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Restoring Business Trust and Confidence

CRAs Must Evolve Alongside Oncology Therapeutics

By **Christina S.T. Wilhoit,** inSeption Group

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As the science surrounding immune and targeted therapies in oncology rapidly progresses, clinical trials in that arena are becoming increasingly complex. Among CAR-T cell therapies in particular, there is an abundance of liquid tumor trials, which require more than just a passing knowledge of pathology, laboratory science, and general medicine to accurately monitor.

In the past, this was not (as) problematic. It was a given that clinical research associates (CRAs, used interchangeably here with "monitors") had the requisite medical knowledge needed to successfully monitor complex oncology studies. This was due to the fact that many monitors were nurses or other healthcare professionals (HCPs) who left their clinical roles to become monitors. However, more recent entrants into the field have been non-medical professionals with little to no clinical experience.

While master's-level programs exist for CRAs, medical training is typically not a part of this coursework. The training focuses more on the job's legal elements, including FDA and international guidelines/regulations, as well as good data management practices. This leaves many new CRAs entering the field with only a master's in clinical research and an expectation they will learn medical concepts on the job. Beginning the job with so little knowledge in the medical field can make it difficult to be an effective monitor that produces high-quality data.

In oncology in particular, this problem has been compounded by recent high turnover rates. High turnover has forced many clinical research organizations (CROs) to place CRAs with no oncology experience into oncology monitoring roles. However, the knowledge required to monitor oncology studies differs greatly from the knowledge necessary to monitor non-oncology studies, leading to sub-par monitoring performance by some CRAs in these situations.

The onus is on sponsors and CROs to implement hiring and training processes that identify and rectify shortcomings in medical knowledge. Some strong monitors and/or those with medical backgrounds may not require additional training, but programs should be established to serve those who do require additional education — ensuring all CRAs on a study have the ability to understand and critically analyze what is recorded within the medical record.

WHY ONCOLOGY CRAs NEED MEDICAL TRAINING

The root of the issue is one sponsors already have recognized: the industry dynamic is shifting from a majority of CRAs who boast some sort of medical background to individuals who have very little, if any, medical training. This has been driven, in part, by the misguided belief that preexisting medical knowledge or training is not necessary to perform CRA duties and/or that the requisite knowledge can be acquired on the job.

Consider that, for liquid tumors/leukemias, accurate monitoring of disease response requires a thorough understanding of bone marrow pathology. Unlike non-oncology studies, wherein relatively simple scales can often be used to monitor endpoints, or solid tumor studies where tumor size measurements are key, liquid tumor/leukemia studies require a monitor to understand the numerous ways sites can test bone marrow, as well as interpret data from those tests. Bone marrow reports are complex, and an understanding of the process followed by a pathologist often is necessary to comprehend what is written in a report. This knowledge generally is difficult to "pick up" without some sort of formal education.

Additionally, CAR-T trials must be monitored meticulously due to the novelty of the science involved, highlighting another area where more-than-average medical experience and knowledge is key. The interplay between the immune system and cancer is a relatively new frontier, and attempts to intervene in this process — as we are doing in CAR-T and other immune therapies — place us in less predictable patient-safety territory compared to more traditional therapies.

As many of these trials are liquid tumor studies, tremendous amounts of inpatient data must be reviewed (i.e., 6-12 or more daily sets of vital signs to review for 2- to 3-week time periods, as opposed to two sets/week for a solid tumor study). A strong medical background and familiarity with leukemias is key to successfully navigating high volumes of data and identifying safety issues that may differ from the norm.

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Two important examples are the main adverse events of interest associated with leukemias: cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). These adverse events are both critical to identify and extremely complex. CRS often presents in a nearly identical manner to febrile neutropenia, a common occurrence in leukemia patients. Thus, familiarity with the disease's typical effects and treatment regimens helps CRAs to avoid missing things like CRS and reduces accidental underreporting of significant adverse events by sites.

In addition to patient safety concerns, CAR-T trials also require thorough monitoring because the FDA is examining these trials with greater scrutiny, which is not unexpected when heading into the unknown. As an example of the

increased scrutiny, the FDA has increased the required length of time that sponsors must follow patients after CAR-T therapy to 15 years. Everything is so new that both short- and long-term effects must be carefully studied and meticulously documented.

Finally, it is critical to ensure that CRAs fundamentally understand what they are monitoring, because the results of their work influence medical practice without their even realizing it. CRA failures to accurately monitor data can impact physicians' treatment decisions, and thus patient lives, because modern physicians rarely practice medicine out of a textbook. When physicians are weighing treatment decisions — especially at large institutions that utilize multidisciplinary teams — they are looking to recent peer-reviewed publications for the most current knowledge in the field. The faster the pace of medicine becomes, the more physicians rely on publications, posters, or information presented at meetings (e.g., the American Society of Clinical Oncology [ASCO]); these are becoming the textbooks of our time.

Less-than-thorough monitoring may lead to published data being inaccurate if, for example, adverse events have been underreported. It is up to CRAs to ensure that the full experience of patients receiving these novel therapies is accurately captured.

TRAINING AND OVERSIGHT MUST MOVE IN REAL TIME

It is difficult to overstate the importance of the high-quality performance a medically knowledgeable CRA can provide. Still, many CRAs do not fully appreciate the importance of their work, its industrywide impact, or the impact of strong medical knowledge on their proficiency in monitoring solid and/or liquid tumor clinical trials.

Oncology moves at blinding speeds compared to other fields in medicine. Approvals may move more slowly in, say, gastrointestinal medicine, because it typically does not deal with life-threatening illnesses. Similarly, specialists in fields with less mortality like dermatology are more likely to wait for a drug to be approved before using it in practice. In oncology, therapies often are applied prior to approval because physicians and patients alike are seeking anything with the potential to keep patients alive or to improve their quality of life. It is a different mindset altogether: CRAs must be willing to pursue continued training to keep their medical knowledge up-to-date with advances in current medical science.

inSeption Group has responded to the issues raised in this article by implementing high-level training for our monitors to ensure they can excel in a complicated realm. Typically, we assess what they know at hire and work to fill in gaps. For example, our courses relevant to leukemia monitoring include an in-depth bone marrow pathology training course that not only covers fundamental hematopathology basics, but covers the bone marrow biopsy procedure, specimen processing techniques and issues that can affect results, different technologies used in testing, how to abstract data accurately from pathology reports, and ways to ensure accurate response reporting.

This micro-level course correction addresses issues in many scenarios, but a fundamental component of providing high-quality monitors for these trials is utilizing the interview process to assess which candidates have the willingness and ability to be more educationally engaged, and to keep up with the scientific learning demanded by these roles. Organizations must use creative interviewing techniques to get candidates to demonstrate their level of medical knowledge so that gaps can be identified up front — before assigning CRAs to studies in areas they have not previously monitored.

Ideally, the industry will progress to a point where there exists a basic CRA standard of knowledge so skillsets are not so varied, especially in oncology. Admittedly, every protocol and every disease area within oncology will be slightly different. Each will come with its own learning curve, but that is to be expected to an extent. As the science progresses, monitors are constantly learning, but it is time to ensure that all CRAs have some baseline level of clinical knowledge on which to build.

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