Infectious Diseases vs. Clinical Researchers. Who is winning?

By Brian Murphy, MD, MPH, Medpace Medical Director, who is an infectious disease physician who has considerable experience as a principal investigator on clinical trials. Dr. Murphy provides leading clinical drug development experience for infectious disease and pediatric specific agents. He has considerable experience in clinical trials of anti-bacterials, anti-virals and vaccines.

The accelerated events of the last several decades prove that our guard against infectious and communicable diseases cannot be let down. However, in the past decade the development of new antibacterial agents has been decreasing dramatically [Spellberg B, Guidos R, Gilbert D, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155-164.]. The expenses and difficulties in designing appropriate clinical trials, offset by the relatively small market size for antibiotics compared to other therapeutics and compounded by regulatory requirements that seem to evolve as quickly as the pathogens, are major hurdles to the development of new infectious diseases therapeutics and diagnostics. Historical-controlled trials are useful only if the clinical setting, including treatment and supportive care, has remained relatively unchanged and the strain of pathogen that is being evaluated has not evolved excessively and still has similar characteristics, antibiotic susceptibility patterns, and virulence factors to the strain in the historical study. For a pathogens that can rapidly adapt to environmental pressures such as Staphylococcus aureus that can divide as quickly as every 30 minutes (and in which the rate of methicillin resistance has increased from 2% in 1974 to 22% in 1995 to 63% in 2004), Mycobacterium tuberculosis which can go from a streptomycin resistant rate of 2% to over 80% within three or four months [Mandell, G. L.; Petri Jr, W. A. Goodman & Gilman's Ninth Edition, International Edition pp. 1155-1174. J.G. Hardman, L.E. Limbird (eds) 1996], and viruses that can mutate even faster (3 x 10^-5 mutations per base per replication cycle for HIV), historical-controlled studies may be a challenge. Noninferiority trials with more stringent margins of noninferiority often face the challenge of comparing an agent to a comparator that first became available in an era before widespread use of placebo-controlled studies and whose efficacy rate is itself unclear. Ethical concerns of superiority studies versus placebo or delaying effective therapy until the pathogen is confirmed are becoming an important performance indicator in many institutions.

To be innovative and succeed against a landscape of infectious diseases that seems to overtake the discovery of new agents and diagnostics, infectious diseases programs and studies must also evolve dynamically. By utilizing extensive population modeling from databases of similar antimicrobial agents against target pathogens or from nonclinical models of infection, companies can effectively optimize study drug dose and timepoints, even before a study begins. Adaptive trial designs can enable real time analysis of the study data and further validate such model’s goodness of fit in such a way to reduce the number of patients required to reach meaningful clinical endpoints. Ongoing active antimicrobial surveillance programs are crucial to manage the added complexity of international enrollment that may arise from variations in the availability and capability of local microbiology laboratories, variations in standard of care, or differences among the quality and reliability of data. Innovative point of care testing to rapidly identify specific target pathogens combined with confirmatory molecular epidemiology techniques is necessary to properly manage the broadened scope of antimicrobial research. An integrative, dynamic, multi-disciplinary approach is fundamental to withstand the tug and pull of the current operational and regulatory environment of global infectious diseases research, the balance of risk and benefit to the patient, as well as the mechanistic issues of the therapeutic agent, the diagnostic tests, and the organism. Adaptability and novel ways of thinking about infectious diseases programs and studies are required for survival.

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