Front & Center

Manage Medication Adherence to Optimize Clinical Trial and Drug Development

Medication adherence is more than a barrier to successful clinical outcomes. Adherence may be the single most significant covariate limiting the successful analysis, evaluation and outcome of clinical trials.

The link between medication adherence and trial outcomes is direct. If a significant portion of patients in a trial do not take the agent as directed, the statistical power of the trial plummets. A trial powered to 90 percent in which 20 percent of participants are non-adherent is transformed into a trial with just 74 percent power. To restore the planned 90 percent power would require altering the methodology, which in many cases may increase complexity, time and cost of clinical trials.

Multiple studies in clinical trial populations suggest that widespread nonadherence persists despite clear and repeated associations between optimal adherence and improved clinical outcomes.

Clinical trial results are based on an implicit assumption that trial participants take medications as directed. Clinical pharmacologists, statisticians and data analysts have long recognized this assumption as a critical vulnerability. Multiple technologies have existed since the 1980s to assess adherence, including electronic medication monitoring systems, image-based monitoring systems, motion monitoring systems, electronic diaries, and more. The biopharma industry seldom applies those technologies to assess actual adherence during trials despite mounting evidence that nonadherence adversely affects the quality of trials, the quality of data generated by trials and the clinical and business decisions based on trial results.

Trials routinely assess body weight, age, sex, smoking status, renal and hepatic function, race, ethnicity, genetics and other recognized covariates, yet still fail to adequately account for variations seen in the data. Simply quantifying when, or if, a trial participant takes the trial agent as directed can eliminate a significant portion of that residual variability in pharmcodynamic response and the underlying pharmacokinetics. The result is more robust trial data and greater statistical power that can lead to better developmental and marketing decisions.

Several major biopharmaceutical firms are incorporating adherence data into trial designs. Evidence continues to mount that objectively measuring medication adherence and taking positive steps to improve adherence can directly improve outcomes.

The Embarrassing Relative

One of the major challenges in clinical trial design is to recognize and account for the multiple covariates that can affect the results. Body mass index, age, sex, smoking status, hepatic function, renal function, race, ethnicity, genetics, blood pressure, medical history, comorbid conditions, socioeconomic status and physical activity level are just a few of the variables that are routinely evaluated to determine if a potential therapeutic agent is effective, at what dose, in which populations and with what side effects.

Trial protocols are designed to enrich populations with patients most likely to provide useful data. Inclusion and exclusion criteria are carefully tailored to demonstrate safety and efficacy with as small a population as possible in as short a time as possible while maintaining robust statistical power.

The biopharma industry has long since abandoned broad assumptions such as similar pharmcodynamic, pharmacokinetic and clinical responses in men and women, young and old, lean individuals and obese, across multiple racial and ethnic groups and without regard to genetic variation. But one broadly accepted assumption continues to underlie nearly every clinical trial: That patients in trials are adherent, that they take their medication, be it active ingredient or placebo, as directed.

The reality is that non-adherence is common. Whether patients forget to take doses, avoid dosing because of side effects or some other reason, a growing body of data show that significant proportions of patients in clinical trials are not adherent.

Clinical pharmacologist Michael J. Fossler, PharmD, PhD, Vice President of Quantitative Sciences for Trevena, a biopharma focused on developing biased ligands, likened adherence to an embarrassing relative. Everyone knows the relative is there, but no one wants to talk about him or her. If we don't talk

about him or her, maybe he/she will just disappear.

Adherence isn't going away and the industry is starting to talk.

When not recognized and accounted for, nonadherence can produce errors in safety signals and effect sizes. The ultimate result is to expose patients to adverse events that might have been avoided, preventing potentially safe and effective medications from being approved and wasting hundreds of millions of dollars in R&D spending.

A recent paper in The Journal of Clinical Pharmacology calculated the statistical effects of nonadherence in clinical trials. A trial powered to 90 percent could be transformed into a trial with just 74 percent power simply by estimating 20 percent nonadherence amongst patients.

Real world data suggest that 20 percent nonadherence in clinical trials is optimistic. A prospective study of imatinib adherence in chronic myeloid leukemia, for example, showed a third of patients to be non-adherent. Patients were told that high adherence is strongly correlated with curative outcomes, yet only 14.2 percent of patients took 100 percent of doses as prescribed. Similar results have been seen in studies of ivabradine and placebo in chronic heart failure, anti-rejection medication in organ transplant patients and numerous other medications and diseases.

Self-Reporting Errors

The clinical trial community is beginning to recognize the importance of adherence. Some trials include adherence data, almost always based on patient self-reporting or pill counts and typically in excess of 90 percent. Both self-reporting and pill counts are easy to falsify.

Multiple studies have found 20 to 30 percent discrepancies between self-reports or pill counts and objective measures such as sampling of drug in urine or plasma. Medication Event Monitoring Systems (MEMS), which provide an electronic time and date stamp when the drug container is opened, show less than a three percent discrepancy compared to biologic fluid assays.

MEMS can also track individual adherence and attempts to falsify adherence. Dr. Fossler pointed to the Lung Health Study, a five-year trial to evaluate the effect of concentrated smoking cessation and bronchodilator use on the progression of COPD. About 30 percent of patients actuated their inhalers more than 100 times in a short period, usually just before a scheduled clinic visit, in order to appear to be adherent. This kind of deliberate deception may occur more frequently than trialists realize and cannot be factored into trial results unless actual medication usage and adherence patterns are documented.

Changing the Trial Paradigm

Some biopharma companies and clinical trialists are changing the way trials are designed and conducted in order to collect and apply adherence data. Global MEMS provider WestRock is working with more than 20 sponsors to apply electronic medication monitoring to clinical programs now in the planning and design phases.

A research-stage company building a once-daily controlled-release oral drug delivery system uses electronic adherence data during a washout period to identify patients who are adherent to study protocol prior to receiving the study drug. Researchers can help nonadherent patients learn more effective adherence behaviors and establish the medication-taking habits that lead to reliable adherence.

In Kenya, pre-exposure prophylaxis (PrEP) HIV investigators use electronic adherence monitoring to gain insights into the actual medication exposure of subjects at high risk of HIV infection. In the US, Merck is among many pharmaceutical companies launching its first studies that bring electronic medication adherence monitoring into the clinical trial data stream.

Merck, like many sponsors, has long used patient diaries and other manual measures of adherence. Electronic monitoring will give researchers a clearer view into patients' actual medication use. The result is a more accurate and more timely assessment of both the safety and efficacy of agents in trial.

The move to electronic data collection is a deliberate and considered investment in improved trial data quality, said Matthew Moyer, MS, MBA, PMP, Associate Director of Packaging Operations at Merck. The cost of MEMS packaging is trivial, but managing and validating the new data stream is not.

Adding data collection from every trial participant requires multiple process checks and validations to support data capture and integrity. There are additional process and validation checks to support adherence data transmission and incorporation into the clinical study report.

The payoff is significantly more robust data from clinical trials that allow more agile decisions regarding compound development, formulation, prioritization and patient therapy. Adding adherence to the data mix allows the company to make better informed decisions around trial results and to make those decisions more quickly. While competitors continue to assume adherence, Merck is generating solid data that can link actual drug exposure to pharmcodynamic and pharmacokinetic measures as well as clinical outcomes.