# Navigating the Role of the "Non-Investigator Provider" in Non-Exempt Human Subjects Research

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The modern clinical research landscape, particularly with the rise of decentralized clinical trials (DCTs), is increasingly characterized by a network of individuals and facilities that extends beyond traditional academic medical centers. Multisite human research studies have been ongoing for many years. However, confusion remains over which sites require IRB oversight, particularly when each site handles different aspects of the protocol.

DCTs and hybrid DCTs add more complexity. Although this distributed model can improve participant access to local providers, thereby boosting study retention, it requires careful planning to ensure compliance with federal regulations.

Under the HHS's regulatory offices, the U.S. Food and Drug Administration (FDA) and the Office for Human Research Protections (OHRP) each specify different responsible parties for the ethical and scientific integrity of the trial, the protection of the rights, safety, and welfare of all participants under their care, and the quality and validity of the data generated.

The FDA identifies the investigator[1] as responsible, while OHRP identifies the "engaged" institution as responsible when the study is non-exempt human subjects research[2]. In guidance issued by OHRP in 2008, OHRP clarified that for the term institutional engagement, "an institution's *employees or agents* refer to individuals who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities."[3] OHRP guidance considers anyone engaging in study-specific activities an investigator.

Engaged institutions usually assign responsibility to the investigator (an institutional employee or agent), but the institution is ultimately held accountable if something goes wrong. When a research study is supported by a federal agency under the Common Rule and regulated by the FDA, both the investigator and the institution are accountable to their respective agencies.

International standards, such as the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), are incorporated into the FDA's stance. ICH E6(R3) 2.3.1 states that while an investigator may delegate tasks, "The investigator retains the ultimate responsibility and should maintain appropriate oversight of the persons or parties undertaking the activities delegated to ensure the rights, safety, and well-being of the trial participants and the reliability of data." Therefore, any framework for using external, non-investigator providers must be based on processes and written agreements that enable the PI to maintain this auditable oversight.

To manage the complexities of a clinical trial, PIs delegate specific duties to a qualified research team member. This team may include sub-investigators, clinical research coordinators (CRCs), research nurses (CRNs), data managers, and other skilled personnel. The official instrument for documenting this delegation is the Delegation of Authority (DoA) log, also known as the

Delegation of Responsibility Log. This log may be combined or also serve as the site signature log. These are auditable documents that must be expertly maintained. There is no one way to document delegation, and numerous companies and tools have been created for this purpose. However, the non-investigator providers are not officially on a DoA log since the services they are providing to the participants should not rise to the level of needing to be delegated. This is addressed in ICH(E6)(R3)[5], “In situations where the activities are performed as part of clinical practice, delegation documentation may not be required.” However, ICH(E6)(R3) 2.3.4 goes on to state that, “Agreements made by the investigator/institution with service providers for *trial-related* activities should be documented.”[5]

### Delegation of Tasks vs. Procurement of Services

A distinction must be made to structure the relationship with an external, non-investigator provider properly. The act of assigning duties to a study coordinator via a DoA log represents a *delegation of research conduct.* This implies that the coordinator is an integral part of the research team, has been trained on the protocol, understands the research objectives, and is operating under the PI's direct supervision as an agent of the institution.

In contrast, engaging a local phlebotomist to draw blood or a neighborhood clinic to perform a standard-of-care ECG represents the *procurement of a clinical service*. This relationship is fundamentally different. The provider is not expected to have detailed knowledge of the protocol, the investigational product, or the broader research context. Their role is transactional: to perform a specific, routine clinical task for which they are already qualified, and to provide the resulting data back to the research team.

This distinction has profound compliance implications. Attempting to manage the procurement of a clinical service through the mechanism of a DoA log would be a mistake. Placing a local, non-investigator provider on the DoA log would incorrectly imply that they are a formal member of the study team, that they have been trained on the full protocol, and that they are performing significant research-specific duties. This could create a substantial vulnerability during a regulatory inspection, as the provider would not meet the expected qualifications or training level for someone listed on the DoA log.

The PI's responsibility for oversight, therefore, is different in these two scenarios. For the formal study team, oversight involves team management, ongoing training, and ensuring protocol adherence. For the non-investigator provider, oversight shifts to vendor management. The PI must ensure that the service was contracted appropriately, that clear instructions were provided, that the service was performed to the required clinical standard, and that the resulting data are accurate and properly integrated into the research record. The governing document is not the DoA log, but rather a service agreement or contract that explicitly defines the limited, transactional nature of the relationship.

### The "Local Health Care Provider" in DCTs

The FDA, recognizing the potential of DCTs to make clinical trials more accessible and efficient, has provided a specific framework for utilizing providers who are not formal investigators. The agency's September 2024 guidance, "Conducting Clinical Trials With Decentralized Elements," introduces and defines the role of the "Local Health Care Provider" (HCP), establishing clear parameters for their activities and the corresponding responsibilities of the PI.[1] There is no such equivalent title in OHRP policy or guidance to date.

The FDA guidance formally acknowledges that DCTs may involve a "network of locations where trial personnel and local HCPs work".[1] It defines a role for local HCPs, such as community-based doctors or nurses, to perform certain trial-related activities, often on a fee-for-service basis.[1] By leveraging local HCPs, sponsors and investigators can facilitate the recruitment and retention of a more diverse and representative participant population, which in turn can expand the recruitment pool of participants and improve the generalizability of the trial's findings.[1]

**Standard of Care**

The term “Standard of Care” seems to imply a clear and simple benchmark, but the term is contentious because it carries multiple, often conflicting, meanings depending on the context.

- **Legal Origin:** "Standard of care" is primarily a legal concept used to determine negligence in medical malpractice lawsuits. In this context, it defines the minimum level of competence and care that a reasonably prudent healthcare professional, with similar training, would provide under the circumstances. It is a legal yardstick for liability, not necessarily a benchmark for optimal treatment. It also presents as “a continuum, with barely acceptable care at one end, and the ultimate in care at the other end.”[4]
- **Medical/Research Usage:** In clinical and research settings, "standard of care “is not a single entity but a combination of various components. These components can broadly be categorized into clinical guidelines, best practices, and ethical considerations.[5]

**“Standard of Care" vs. "Routine Clinical Practice"**
These two terms are often used interchangeably, but they are not synonymous, which adds to the confusion.

- **Standard of Care (Normative):** This refers to what *should* be done.
- **Routine Clinical Practice (Descriptive):** This refers to what is *actually* and *typically* done by practitioners in a given community.

The FDA's guidance for decentralized trials states that tasks delegated to a local HCP "should not differ from those that they are qualified to perform in clinical practice" and, crucially, "should not require a detailed knowledge of the protocol, investigator's brochure, or IP".[1] This phrasing focuses on the provider's routine activities rather than a rigidly defined, evidence-based "standard of care," acknowledging the practical realities of varied clinical practice.
This creates an inherent ambiguity, especially if sponsors use the term: standard of care when they are trying to address routine clinical practice.

**Routine vs. Research-Specific Activities**

The FDA establishes a bright-line test for determining which activities are appropriate for a local HCP. The central principle is that the tasks performed by a local HCP "should not differ from those that they are qualified to perform in clinical practice."[1]

**Permitted Activities**[1]**:** Based on this principle, local HCPs can be engaged for a range of routine procedures. Examples explicitly mentioned in the guidance include:

- Performing standard physical examinations.
- Obtaining vital signs.
- Collecting biological specimens, such as blood or sputum, for analysis at a designated laboratory.
- Overseeing routine safety monitoring involving well-standardized laboratory tests or imaging at local facilities.

Perhaps the most significant activity permitted by the FDA is the administration of the investigational product (IP). The guidance states that it "may be appropriate for local HCPs," but this permission comes with a critical caveat: it is only appropriate if the "safety profile of the IP is well characterized and specialized monitoring during the immediate period following administration is not needed."[1]

**Prohibited Activities:** Conversely, any activity that is "unique to a research study" or that requires a detailed understanding of the protocol, the investigator's brochure, or the IP must be performed by qualified trial personnel who have been formally trained on the protocol and listed on the delegation log.[1] This would include tasks such as assessing clinical outcomes using a protocol-specific rating scale or evaluating adverse events for causality and severity, which are core research functions.

Furthermore, the FDA carves out one activity as inappropriate for a local HCP: obtaining informed consent. The guidance states that because the individual obtaining consent must have detailed protocol knowledge and be able to address any questions a subject may have about the research, "FDA...does not consider obtaining informed consent to be an appropriate activity for a local HCP to perform".[1] This responsibility must remain with the investigator or a properly trained and delegated member of the formal study team.

While the PI can utilize local HCPs, they can never abdicate their oversight responsibility. The guidance reiterates that the investigator "remain[s] responsible for the adequate supervision of those to whom they have delegated these activities."[1] This supervision must be active and documented.

Specific oversight duties for the PI include:

- **Data Review:** The PI must "review data from other trial personnel and local HCPs, as applicable, and follow up on any data that are missing, concerning, or appear to be in error."[1] This review should be timely and regular to ensure data quality and participant safety.
- **Task-Specific Instruction:** To limit variability in data collection, the PI must "communicate any specific instructions included in the protocol to local HCPs for trial-related activities they are delegated to perform".[1] A prime example is providing a directive like, "have participants rest for 5 minutes before measuring blood pressure."[1]
- **IP Accountability:** When an HCP is involved in IP administration, the PI must "authorize the release of the IP" from the distributor and implement procedures to "ensure receipt by

trial participants or local HCPs."[1]

- **Case History Documentation:** The PI is responsible for ensuring that adequate case histories are prepared and maintained. This includes making sure that any reports received from local HCPs are incorporated into the subject's research record and that these reports clearly identify the "name of the local HCP and the date when activities were performed."[1]

### "Supervisory Paradox"

The FDA's model, while pragmatic, creates a challenging operational dynamic. It permits a PI to engage an HCP for a critical research function—such as administering the IP—precisely because that HCP *lacks* detailed protocol knowledge. Simultaneously, it holds the PI responsible for supervising that same function to ensure it is performed in accordance with the protocol's requirements for safety and data integrity. The PI must ensure a research-critical task is performed correctly by someone who is intentionally kept at arm's length from the research itself.

This structure places an immense burden on the sponsor and the PI to design robust systems that can bridge this knowledge gap. The solution cannot be to train the HCP on the protocol, as that would transform them into a subinvestigator. Instead, success hinges on the quality and clarity of the supporting infrastructure. This includes creating particular, task-based instructions that provide objective directives without revealing sensitive protocol details. For example, instead of asking an HCP to "monitor for signs of hepatotoxicity," the instruction might be, "If the subject reports nausea, abdominal pain, or jaundice, or if you observe these signs, contact the PI immediately." The safety monitoring plan must be meticulously designed to instruct the HCP on *what* to report and *how* to report it, without requiring them to perform a research-based assessment of causality or severity.[1]

### The HHS/OHRP Framework: Determining Institutional "Engagement"

The Federal Policy for the Protection of Human Subjects is commonly known as the Common Rule (45 CFR Part 46) because 21 Federal agencies have adopted Subpart A in full. When a research study is conducted or supported by any of the Common Rule agencies,[6] it generally falls under the purview of the OHRP. The OHRP responsibility framework, as alluded to in the opening of this paper, operates on a different principle from the FDA. The OHRP framework centers on the concept of institutional "engagement." Understanding this doctrine is paramount, as inadvertently "engaging" a collaborating provider's institution can trigger significant and often unforeseen regulatory obligations.

### "Engagement"

The concept of "engagement" applies to *institutions*, not to individuals. An institution can be a hospital, a private clinic, a university, or a commercial entity.[3] The determination of whether an institution is "engaged" in a non-exempt human subjects research project is a threshold question with serious consequences.[3]

When an institution is determined to be engaged, it must satisfy two primary requirements under 45 CFR 46.103:

1. It must hold or obtain an OHRP-approved Federalwide Assurance (FWA), which is a formal commitment to comply with the Common Rule.
2. It must certify to the funding HHS agency that the research has been reviewed and approved by an Institutional Review Board (IRB) designated under its FWA, and that the research will be subject to continuing IRB review.

Therefore, a PI conducting federally funded research must carefully analyze whether their collaboration with an external provider will cause that provider's home institution to become engaged in the research.

### Activities That Trigger Engagement

According to OHRP, an institution generally becomes engaged in research when its employees or agents (which can include staff, contractors, or volunteers acting on the institution's behalf) perform certain activities for the purposes of a specific research project.[3] The 2008 OHRP guidance on engagement outlines the specific actions that typically trigger this status.

The three core triggers for institutional engagement are:[3]

1. **Intervention or Interaction for Research Purposes:** This includes performing invasive procedures (e.g., drawing blood, administering a drug) or noninvasive procedures (e.g., administering a psychological test), as well as manipulating a subject's environment (e.g., controlling lighting or sound for a study). It also includes interacting with subjects for research, such as conducting interviews, administering questionnaires, or asking them to provide a specimen.
2. **Obtaining Identifiable Private Information (IPI) or Identifiable Biospecimens:** An institution is engaged if its employees or agents obtain IPI or identifiable biospecimens for the research from any source. This applies even if there is no direct contact with the subjects. Examples include observing private behavior, or using, studying, or analyzing identifiable data or specimens provided by another source.
3. **Obtaining Informed Consent:** If an institution's employees or agents obtain the informed consent of human subjects for the research, that institution is considered engaged.

### Not Engaged

The OHRP guidance also provides a list of specific, narrowly defined scenarios in which an institution's involvement would *not* constitute engagement.[3] For a PI to compliantly use an external provider without triggering engagement for that provider's institution, the provider's activities must fit wholly and squarely within one of these "safe harbors."

Key "not engaged" scenarios from the OHRP guidance include[3]:

- **Commercial or Other Services:** An institution is not engaged if its employees perform commercial or other services for investigators, provided that all of the following conditions are met: (a) the services performed do not merit professional recognition or publication privileges; (b) the services are typically performed by the institution for non-research purposes; and (c) the institution's employees or agents **do not administer any study intervention** being tested or evaluated under the protocol.

- **Clinical Trial-Related Medical Services:** A private practice or other institution is not engaged if its employees provide medical services that are dictated by the protocol but are part of routine clinical monitoring (e.g., a follow-up visit), provided that they **do not administer the study intervention**, do not enroll subjects or obtain their consent, and the PI from the engaged institution retains full responsibility for oversight and data reporting.
- **Recruitment Activities:** An institution is not engaged if its employees merely inform prospective subjects about the availability of research, provide them with information (including a copy of the consent form), or seek permission for the investigators to contact them, as long as they do not obtain consent or act as representatives of the investigators.
- **Release of Information:** An institution is not engaged if its employees release identifiable private information or biospecimens (e.g., copies of medical records or existing tissue samples) to investigators at another institution, as this does not involve obtaining the information *for research purposes* but rather fulfilling a request.

### Conflict Between the FDA and OHRP Models

A direct and critical conflict emerges when comparing the flexibility of the FDA's DCT framework with the strictures of the OHRP engagement doctrine. This conflict is most apparent in the context of IP administration. The FDA's "local HCP" model explicitly permits a non-investigator provider to administer an IP, provided its safety profile is well-understood.[1] This is a cornerstone of making many DCTs feasible.

However, under the OHRP framework, the act of "administer[ing] any study intervention being tested or evaluated under the protocol" is a specific disqualifying condition for two of the most relevant "not engaged" safe harbors: the "commercial services" and "routine clinical services" scenarios.[8]

The implication is unavoidable. Suppose a PI conducting an HHS-funded study asks a provider at an external clinic to administer the investigational drug. In that case, that provider's institution has, by definition, become "engaged" in the research. The flexibility offered by the FDA for DCTs does not override the more restrictive institutional requirements of the Common Rule. For a study subject to both regulations, the OHRP engagement rule is the controlling factor for this specific activity. Consequently, the provider's institution would be required to obtain an FWA and secure IRB review and approval for its role in the study. This fundamental incompatibility means that strategies for designing DCTs must be tailored based on the funding source of the research.

It is important to note that not all federal agencies follow the guidance issued by OHRP, even if they hold a federalwide assurance. OHRP enforces the applicability of the OHRP guidance for HHS-funded research, but the applicability of the OHRP guidance would be subject to the interpretation of other federal funding agencies.

### The Functional Role of the Non-Investigator Provider in Dual-Jurisdiction Studies

For studies subject to both FDA and HHS regulations, the functional role of a non-investigator provider is dramatically curtailed. The FDA's 2024 DCT guidance appears to open a wide door for leveraging local providers to perform a variety of trial-related activities, including core interventions like IP administration. However, the OHRP engagement doctrine acts as a powerful brake on this flexibility.

Because the most meaningful research activities—administering interventions, performing research-specific procedures—are the very activities that trigger institutional engagement under the Common Rule, the PI in a dual-jurisdiction study is left with a much narrower set of permissible tasks for an external provider. The provider's role effectively shrinks from that of a decentralized extension of the trial site to that of a simple service vendor. They can be used for indisputably routine tasks, non-interventional (in the research sense), and fit cleanly into an OHRP "not engaged" safe harbor. This primarily includes standard-of-care diagnostics (e.g., getting a routine x-ray or ECG), standard laboratory tests, and data retrieval (e.g., obtaining medical records). The expansive vision of the DCT model, where complex trial activities are seamlessly distributed into the community, is thus heavily constrained by the foundational principles of institutional accountability that underpin federally funded research.

### Operationalizing the Relationship

A deep understanding of the parallel regulatory frameworks is essential but alone does not ensure compliance. PIs and sponsors must turn this knowledge into concrete operational practices. The key to effectively and compliantly working with a non-investigator provider is to formalize the relationship, give clear instructions, and maintain careful oversight. These practices are not just recommended; they are critical risk mitigation strategies that create an auditable and defensible compliance foundation.

### Structuring the Service Agreement

The relationship with a non-investigator provider must not be based on an informal understanding or a simple purchase order. It must be formalized in a legally sound, written service agreement. This document serves as the cornerstone of the PI's compliance strategy, as it prospectively defines the limited nature of the relationship and provides clear evidence of a systematic plan for oversight.

A robust service agreement should, at a minimum, include the following essential clauses:

- **Precise Scope of Work:** The agreement must specify the exact tasks to be performed. Vague language, such as "provide clinical support" or "perform cardiac assessments," is insufficient. The scope should be detailed, such as: "Perform one standard 12-lead electrocardiogram (ECG) according to standard clinical practice and transmit the electronic tracing" or "Collect one 5 mL tube of whole blood via standard venipuncture." This level of detail prevents scope creep and clearly defines the boundaries of the provider's role.
- **Regulatory Status Declaration:** The agreement must include a clear statement confirming the provider's status. It should specify that the provider and their institution function as independent service vendors, are not investigators, sub-investigators, or agents of the PI's research institution, and are not formal members of the research team. This clause is essential for protecting against claims of improper delegation or unintended institutional

involvement.

- **Data and Reporting Requirements:** The agreement must specify the necessary data elements that must accompany any results. In accordance with FDA guidance, this should include the name of the provider who performed the service and the date of the service. It should also define the required format for the data and the secure method of transmission to the PI's site to ensure data integrity and protect participant privacy.
- **Safety Reporting Protocol:** The agreement must include clear, objective, and unambiguous instructions for how the provider should respond to urgent medical events. This protocol should not require the provider to make research-based judgments (e.g., assessing causality or severity). Instead, it should consist of direct commands. For example: "If the subject experiences syncope, seizure, chest pain, or severe shortness of breath during or within 30 minutes after the procedure, you must contact the Principal Investigator, Dr. [Name], immediately at [emergency contact number]." This meets the PI's safety oversight responsibility without improperly delegating a research assessment function.
- **Confidentiality and Privacy:** The agreement must include standard clauses requiring the provider to safeguard all participant information in accordance with HIPAA and other relevant privacy laws.

### Training and Communication: Task-Specific Instructions, Not Protocol Education

The training for a non-investigator provider must be fundamentally different from the comprehensive protocol training given to a formal study team member. The aim is not to teach the provider about the research but to instruct them on a specific task. The PI should "communicate any specific instructions included in the protocol" that are relevant to the task at hand but should not have to provide the protocol itself.

This can be implemented using just-in-time, task-specific instruction sheets or checklists that accompany the order for the service. For example, a request for a blood pressure measurement might include a one-page sheet that specifies:

1. Have the participant sit and rest quietly for 5 minutes.
2. Use the provided calibrated electronic cuff on the left arm.
3. Record the first reading.
4. Wait 2 minutes.
5. Record the second reading.
6. Transmit both readings.

This ensures standardization and data quality without requiring the provider to read and interpret the full study protocol.

Communication should be streamlined through a single, designated point of contact at the PI's site, typically the CRC. This prevents conflicting instructions and ensures that all interactions are documented. If the provider will be using any electronic systems to submit data (e.g., a portal for uploading ECG tracings), they must be provided with specific training on that system.[2]

Non-investigator providers should insist that the PI attest to them that they are not being asked to perform any task that would rise to the level of being an investigator.

### A PI's Checklist for Quality Oversight

The PI's oversight cannot end once the service agreement is signed. They must implement and document a continuous process for reviewing the work performed by external providers. This oversight process should be systematic and can be guided by a checklist that includes the following items:

- **Timely Review of Incoming Data:** Is there a defined process and timeline to ensure that all reports, lab results, and other data received from external providers are promptly reviewed by the PI or another qualified, delegated member of the study team (e.g., a sub-investigator)?
- **Data Completeness and Consistency Check:** Does the submitted data contain all the elements required by the service agreement (e.g., provider's name, date of service)? Is the data plausible and consistent with other data collected for that participant? Are any missing or concerning data points being followed up on immediately?
- **Integration into the Case History:** Is there a reliable workflow to ensure that every report from an external provider is correctly filed in the participant's source documentation and integrated into their official case history, creating a complete and accurate record of the participant's journey through the trial?
- **Billing and Payment Reconciliation:** Is there a process to ensure that invoices are reconciled against the services performed and that payments are made correctly according to the terms of the service agreement? This helps maintain a clean, professional relationship and avoids any appearance of undue influence or financial coercion.

### The Service Agreement as the Primary Audit Defense

In the event of an FDA inspection or an OHRP audit, the PI will inevitably be asked to describe the roles of all individuals and entities involved in the study and to demonstrate how they maintained proper supervision. In this context, a well-crafted service agreement becomes the PI's most important piece of exculpatory evidence regarding the use of non-investigator providers.

Presenting this document allows the PI to demonstrate, with documentary evidence, that they proactively and systematically managed the relationship. The agreement proves that the PI:

1. Clearly defined the provider's role as a limited, non-investigator service vendor, satisfying the FDA's distinction between a "local HCP" and a subinvestigator.
2. Strictly limited the provider's activities to specific, routine tasks that do not require protocol knowledge, aligning with the FDA's definition.
3. For federally funded studies, carefully select only those tasks that fall squarely within an OHRP "not engaged" safe harbor, thereby protecting the provider's institution from unintended regulatory burdens.
4. Established clear, pre-defined channels for data reporting and urgent safety communications.
5. Defined the exact data deliverables needed to maintain a complete and accurate research

record.

The service agreement, therefore, transforms what could be perceived as an ambiguous and high-risk collaboration into a well-documented, auditable, and compliant business transaction. It is the essential tool that protects the PI, the sponsor, the research institution, the participant, and the collaborating provider's institution by creating a clear and defensible record of a properly managed relationship.

### Conclusion

Ultimately, leveraging non-investigator providers is a powerful and valuable tool in modern clinical research. However, its successful implementation is not a matter of informal collaboration. It requires a rigorous, proactive, and well-documented compliance strategy. This strategy must be based on two pillars: first, a detailed understanding of the applicable regulatory frameworks, and second, the implementation of precise operational controls. The foundation of these controls is the service agreement, which defines the limited scope of the relationship and serves as the main evidence of the PI's diligent oversight. By combining regulatory expertise with meticulous operational planning, investigators and sponsors can leverage the benefits of a distributed research model while upholding their primary responsibility to protect research participants, abide by applicable regulations, and maintain the integrity of the scientific process.

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