Katarina Eghan

Karen Martin

COMPLIANCE, QUO VADIS?

The Cambridge Dictionary defines compliance as 'the act of obeying an order, rule, or request'[1]. The word compliance has a similar meaning in the world of drug development and manufacture; organisations developing or manufacturing medicines generally exert a lot of effort on ensuring compliance with legislative and other requirements. However, looking at inspection metrics and based on direct experience from audits, it seems that there are still areas where the efforts of the industry are not as effective as would be hoped.

This article sets out to explore the possible causes of ineffective application of quality and compliance management principles and provide some food for thought on how to reduce the time, money, effort and resource spent on managing compliance. The examples used are related to the conduct of clinical trials however, the ideas can be extrapolated easily beyond the boundaries of Good Clinical Practice (GCP).

COMPLIANCE LANDSCAPE

As noted in the article 'Causes of Effects – What Should we Measure?' published in Quasar 129, inspection metrics between 2008 and 2013 had not shown marked improvements in the compliance levels of organisations and there had been repeated issues uncovered during reactive compliance verification activities, such as monitoring, audits and inspections[2]. A comparison of a sample of the UK Medicines and Healthcare products Regulatory Agency (MHRA) GCP inspection metrics from 2008 to 2013 was made in that article, where the mean and maximum number of findings per inspection (of commercial sponsors – routine systems, study specific and triggered) were more or less the same. The authors also looked at the trends in percentage of 'any' findings (critical, major and other) for three randomly selected observation categories from UK investigator site inspections. The original data have been reproduced in Figures 1-3, together with additional data from 2013-2016, which again do not show a clear downward trend.

FIGURE 1. METRICS FROM MHRA INSPECTIONS OF COMMERCIAL SPONSORS (ROUTINE SYSTEMS, STUDY SPECIFIC AND TRIGGERED)[3,4,5,6,7,8,9]

METRICS PERIOD	NO. OF INSPECTIONS	NO. OF OBSERVATIONS*					
		CRITICAL		MAJOR		OTHER	
		MEAN	MAX	MEAN	MAX	MEAN	MAX
01 Apr 08 – 31 Mar 09	22	0	1	3	8	7	14
01 Apr 09 - 31 Mar 10	32	0	1	2.2	7	6	12
01 Apr 10 - 31 Mar 11	30	0	1	2	8	6.5	11
01 Apr 11 - 31 Mar 12	27	0	1	2	5	6.5	11
01 Apr 12 - 31 Mar 13	19	0	1	1.5	6	7.5	13
01 Apr 13 - 31 Mar 14	22	0.1	1	2.5	6	6.5	12
01 Apr 14 - 31 Mar 15	11	0.2	1	3.0	13	7.7	13
01 Apr 15 - 31 Mar 16	10	0.3	1	2.9	8	7.0	11

* Approximate figures used

Although the sample size used for comparison purposes was relatively small and bias was introduced by the authors selecting which data to include, the above is nevertheless indicative of a stagnating compliance landscape.

POSSIBLE CAUSES OF ONGOING ISSUES

1. CUMBERSOME PROCEDURAL DOCUMENTS

Hand on heart, do you ever get overwhelmed by the length of procedural documents or the language used? Or by the extremely prescriptive nature which makes you almost instantly non-compliant (because you did not perform the process steps in the prescribed order for example)? Unfortunately, many procedures are still very complicated, hard to follow and are often written by people not doing the job that the procedure is trying to define.
This results in user unfriendly documents that pose a high risk of non-compliance. On the other hand, some procedural documents can be so vague that they provide no meaningful instruction to the reader.

2. CUMBERSOME TRIAL DOCUMENTATION

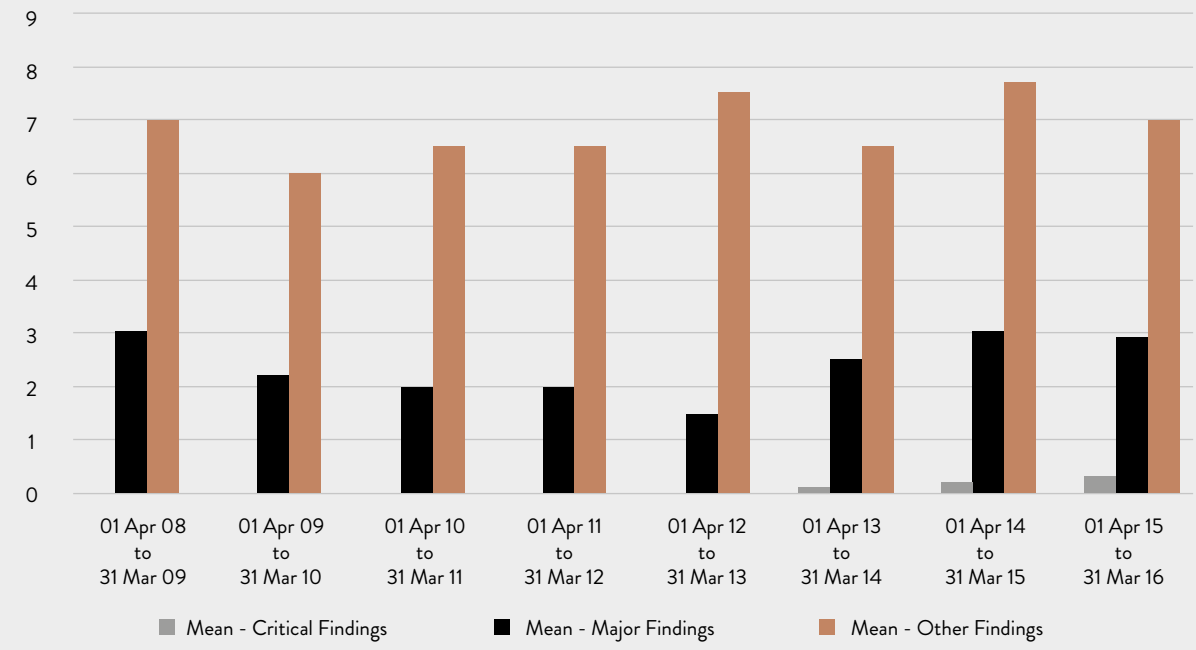
Ask yourself the following questions: how many pages does the trial protocol have, how many study objectives or sub-studies does it include, how many amendments to the protocol have there been and how many pages of manuals and guidelines have been produced to tell investigators and their staff what to do? Do the answers make your head spin? If the answer is yes then there is a high probability that the trial will be non-compliant with some of the requirements set out in the trial documentation. The incidence and frequency of substantial protocol amendments remains high, with one study revealing that 57% of all protocols, across all phases, have at least one global, substantial amendment, some of these occurring before enrolment of the first subject and almost half of these deemed avoidable[10].

3. INEFFECTIVE SITE SELECTION, MONITORING AND MANAGEMENT

Site evaluation and selection is critical to the success of clinical research. As per the International Council for Harmonisation (ICH) E6 Guideline for GCP, investigators participating in a clinical trial have numerous responsibilities. Each element of the trial conduct should be thoroughly discussed with sites and their ability to meet all the requirements and expectations determined prior to their selection.
For example, with the increasing use of Electronic Health Records (EHRs) by sites, an adequate assessment of the set-up must be performed during site evaluation and the sponsor/contract research organisation (CRO) staff should be asking the right questions to ensure they have a complete picture of what trial subjects' source medical records comprise and how these are maintained. A thorough review of the format and composition of source records will help reduce the likelihood of unwelcome surprises during the trial, such as the discovery of additional medical records maintained on a system that was not identified during site evaluation.
ICH E6 specifies in point 6.10 that 'the sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, Independent Review Board/Independent Ethics Committee review and regulatory inspection(s), providing direct access to source data/documents'[11]. Should the site be unable to give monitors/auditors/inspectors unaided direct access to the EHRs of trial participants, an appropriate process must be put in place to assure completeness of the records made available for review.

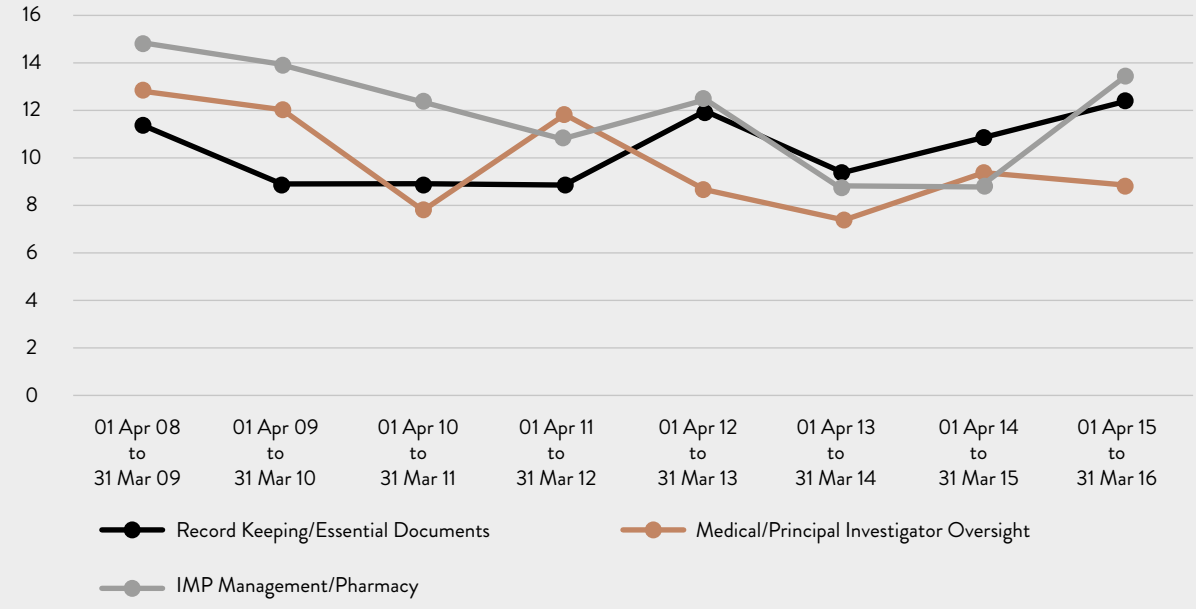
Ineffective monitoring may often be the result of a poorly thought out monitoring approach, resulting in the requirements of the monitoring plan being excessive, inappropriate, unreasonable or unattainable. For example, the monitoring frequency should be such that the monitor can efficiently review the key elements, such as the subjects' eligibility to participate in the trial, in a timely manner (i.e. not months after inclusion). Also, the requirements for the monitor's review of certain less critical aspects of trial conduct, such as the investigator site file (ISF), should be proportionate.

FIGURE 2. MEAN* NUMBER OF FINDINGS FROM MHRA INSPECTIONS OF COMMERCIAL SPONSORS (ROUTINE SYSTEMS, STUDY SPECIFIC AND TRIGGERED)[3,4,5,6,7,8,9]



* Approximate figures used

FIGURE 3. TRENDS IN PERCENTAGE* OF ANY FINDINGS (CRITICAL, MAJOR, OTHER) FOR THREE FINDING CATEGORIES FROM UK INVESTIGATOR SITE INSPECTIONS[3,4,5,6,7,8,9]



* Approximate figures used

Some organisations now adopt a risk-based approach to monitoring, but examples have been seen where the risk-based approach is too complex to manage and to enable measurement of compliance with the monitoring requirements.

Also, the demands placed on sponsor/CRO staff in today's environment can be excessive, particularly with regard to the number of projects and sites that staff have responsibility for. Unfeasible requirements of the monitoring/project plan can place unnecessary burden on monitors and others, ultimately leading to high staff turnover or staff burn-out.

Effective site management, i.e. issue resolution, is the key! Numerous examples have been seen on audit of CRAs doing a great job of identifying issues, retraining the site and performing other supporting activities, as required by ICH E6 5.18.4. However, there are subsequent failures to fulfil the requirements of 5.20.1 ('non-compliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance') and 5.20.2 ('if the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial')[11].

4. DEFICIENCIES WITH E-DIARIES, ELECTRONIC PATIENT REPORTED OUTCOMES (EPROS) AND OTHER ELECTRONIC TOOLS

The use of e-diaries, ePROs and other e-solutions is commonplace in today's clinical trials and these are often used to collect key trial data. However, the use of these data collection tools is often fraught with technical challenges and much of the monitor's time is spent trying to help site staff resolve these issues. Examples have been seen on audit where subjects were unable to submit e-diary data over long periods of time due to technical issues which were not resolved in a timely manner. This can lead to lack of motivation of the trial subject as well as site staff, not to mention missing key data or the risk of safety data not being available for real-time evaluation by the investigator. Similarly, issues with e-data not being captured due to issues with user login are not uncommon. This can often be due to inadequate setup and/or testing of the devices.

5. INEFFECTIVE ISSUE MANAGEMENT

How often have you seen 'retraining' as a 'corrective and preventive action' ('CAPA') for a monitoring audit or inspection observation? When seeing such CAPAs, one often wonders about the underlying root cause(s). Could these be inadequate initial training or unclear instructions? If this is possibly so, one should look at the root causes of such failures and arrive at a more wholesome CAPA than 'retraining'.

Also, as postulated in the 'Causes of Effects – What Should we Measure?' article[2],

- Issues are often viewed in an isolated manner and within functional areas or per trial and with no assessment of the impact on other sites/countries involved in the same trial
- Organisations often monitor quality data for trends using aggregate reports which contain monitoring, audit or inspection findings (i.e. effects). However, it is less commonplace to peruse root causes which would (also) provide valuable information about the quality and compliance health of the organisation.

Similarly, one is justified to ask why issues are recurring. The first answer that springs to mind and one that is possibly only a part of the problem, is that we as an industry do not deal with issues effectively. We are good at identifying them but are not so good at determining and addressing the root causes and ensuring that the issues do not recur. Developing solutions to problems is not easy and CAPA plans should not be a paper pushing exercise. There is an argument that lots of little costs associated with fixing individual errors can be overlooked but the investment to prevent such losses may not be approved. Therefore, it is easier to keep fixing things rather than plan and invest to prevent them.

It should be remembered however that not every finding requires a CAPA, sometimes a correction is all that is necessary for an individual finding. However, a sufficiently large collection of findings relating to a regulated activity should prompt appropriate individuals to look at the 'bigger picture' and put an effective plan in place to remove or mitigate the cause of the problem or anticipate and prevent similar problems occurring in the future. Correcting errors ('correction') wastes time and money, preventing recurrence ('corrective action') saves money in the future though still results in waste, but only prevention of occurrence ('preventive action') avoids waste. Treating the symptoms is not the same as treating the patient!

The question that also needs to be asked is whether the persons responsible for CAPA development possess the necessary skills to investigate issues effectively and if there is adequate support to allow for efficient investigations to take place. After all, there is nothing worse than a badly thought out CAPA plan which has been put in place under duress to fulfil the requirements of the QA department.

POSSIBLE SOLUTIONS

1. SMART PROCEDURAL DOCUMENTS

Keep it simple and user friendly. For example, do not describe a process in text if you have already spent time on defining it in a process map. Also, 'a picture paints a thousand words' - why not use videos as procedural 'documents'? The purpose of procedural documents is to explain to the persons carrying out the processes how to perform the individual steps so as to obtain the optimal outcome. Their purpose isn't to be kept in a binder on a shelf and be dusted off for inspectors and auditors. The key to success is for the persons using them to love them, so make sure they do!

2. SMART TRIAL DOCUMENTATION

- Produce clear protocols without excessive complexity (including focused objectives), avoiding duplication and the use of imprecise terminology such as 'should'; the protocol must contain clear instructions on what is required and nice-to-have elements are to be avoided
- Produce clear and streamlined auxiliary reference materials such as plans/manuals (without duplication and contradictory information)
- Develop forms that are fit for use and which comply with the relevant requirements. Forms that do not meet basic requirements are frequently seen on audits.

After all, ICH E6 now specifies that 'quality management includes the design of efficient clinical trial protocols and tools and procedures for data collection and processing, as well as the collection of information that is essential to decision making'[11].

3. EFFECTIVE SITE SELECTION, MONITORING AND MANAGEMENT

- Ensure effective site qualification prior to site engagement. The individuals performing the related activities should be making informed decisions based on historical performance data and the results of any improvement or oversight plans, if applicable
- Monitors should be equipped with adequate understanding and tools to effectively evaluate sites, including the assessment of EHRs

- Ensure appropriateness of monitoring plans and frequency and/or length of initiation and monitoring visits. Site staff should take responsibility for the work being done by them, reducing over-reliance on monitors. It should be remembered that investigators and their staff are responsible for the conduct of the clinical trial at site (including, for instance, the filing of essential documents in the ISF) and these responsibilities must not be dispensed of and placed upon the monitor. Monitors should be sufficiently supported in order to ensure that issues reported by them are managed in an effective manner
- Non-compliant sites are required to be managed optimally, including the closure of sites where significant issues have been identified or which are continually non-compliant (alternative arrangements for ongoing subjects need to be determined). There should be appropriate documentation in place evidencing all steps taken and decisions made, including why sites are kept open despite ongoing non-compliance. Management play a key role in this process and there should be evidence of their oversight, including ongoing risk evaluation (i.e. mitigation, elimination, acceptance), in cases where sites continue their trial conduct.

4. ADEQUACY OF E-DIARIES, EPROS AND OTHER E-SOLUTIONS

- Electronic tools to be used by subjects should undergo complete validation and user acceptance testing (UAT). It should be ensured that UAT is performed by the end users
- Devices should be correctly set-up and access and audit trails should be adequately managed
- Appropriate metadata should be available and reviewed on an ongoing basis to assure data integrity
- Issues with third-party providers should be appropriately addressed (e.g. to avoid delays by helpdesks in resolving technical issues).

5. SMART ISSUE MANAGEMENT

'Only if individual processes and systems are perused as an interlinked web forming an entire organisation and by looking at often complex interfaces may the overall root cause of the individual 'smaller' causes be identified.'[12]

- Identify potential issues and prevent them from occurring (e.g. at trial set-up stage)
- Be smart when deciding what findings need a correction and when there may be a bigger underlying issue requiring a robust corrective action
- Ensure people identifying root causes and developing solutions have sufficient skills, influence and resources to think beyond the boundaries of individual audits
- Be smart when deciding what you look at for trends; quality data that are easiest to obtain in summary format are probably not the only ones that would benefit from ongoing review
- If you identify systemic issues at a couple of audits, don't automatically increase the number of audits that yield the same or similar results. Rather, focus your energy on effective root cause investigation, the development of appropriate 'CAPA' plans and the monitoring of their effectiveness. Effectiveness of such plans can be verified through audits but also by other means (e.g. self-reported progress by monitors)
- Empower people to make decisions. Auditors who do not know the processes first hand are rarely the best individuals to decide whether the proposed CAPA plan is optimal.

One element that we have not yet touched upon is the importance of a quality and compliance-focused company culture, i.e. one that entrusts people to make informed decisions and holds people accountable for their actions, while encouraging them to take measured risks and is (relatively) blame-free. We all make mistakes but constantly referring to human error as the underlying cause of non-compliance is hopefully a thing of the past.

As an industry, more energy should be spent on determining and addressing the root cause(s) of recurring issues rather than repeatedly reporting them.

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PROFILES

Katarina graduated from the MSc in Quality Management in Scientific Research and Development from Cranfield University in 2013 and is presently a Principal Associate with TMQA, an independent QA consultancy located in Edinburgh, UK, where she is responsible for their Central European operation in Bratislava, Slovakia. Previously, she held the position of a clinical quality auditor at Janssen, Pharmaceutical Companies of Johnson & Johnson. She started discovering clinical research and quality assurance within Phase one commercial CROs. She has over 13 years' experience in clinical research (nine years in QA) and has conducted GCP audits in Europe, Asia, North America, Latin America and Africa.

Karen graduated with an Honours degree in Medical Microbiology from the University of Edinburgh and a Masters in Immunology from the University of London. She began her career working in pre-clinical research before moving into clinical development where she held positions in data management before moving into QA. She has worked for both pharmaceutical companies and CROs and has over 15 years' experience in clinical QA, having conducted GCP audits across the globe, including Europe, Asia Pacific, North America, Latin America and Africa. She is currently a Principal Associate with TMQA.