

PHASE IV—SAFETY AND VALUE

PHASE IV: TABLE OF CONTENTS

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PHASE IV: OVERVIEW

UNIQUE SOLUTIONS FOR UNIQUE NEEDS.

PharmaNet's Phase IV leaders help world-class companies bridge the gap from development to commercialization. The key is recognizing that Phase IIIb/IV research is undertaken for different reasons than pre-approval studies. Indeed, post-approval success is achieved through documentation and persuasive demonstration of safety and value and through an operational approach that reflects the unique characteristics of Phase IV: different goals, different measures, different stakeholders, and different time frames.

At PharmaNet, we strive to ensure our clients' Phase IV initiatives achieve both strategic and scientific objectives by leveraging our unique perspectives and global resources. With expertise in Observational (non-interventional) Research and Patient Registries, Interventional IIIb/IV studies and Endpoint programs, Health Economics and Outcomes Research, and Risk

Management and Epidemiology, PharmaNet covers the full range of Phase IV services.

Of critical importance, we have unique perspective and insight into the organizational dynamics that can make or break a Phase IV initiative, and we are regularly called on to provide leadership, vision, and training. This added dimension has enabled our clients to achieve consensus and clarity and highly effective Phase IV initiatives that often commence well before product approval.

Our goal is to support our clients in achieving both commercial and scientific success through a balanced and operationally cost-efficient approach that recognizes the unique attributes of the post-approval landscape.

Our services span the spectrum of capabilities to support documentation and demonstration of "real world" safety and value. In Phase IV research, *PharmaNet works for you.*

PHASE IV: OVERVIEW

Clinical Performance	Health Economics and Outcomes Research	Risk Management and Epidemiology
<ul style="list-style-type: none">• Observational (non-interventional) research and patient registries• Interventional IIIb/IV studies• Comparative effectiveness research• Retrospective data analyses• Expanded access and compassionate use programs• Label extensions• Endpoint studies	<ul style="list-style-type: none">• Cost-effectiveness studies• Economic analyses and models• Global value dossiers• Patient-reported outcomes research• Direct-to-patient disease registries	<ul style="list-style-type: none">• Post-approval safety surveillance• REMS/RMPs - consulting and implementation• Meta-analysis• Signal detection

PHASE IV: SERVICES

OBSERVATIONAL RESEARCH AND PATIENT REGISTRIES

Increasingly, health authorities, insurers, regulators, policymakers, physicians, and patients are all seeking information to better understand “what works” in the real world; that is, in settings that reflect how diseases are treated and how products are actually utilized without the controls and constraints of traditional clinical trials. Thus, studies must be designed to observe processes and outcomes in actual medical practice settings without disrupting the very practices being observed. This requires a truly unique experience.

Our Phase IV team’s approach to Observational Research begins by affirming the strategic foundation for a study: *why* a non-interventional project is being undertaken impacts *how* operational components should be structured. An understanding of both the opportunities and the limitations of observational research is crucial to the organizational alignment necessary for success. Our experts provide our clients with valuable insight and perspective throughout the study, ensuring expectations are appropriately set and met through pragmatic, yet scientifically sound, design and operational cost-efficiency. Indeed, by applying design and operational approaches specifically focused on Observational Research, we can ensure outstanding results in the management of participating sites, data management and analytical processes, and in the overall project.

Services include:

- Study design
 - Statistical analysis planning
 - Communications planning
- Overall project management
 - Notifications
 - Management of Scientific Advisory Panel
- Protocol/guidelines development
 - Informed consent
 - Case report forms
- Site recruitment and management
 - Site agreements
 - EC/IRB approvals
- Data management
 - EDC, EMR
 - Paper, hybrid
- Quality management
 - Site interaction
 - Data quality monitoring and SDV
 - Safety reporting
- Analysis and reporting
 - Presentations
 - Abstracts
 - Manuscripts

PHASE IV: SERVICES

INTERVENTIONAL IIIB/IV STUDIES

Transitioning from product development to the commercial setting merits a variety of research approaches, including additional “traditionally” structured interventional studies to address specific uses and/or populations. These initiatives often are developed within the context of forging new relationships with key providers, opinion leaders, and/or payers and, hence merit both precise and sensitive execution.

Our Phase IV team assesses our dedicated and broader clinical research resources for the specific needs of these critical studies from design to regulatory support and from site recruiting to data management and statistical analysis.

Expanded Access and Compassionate Use Studies

PharmaNet’s Phase IV team has industry-leading experience in the development and implementation of these specialized initiatives designed to ensure at-need populations can continue to benefit from innovative therapies, even as they are receiving final regulatory evaluation. By ensuring these studies generate valuable experience data, we can maximize their value for our clients while maintaining a focus on overall safety and patient access.

Endpoint Studies

Our endpoint management team includes registered nurses and clinicians who work in close collaboration with our clients to collect critical information from sites and manage the flow of the event data to the Adjudication Committees.

The endpoint management team works closely with sites throughout a study to rapidly obtain the critical source documents needed for immediate reporting of potential clinical events. Using state-of-the-art online tracking tools to effectively manage the collection and review of event information, the team collaborates with data management and monitoring teams to ensure that all events are reported and documents are submitted as quickly as possible.

The endpoint management team has significant experience in:

- Developing adjudication charters and guidelines for the endpoint review process
- Conducting endpoint programs requiring adjudication of events in multiple therapeutic areas
- Preparing, disseminating, and tracking outcome packages, including:
 - Copies of CRFs
 - Query responses
- Supporting source documents for review by Clinical Events Committees

PHASE IV: SERVICES

HEALTH ECONOMICS AND OUTCOMES RESEARCH (HEOR)

Generating relevant economic and humanistic evidence for a variety of different stakeholders, health authorities and technology assessment agencies require a multidisciplinary approach to the design, execution, and analysis of data. Using internal resources and external global partners, PharmaNet's Phase IV HEOR team addresses such complicating factors as the differing approach to healthcare delivery and the cost of healthcare resources in different countries. PharmaNet's HEOR studies and analyses focus on the economic impact of treatments, diseases, and conditions, including the direct costs of medical expenditures and indirect costs, such as those associated with work loss and disability.

PharmaNet examines and establishes product value through a broad range of services, including:

- HEOR portfolio planning
- Comprehensive economic and outcomes literature reviews
- Burden/cost-of-illness studies
- Treatment pattern analyses
- Trial/market simulation modeling
- Global cost-effectiveness models
- Management of economic endpoints in clinical trials
- Patient Reported Outcome (PRO) studies, including Quality-of-Life and health utility studies
- Retrospective cost-effectiveness and resource utilization studies
- Global and country-specific value dossiers

PHASE IV: SERVICES

RISK MANAGEMENT AND EPIDEMIOLOGY

The monitoring of product safety is a key concern throughout the development cycle, but never more so than after product approval. In today's environment, more and more drug development teams are adding post-approval activities as part of their risk management and epidemiology planning.

Risk management considerations include the number of potential users of the product, the seriousness of the disease being treated, the expected effectiveness of the product, the length of time patients will be treated, the seriousness of known or potential adverse events, and/or whether alternative agents exist. PharmaNet's Phase IV specialists advise clients to be proactive, bringing progressive, scientifically-sound risk management plans to regulatory agencies rather than facing the imposition of a mandate that may be overly restrictive.

PharmaNet's risk management and epidemiology professionals develop programs to monitor and manage product utilization and safety, mitigate risk, establish a product's risk-benefit profile, and ensure understanding of its market value.

Services include:

- Post-approval safety studies
- Risk Evaluation and Mitigation Strategies (REMS)/RMPs
- Signal detection/database analyses
- Epidemiological assessments
- Label comprehension and physician compliance studies
- Restricted distribution/access programs
- Natural history studies
- Burden of illness studies
- Meta-analyses of potential safety signals during clinical trials
- Retrospective and prospective post-approval pharmacoepidemiology and drug safety studies
- Database "mining"
- Development of medication guides
- Implementation and evaluation of Elements to Ensure Safe Use (ETASU)

PHASE IV: VISION

A COMMITMENT TO LEADERSHIP

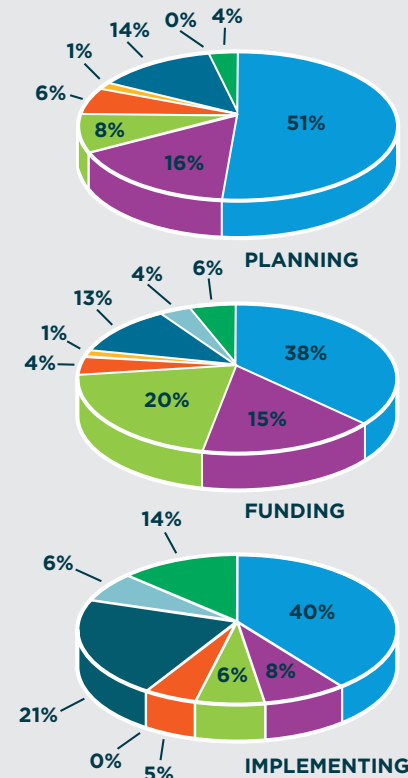
The Phase IV landscape continues to evolve. As such, today’s solutions need to be regularly assessed for on-going relevance. At PharmaNet, we continually challenge ourselves to develop and “operationalize” innovative yet strategically and scientifically sound solutions for our clients. Moreover, we take seriously our responsibility as industry leaders to provide direction, vision, and clarity. And while the Phase IV landscape reflects an increasing level of regulatory requirements, we welcome the responsibility of helping our clients transform requirements into opportunities. We believe there is no better or more important setting than Phase IV.

- Health Economics/Outcomes Research ■
- Medical Affairs ■
- Product Management/Marketing ■
- Epidemiology ■
- Pharmacovigilance ■
- Clinical Study Operations ■
- Outsourcing/Procurement ■
- All Responsibility is Outsourced ■

Observational Research Survey

PharmaNet surveyed over 5,500 Phase IV industry professionals from large to small pharma, biotech, CRO, and consulting organizations.

Who, in your organization, has primary responsibility for planning, funding, implementing observational research?



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