



○ Featured Article

Clinical Trials for Community-Acquired Pneumonia: Navigating Regulatory Turmoil

By Michael Corrado, MD, FIDSA
Chief Scientific Officer
INC Research



Designing successful clinical trials is difficult in the best circumstances. Add a bit of regulatory uncertainty, and the task becomes nearly impossible, as antibiotic developers know all too well.

Over the past few years, the FDA has re-evaluated its stance on antibiotic clinical trial design issues such as appropriate endpoints, acceptable noninferiority margins, and superiority requirements. The upheaval has led to trouble for cethromycin, iclaprim, ceftobiprole, dalbavancin, faropenem, oritavancin, telavancin and other products.

The dust is finally beginning to settle, as evidenced by Theravance's long-awaited telavancin approval last fall. Additionally, the FDA recently issued guidance documents for community-acquired pneumonia (CAP) and acute bacterial infections of skin and skin structures, and other guidance documents are in the works. The CAP field gained additional clarity last December, when the FDA convened a meeting of its Anti-Infective Drugs Advisory Committee to discuss the CAP guidance document and provide input on endpoints and other clinical trial design issues.

Evolving Endpoints

A clear endpoint demonstrated during the pre-antibiotic era in studies of pneumococcal pneumonia was time to defervescence of fever. Untreated pneumococcal pneumonia clearly took 7 days to resolve fever, so a drug could easily be compared to placebo with the goal of reducing fever faster.

In the modern world, several factors complicate the use of fever reduction as an endpoint in antibiotic trials. First, most modern households keep an over-the-counter antipyretic like Tylenol readily available, so only about 20 percent of pneumonia patients present to their doctor with a fever. Screening for fever at baseline could capture those patients who still had fever, but it would increase average trial enrollment time from one year to about three or four years.

Second, even if a pneumonia patient did have a fever when they reached the emergency room, American regulations require treatment within six hours. Such early pre-emptive treatment with an effective antibacterial may modify the clinical presentation of the patient prior to consideration for trial enrollment.

Third, fever is inherently variable: there are no rules regarding what temperature constitutes a fever, or if a 100.8 degree fever and a 102 degree fever should be expected to return to normal within the same timeframe. Add to that the fact that today's CAP population is older than it was in the 1930s, and thus less capable of mounting as brisk a fever response as younger patients, and it becomes apparent why fever has failed to carry forward as a relevant primary endpoint.

But another original CAP endpoint is still used today: mortality. The FDA's Anti-Infective Drugs Advisory Committee voted that mortality is an acceptable endpoint in a noninferiority trial for CAP, with a noninferiority margin of 10 percent.

Of course just because mortality is an approved endpoint doesn't make it easy.



The main complication with using mortality as an endpoint in a CAP trial is that CAP patients do not have high mortality to begin with. Patients with mild disease (PORT Scores 1-2) are generally not sick enough for inclusion in clinical trials (although PORT Score 2 subjects may constitute a part of the enrolled population), while patients with severe disease (PORT Score 5) are generally too sick. That leaves patients with PORT Score 3, who have about a three percent baseline mortality rate and patients with PORT Score 4, who have about an eight percent baseline mortality rate as relevant populations for study.

The problem with using mortality as an endpoint becomes immediately apparent. If a trial enrolls 400 PORT Score 3 patients, with 200 in each arm, six deaths would be expected in the control arm. If there are seven deaths in the active drug arm – just one more death due to any circumstance – the noninferiority delta will exceed 10 percent and the trial will be deemed a failure.

Thus to have a shot at statistically significant success, sponsors must either enroll thousands of patients into their clinical trials, or they must focus on enrolling patients with higher baseline mortality rates. For financial reasons, the latter is obviously preferable.

But the variability within PORT Score classifications makes it difficult to use this measure alone to focus on high mortality patients. For example, PORT Score 3 covers patients with PSI scores ranging from 71 to 90. Those with PSI scores in the 85 to 90 range should actually have a mortality rate closer to PORT Score 4 (eight percent) than PORT Score 3 (three percent). So if a trial enrolls only PORT Score 3 patients, but the average PSI Score of patients in the active drug arm is 86 versus 73 in the control arm, then the active arm will be biased to have higher mortality, making it extremely difficult to establish a mortality benefit. One could choose to have hopeful expectations of comparability between arms met by the laws of random chance. But what is held in the brink is the value of the drug and the company if chaos rules.

The solution is to stratify patients by PORT Score and within the PORT category. Study drug can be stratified in such a manner so that the trial can be enrolled in a blinded manner, yet the baseline mortality of patients in each arm will be more discreetly balanced.

Ideal Protocol

Another endpoint approved by the FDA's Anti-Infective Drugs Advisory Committee is clinical outcome, or cure. A cure is typically defined by a return to afebrility, normal respiratory rate, no pleuritic pain, a normal white cell count, and similar measures. The benefit of measuring cure over mortality is that everyone will have a clinical outcome, so not nearly as many patients are needed as when measuring mortality. But there is some degree of subjectivity, so certain steps should be taken to make clinical outcomes more objective thereby allowing clinical outcome as a primary endpoint.

Clinical cure is usually measured against a comparator drug, and a clinical trial will have an edge if that comparator can function as a surrogate placebo. For example, if a new drug works against amoxicillin-resistant strains, and an estimated 40 percent of bacteria are amoxicillin-resistant, then using amoxicillin as the comparator allows a cleaner look in comparing the two drugs for that subgroup of pathogens, as if a placebo had been used.

As the trial enrolls, it is important to monitor how many patients present with amoxicillin-resistant strains, as you might be able to stop the trial early if the number is higher than anticipated.

While there is some degree of subjectivity with clinical outcome, particularly with respect to returning the patients to "normal baseline," this can be compensated for by using as many objective parameters as possible. Thus sponsors might want to consider evaluating mortality as a secondary endpoint.

One efficient way in which to do this is to focus on a subgroup of patients with bacteremia. An estimated 20 to 30 percent of subjects with pneumococcal pneumonia are likely to have bacteremia, in contradistinction to other pneumonia causes including H. Influenzae pneumonia where bacteremia is far less common. Tracking these patients with bacteremic pneumococcal pneumonia results in a higher baseline mortality rate for such cases. This group becomes an important secondary population endpoint for mortality and for clinical cure. But multiple blood cultures are needed to identify bacteremia: we recommend a minimum of three blood cultures prior to treatment.

Although regulations regarding antibiotic clinical trials are still evolving, this is one example of a clinical trial protocol that would be reasonable to present to the FDA. A good CRO partner can recommend additional protocol design elements that comply with the latest agency thinking. At INC Research, we understand the intricacies of clinical trials for infectious diseases, and our experience spans pediatric and adult trials of all levels of complexity for drug candidates at all stages of development. Our regulatory experts stay abreast of all the latest rules and regulations, whether they affect anti-bacterials, anti-virals, anti-fungals or vaccines.

To understand how the infectious disease team at INC Research can support your clinical trial needs, please contact Michael Corrado, MD, at mcorrado@incresearch.com or visit www.incresearch.com.

About the Author

Michael L. Corrado, MD, FIDSA, is Chief Scientific Officer at INC Research. After spending eight years with Merck and eight years with Johnson & Johnson, where he was the Vice President of Regulatory Affairs, Dr. Corrado co-founded Advanced Biologics and established himself as an infectious disease expert. He has been intricately involved in the complete development of numerous infectious disease compounds, from preclinical work through marketing application submission. Dr. Corrado has served as Primary Medical Author of seven NDAs, ten sNDAs, and several expert reports submitted to European regulatory bodies. He worked on an extensive list of infectious disease compounds, and is involved with local and regional authorities to combat bioterrorism and supports their efforts for bio-preparedness. In addition to infectious disease compounds, Dr. Corrado has also been involved in other therapeutic areas such as CNS, pain, and dermatology. Dr. Corrado is frequently published as anti-infective authority and is a member of the IDSA-FDA Anti-infective Guidelines Committee. Dr. Corrado attended the University of Pittsburgh for his undergraduate degree and received his medical degree from Meharry Medical College.