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Achieving GCP Compliance in Oncology Trials: The Balance between Obligation, Idealism and Realism

Compliance with GCP provides assurance that the data and reported results of clinical investigations are credible and accurate and that the rights, safety, and confidentiality of participants in clinical research are respected and protected. Hence, to protect public health, only sufficiently and verifiably GCP-compliant studies are accepted by regulatory authorities. Oncology trials, with their inherent complexity, length and number of amendments have a higher risk of protocol non-compliance. Many of these challenges can be mitigated through study-specific risk-based measures including; adaptive trial designs, risk-based monitoring, protocol-based GCP training, vigorous feasibility process (at programme, protocol, site and investigator level), correcting and preventing root causes, administrative tools and other measures.

Inherent GCP Compliance Challenges in Oncology Trials

Good Clinical Practice (GCP) provides an internationally accepted standard to ensure subject safety and data integrity in clinical trials incorporating ethical and scientific guidelines. GCP, which is incorporated into regulations, must be followed when generating clinical trial data that are intended to be submitted to regulatory authorities for marketing authorisation. Sufficiently and verifiably GCP-compliant studies can detect and mitigate against biases that may confound analysis of clinical trial outcomes. While each therapeutic area has its own unique intrinsic challenges when conducting clinical trials, oncology can be particularly testing with many inherent characteristics including:

A. Trial Design:

Cancer therapies can have highly variable modes of action which sometimes necessitates:

- Complicated inclusion and exclusion criteria; while some exclusion criteria are fact-based, others might be with no clear delineation (e.g. theoretical, precautionary) in the respective protocols, as to which exclusion criterion has been drawn from known fact/data (which means that non-compliance could impact patient safety) and which is theoretical. While investigators must comply strictly with all exclusion criteria, this has often led to non-compliance by many investigators.
- Frequent dose modifications caused by toxic effects.
- Numerous prohibited concomitant medications: In Phase I oncology trials, for example, where patients' cancers have proved refractory to standard therapies, and where patients' prognoses at trial entry are very poor, many investigators (in agreement with or upon request from the patients) try or add another (protocol-prohibited) therapy if they do not perceive the trial therapy to be successful after a few doses. Again, while the default setting is for investigators to strictly comply with the protocol, the final decision on a patient's therapy belongs to the patient and her/his physician in such difficult circumstances. Being a study investigator is not, in all its dimensions, above the fact that the investigator is the patient's physician.
- Tight schedules of clinical assessments for patients who may already be enduring disease-related and drug-related fatigue. The potential negative impact of this issue can sometimes be mitigated by aligning study schedules with those of the clinical site to minimise the burden on site staff and patients, and can improve compliance.
- Numerous laboratory tests; this can obviously have a negative impact on the compliance/willingness of patients but can also be a burden for the investigators who could miss the review and/or its documentation of some of the numerous laboratory reports which, in turn, can be considered as a serious GCP non-compliance as it could mean lack of safety monitoring in general or, in particular, for dose escalation purposes. This challenge can be mitigated by avoiding excessive tests which are not required to substantiate safety or efficacy endpoints.
- Long trial duration: The length of oncology trials (and/or follow-up) can have a negative impact on the patients' compliance and drop-out rates. The long duration of trials can also result in the need to deal with potential changes in trial personnel (sponsors, monitoring staff, investigators, site coordinators, suppliers, service providers, etc.) with associated potential impact on continuity, experience, familiarity with procedures, knowledge, training needs, etc.

B. Pharmacological Factors:

Since the pharmacological effects of some oncology investigational medicinal products (IMPs) generally influence cell proliferation or cell division, a large number of adverse events (AEs) are frequently reported. The high number of AEs together with, at times, the difficulty to discern AE causality (whether the AE is disease- or comorbidity- or concomitant drug-related or is an IMP-related AE), can result in either over- or under-reporting of AEs. The newness of some oncology therapies adds to this challenge as the knowledge of their pharmacology is more limited than that of those with known pharmacology or pharmacological class rendering the investigators' AE causality assessment to be more speculative. Regardless of its cause, there should be no delay in reporting the event within the specified timeframe.

For immuno-oncology trials, implications of delayed onset of related adverse events are not always foreseen in study design and there is often a lack of clarity about "standard vs. study-specific" toxicity management. When study protocols do not mitigate these issues, indirect non-compliance can invariably occur. Treatment-related AEs also often contribute to patients' non-compliance. Mental health and educational specialities could play a considerable role in mitigating cancer patient non-compliance.

The toxicity profile of many cancer drugs as well as the various schedules and routes of administration used pose additional design challenges to blinding.

C. Recruitment Challenges:

Patients recruited to the study frequently have constrained treatment choices.

- Patients' disease already at advanced stage and refractory to existing therapies.
- Patients' awareness that they may not derive benefit from participation per se or because optimal dose of the

- investigational therapy is unknown at that stage (could be one of the trial objectives) so low (perhaps sub-therapeutic) doses are used which can cause patients' reluctance to participate and/or to drop-out. The latter issue can sometimes be mitigated where multiple ascending dose (MAD) studies, to determine the maximum tolerated dose (MTD), can be designed, where possible, to use a starting dose which is considered to be potentially beneficial.
- Where standard therapies have failed, some patients are in such a desperate state to receive a "novel therapy" that they may resort to hiding certain medical history or data to be eligible for the trial. Some of these situations can be mitigated by the introduction, where possible, of expanded access so long as the patients do not meet any safety exclusion criteria.
- Oncology trials often face particularly high competition for patients and sites.
- Trial duration might not be clear at the beginning, which may dissuade some patients from participation and/or increase drop-outs.

D. Requirements of Clinical Research versus Common Clinical Practice:

- Administrative/documentation requirements: By far, the additional and particularly detailed documentation, records and data required in oncology clinical trials pose a big challenge to investigator sites' personnel. In clinical research, while all data are equal … some data are more equal than others!
- A major issue typically is encountered when source documentation, to support critical data entered into the CRF, is missing; for example, to confirm eligibility that a subject had received at least one first-line chemotherapy or if they had radiation regimens treatment prior to enrolment in the study.
- Also, a protocol may require that an anti-emetic be given along with study chemotherapy and this would need to be documented (drug, administration time, route, and amount given). However, the standard at some oncology clinics is not to document dosing times of such standard medications. Other administrative requirements may be perceived by the site team as challenging their integrity. For example, while obscuring erroneous data entry, destroying a wrong record or backdating information might only be considered as bad administrative management in normal clinical practice, it could be construed as a potential sign of "scientific misconduct" in clinical research. The most efficient means to tackle data quality issues is a preventive approach through planning prior to and at study site start-up. Effective Good Documentation Practice (GDP) training on "Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring and Available" (ALCOACCEA) together with the provision of efficient templates and simple, clear procedures for entering sequential observations and making insertions or corrections that enable timely collection of important source data can pay dividends in mitigating several problematic compliance issues.
- Regulatory requirements such as having trial monitors, auditors and potentially regulatory authority inspectors monitor, audit and inspect clinical sites to ensure/verify compliance with GCP, patients' safety and data integrity are invariably above and beyond the norms of standard clinical practice. The perception and, consequently, the interaction of some oncology investigators do not always align with the obligations of the sponsor and/or regulators. These issues are best mitigated with smart interactive pre-trial training that should aim to raise awareness of the rationales for the regulatory requirements and their applicability to all therapeutic areas regardless of disease severity, regimen complexity, and acute care requirements, remove misunderstandings and align the common objectives. Unfortunately, very often the time allowed and quality of the GCP training provided during investigator meetings leave a lot to be desired: typically scheduled at the end of the agenda, confined to 25 minutes, and "clinically" tiresome in content and/or delivery style. GCP training at investigator meetings and site initiations should, at a minimum, be: A. designed based on the protocol to highlight "what matters" and what could go wrong so that it can be avoided; B. Interactive, to engage the investigators and their team.

Common Audit/Inspection Findings, Possible Contributing Factors, and Mitigation Strategies:

- **Lack of documentation of the consent process and/or not using the 'current' version of the informed consent document:** No record describing how the consent was conducted. As oncology trials tend to be long, there could be a high number of protocol amendments and hence (where warranted, e.g. new safety information) several corresponding informed consent forms. In a busy oncology clinic, this may lead to forgetting to document the informed consent or some other oversight, or using the wrong (superseded) version of informed consent form.

- **Possible remedies/prevention:**
  Include emphasis in the initial training and subsequent reminders (where needed) that consent is a process rather than an administrative task. This may impact how consenting and re-consenting is conducted and documented. The site can also incorporate a brief description of the consent process into the patients' notes.
  Use tracking methods/tools for ICF versions. An electronic method accessible to the research team can also help eliminate these issues.

- **Missing source documents:** This issue is usually particularly amplified in oncology trials where there could be substantial volume of medical records for each patient. If, for example, a biopsy report is missing, the monitor cannot verify important elements such as the diagnosis (e.g. if based on biopsy data).

- **Possible remedies/prevention:**
  Plan and execute, in collaboration with site staff, a robust trial-specific documentation system prior to trial start.

- **Incomplete medical history:** For example, the medical history records available do not support protocol-required documentation of failure of at least two prior chemotherapy regimens; records of previous therapies are missing.

- **Possible remedies/prevention:**
  The site can be encouraged to use a progress note template to capture protocol-required histories in addition to standard clinical data. Also, one can integrate the request for pathology reports, from referring oncologists at the preparatory/recruitment stage.

- **Source documentation not appropriately signed and dated.** Oncology trials have exceptionally large volumes of records. If, for example, laboratory reports have not been signed and dated, this could, in the first instance, mean that they were reviewed but the review was not documented/confirmed (by signature and date). However, unless proven otherwise, it could also mean that the omission was the result of failure to review these reports. The latter is a more serious type of non-compliance as it could have potential safety implications.

Other examples include situations where a patient is seen by a physician who has not been delegated by the principal investigator, or was delegated but the delegation was not documented on the site delegation log. Naturally, the former is problematic as it could imply that a physician, who is not assigned (and not trained on the trial protocol) may have conducted a trial procedure.

- **Possible remedies/prevention:**
  Create forms with places for signatures and dates when possible to act as a reminder to sign and date. Strengthen the clarity in the patients' notes that the patient is in a research project and the importance of data verification, etc.

- **Repeated similar protocol non-compliance:** Oncology trials, with their inherent complexity, length and number of amendments have a higher risk of protocol non-compliance. If a pattern is identified across sites in a trial, possible root causes could, in fact, reveal inadequate or improper protocol feasibility (impractical or hard to follow), too many amendments without corresponding re-training, as well as lack of initial involvement of some stakeholders (e.g. oncology site staff, etc.) who would be tasked with the practical implementation of the protocol.

- **Possible remedies/prevention:**
  A vigorous feasibility process (at programme, protocol, site and investigator level) can afford a realistic of assessment of the capability to conduct the clinical trial through seeking a review from additional relevant stakeholders such as a site study coordinator and/or an experienced sub-investigator, i.e. triallists, not just opinion leaders. Likewise, ensuring assessment for the need for re-training, could also pay dividends.

- **SAEs inadequately processed, not reported, or reported late to the sponsor:**
  The high volume of adverse events typically seen in oncology settings, together with the heavy workloads in oncology clinics, frequently impinge on the compliance with the required processing of adverse events. Other factors include inadequate awareness/training of site personnel on the reporting requirements of adverse events in clinical research compared to non-research settings. Changes in personnel with no training given invariably compounds this deficiency. Other factors include lack of clarity in trial protocols on which adverse events need not be reported (e.g. because they are considered to be due to the cancer, etc.).

- **Possible remedies/prevention:**
  Ensuring that the training given to investigator sites (at investigator meetings or site initiation visits, etc.) is "effective", i.e. using certain smart training strategies such as the provision of examples or case studies which are created based on the trial protocol and therapeutic area, verification of understanding and evaluation of the training with tests at the end of the training. These strategies have been shown to be very effective as both motivational and as a deterrent against the endemic lack of attention during the training sessions and most importantly in mitigating the non-compliances under question. They are also well-appreciated by regulators.

- **Lack of or late responses to data queries from sponsors:** While the lack of or late response to data queries is noted in all trials, the prevalence in oncology trials is much higher and, regardless of the root causes, is considered to be a non-compliance by the site with their GCP and also contractual obligations which can, in severe cases, negatively impact the conduct of the trial particularly when the resolution of the queries and resultant data, or data correction, have an impact on safety assessment and reporting. While this remains a clear non-compliance by the site, abnormally very high numbers of data queries across trial sites should warrant investigating whether, amongst other possible root causes, the CRF itself is badly designed or the respective part of the protocol is lacking clarity.

- **Possible remedies/prevention:**
  Adequate dry runs of the CRF as well as seeking CRF reviews from, often missed, direct stakeholders such as a site study coordinator could well pay dividends to avoid such situations. Also, there could be unexpected benefits and useful feedback from the provision of interactive training workshops, which incorporates examples of potential wrong CRF entries to verify understanding to better identify deficiencies in the CRF design. Such trainings prove particularly productive if accompanied by a training effectiveness test at the end which provoke lateral thinking and identification of otherwise invisible problems.

- **Ineffective monitoring:** For example, the source data verification (SDV) is conducted well by the site monitor, but major or even critical non-compliance could be missed. For example, SDV is almost 100% healthy but, unlike most sites in the trial, neither serious adverse events (SAEs) nor AEs have been reported from the site – very unusual in oncology trials. Tick-box monitoring is often a contributing factor and/or lack of awareness of AE identification and/or reporting.

- **Possible remedies/prevention:**
  Effective smart risk-based monitoring has been shown to mitigate this and similar issues as it focuses on the global picture rather than non-critical data or processes.

Major GCP compliance issues can be prevented by adapting a risk-based approach for all trial procedures taking into account key factors including, but not limited to; novelty of the therapy, complexity of procedures and respective schedules, eligibility peculiarities, consent, safety, primary end points, randomisation/blinding, etc:

- Risk-based approach to GCP training which is created after an assessment of the potential risks related to the specific protocol.
- Outsourcing-related risks and required oversight.
- Smart fact- and data-driven risk-based oversight and quality assurance programme (including but not limited to audits).

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