The Future of Audits

by Melvyn Rapprecht June 2022

Do note this is written from an independent consultant perspective and therefore the auditing experience if you work within a pharmaceutical company will differ as independent consultants are normally not involved in risk assessment, audit selection of studies and sites, study related process or systems audits and but not always in the review of the CAPAs to audit observations.

With the introduction of ICH GCP in the 1990s the road to inspections and audits was opened in Europe. The FDA already had established an inspection program, but this was rather new to Europe and the rest of the world. Pharmaceutical companies embarked on setting up the auditing function, its scope, its independence, the auditing processes and deliverables and of course the associated standard operating procedures, tools and templates. Looking back the auditing process consisted of writing the audit plan, audit confirmation letter to auditee, preparation (and more time was allowed compared to today as we reviewed SOPs, Protocol, Informed Consent and Investigator's Brochure and monitoring plan when we conducted Investigator Site Audits), conducting the audit, writing the audit report with recommendation, review of the actions and issuance of the audit certificate or a similar process. Do note, in the 90s there was less to no outsourcing so less stakeholder's involvement in the clinical trials, less systems, no CSV requirements, regulatory and IRB/IEC were mostly not centralized, no translations, and no DIA structured Trial Master File (TMF). If memory serves me right, the auditing function was already established in Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) and in clinical development the GLP and GMP frameworks were adopted to within Good Clinical Practice (GCP).

Auditing 30 years ago consisted of sometimes review of the country TMF and the general TMF which was kept in-house and interview of the project team and/or monitor/CRA prior to the audit, conducting an opening meeting, to discuss the audit objectives, scope and audit logistics, interviewing the Principal Investigator and his team, tour of the facilities, review of the ISF almost 100% with, tour and review of the pharmacy and pharmacy file, and Source Document Verification (SDV) 100% for $\sqrt{n}$+1 subjects' CRF where n is the total number of subjects enrolled into the clinical trial at the site in question. This was conducted by 1 or 2 auditors over a period of 2 to 5 days. The audit was concluded by a close out meeting with the investigational team in which the scope, the reporting process and observations were discussed including the potential severity classification. And the medium used was paper.

Now 30+ years later, the overall process has not changed. We still prepare, conduct and report in spite of some key differences, one being that data and records are in different mediums and across different platforms and outsourced stakeholders.

So before listing other differences one needs to understand how the clinical development landscape has changed in the last 30 years. Here are some key (regulatory) milestones/differences:

1. ICH GCP E6 R1 shaped the responsibility of sponsors, IRB/IEC and investigators to conduct clinical trials
2. 21 CRF Part 11 shaped the Computerized System Validation
3. ICH GCP E6 R2 introduced risk within clinical trials
4. MHRA introduced the Serious Breach reporting requirement

5. EMEA (now called EMA) shaped the inspection landscape within Europe which is process based with differs from the FDA approach which is mainly data/record based
6. Clinical Trials are far more outsourced
7. More systems are used, eCRF, eDiary, ePRO, other monitoring devices (some 24hrs), eTMF, more central laboratories and reporting system, systems for safety reporting, sponsor/client LMS, sharepoint/box
8. Complexity of clinical trials have changed e.g., gene modified products with often a different regulatory landscape
9. Study management documentation such as the monitoring plan (which describes the risk-based approach), eTMF plan, Pharmacy Manual, eCRF completion plan, Laboratory manual and training are provided continuously

Going forward, the ICH guidance and regulations are now more frequently being updated to keep up with technological changes and clinical trial complexities. Notably ICH E8 General Considerations for Clinical Trials and EU No 536/2014 Clinical Trial Regulations which were introduced in 2022.

Taking the above into consideration one would have thought that the audit process would have adapted to accommodate those complexities and changes overtime. What I see as an independent consultant, the time used to prepare, conduct and reporting audits as a consultant is still the same when ADAMAS Consulting was set up in Europe for which I was the CEO in its first couple years of existence.

Consulting auditors are given in general between 1 and 2 days to prepare for an audit and that includes the set up and training in the systems/platforms and its access and used in the clinical trials which could be quite a few; reading and understanding the protocol, monitoring plan, laboratory and IMP Manual in detail is expected, the writing of an Audit Plan and/or Confirmation Letter and/or Agenda which includes meetings and communication between sponsor and auditee. This is the minimum and all to be done within 2 days…. Is this realistic? And how does this affect an audit from a value perspective?

Taking the time to set up, train and familiarize yourself with the systems and platforms, issuing the audit plan (if required), Confirmation Letter and agenda leaves little time to read the protocol synopsis and key study elements such as the inclusion and exclusion criteria, and visit and scheduled assessments, primary and secondary endpoints, IMP preparational and dosing requirements and navigate the complexity of the Monitoring Plan(s), access the eTMF for monitoring insights and IEC/IRB regulatory submissions. One thing we do not get to read most of the time, is the key sponsor SOPs in managing clinical studies and sites.

It is most of the time not possible to read and familiarize this all in the allotted time. And will have an impact on the audit outcome in my opinion.

Two to 3 days are given to conduct the audit which includes the opening meeting, tour of the facilities, checking of the calibrated status of equipment, temperature excursion of the fridge and freezers used in the clinical trial, shipping process and responsibilities, pharmacy, pharmacy file and drug accountability, interviews, review of the ISF mostly 100% regulatory and IRB/IEC approval records, 100% monitoring documentation (actually 100% of checking dates on the monitoring reports vs monitoring visit log and Follow-up letters but we have no time to read the content of the monitoring reports), Qualification, medical licenses and training records, financial disclosures, FDA 1572 if the study is conducted under an IND, Non-disclosure Agreements, Clinical Trial Agreements, insurances and the site delegation/responsibility log. Not to mention checking the safety

notifications including the process and evidence, SUSARs, DSURs and Annual Reports. All this is checked 100% and providing you had time to prepare or are an experienced auditor to assess these documents against the eTMF for consistency and completeness. Leaving very little time to determine if the system used at the site was properly implemented and were stable during the clinical trial. eDiary and ePRO appear glitchy and raises potentially the non-compliance of subjects unnecessarily. And then of course trying to verify how and when the protocol amendments and informed consent and amendments were introduced, trained upon, implemented and managed by the site. Followed by the checking of SAEs, informed consents and SDV part is conducted on the second day. Often one is expected to conduct 100% of one subject irrespectively of the volume and study progress of that subject and irrespective of the type of study whether it is an oncology, a gene therapy study or other therapeutic studies either with biologics or manufactured products. Finally, a closing meeting for which you need time to analyze the observations and to determine what you will be saying to the site team, who is often nervous as to what they will be fed back. I have focused on Investigator Site Audits, but the same analysis would apply to Qualification and CSV Audits.

The overall conclusion that can be drawn is that the overall process how audits are conducted has not changed. But the level of information, the operational and changing regulatory landscape has.

In my opinion the audit process should be changed with the focus to determine the critical risk elements prior to the audit and asking different questions which would target compliance, efficiencies, patient safety and well-being whilst reducing the clinical trial administrative burden whilst safeguard the safety and well-being and clinical trial experience of the subjects; and the scientific integrity of the clinical trial design and the robustness of the data, of course.

So, what should change?

In order for the Investigator Study Audit, but all other audit types, to be of value-added we should be embracing current/future technologies far more to prepare for audits. The number of data and records available to auditors and that we still manually process should become a thing of the past. Auditors should be able to utilize technology more and more to assist with the preparation of audits.

Machine Learning and Artificial Intelligence could be utilized to examine and analyze records and data and provide a summary of potential (un)detected quality risk elements which would assist in the prioritization when auditing. This would require changing the audit process from a static model to a more dynamic model. Thus, it is time to relook at the auditing objectively and going forward going from a static auditing model to a more dynamic model where possible of course. *Aut viam inveniam aut faciam* (Anibal).