinical resolution rates out to day 7 [27].

[¶]Assuming no difference in mortality rate with the mortality rate reported in the sulfonamide study.

Sulfa: Sulfapyridine.

antibacterial agents is 10% [16]. Thus in the base case estimate (Table 1), assuming a 3% mortality rate in the antibacterial arm (based on the one sulfonamide study that reported both day 7 clinical response data and mortality data [27]), an absolute 10% increase would result in a 13% mortality rate in patients treated without antibacterial agents. Since 13% of the original group is estimated to have died, the 662 patients in the cohort represent the 87% who survived. Thus, the original total CABP control cohort can be estimated to have had 761 patients, with 99 deaths and 662 survivors, and a 39% day 7 clinical response rate among the survivors [23]. Adding together the failures resulting from deaths and lack of clinical response results in a composite success (alive plus clinical response) rate of 26% in the absence of antibacterial therapy versus 90% with antibacterial therapy, for a day 7 absolute antibacterial treatment effect size of 64% (95% CI: 53–75%) (Table 1).

In a sensitivity analysis, decreasing the modeled mortality rate in the pre-antibiotic control cohort so that it was the same as in the antibacterial-treated cohort (3%) results in an estimate of a 53% (95% CI: 42–64%) absolute increase in composite success with antibacterial therapy versus background medical therapy at day 7 (i.e., end of therapy). This sensitivity analysis is extraordinarily conservative given the overwhelming evidence of excess mortality without antibacterial therapy. In another sensitivity analysis, mortality rates were imputed from the previously published systematic review of concurrent controlled studies of antibacterial therapy versus no antibacterial therapy for CABP (7% mortality with antibacterial agents vs. 23% without [16]). Use of these mortality rates results in an estimate of a 71% (95% CI: 59–83%) absolute improvement in composite success with antibacterial therapy at day 7.

Hence the smallest estimate (lower bound 95% CI) of the absolute difference in a day 7 composite end point of alive and clinical success between patients treated with and without antibacterial therapy is 42% in favor of antibacterial therapy. This is an extremely conservative estimate, since it presumes no difference in mortality in patients treated with or without antibacterial therapy, it does not include patients in the control group who survived but with purulent complications, and it uses the 95/95 method (i.e., comparing the lower bound of the 95% CI of success rates with antibacterial therapy with the upper bound of the 95% CI of success rates without antibacterial therapy). The 95/95 method is recognized by the FDA to be highly conservative [102]. Reducing by half the difference in success rates with or without antibacterial therapy, to preserve at least half of antibiotic benefit, would still easily allow for a 10–15% absolute noninferiority margin for the composite end point at day 7 of therapy [108].

What elements should be incorporated in a composite primary efficacy end point?

Resolution of fever, cough, chest pain, dyspnea, malaise or hypoxia are important clinical end points because they cause patients substantial discomfort and distress, and their resolution has been shown to predict when patients can be safely discharged home with minimal risk of recurrence or readmission to the hospital [19,20,33–39]. Furthermore, resolution of these signs and symptoms is concordant with the descriptions in the historical literature of resolving illness in patients with CABP after the 'crisis.' Finally, use of clinical improvement to guide the timing of the switch from intravenous to oral antibacterial agents and of hospital discharge has been incorporated into national guidelines for the treatment of CABP [40].

Therefore, a composite end point should consist of survival and resolution of all individual signs and symptoms present at baseline due to the CABP, to include fever (or hypothermia), cough, chest pain, dyspnea, malaise or hypoxia, and leukocytosis or leucopenia (based on the latter's incorporation in sepsis/systemic inflammatory response syndrome criteria, which are validated in tens of thousands of patients to correlate with severity of illness for infections [41]). Signs and symptoms determined to be 'due to' the CABP are those that are acutely new/different from the patient's baseline clinical status. Presence or absence of each of these individual components should be documented at baseline and again at end of therapy (i.e., approximately day 7, or before if a short course therapy is under study) when the primary efficacy analysis is conducted. Definitions for each symptom or sign should be prospectively established to allow unbiased assignment to the binary outcomes of present versus absent. Global success would require that patients be alive and have resolution of each individual sign or symptom documented to be present at baseline, and no new related signs or symptoms.

Whenever a composite end point is used it is important to recognize that the individual components of the end point may not be equivalent in importance. For example, in the case proposed, "dead-at-day-7" has greater impact than being alive with a persistent fever at day 7. One strategy to account for this difference in importance of composite components is to weight the individual components to form a simple utility function. For example, all patients might be assigned a numerical value at day 7: 2 = alive with clinical resolution, 1 = alive without resolution, 0 = dead. Outcome scores could then be summed and compared. This approach is likely to yield a higher trial power for a given sample size than using a simple dichotomous primary outcome measure. Regardless, all components of the end point should be individually tabulated as secondary end points, with any adverse trend in mortality meriting closer examination. Indeed, it would be appropriate for a substantial trend towards an adverse mortality effect in patients receiving experimental therapy to preclude approval of the drug, irrespective of the primary efficacy analysis using the composite end point.

Debate over selection of the M2 margin from the M1 margin

The ICH E9 and E10 guidance documents [103,104], and a recent FDA guidance on noninferiority clinical trials [102], describe the process by which the noninferiority margin (M2) for a clinical trial can be selected after knowing the historical effect size of the comparator regimen versus placebo/no therapy (M1). The key principles are that the noninferiority margin (M2) selected for a clinical trial must: be smaller than the historical effect size of the comparator versus placebo/no therapy (M1); and in addition to being smaller than M1, M2 must also preserve a clinically meaningful fraction of M1. In practice, it has commonly been suggested to set M2 so that it is half of M1, preserving 50% of the effect size of the comparator drug (Figure 2A). More recently, some have begun adding an additional "discount" step, in which the historical effect size (M1) is first cut in half to account for methodological limitations in the data resulting in the calculation of M1. After that discount step, a further 50% reduction is applied to 'preserve' a clinically meaningful fraction of the discounted M1.

These approaches are arbitrary and overly conservative, especially when the original estimate of efficacy is already highly conservative, as discussed above. We are not aware of any specific scientific evidence or legal statute indicating the need to further discount by 50% M1, or for requiring preservation of 50% of M1 when setting M2. The resulting calculation may appear mathematically precise, but in reality it is merely arbitrarily and overly conservative based on subjective selection of how much to discount M1 to account for methodological issues in determining M1 and how much to further reduce the discounted M1 in setting an M2.

Thus, as long as the effect size of the comparator drug (M1) is substantially greater than the proposed noninferiority margin (M2), it is more logical to simply select an M2 that preserves a clinically meaningful component of M1, rather than using an arbitrary mathematical calculation to derive the M2 margin. For example, it generally has been agreed by clinicians and multiple medical societies that an M2 for mortality should never be larger than 10% (absolute, not relative), because it is never acceptable to approve a drug that could result in more than a 10% absolute increase in mortality rate than a comparator drug [16,42]. Therefore, if the mortality benefit of a comparator drug is substantially larger than 10% relative to placebo, the M2 margin for a noninferiority study should still be no more than 10% (absolute, not relative) for mortality. We and others have suggested that a 15–20% margin may be acceptable for nonmortality clinical end points, particularly if the experimental drug offers specific advantages over available therapy, such as superior safety, dosing considerations, or for antibacterial agents, activity against antibiotic-resistant bacteria [16,43,101,102]. Thus, the noninferiority margin should be set and justified for each study based on the individual new drug and its potential clinical utility, with a composite mortality/clinical response end point ranging from 10 to 15% being reasonable.

One concern raised about setting noninferiority margins of 10–15% is based on the impression that such a margin means that society is willing to use, and the

FDA will approve, drugs that are 10–15% less effective than comparator drugs. Substantial consternation has been expressed in public settings regarding whether regulatory standards should be satisfied by drugs that are so substantially inferior in efficacy [110]. However, enabling use of a 15% absolute noninferiority margin in a pivotal Phase III clinical trial does not mean that the agency is likely to approve a drug that is 15% worse than the comparator drug. Rather, the key to understanding the implications of a 15% noninferiority margin, in terms of the likelihood of regulatory approval of a substantially inferior antibacterial agent, is to examine the power curve for such a trial (Figure 2B). In the example shown, the trial is designed to have a power of 95% to demonstrate noninferiority with a margin of 15%, an α of 0.05 and a treatment success rate of 80% with the comparator drug. As is commonly done, the power is defined for the alternative hypothesis that the two drugs are exactly equivalent in efficacy. Although the preplanned noninferiority margin is -15%, the actual probabilities that a positive trial result will be obtained if the true effect of the new agent is -15, -10 or -5% relative to the comparator drug is 5, 26 or 67%, respectively. Hence, it is highly unlikely that an experimental drug, which is 15% less effective than the comparator drug, would result in a positive trial result.

Furthermore, the FDA typically requires that two noninferiority trials be conducted to support approval of a new drug. If the true effect of the new agent is -15, -10 or -5% relative to the comparator drug, the probability of obtaining two positive noninferiority trials is 0.25, 6.7 or 44%, respectively. Thus, with a margin of -15% a new agent that was truly 15% inferior has only a 1 in 400 chance to achieve noninferiority in two trials, and the agent

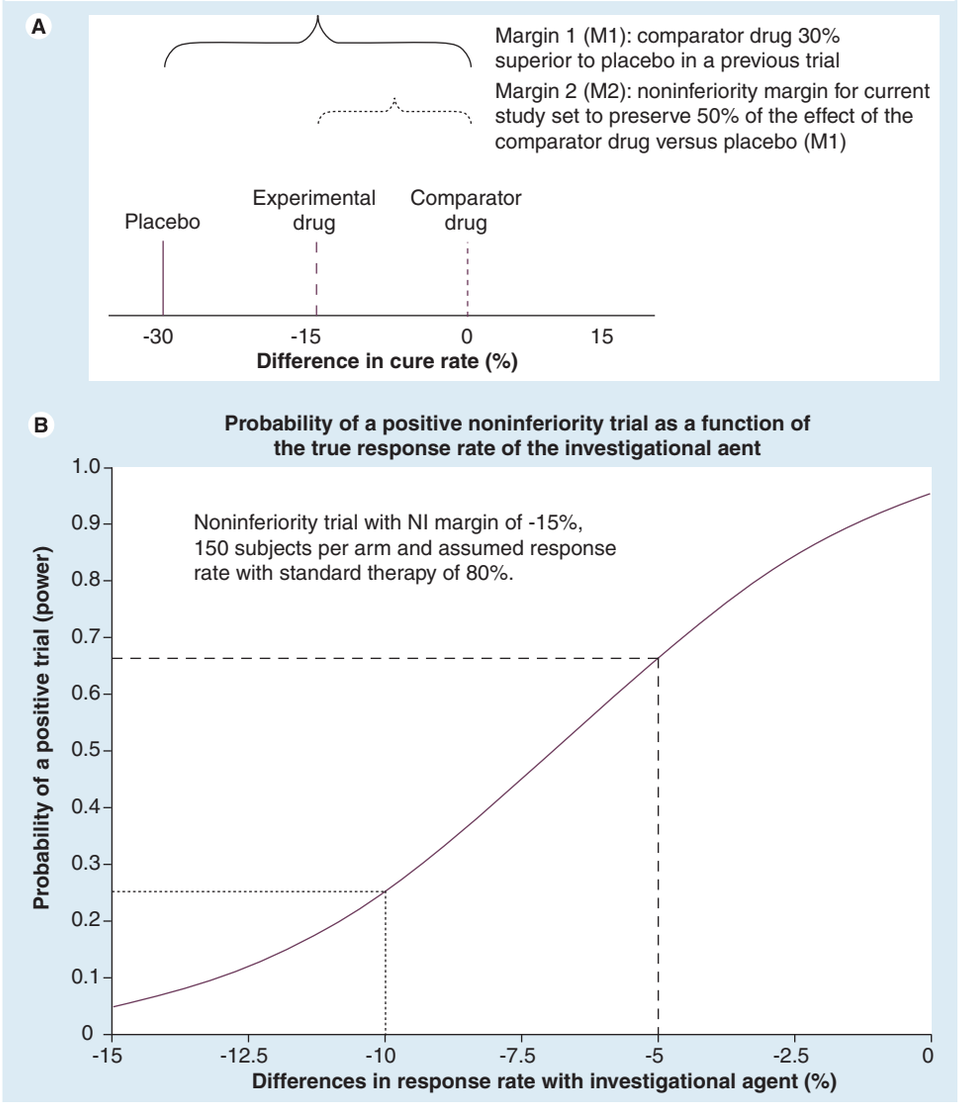

Figure 2. Determination of non-inferiority margins. **(A)** Difference in efficacy between a comparator drug, an experimental drug, and placebo. The M1 margin is the lower bound of the 95% CI of the difference in efficacy between the comparator drug versus placebo based on previous studies. The M2 margin is the pre-planned noninferiority margin for the current study, and is often set to preserve 50% of the effect of the comparator drug (i.e., it is set to be 50% of the magnitude of M1). **(B)** The power curve for a clinical trial with a noninferiority margin of -15%, an α of 0.05, and an expected 80% success rate in the comparator arm. The power curve shows the probability of demonstrating noninferiority as a function of the true difference in efficacy between the treatment arms. In the example shown, the trial has a power of 95%, or a probability of 0.95 for demonstrating the noninferiority of the experimental drug if both the experimental and comparator drugs yield a success rate of 80% (a difference of 0%). The probability of a positive trial (i.e., establishing noninferiority of the experimental to the comparator drug) is graphed on the vertical axis against the true difference in success rate between the experimental and comparator drugs (i.e., experimental drug success rate - comparator drug success rate) on the horizontal axis. For example, if the experimental drug is associated with a true absolute difference of -5, -10 or -15% relative to the comparator drug, the trial has a 67, 26 or 5% chance of achieving a positive outcome (i.e., establishing noninferiority), respectively.

must have an effect better than -5% relative to the comparator drug to even have a 40% chance of yielding two successful trials to support regulatory approval.

Why take any chance that the approved drug could be inferior in efficacy to the comparator drug? As the noninferiority margin shrinks, the required study sample size – and hence study cost and required time to complete enrollment – markedly increases. If new antibacterial agents are critically needed, we must balance feasibility of conducting studies (and the resultant public health benefit of facilitating approval of effective new antibiotics) against a desire to narrow the noninferiority margin. While patients may be harmed if ineffective drugs are allowed to reach the market, they may also be harmed if they have an infection for which no effective antibacterial agents have been developed. Furthermore, if the criteria for study conduct are so strict that it is infeasible to enroll meaningful numbers of patients in the USA, or the trial results are not generalizable post-approval, then we run the risk that the observed safety and efficacy of the drug in its pivotal studies will not be informative regarding the safety and efficacy of patients in the USA actually exposed to the drug. The key is to create a regulatory path that balances these competing risks.

It is also important to emphasize that the FDA is not obligated to approve a drug simply because it meets its prespecified noninferiority margin in its pivotal studies. For example, a drug with a point estimate for efficacy of -7.5% and a 95% CI of -1–14% relative to the comparator drug will have been shown to be inferior in efficacy to the comparator regimen, and such a drug is unlikely to be approved despite the fact that it met its prespecified noninferiority margin of -15%. Rather, the FDA appropriately considers the totality of the evidence of safety and efficacy when deciding whether or not to approve a drug. A greater tolerance should be granted for potential inferiority for an experimental drug with meaningful advantages in safety, antibacterial spectrum of action, dosing interval or other important clinical parameters, relative to comparator drugs available. By the same token, for a drug with no meaningful clinical advantages over available therapy, tolerance for potential inferiority or uncertainty with respect to safety should be minimal.

A reasonable compromise between the need to ensure that a newly approved drug is safe and effective and the need to enable feasible-to-conduct studies may be to accept as a general benchmark a 10–15% margin of noninferiority for the composite end point. Of course, the margin specifically must be justified for each individual drug and noninferiority study. For example, a margin of 10% may be justified for drugs with few to no clinical advantages over other drugs on the market, while a margin of 15% may be justified if the drug has substantial advantages over other drugs on the market (e.g., activity against extreme drug resistant or pan-drug-resistant bacteria that cannot be treated by any other drugs on the market, substantial safety advantages).

In summary, when considering the design of a clinical trial, sponsors should justify the noninferiority margin (M2) by providing an analysis of the potential benefits of the experimental drug relative to other drugs on the market. The historical data providing an estimate of antibacterial effect size versus placebo/no therapy have already been summarized and discussed for 3 years, and there is little point in sponsors repeating these analyses. The summarized data can be used by sponsors, as appropriate, to further support the specific design features of their study. From highly conservative analyses, it is clear that the effect size of antibacterial agents in CABP for both mortality and clinical end points is very large at the end of therapy. Sponsors and regulatory agencies should avoid unjustified statistical discounting of the already conservative estimates of historical effect size, and should avoid arbitrarily selecting the fraction of the discounted clinical benefit to 'preserve' in the noninferiority margin (M2). Rather, sponsors and regulatory agencies should select the margin for an individual study based upon an assessment of the relative merits of the specific candidate drug and key features of the proposed study design. Factors to be considered include relative advantages of the experimental drug versus drugs already on the market (e.g., antibacterial spectrum of activity, novel mechanism of action, safety and dosing) as well as trial design features, such as the percent of microbiologically confirmed CABP required in the preplanned primary efficacy analysis population and the disease severity of the enrolled patients (see below).

Biocreep

Another concern regarding the use of noninferiority margins of more than 10% has been the potential for wider margins to increase the risk of 'biocreep'. Biocreep is a theoretical process in which decreasingly effective drugs are sequentially approved over time. As each new generation of less effective, approved drugs becomes the standard comparator for the next NI clinical trial, the true difference in efficacy between placebo and the original comparator drug disappears. However, there is no evidence that biocreep has occurred for antibacterial agents for the treatment of serious and life-threatening infections such as CAPB [1,44,45]. Indeed the US Government Accountability Office (GAO) recently completed a Congressionally requested review of this issue and they also found "no evidence of biocreep" [113].

Furthermore, there is compelling evidence that noninferiority studies do detect inferior antibacterial agents, preventing their approval. For example, in the last 3 years tigecycline and ceftobiprole failed to achieve noninferiority in their pivotal studies in patients with ventilator-associated pneumonia due to inadequate dosing in critically ill patients [46,47], daptomycin failed to achieve noninferiority in its pivotal trials of CABP due to the drug's inactivation by pulmonary surfactant [48], and iclaprim failed to meet noninferiority in its pivotal complicated skin infection studies. None of these drugs were approved for these indications, which prevents their use as comparator drugs in future noninferiority trials, mitigating the risk of biocreep.

In the absence of evidence that biocreep has actually occurred, and given the evidence that noninferiority studies with previously used margins can detect inferior antibacterial agents, narrowing noninferiority margins is not an optimal means of reducing the risk of biocreep. In the case of CABP, the benefit of narrowing margins below 10% is offset by the deleterious affect on public health by reducing the availability of needed new antibacterial agents.

We also emphasize that approving an inferior drug does not lead to biocreep unless that drug is allowed to be used as the comparator agent in a future noninferiority clinical trial. Thus, focusing on the margin for a noninferiority study only indirectly addresses the concern of biocreep. The only way to directly protect against the risk of biocreep is to ensure that the comparator drug used in a NI clinical trial is actually the best candidate available based on robust efficacy data [45]. Selecting the most effective comparator drug is advantageous because it will protect against biocreep without further impeding the development of critically needed new antibacterial agents.

Primary efficacy analysis population

In a superiority study, the enrollment of patients who do not actually have the disease under study biases the trial towards the null result (no difference between treatments and thus no evidence of drug effect). By contrast, in a noninferiority study, the enrollment of patients who do not have the disease under study will have the effect of masking true differences in efficacy between the experimental and comparator therapies, increasing the risk of falsely concluding that the new drug is not unacceptably inferior in efficacy. Therefore, for noninferiority clinical trials of antibacterial agents for the treatment of CABP, it is critical that patients have bacterial pneumonia, rather than any of a variety of confounding diagnoses that may present similarly to CABP but not respond to antibacterial therapy (e.g., viral or fungal pneumonia absent a co-existing bacterial infection, pulmonary embolus, pulmonary edema and hypersensitivity pneumonitis).

The 2009 FDA draft guidance on trials of antibacterial agents for the treatment of CABP indicated that 100% of evaluable patients must be confirmed to have bacterial infection, which is scientifically valid and would help ensure that noninferiority will not be driven by spontaneously resolving nonpneumonia diseases in both arms of the study. However, as the IDSA emphasized in its position paper, the concurrent controlled historical data that provide much of the efficacy justification for establishing the noninferiority margin did not include 100% microbiologically confirmed pneumonia [16]. Rather, approximately 50% of the patients in the concurrent controlled studies were confirmed to have bacterial pneumonia (not all of which was due to the most aggressive pathogen, *S. pneumoniae*), and still the antibacterial treatment effect size was very large. Not surprisingly, in historically controlled studies, where almost 100% of patients were confirmed to have *S. pneumoniae* CABP, the effect size of antibacterial therapy was even greater [16].

Requiring that over 50% of patients in the primary efficacy analysis population be confirmed to have a bacterial etiology of pneumonia would be commensurate with the rate of confirmation in the concurrent controlled historical studies comparing antibacterial therapy to background therapy. Furthermore, such a requirement would substantially, and appropriately, raise the bar versus previously conducted studies, which have often had a 20–30% rate of bacteriological confirmation of infection [22]. Given the low bacteriological confirmation rate with standard microbiological diagnostic testing, requiring a 100% confirmation rate may result in an infeasible study design, increasing the enrolled population by fourfold compared with studies conducted over the past several decades. As mentioned, one potential compromise would be to allow a variation in the noninferiority margin based on the proportion of evaluable patients with bacterial confirmation, for example, requiring a 10% noninferiority margin if 50% of patients are bacteriologically confirmed and allowing a 15% margin if more than 75% of patients are bacteriologically confirmed. This is an example where study design must be an integral component defining the margin for an individual drug development program.

In the past, patients in CABP trials were often excluded from the primary end point analysis if they received an insufficient number of days of therapy (usually ≤ 3 days), due to the assumption that patients dying within that time frame were sufficiently ill to have been unlikely to have benefited from any antibiotic therapy. However, in today's environment of early goal-directed therapy, and other critical care supportive measures, it is not clear that this assumption is valid. Furthermore, early deaths on

therapy may reflect an exacerbation of underlying disease, toxicity of the trial drug or worsening sepsis caused by sudden lysis of bacteria. Therefore, patients with early termination of study treatment should not be excluded from the primary analysis dataset.

In summary, the population used for the primary efficacy analysis should be the modified (patient has received at least one dose of therapy) intention-to-treat (mITT) population. Furthermore, for the primary efficacy analysis, the mITT population should be enriched (i.e., ≥50%) for patients in whom bacterial confirmation of infection has been achieved, referred to here as the modified microbiological ITT (mMITT) population.

■ Enrollment criteria

Disease definition

Pneumonia is commonly defined by the presence of signs and symptoms of infection, including fever, tachycardia, tachypnea, hypoxia, cough, chest pain, and/or production of purulent sputa, in the presence of an infiltrate on chest x-ray (CXR) [40]. These criteria are sensitive but not necessarily specific for CABP. They are necessary to enrich the pretest probability of CABP, which can then be confirmed with microbiology testing (culture, antigen testing or molecular diagnostics).

A sputum gram stain may be useful to include as an enrollment criterion, as a positive sputum gram stain (defined by standard means [49]) increases the probability that the patient has bacterial pneumonia. However, obtaining gram stains is cumbersome and many specimens are rejected for inadequate quality [40]. An alternative test is serum procalcitonin, which has been shown to be highly specific for bacterial infections and can be available within several hours from the time the blood is drawn [50–52]. Therefore, procalcitonin may also be useful to enrich microbiologically evaluable patients.

Other laboratory methods to confirm a bacterial etiology of infection include blood cultures, sputum culture (of adequate sputa) [49], urinary antigen testing and pleural cultures. Serologies have become less useful now that a reliable urine antigen test is available for *Legionella*, and since there is increasing regulatory reluctance to accept patients with pneumonia caused by other atypical pathogens, such as *M. pneumoniae* and *Chlamydophila pneumoniae*, which are typically detected by serology [108]. Of note, detection of atypical pathogens by serology does not rule out the possibility of dual infection with a typical pathogen, so such serologies may not be useful for exclusionary purposes either.

Evaluation of novel molecular diagnostic tests, such as those based on real time quantitative PCR, other nucleic acid screening methods and protein/biochemical methods, should be strongly encouraged. Such tests may be more sensitive than standard methods, resulting in a greater rate of microbiological confirmation of infection [53], and the FDA has publicly indicated that a single trial could be used to simultaneously support approval of a new antibacterial agent and a new molecular diagnostic test. Pharmaceutical companies should strongly consider partnering with diagnostics companies in designing and conducting these studies [53].

Severity of illness score or age as enrollment criteria

It is important that the patient population enrolled reflect a sufficient severity of illness to ensure validity of the constancy assumption that underlies historical comparisons of antibacterial efficacy versus placebo/no therapy [16,108]. Complexities of using scoring systems such as the Pneumonia Severity Index (PSI) and CURB-65 scores have been previously discussed [16]. From the perspective of defining disease severity for a CABP clinical trial, there are advantages of the PSI scoring system over the CURB-65 scoring system. First, and most important, the PSI scoring system correlates with mortality despite antibiotic treatment in patients in both historical and modern datasets, providing additional assurance of validity of the constancy assumption in conducting the clinical trial [16]. Second, the PSI score separates disease severity into more categories than does the CURB-65 score, and hence PSI is more flexible than CURB-65 in stratifying patients by severity of disease.

However, since the original publication of the IDSA position paper on clinical trials for CAP [16], the dialogue regarding severity of illness stratification has matured. The PSI score requires information to be gathered that can take several hours to collect, and the scoring calculation is sufficiently complex that it typically must be done electronically. Given the increasing impetus to rapidly administer antibacterial therapy to patients with CABP, and the fact that antecedent antibacterial therapy is highly discouraged by the FDA for these trials [108], it may become practically impossible to complete PSI score evaluation without administering antibacterial therapy while attempting to enroll a patient in a clinical trial.

By far the largest driver of the PSI score is age [53]. Furthermore, age was understood to be a primary predictor of outcome from pneumonia well before the availability of antibacterial agents, and it remains so today [16,54–57,108]. As mentioned, the historical data document a substantially larger antibiotic benefit for patients aged 30–59 and 60 years or older versus younger patients. Hence, a reasonable alternative is to require that a minimum percentage (e.g., >50% or >75%) of randomized patients be over the age of 50 or 60 years, *in lieu* of using PSI scores to facilitate constancy with the historical data.

Another method to ensure sufficient representation of severe illness is to require that patients be enrolled who meet criteria for sepsis/systemic inflammatory

response syndrome, and to attempt to enrich enrollment of patients being admitted to the Intensive Care Unit. The presence of hemodynamic instability (e.g., low blood pressure) and respiratory failure (e.g., requirement for >10 l/min of supplemental oxygen or mechanical ventilation) could also be used as enrollment criteria, although consenting such patients would provide another challenge to study conduct.

Prior antibacterial therapy

The 2009 FDA draft guidance on CABP indicated that no antibacterial therapy should be allowed prior to enrollment in a CABP clinical trial due to the risk that even a single dose of effective therapy could interfere with assessment of the efficacy of an experimental drug [108]. However, the dataset upon which this assertion is based was limited and the conclusion was dependent on a *post hoc* analysis of the subpopulation of patients in the failed daptomycin pivotal Phase III trials who had received antecedent ceftriaxone therapy [48]. Furthermore, antecedent therapy with short half-life antibacterial agents did not affect outcomes in the same study [48]. From the data available, it remains unclear what effect a single dose of previous antibacterial therapy has on clinical trial outcomes, particularly if the antibacterial agent has a relatively short half-life.

Ideally, no antibacterial therapy would be allowed in patients prior to enrollment in CABP studies, given the potential for such treatment to affect outcomes. The primary challenge in not allowing a single dose of prior therapy is in the great time pressure in the US to rapidly administer antibacterial agents to patients who may have pneumonia, in order to comply with the Center for Medicare and Medicaid Services mandate to administer such drugs within 6 h of patient presentation. Therefore, not allowing a single dose of prior therapy may preclude conduct of these studies, or at least cause the studies to be conducted primarily outside of the USA. There is no clear solution to this problem, as the potential for even a single dose of previous antibacterial therapy to affect clinical outcomes is a legitimate concern. As with many issues discussed in this manuscript, regulatory agencies must balance the desire for conduct of the trial with highest rigor while still enabling the trial to be informative for use of the drug in patients in the USA.

Future perspective

The standards for clinical trial conduct to study antibacterial agents for the treatment of CABP have dramatically changed in recent years. In the coming 5–10 years, trials will become larger and scientifically more rigorous, which will provide additional protection of the public against the possibility of a relatively ineffective drug being approved.

It is critical that a balance be achieved to ensure that such trials lead to scientifically valid, statistically sound and clinically meaningful results, while allowing the development of new, urgently needed antibacterial agents. Clinical trials using a composite end point of alive and resolution of clinical signs and symptoms of infection at the end of therapy, using a 10–15% margin of noninferiority (evaluating efficacy in the mMITT population) have the potential to achieve this balance in specific, appropriate cases. The scientific standards requiring a marked increase in microbiological confirmation of infection, a greater level of detail in documenting individual elements of the clinical response component of the end point, elimination or near elimination of antecedent antibacterial therapy, and a greater required sample size, are all commensurate with raising the scientific standards for conduct of these studies. Maintenance of a clinical component to the composite primary efficacy end point, and analysis of the end point at end of therapy (e.g., day 7) is critical to ensure that trial results are clinically relevant and informative regarding the use of new drugs post-approval.

Disclaimer

Opinions expressed in this article are those of the authors alone, and not of any medical society or professional association.

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Executive summary

- Placebo-controlled trials of antibacterial agents for the treatment of community-acquired bacterial pneumonia (CABP) are unethical and should not be conducted.
- New antibacterial agents are needed because of rising rates of resistance to currently available antibacterial agents.
- However, patients ethically cannot be randomized to treatment with a comparator antibiotic for which there is prevalent resistance when antibacterial agents without this limitation are available.
- Available antibacterial agents are extremely effective in the treatment of CABP caused by susceptible bacteria and it is unlikely that new drugs will be substantially superior in efficacy when tested in patients infected with such susceptible bacteria.
- Thus, active-controlled superiority studies are impractical in the setting of CABP, and noninferiority studies are the only ethical and practical means to make new antibacterial agents available for this disease.
- Despite a lack of placebo-controlled trials, sufficient historical data document that antibacterial agents mediate unequivocal, large improvements in mortality and clinical resolution of CABP versus background medical therapy.
- Based on the historical data, the primary efficacy end point for noninferiority trials should be a composite of alive and resolution of clinically-important signs and symptoms of infection present at baseline.
- The primary efficacy end point should be assessed at the end of therapy, not early in the course of therapy.
- In general, a noninferiority margin of 10–15% is justified for the primary composite end point; the margin appropriate for individual studies should be separately justified based on the potential, relative clinical advantages of the experimental agent and design features of the proposed study.
- The primary efficacy analysis population should consist of patients who have received at least one dose of study drug and the majority of whom have had confirmation of a bacterial etiology of pneumonia (the microbiological modified intention to treat population).
- The higher the percentage of patients in the primary efficacy population who have microbiologic confirmation of CABP, the more robust any noninferiority conclusion will be.
- It may be reasonable to use a narrower noninferiority margin (i.e., 10%) if less than 75% of patients are microbiologically confirmed in the primary efficacy analysis population, and a wider margin (i.e., 15%) if 75% or more of patients are microbiologically confirmed.
- Enrollment criteria should include clinical and laboratory features designed to enrich the evaluable population for microbiologically-confirmed CABP.
- Severity of illness may be assessed by use of the Pneumonia Severity Index (PSI) or more simply by age.
- Allowing administration of one previous dose of antibacterial therapy prior to enrollment is one of the most controversial areas in clinical trial design for CABP.

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