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Concomitant medications in clinical trials:

Why the stakes are high

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Almost every reported concomitant medication has a reason – and many, if not all of these reasons should be reported as adverse events. Concomitant medications (a.k.a., con-meds) are other prescription medications, over-the-counter (OTC) drugs or dietary supplements that a study participant takes in addition to the drug under investigation. Con-meds may be used by study subjects for the same indication as the study or for other indications.

Nothing but the most casual review of concomitant medications is required for every trial. As con-meds may interact with the study medication (thus leading to faulty conclusions regarding safety and efficacy) Good Clinical Practice (GCP) regulations mandate that investigators pay attention to con-meds used by study participants. According to protocol requirements, the monitor, acting as the sponsor's representative, is responsible for checking the accuracy of data entered into case report forms (CRFs) regarding "adverse events, concomitant medications and intercurrent diseases."

In addition to preventing misleading conclusions about the efficacy and/or safety of the drug in question, concomitant medications may also indicate a patient condition (like hypertension) which potentially affects the pharmacokinetics of the study drug. Beyond that, the earliest indication of a serious adverse event may have been self-treated with an OTC concomitant medication. Hence, there is a point where a thorough concomitant medication analysis is absolutely appropriate and may ultimately act as a supporting piece of evidence. A good concomitant medication analysis will highlight issues to be considered for contraindication, for inclusion on label, or for further investigation in later stage studies.

Con-meds are important for another reason: they can contribute to the problem of patient enrollment and delays, as they are typically part of a clinical study's inclusion and exclusion criteria. Con-meds are used to determine whether patients are allowed to take part in trials, and this is essential in order to avoid adverse reactions between two drugs that are known to exist. Medication-related exclusion criteria are among the most common barriers to enrollment in clinical trials.

The bottom line is that con-med tracking warrants more attention in clinical research.

Challenges in tracking concomitant medications

While the issue of concomitant medications during clinical trials is clearly an important consideration for pharma companies looking to validate the safety and efficacy of their products, many clinical studies still do not adequately track and/or analyze con-meds. Concomitant medications are used by nearly 100% of subjects involved in Phase 1 cancer clinical trials, for

con-meds. Concomitant medications are used by nearly 100% of subjects involved in Phase 1 cancer clinical trials, for example, but the topic of con-meds is not given much attention in medical literature. Most reports of Phase 1 trials do not contain a description of the types of concomitant medications taken by the study participants in the trial, or any kind of analysis as to whether those medications might interact with the drug under study.

One of barriers to collecting quality con-med information commonly occurs during the data collection process. Con-meds may be tracked as both a history item, as well as, during the study. This makes it difficult to correlate the data with primary endpoints of the study, particularly if there is a lack of consistency on con-med reporting across sites and geographies. For example, con-meds are often collected by nursing staff, but after randomization, the con-med data is typically collected as part of the medical doctor's consultation with the patient. In these cases, the initial con-med data quality is very high and then may drop off dramatically after randomization. The data often improves as the CRA performs the source data verification (SDV) and makes inquiries related to new adverse events and medications in the patient health record. As such practices vary across sites, study teams are often left with inconsistent con-med data, making it difficult and time-consuming to analyze.

Until recently, effective tracking and analysis of con-meds in clinical trials was simply not on the radar for many pharma companies. As prescription medication, over-the-counter drug, and supplement use by the general population continues to increase, the potential impact of con-meds on the validity of clinical trial data is becoming more apparent. As such, both pharma companies and regulators are beginning to take notice and pay more attention to con-med use by study participants.

Part of the resistance to tracking con-meds may simply be lack of technology adoption. Traditionally, if con-med information was collected at all during a clinical trial, it was done on paper. Trial participants might be asked to bring in a personal diary of any additional medications they might be taking, or even to bring their medications in for documentation at the site. This kind of paper-based documentation is cumbersome, and certainly does not lend itself well to any kind of effective or efficient analysis of possible con-med-study drug interactions.

Fortunately, new electronic technologies are now available to address this challenge. If study participants were given access to an eDiary, for example, they could electronically access lists and dosage amounts of various medications, and then immediately upload their con-med information into a trial database – enabling sponsors and CROs to capture data effortlessly and have it easily accessible for analysis, thus enabling greater insights into the different variables impacting a patient.

Impacts on patient eligibility

With almost 80% of clinical trials failing to meet patient enrollment timelines, fiscal budgets are stressed and the process of translating lab research into potentially life-saving treatments is often severely delayed. Concomitant medications can contribute directly to the issue of patient enrollment delay, as they are typically part of a clinical study's inclusion and exclusion criteria that are used to determine whether patients are allowed to take part in trials. This is essential to avoid adverse reactions between two drugs that are known to exist. Medication-related exclusion criteria are among the most common barriers to enrollment in clinical trials. A systematic review of randomized controlled trials identified 54.1% of trials to have at least one medication-related exclusion criterion.

This issue is compounded by the fact that potential study participants are usually taking concomitant medications. A recent review of Phase 1 cancer trials noted that nearly 100% of 274 study participants in the trials studied used concomitant medications. This review also cited statistics on con-meds for studies conducted on medications for a number of other diseases: 78% of subjects enrolled in a trial of ziprasidone, an antipsychotic agent for treatment of schizophrenia, were found to be taking concomitant medications. 76% of patients in a study of the pharmacokinetics of escitalopram, a drug used for treatment of major depression, were taking additional medications. 83% of study participants in a study of levetiracetam, an anticonvulsant agent, were taking at least 1 concomitant medication. Studies of concomitant medication use in epilepsy and Alzheimer's disease have reported rates of concomitant medication use to be in the 70-75% range.

In order to avoid con-meds negatively impacting patient enrollment due to medication-related exclusion criteria, it is important for clinical trials to have an investigational pharmacist on hand to conduct a review of patient medications for potential investigational drug and concomitant medication interactions. In most cases, acceptable solutions (con-med discontinuation or substitution) may be found for patients taking concomitant medications either prohibited by a study protocol or having potential interactions with the investigational drug. In well conducted clinical trials with an investigational pharmacist on staff, it should be uncommon for a patient to be excluded from a clinical trial due to concomitant medication use. Appropriate input from pharmacy colleagues enables sponsors to conduct a scientifically rigorous clinical trial, address the needs of the study patient, and conduct an efficient study startup process with minimal delays.

The future of con-meds in clinical trials

Although FDA guidelines have always called for an analysis of the impact of con-meds in clinical trials, this has not always been strongly enforced. Concomitant medications have always been a part of inclusion and exclusion criteria used to allow patients to take part in trials, but once an individual was admitted to a study, there was typically very little, if any, tracking by sponsors of the subtle impacts those medications might have on trial results. This is beginning to change as regulators are starting to encourage more thorough con-med analysis in clinical study reports. Concomitant medication analysis requirements are in turn fueling adoption of electronic tracking technology that is serving to make this analysis easier to accomplish. The key is to track the concomitant medication data correctly and routinely across sites, so that the appropriate conclusions can be drawn – to enable further studies or inform potential side effects.

Accurate con-med documentation does more than just make it easier to characterize adverse events and drug interactions for an investigative drug's safety profile. The reality is that almost every person participating in a clinical research study uses some form of concomitant medication, whether it be a multi-vitamin, dietary supplement, or common OTC medications used to treat pain or allergies. With sponsors facing tremendous financial pressures to run their trials on-time and on-budget, we need to recognize the importance of concomitant medications in meeting patient enrollment timelines. The fact is we can no longer afford to rigidly apply inclusion/exclusion criteria to studies, without taking a critical look at the nuances involved. This is important for, not only reducing the overall cost of healthcare, but speeding the delivery and quality of life-saving therapies to patients.



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