



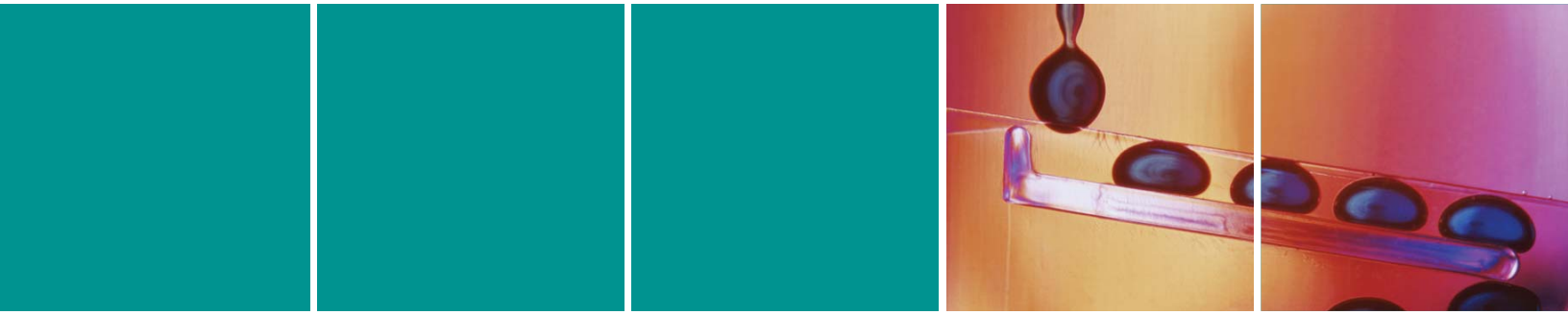
A Symbol of Excellence

Clinical Research




Excellence in Infectious Disease Clinical Trials

We work to find better solutions.
We work to exceed expectations.
We leverage our experience and expertise to ensure quality deliverables.



ICON is a global provider of outsourced development services to the pharmaceutical, biotechnology and medical device industries. We specialize in the strategic development, management and analysis of programs that support Clinical Development from compound selection to Phase I-IV clinical studies.



Anti-viral agents are becoming an increasingly important sector of the global anti-infective market. Currently, the market for anti-infective drugs is \$66 billion, with non-vaccine anti-viral agents accounting for 24% of sales. The vaccines market is also growing rapidly, and is expected to double over the next five years to approximately \$20 billion by 2010.¹

Excellence in Infectious Disease Clinical Trials

Despite decades of “breakthrough” treatments, infectious disease is still the third leading cause of death in the world. Newly emerging diseases and the rise of drug-resistant bacterial strains have added to the problem.

After years of slowed activity, new drugs to combat infectious diseases are once again starting to enter the development pipeline. Experts estimate that the market for anti-infective therapies will grow steadily in the decades ahead, driven by increasing needs for effective treatments of HIV, hepatitis and other serious, treatment-resistant conditions.

Challenges and Solutions

Infectious Disease Therapies: The Opportunity

Antibiotic drugs were one of medicine's major success stories in the 20th century. Penicillin, streptomycin and their successors were so effective at fighting infections that many doctors and patients assumed the battle was won, and research efforts declined accordingly. And yet, as the 21st century unfolds, infectious disease is on the rise again – and researchers are returning to their labs.

Many factors are involved in the global rise of infectious disease:

- The emergence of new diseases not previously seen, such as SARS (Sudden Acute Respiratory Syndrome), Ebola, Hantavirus and new strains of influenza, including avian flu.
- The increasing number of treatment-resistant strains of bacteria and viruses. Most bacteria are killed by antibiotics, but the few that survive treatment are more robust, or possess a mutation that makes them impervious to the antibiotic. When these survivors reproduce, they pass on their genetic resistance to a new generation, thus creating a variant of the disease that no longer responds to the original antibiotic.
- Abuse of antibiotic drugs has led to widespread resistance to these drugs.
- It is estimated that in developed countries, as many as 70% of the population harbors an organism that is resistant to at least one antibiotic. One of the most troubling of these drug-resistant bacteria is Methicillin-Resistant Staphylococcus Aureus (MRSA), which can be fatal.
- The rise of hospital-acquired bacterial infections. Each year in the US alone, over 2 million people contract a bacterial infection in a hospital setting, resulting in over 90,000 deaths.

Clearly there is a need for a new generation of anti-infective drugs, and in recent years several leading pharmaceutical companies have stepped up their research efforts in response. Governments, faced with real or threatened pandemics, are also beginning to respond, with fast-tracking, tax incentives, subsidies or other measures to promote anti-infective development.

Unique challenges in Infectious Disease Trials

Some infectious diseases are seasonal, others are regional and the complex protocols and brief enrollment windows of most infectious disease studies make these projects difficult to manage.

Changing or unclear interpretations of clinical trial data needed to demonstrate the effectiveness and safety of antimicrobial drug products have at times led to confusion and present additional challenges. In an effort to introduce a more objective approach for interpreting "equivalence" or "superiority" of antimicrobial drug products, more rigorous statistical analyses and better database review procedures have been employed by the FDA. These changes, along with the tightening of evaluability criteria and more definitive delineation of infections under investigation, have resulted in the need to enroll more patients in clinical trials of antimicrobial drug products and address issues regarding labeling and adequacy of trial design and conduct of these studies.

A more serious challenge, especially where the treatment is for a life-threatening condition, are issues relating to regulatory requirements and study ethics, including informed consent. It is imperative that clinical researchers are in full compliance with all applicable regulatory and ethical requirements in the conduct of the study.

ICON provides the experience and expertise across multiple classes of infection to address these and other critical issues of infectious disease research – and our global reach assures that your study will meet the regulatory standards of each country.



Expertise and Support

Anti-Infective/Anti-Viral Therapeutic Area Group (TAG)

ICON's anti-infective/anti-viral TAG is comprised of international therapeutic specialists who are experienced in clinical research and drug development. They provide strategic knowledge and expertise in the development of anti-infective drugs and are involved in all stages of the study:

- Global project feasibility
- Protocol development, review and evaluation
- Clinical trial planning
- Therapeutic training and advice
- Project oversight
- Consulting, medical monitoring and advisory board representation
- Interpretation of the clinical data
- A 24-hour, global physician "on call" system to assure that no enrollment opportunity is missed

Diagnostic procedures, clinical trial methodology and assessment methods in anti-infective drug development differ in many respects from those in other therapeutic areas. ICON's infectious disease TAG can provide the specialized knowledge required to ensure these factors are taken into account. They provide insight into:

- Diagnoses and treatment of infectious diseases
- Currently available anti-infective drugs; their mode of action, efficacy and safety
- Specific risks of anti-infective drug development and how to manage them
- Specialized knowledge of clinical trial methodology and efficacy assessment methods
- Relationships with key opinion leaders around the globe
- Access to a well established world-wide network of investigators in infectious diseases and public health
- Business intelligence information of the market for anti-infective therapies

ICON also has a team of clinical project managers and clinical research associates with experience in all major anti-infective drug classes across all key areas of anti-infective drug development.

ICON's experts have conducted over 200 studies representing 45,000 patients and 5,400 sites across the globe over the past five years.

Excellence through Experience

ICON has extensive experience in global clinical trial management including a wide range of antibiotic, antimicrobial and antiviral agents. These trials have consistently been completed on or ahead of schedule and within budget. Our clients know they can rely on us for flexibility, efficiency and unsurpassed quality.

ICON's capabilities in infectious disease research include:

- Development, advisory and regulatory services
- Phase I clinical pharmacology services including unique pharmacodynamic models for infectious disease
- Full service Phase I-IV clinical trial management
- Extensive testing facilities at central laboratories that are ISO 17025 certified
- Customized interactive voice response systems (IVR) and interactive web response systems (IWR)

Case Study 1: Infectious Disease

ICON's proactive response to lagging enrollment resulted in achieving enrollment goals 14 weeks ahead of schedule.

Number of patients: 469

Territory: North America, Eastern Europe

ICON's services:

Clinical Research

- Project Management
- Study Set-Up
- Clinical Monitoring
- Quality Assurance - sites & deliverables
- Biometrics
 - Data Entry
 - Statistical Analysis
- Medical & Safety Services
 - Medical Monitoring - site queries
 - Medical Writing - CSR
 - Laboratory Report Review
 - SAE Reporting

Key Challenges & ICON Solution:

Solving the problem of lagging enrollment

Initial patient enrollment numbers in the four treatment arms of a Phase III complicated skin and soft tissue infection study were behind the study plan. ICON met with the sponsor to discuss initiatives that could help turn the study around.

ICON's recommendations

- More frequent study teleconferences with sites focusing on enhanced patient screening initiatives
- Increased number of motivational visits
- Major emphasis on competitive enrollment
- Development of advertising strategies specific to individual sites

Amending the study protocol to expand enrollment

ICON also recommended two protocol amendments. The first opened enrollment to patients in countries outside of North America, and the second addressed extraneous exclusion criteria that were hampering the recruitment process.

Outcome:

ICON provided timely and effective corrective actions to help get this study back on track and achieved a targeted milestone of 469 randomized patients 14 weeks ahead of schedule.

Case Study 2: Infectious Disease

ICON's comprehensive investigator database allowed for the selection of the most appropriate and productive centers for this difficult indication.

Number of patients: 315

Territory: North America

ICON's services:

Clinical Research

- Project Management
- Study Set-Up
- Clinical Monitoring
- Study closeout
- Quality Assurance - sites & deliverables

Key Challenges & ICON Solution:

Site selection and subject enrollment were critical factors in the success of this randomized, double-blind, Phase III, Infectious Disease study encompassing 101 sites with 315 patients.

Available incidence data for the emerging pathogen was very limited throughout the study. This fact, coupled with the aggressive treatment regimen for potential subjects, made subject identification, screening, and recruitment particularly difficult, and therefore appropriate site selection was key to the success of this trial.

Outcome:

ICOSite, ICON's global investigator database with more than 14,000 investigators, captures many parameters including enrollment performance, therapeutic specialty and indication experience.

Site selection for this study was limited to motivated sites with access to a pool of patients meeting the inclusion criteria, having demonstrated the ability to enroll patients in a timely manner, with no competing studies which could reduce the ability of the site to enroll patients. The use of ICON's investigator database coupled with several patient recruitment initiatives proved effective, and ICON met all projected timelines.

ICON's Infectious Disease Experience over the past 5 years

| | No. Trials | Phase | Regions | Patients | Sites |
|---------------------------------|------------|-----------------------------------|--|---------------|--------------|
| HIV | 55 | Consulting, I, II, III | Asia Pacific, North America, Latin America, South Africa, Western Europe | 9,258 | 1,026 |
| CMV Retinitis | 1 | III | North America | 500 | 15 |
| Hepatitis B & C | 65 | Consulting/Regulatory, I, II, III | Asia Pacific, North America, Latin America, South Africa, Eastern Europe, Western Europe | 13,763 | 1,736 |
| Pneumonias | 8 | Consulting, III, IV | Asia Pacific, North America, Latin America, Eastern Europe, Western Europe, South Africa | 3,373 | 363 |
| Bronchitis and URIs | 6 | I, III | North America, Western Europe | 1,044 | 87 |
| VRE, MRSA, MRSE | 5 | III | Asia Pacific, North America, Latin America, Eastern Europe, Western Europe, South Africa | 760 | 181 |
| Skin & Soft Tissue Infections | 20 | Consulting, I, III, IV | Asia Pacific, North America, Latin America, Eastern Europe, Western Europe, South Africa | 6,957 | 990 |
| Urinary Track Infections | 4 | Consulting, I | Asia Pacific, North America, Eastern Europe, Western Europe | 2,293 | 139 |
| Otitis Media | 4 | II | Asia Pacific North America, Latin America | 1,641 | 92 |
| Tonsilitis | 4 | II, IV | Asia Pacific, North America, Latin America | 1,075 | 152 |
| Fungal Infections | 12 | Consulting, I, II, III | Asia Pacific, North America, Western Europe | 668 | 70 |
| GI Infections | 17 | Consulting/Regulatory, I, III | Asia Pacific, North America, Latin America, Western Europe, Eastern Europe, South Africa | 3,812 | 524 |
| Wound/Post Operative Infections | 7 | Consulting/Regulatory | North America, Western Europe | N/A | N/A |
| Sepsis, CR-BSI | 4 | II, III | Asia Pacific, North America, Latin America, Eastern Europe, Western Europe, South Africa | 440 | 112 |
| Totals | 212 | | | 45,584 | 5,487 |

As of July 2007

For more information on ICON's experience in infectious disease, contact our Business Development Department:
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