

## Statement of Clinical Investigator Competence

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### Introduction

Physician investigators accept far-reaching responsibilities when they sign on to participate in sponsored or academically initiated clinical research projects. Legally and morally, investigators hold ultimate accountability for the conduct of the research that occurs under their supervision. Given this weighty obligation, an important question arises as to “What qualifies an investigator to lead and participate in clinical trials?” Is a curriculum vitae documenting clinical credentials in the therapeutic area under study enough, or should a higher standard of demonstrated competence prevail?

All parties involved in clinical research agree that investigators require an appropriate knowledge base and training to carry out their duties. Yet, the current qualification standards for investigators are vague. Therefore, The Academy of Physicians in Clinical Research (APCR) assembled a working group to study the areas of proficiency that we believe should define competence for qualified clinical investigators. APCR represents nearly 1,000 physicians who work in the field of developing new medical products. APCR members with experience from academia, industry, research practice, government, and consulting contributed their expertise to this working group.

### Policy Statement

Competence in clinical investigation requires mastery of specific skills and knowledge beyond those learned when training for clinical practice. These skills may not be obvious to even the well-trained clinician who has not received significant clinical research exposure. Competent investigators must understand and integrate research ethics, regulatory considerations (i.e., Good Clinical Practices or GCPs), scientific principles, and management skills in addition to their clinical

training to apply their therapeutic area expertise and patient care skills effectively in a research setting.

APCR has defined the areas of proficiency of a qualified investigator into five broad categories: I) Ethics and Subject Protections; II) Scientific Concepts; III) Subject Care; IV) Operational Excellence and Regulatory Compliance; and V) Leadership and Business Management—each with supporting details. We believe that qualified investigators should be able to demonstrate proficiency in each outlined area. We recommend that proof of these proficiencies, when physicians choose to formalize them, should occur through a certification process. After having successfully completed a certification process, the certified investigator should be deemed qualified to pursue clinical investigation within his or her therapeutic field of expertise without any further general research training.

While these competencies have been established specifically to guide physician clinical investigators, we believe they are broadly applicable to professionals who participate in the clinical trial enterprise from industry, academia, government, or the consulting sphere for both sponsored and investigator-initiated studies. Further, we hope these outlined areas of proficiency provide guidance for clinical medicine trainees who wish to receive exposure to the knowledge needed for success in clinical research practice.

### Areas of Proficiency

#### I. *Ethics and Subject Protections*

Contemporary clinical research builds from a foundation of core ethical principles that guide study conduct and provide subject protections. Without complete understanding of these core principles and their manifestations, an investigator will inevitably fall short of his or her obligations and fail to provide appropriate guidance to co-workers,

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The Board of Trustees of the Academy of Physicians in Clinical Research (APCR) has endorsed this consensus statement, entitled “Academy of Physicians in Clinical Research (APCR) Statement of Clinical Investigator Competence.” This statement expresses the guidance of an academy working group assembled at the request of APCR’s president and chairman, Jonathan Seltzer, MD, MBA, FACC, to address the uncertain standards and piecemeal training efforts that currently apply to clinical investigators. The working group sought input and feedback from numerous parties involved in clinical research, and created this aspirational document to define the elements of knowledge and path to proficiency of competent clinical investigators.

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This document will be made available on the APCR website ([www.apcrnet.org](http://www.apcrnet.org)).

sponsors, and patients. Core knowledge includes:

- a.) Ethical principles that underlie clinical research
  - What makes experimenting on human beings ethical?
  - How ethical principles translate to regulations
  - Identification of unethical research practices
- b.) Informed consent
  - Historical perspective as to why we get consent as we do
  - Consent process logistics and safeguards
  - GCP requirements of the consent process, including defined elements addressed within consent forms
- c.) Vulnerable populations
  - Definition of vulnerable populations
  - GCP requirements related to vulnerable populations
  - Practicality of enrolling vulnerable populations into clinical trials
- d.) Institutional review boards (IRBs)/Institutional ethics committees (IECs)
  - Rationale, regulatory definitions, and rules applicable to IRBs/IECs
  - Practical issues concerning investigator interactions with IRBs/IECs
  - Other review committees that provide safeguarding functions in clinical research
- e.) Legal and jurisdictional rules regarding research
  - Government oversight agencies—knowledge of their structure and jurisdiction
  - Reporting requirements (e.g., EudraCT, ClinicalTrials.gov, Federal Wide Assurance)
  - Referral laws and ethics
  - Local laws and disclosure requirements
  - Tort exposure and redress
  - Payment issues for clinical research subjects

## II. Scientific Concepts

Clinical trials are designed mindful of vital scientific concepts. Investigators must understand these constructs because studies that do not adhere to them can fail patients or prove to be unethical. Scientific concepts within specific therapeutic areas also greatly influence clinical trial design and conduct. Core knowledge includes:

- a.) Elements of study design
  - Posing a primary research question
  - Defining primary and secondary endpoints
  - Intention to treat concept and implications
  - Enrollment/randomization/screen failures/dropped subjects /completion
  - Basic statistical knowledge and considerations
- b.) Applying therapeutic area knowledge to research success
  - Feasibility analyses
  - Appropriate use of inclusion and exclusion criteria
  - Outcomes analyses
- c.) Pharmacology principles
  - Half-lives, volumes of distribution
  - Pathways of metabolism and excretion
  - Drug–drug interactions

- d.) Epidemiological principles
  - Selection biases
  - Bayesian considerations
  - Relative and absolute risk
- e.) Reading and understanding research journal articles

## III. Subject Care

Ethical considerations mandate that clinical investigators have the same concern and care for research subjects as for all patients. Investigators must also acknowledge that care considerations should outweigh research considerations even as they ask subjects to comply with rigid protocols. Questions frequently arise in clinical trials as to when research begins and ends and when research considerations give way to subject care. Core knowledge includes:

- a.) Distinctions between research and care
  - How and where to draw lines for clinical patients?
  - Explaining and managing blinding and unblinding
  - Explaining and managing placebo/control issues
  - Interpreting inclusion and exclusion criteria for sponsors and subjects
- b.) Understanding and interpreting standards of practice
  - Acceptable elements of pre-consent patient preparation for research
  - Advocating for subjects during the conduct of trial
  - Communicating the acceptance of uncertainty to subjects during research participation
- c.) Confidentiality
  - Confidentiality considerations during preparation to research
  - Understanding and implementing privacy protections (e.g., HIPAA)
  - Protecting confidentiality during research conduct
- d.) Recruiting for clinical trials
  - Psychology and ethics of recruiting patients
  - Diversity considerations when recruiting patients
  - Summarizing features of trials for patients
  - Articulating research value proposition for patients
- e.) Clinical management of research subjects
  - Meeting patient expectations while complying with research requirements
  - Interfacing with other providers
  - Managing changes in patient status during research participation
- f.) Identifying and managing side effects and lab abnormalities
  - Working with patients to assess causality of adverse events
  - Treating side effects within study context

## IV. Operational Excellence and Regulatory Compliance

Investigators must have an excellent working knowledge of the regulatory requirements (GCPs) and operational demands to conduct clinical research. Throughout the

data collection process, investigators must establish a culture of quality. Core knowledge includes:

- a.) Understanding processes and priorities during each stage of the medical product development cycle
  - Preclinical
  - Phases I–IV
  - Device, diagnostic, and nontraditional trials
  - Genetic and biotechnology considerations
  - Role of oversight and regulatory authorities/agencies/ICH guidelines
- b.) Study start-up requirements
  - IRB/IEC submission process
  - Prestudy preparations
  - Regulatory documents
  - Site training
  - IVR systems
- c.) Classifying and reporting adverse events and lab abnormalities
  - GCP definitions and responsibilities for adverse events reporting
  - Methods of assigning causality for adverse events and lab abnormalities
  - Severe adverse event reporting requirements
  - Understanding regulatory agency safety focus and adverse event classifications (e.g., “black box” warnings, QT prolongation, Hy’s Law, etc.)
- d.) Delegating authority and tasks
  - Working with and availability to study coordinators and monitors
  - Electronic data capture systems in clinical research
  - Delegation and training logs
- e.) Elements of regulatory compliance (GCP)
  - IRB correspondences
  - Investigational product security
  - Drug accountability
  - Study file notebooks
  - Standard operating procedures
  - Sub-investigator and staff training
  - Record storage
  - Audit preparation
  - Audit conduct
- f.) Recruitment of subjects
  - Staff involvement and oversight
  - Advertising issues
  - Data base issues
- g.) Assuring data quality
  - Systematic approaches to assure accuracy throughout the data collection process
  - Understanding quality assurance and continued quality improvement methods
- h.) Facility management
  - Assessing facility requirements of sites based on studies and therapeutic areas
  - Oversight functions for facility management

## V. Leadership and Business Management

The clinical investigator must provide leadership for all participants in the research process and understand basic financial and business management concepts regardless

of his or her employment status or place of work. Understanding local community sensibilities towards research and outreach to advocacy groups breeds success. Core knowledge includes:

- a.) Conflicts of interest
  - Financial disclosures—regulatory obligations and sponsor-specific requests
  - Managing nonfinancial conflicts of data ownership, publication rights, time conflicts, confidentiality of results, and proprietary trade secrets
  - Understanding patients and local community conflicts, real and perceived
- b.) Research contracts
  - Understanding standard elements
  - Financial management
  - Legal principles—indemnification, liability, jurisdictions
  - Responsibilities and risk exposure of involved parties
- c.) Staff management
  - Creating a culture of ethical practices
  - Balancing staff work load while maximizing efficiency
  - Specialization within the research enterprise
  - Training of and communication with staff and sub-investigators
  - Detecting and reporting fraud
- d.) Compensation standards
  - Staff
  - Subjects
  - Sub-investigators
  - Vendors
  - Record storage
- e.) Understanding and assigning financial obligations of institutions and sponsors
  - Insurance coverage analysis—what is and is not covered
  - Indemnification and cross-indemnification issues
  - Employee, institution, and sub-investigator liability
- f.) Investment environment
  - Understanding medical product financing
  - Interactions between investment community and clinical trials industry
- g.) Community interface
  - Interacting with patient advocacy groups
  - Communicating clinical trial issues with key local constituencies
  - Understanding local laws and sensibilities

## Levels of Competence

APCR recognizes that physician investigators can make varying worthwhile contributions to clinical research. In many circumstances, investigators can competently contribute to clinical research without complete mastery of the extensive knowledge base that we have detailed above. Consequently, APCR recommends acknowledgement of distinct levels of investigator research training and proficiency. Recognized levels of achieved proficiency will help align clinical inves-

tigators with appropriate roles and responsibilities during the conduct of clinical trials. Moreover, the acknowledgement of clearly defined, tiered levels of proficiency will provide a pathway for career development and should obviate piecemeal “window dressing” GCP training requirements.

APCR recommends three levels of training:

**Level 1**—Level 1 training reflects the exposure to clinical research concepts, terminology, and interpretation that most physicians currently receive as part of an accredited clinical residency or fellowship program. Without formal research training, physicians still learn about the conduct and principles of clinical trials when they discuss and apply research findings in practice. By virtue of this exposure, Level 1 trained physicians can competently serve as sub-investigators in clinical trials and participate in study-focused exams and procedures. Level 1 trained investigators are generally competent to refer to and explain salient features of studies to patients who may express interest or receive solicitation from a research program. In general, Level 1 trained physicians should not serve as principal investigators, though exceptions to this rule could occur for Phase IV studies, observational research, or studies in which the Level 1 investigator has direct and clearly defined mentoring available from an investigator with higher level training.

**Level 2**—Level 2 training represents the commitment to research education and proficiency typical of a physician who has participated in 5–20 studies in his or her career. In addition to experience as a significant contributor to several trials, physicians with this level of training should have completed a formal GCP program and commit to participate in ongoing CME experiences related to clinical research training topics that occur over a period of no less than 10 hours every two years. Level 2 training should qualify physicians as clinical investigators for most studies within their therapeutic areas. Level 2 investigators should have a good to excellent working knowledge of the areas of proficiency defined in the Areas of Proficiency (see above). Level 2 trained physicians are qualified to serve as principal investigators for most Phase III studies, investigator-initiated trials, and observational and postmarketing studies.

**Level 3**—Physician investigators committed to clinical research participation as a major element of their professional activities should strive to achieve Level 3 status. Level 3 investigators typically have more than 20 studies of clinical trial experience and have served as a principal investigator for at least 10 trials. In addition to robust experience, acknowledgement of Level 3 investigator status should require successful completion of a qualifying examination to demonstrate proficiency in the areas APCR has detailed.

Level 3 investigators are qualified to participate in and lead all clinical research projects as a principal investigator. Level 3 investigators should be preferentially sought to conduct Phase I and early Phase II studies, as well as perform in a supervising capacity for pivotal Phase III work. Level 3 investigators will be expected to provide training functions to staff and sub-investigators on an ongoing basis and participate in formal training initiatives. Level 3 investigators should be encouraged to maintain certification through an ongoing qualification process that may involve further examination and/or recognition of professional accomplishments every 5–10 years. The Level 3 investigator should not suffer any loss of privileges if he or she chooses not to recertify, but should be encouraged to pursue life-long education through a process of acknowledging each subsequent recertification.

## Public Health Considerations

At all levels of competence, physician investigators have the obligation to contribute to the system of collecting and disseminating clinical research information without bias or preconceived notions. Every investigator advances the greater good when he or she participates in the process by which clinical research uncovers truths, informs medical decision-making, and improves community health outcomes. APCR believes that Level 1 investigators can significantly contribute to this process through the referral of appropriate subjects and technical support of clinical research initiatives. Moreover, Level 1 investigators who commit themselves to learning and the dissemination of clinical trial results to patients and peers enhance the state of public health. Level 2 and 3 investigators are expected to participate in the detailed operational aspects of clinical trial design and reporting. These elements include trial registration, methodological discussions, presentations at professional meeting, and publications of results. Whether or not a clinical trial is successful, the physician investigator, without threat of penalty or motivation by financial reward, should disclose results impartially, and discuss the reasons for implementation of the results or the lack of success. Investigators must apply integrity throughout this process to protect the public from misinformation and advance our common goals of improving public health.

## Conclusion

This policy statement reflects APCR’s position and guidance on investigator competence. Because of the central role of investigators in the conduct of clinical research, we strongly support measures that define areas of investigator proficiency, encourage career-long learning, and recognize the levels of achieved competence of physician clinical research professionals.