A Cost of Crossing Lanes:
Clinical QA and the PV World

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Let's face reality. The scarcity and expense of Pharmacovigilance (PV) Quality talent will, more often than not, result in assigning a Good Clinical Practices (GCP) Quality professional, or, less often, a Good Manufacturing Practice (GMP) Quality professional. This person must recognize the limits of their PV knowledge and experience and proactively seek appropriate collaboration for PV Quality-related matters; everything in PV involves distinct PV Quality mechanics. Absent a PV Quality professional, the only appropriate reservoirs of PV knowledge and experience are the PV Team and the Safety Services Provider.

Issues arise when non-PV Quality professionals step into the PV world without a clear understanding of the differences. A recent incident illustrates what happens when disparate GCP Quality Assurance (QA) attempts to cross into PV Quality. I bring this up because it occurs more often than it should and because this incident epitomizes that lane-crossing: A GCP Quality professional asserts that PV maintains Standard Operating Procedures (SOPs) for entries into the electronic Trial Master File (eTMF, or simply TMF).

PV Quality is often operationally grouped alongside or considered a subset of the broader Clinical Quality function. While not an error in assumption, the two are more distinct than they appear on the surface. PV Quality requirements are often not fully considered by clinical-focused QA professionals. PV Quality in the clinical development stage is a more focused discipline than broader clinical quality, with its own guidelines and regulatory requirements.

Although uncommon, some GCP QA professionals do have the requisite PV training and experience. These individuals are rare because PV Quality takes years to master, and much of it relies on deep expertise in drug safety, a discipline that accounts for the other half of the drug approval equation.

The Quality Agreement Disagreement

Risk to the program occurs when sponsors operate solely under a Clinical Quality Agreement with the Contract Research Organization (CRO). Generally, there is little consideration of their PV colleagues' need to develop a PV Quality Agreement with the CRO or their Safety Services Provider.

The PV Quality Agreement emphasizes the distinct, highly specialized needs of PV for safety oversight, governance models, surveillance, KPIs, and separate operational rules. As we all know too well, classical clinical vendor oversight SOPs do not extend to the deep requirements for safety vendor oversight.

Crossing into the PV Lane — The Well-Known TMF Example is Enough

Exposing PV professionals to unblinded trial data in the TMF creates a serious risk of bias and data integrity compromise, potentially jeopardizing the validity of the trial dataset, a risk well recognized

under ICH E6(R3) and reflected in FDA and EMA guidance on blinding and trial conduct. Further, TMF entry requires highly precise indexing, metadata tagging, and quality control (QC) workflow. To prevent indexing errors, organizations appropriately restrict file upload rights to a gatekeeper (e.g., a Clinical Trial Assistant (CTA) or TMF Officer). The official source of truth for safety information over the product's lifecycle is the safety database.

I am unaware of any PV professional who has ever encountered a TMF officer who would allow them to make direct entries into either of the two TMF zones that contain safety information. Nor do PV professionals have a desire or training to venture into this territory. That has always been a firm "**NO GO**."

Similarly, I am unaware of any SOP that assigns PV ownership for making TMF entries. PV documents related to safety might be referenced or cross-referenced within the TMF, but TMF entry rights and responsibilities have never extended to PV professionals as an ownership function, nor should they.

Industry guidance is consistent on this point: PV professionals are excluded from making direct entries into the TMF to prevent trial unblinding, protect data integrity, and maintain strict system segregation. While safety documents must eventually be accounted for in the TMF, direct system access is restricted to Clinical Operations or specialized TMF teams. (TFS Healthcare: *website source used as an example of industry best practice*)

Why Not Throw a Vendor Audit in for Good Measure?

Requiring PV to maintain SOPs for TMF entries has no basis in applicable PV legislation or guidance. There is no provision in 21 CFR Part 312, ICH E6 R3, GVP Module I, GVP Module VI, or the CDISC/DIA TMF Standard Model that requires PV functions to own or make entries in TMF zones. Adding such a requirement to audit criteria as if it were a regulatory obligation is factually incorrect and procedurally improper.

Despite strong PV pushback during a vendor audit, the same GCP QA professional elevated herself from observer to co-lead auditor. There are at least **four problems** with this action:

> **First**, she added to the audit plan a review of documented procedures to ensure that requirements exist for PV to make TMF entries, a standard with no regulatory basis whatsoever.
>
> **Second**, under GVP Module IV, the auditor must be PV-qualified through training and experience, **and third**, be independent of both the trial and the processes being audited. She was neither.
>
> **Fourth**, the audit was not proportionate to the risks associated with the trial and was not scoped to ensure compliance with the protocol, GCP, or applicable regulatory requirements, thereby itself constituting a violation of ICH E6(R3).

GVP Module IV is unambiguous on this point. It defines auditor independence as freedom from conditions that threaten objectivity or the appearance of objectivity and requires that such threats be managed at the individual auditor, engagement, functional, and organizational levels. An auditor who helped write the very processes under review and then assumed a co-lead role in auditing them fails that test at every level simultaneously.

Note on GVP Applicability to Clinical-Stage Programs

> *The GVP modules are formally directed at marketing authorization holders. However, GVP principles, particularly those governing quality systems (Module I) and audits (Module IV), are broadly applied to sponsors conducting clinical trials, and pharmacovigilance systems are widely expected to meet GVP standards regardless of authorization status. Importantly, GVP Module VI addresses safety reporting in the pre-authorization period and*

> *governs solicited adverse reaction reports from organized data collection systems, including clinical trials, in contexts where the full clinical trials directive framework does not apply.*
>
> *Beyond that regulatory basis, GVP modules are widely applied by sponsors and PV service providers as the accepted industry standard for structuring and auditing PV systems at any stage of development. The references to GVP in this article reflect both that regulatory alignment and industry consensus.*

Here's the Rub

An extremely reputable vendor, vetted through the company's own RFP process and operating under processes written by the auditor herself, was disqualified for failing to maintain TMF entries in their PV case processing SOPs. In other words, they were penalized for failing to comply with a sponsor QA requirement that should never have existed.

The Solution for Guaranteeing Safety Entries into the TMF

The most appropriate location for recording Clinical-owned activities and processes, such as TMF entries from all requisite sources, is within Clinical Operations SOPs. PV personnel must be included in the training matrix for these SOPs, and training records should be properly archived for inspection purposes to ensure that the required safety documentation is requested by the Clinical Team and received at the appropriate time and in the prescribed format.

Shifting the Narrative: Positive Language Guidance

When transitioning from a "lane-crossing" approach to a specialized PV oversight model, the language used in Quality Agreements and audit reports should emphasize this collaboration and regulatory alignment.

Avoid This (The "Lane-Crossing" Tone)	Use This (The Specialized PV Tone)
PV must follow standard Clinical TMF entry procedures to ensure general QA consistency.	PV maintains a distinct safety database as the official source of truth, with controlled cross-referencing to the TMF to protect data integrity and blinding.
The auditor will apply general GCP standards to evaluate all vendor safety functions.	A PV-qualified auditor will assess the vendor's safety systems against GVP and ICH E2 standards to ensure specialized compliance.
Vendors are disqualified for failing to meet sponsor-specific operational preferences.	Vendor performance is evaluated against applicable PV legislation and industry consensus standards to ensure patient safety.
Clinical QA has final ownership over safety vendor oversight SOPs.	Safety vendor oversight is governed by a dedicated PV Quality Agreement and SOP that addresses the unique requirements of surveillance and governance.

Why Is This Lane-Crossing Dangerous?

Conflict of Interest and Audit Integrity

The auditor's self-elevation from observer to co-lead constitutes a serious procedural breach. Independence is a foundational requirement for audit validity. An auditor who effectively wrote or influenced the processes under audit and then assumed a leadership role in auditing those same

processes has compromised the integrity of the entire exercise. The findings are tainted and indefensible if challenged.

Regulatory and Compliance Risk

Audit findings generated without appropriate PV competency may lack credibility and be difficult to defend during regulatory inspections. If a regulatory authority reviewed the audit trail and found that PV processes were assessed by someone lacking PV competency, the sponsoring organization could face serious scrutiny, not for what the vendor did wrong, but for what the audit program itself got wrong.

Organizational and Strategic Risk

The sponsor organization now holds a distorted quality record, has wrongly disqualified a vendor, and has audit findings built on a flawed regulatory interpretation. Correcting this will require significant resources, may require legal or regulatory counsel, and could delay the clinical program. If the disqualified vendor possessed specialized capabilities in safety case processing, replacement may not be straightforward or fast.

Vendor Disqualification Based on a False Standard

This is perhaps the most immediately dangerous outcome. A reputable, vetted vendor was disqualified not for an actual deficiency but for failing to meet a requirement that was incorrectly imposed and has no regulatory basis in PV guidance. TMF ownership and entry rights are tightly controlled under GCP, and PV professionals have historically and appropriately been excluded from direct TMF entries in the two zones containing safety data. Disqualifying a qualified vendor on these grounds removes a potentially critical resource from the clinical program and exposes the sponsor to gaps in coverage for safety case processing.

Patient Safety Implications

PV exists precisely to protect patients by ensuring that adverse event data is captured, processed, reported, and analyzed correctly and on time. Disrupting the vendor ecosystem responsible for safety case processing, or imposing SOPs that misalign PV workflows with TMF governance, creates a real risk of delayed or missed expedited safety reports, inconsistent adverse event coding and narrative development, and breakdowns in signal detection and aggregate reporting timelines. Any of these failures can directly result in harm to trial participants or post-market patients.

The Broader Danger

The core danger is this: when unqualified oversight is applied to a highly specialized discipline like PV, the consequences are not merely procedural. Safety data integrity and regulatory reporting timelines are at stake. PV quality failures can reach regulators, ethics committees, and ultimately patients.

> ***Getting PV quality oversight wrong is not a paperwork problem. It is a patient safety problem dressed in a compliance uniform.***

Regulatory Frameworks Referenced

- 21 Code of Federal Regulations (CFR) Part 312 (US FDA)
- Clinical Data Interchange Standards Consortium (CDISC)/Drug Information Association (DIA) TMF Standard Reference Model
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 R3
- ICH E2A, E2B, and E2E
- EU Good Pharmacovigilance Practices (GVP) Modules I, IV, and VI