

How to Better Manage the Complexities of Clinical Trials in the Dialysis-Dependent CKD Population

Strategies for Addressing the Patient, Trial Site, and Data Collection Complexities in the Development of Treatments for Renal Disease



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Chronic kidney disease is a serious, slowly progressing condition, culminating in end-stage renal disease. Developers of treatments for this condition face a range of challenges in the clinical development process. Ensuring timely, quality, cost-effective execution of Dialysis-Dependent CKD clinical trials requires a research organization to leverage the right people, processes, and technology infrastructure to overcome the trial complexities inherent in Dialysis-Dependent CKD drug development.

Affecting more than 20 million people in the United States, chronic kidney disease (CKD) is a condition in which the kidneys are damaged, hindering their ability to filter blood effectively and causing wastes to build up in the body. As a result of this waste build up, CKD can lead to other health problems, including cardiovascular disease (CVD), anemia, and bone disease.¹

CKD progresses slowly over time. The National Kidney Foundation (NKF) has divided kidney disease into five stages based on a patient's glomerular filtration rate (GFR), a formula based on an individual's age, race, gender, and their serum creatinine—a waste product from muscle activity that rises in level as kidney function slows.² Stage 5 End Stage CKD is also known as kidney failure or end-stage renal disease (Dialysis-Dependent CKD). At this stage, the kidneys have stopped working well enough for a patient to survive without dialysis or a kidney transplant.

While some common challenges exist when conducting clinical trials in CKD across the progression of the disease, trials become especially complex to execute in Dialysis-Dependent CKD due to the complications inherent in dialysis treatment. This article will explore the complexities of running clinical trials in advanced CKD and the Dialysis-Dependent CKD population in more detail and look at the solutions that can be employed to overcome challenges.

Patient Population Complexities

Recruitment

While diabetes and high blood pressure are the first and second most common causes of Dialysis-Dependent CKD, it can also result from a number of other problems, including autoimmune diseases (such as lupus and IgA nephropathy), genetic diseases (such as polycystic kidney disease), nephrotic syndrome, or urinary tract problems.³ Because kidney disease is a sequela of a range of different conditions and patients with Dialysis-Dependent CKD suffer from a wide range of physical and psychological challenges, it is extremely challenging to recruit patients for a trial investigating a treatment for Dialysis-Dependent CKD or any of its comorbidities. Patients on dialysis are widely studied, and thus there is great competition to recruit



these highly fragile subjects. Even pre-dialysis patients with CKD that has not advanced to Stage 5 might occasionally need a “rescue” dialysis treatment. Thus, studies in the CKD population often necessitate a Phase II study in dialysis to prove the drug’s safety in the dialysis population. Dialysis-Dependent CKD patients will likely already be prescribed a number of concomitant medications that could cause them to fail the recruitment screening process due to the potential drug-drug interactions. Other patients may be awaiting a kidney transplant, which will often be an exclusion trigger as these patients would likely need to drop out of the trial prior to completion. Ultimately, only about 4% of patients available at a given trial site will qualify for enrollment.

Site selection is a critical enrollment concern as some study sites do not have adequate staff to handle recruitment. It is important to develop strong relationships with large dialysis organizations and to seek out the strongest independent dialysis sites and networks with research experience and a history of high performance when it comes to enrollment. It is also useful to work with coordinators in the recruitment process and provide them with materials that encourage their patients to want to join a study.

Retention

Clinical studies in Dialysis-Dependent CKD tend to have a longer than average duration, making retention another significant challenge. The longer the study, the higher the dropout rate will be. Dialysis-Dependent CKD has a high morbidity and mortality rate. These patients have a five-year life expectancy, so a one-year trial could lose 20% of its population due to patient death. Meanwhile, other patients may be withdrawn from the study because they require emergency treatment and either be hospitalized or require medication that is prohibited by the study protocol.

Monitoring and safety

Monitors and Safety and Pharmacovigilance teams face challenges as a result of dialysis patients’ high number of concomitant medications and procedures, the high number of Adverse and Serious Adverse Events (SAEs), the high morbidity and mortality rates, and the difficulty in scheduling around possible hospitalization. Trial sponsors increasingly expect monitors to have prior experience with this patient group. Of all the factors complicating the job of trial monitors in Dialysis-Dependent CKD, one of the biggest factors is the extensive medical histories that patients bring. As the trial gets underway, project managers will need to ensure adequate time is given for monitors to review patients’ medical histories.

Whereas for many types of studies, the medical monitor can be a general M.D., in dialysis trials, the medical monitor almost always must be a nephrologist in order to adequately read and understand the high volume of data produced by Dialysis-Dependent CKD trials. Safety monitoring alone must contend with an enormous amount of data, with as many as 80% of patients typically experiencing some kind of SAE. It is prudent to utilize an electronic safety database that integrates well with the Electronic Data Capture (EDC) platform being used.



Trial Site Complexities

Conducting research in a dialysis center environment is considerably different than working within a multi-specialty clinic. Dialysis centers are in the business of critical care, with the overriding purpose of keeping people alive. Research is not the primary focus. Although specifically designated research dialysis centers do an excellent job, the focus is on dialysis, which means that the units are generally not equipped to perform other routine clinical procedures, such as obtaining PK blood draws over a time period exceeding the three-hour dialysis visit. (Typically, no beds or overnight housing are available in the clinic.)

Unlike most multi-specialty clinics, dialysis units operate Monday through Saturday, generally with two three-hour shifts per day (some sites run three shifts per day, but that is less common). Dialysis patients need to undergo treatment three times per week. Accordingly, a typical site with 50 chairs operating on two shifts per day has a capacity to serve 100 patients on a M-W-F schedule and 100 patients on a T-Th-Sat schedule, for a total of 200 patients. This means that site study personnel will need access to CRO study staff at all times, including weekends. (Smaller studies requiring fewer subjects could consider randomizing subjects only on Mondays or Tuesdays, but this could curtail enrollment and place a greater burden on site personnel). Dialysis units typically do not have an abundance of unused space, and since research is not their primary focus, it can be difficult to schedule ample time for study monitors to be on site. Careful planning and advance warning, as well as strict adherence to schedules, is greatly appreciated by site personnel.

Meanwhile, some dialysis networks have automated protocols that control the treatments patients receive. A fluctuation in hemoglobin rate, for example, could trigger an automatic change in dosing. In order to enroll patients into a trial, it will be necessary to take them off the automated protocol, but because the primary focus is treatment over research, a staff member may instinctively revert from the study protocol to the automated protocol.

In dialysis studies where many non-study site personnel are interacting with the subjects during the visit, it is important to establish a clear delineation between study staff and non-study staff, identifying, training, and limiting the staff responsible for study related activities. Likewise it's very important to identify a means to distinguish study subjects from patients who are not in the study. This can help to prevent potential dosing and treatment errors.

Rather than monitors waiting to verify during on-site visits, EDC data can be monitored remotely to ensure sites are doing dose adjustments on time as per the study protocol. Follow-up calls should be made to individual sites if the EDC is not updated, and study-wide training should be conducted with sites that need reinforcement.

Whenever possible, the site initiation visit should be performed with the Principal Investigator (PI) on site to re-inforce PI dosing procedures and ensure understanding and compliance with the protocol. This will help to minimize errors at the site level associated with dosing. Clarity needs to be established prior to study start on acceptable dosing windows, and options for make-up doses must be communicated clearly, considering the fluctuating schedules of the dialysis patients, holidays, and missed sessions.

It is not uncommon for dialysis centers under one PI to have multiple satellite locations. While this can be beneficial to enrollment by providing access to a larger patient population, the scenario may tax the resources of the PI, the coordinator, and the study monitors attempting to manage a study at multiple locations. It is important for research organizations to ensure these sites have adequate clinical staff, coordinators, and assistants to manage the study at multiple locations while also ensuring an adequate clinical monitoring staff is on hand to accommodate these types of sites. In addition to the PI, it would also be beneficial to have sub-investigators in a multi-site scenario. The staff from all of the locations will need to be coordinated during the site initiation visit.

Data Collection Complexities

Monitoring of Dialysis-Dependent CKD clinical trials is further complicated by the variety of source documents and source media, including paper and electronic. Examples are dialysis flow sheets and electronic medical records (EMR), all of which can differ from site to site. It is vital to have an EDC platform that is user friendly and that the site staff and coordinators are comfortable with, as well as providing monitor access to EMR systems.

The data collected by the EDC platform can be fed into interactive data analytics software capable of generating reports for the purposes of risk-based monitoring. By flagging sites reporting data that stands out from the norm or is otherwise questionable, data analytics reports can show where monitors are needed most urgently and arm the monitors with the information they need to ask the right questions so that they can quickly identify problems and address them before they become uncorrectable and compromise the study.

While the clinical research industry is moving toward the use of mobile devices for data capture, this presents somewhat of a challenge in the Dialysis-Dependent CKD environment, as this patient population tends to be older and slow to uptake some of the new electronic means of collecting patient reported data. Use of Electronic Patient Reported Outcomes (ePRO) is not ideal for this population, so paper PRO forms should be used, with reminders given to patients to complete them in a timely manner.

In studies with a heavy burden of questionnaires, subjects can be prone to a lack of compliance. Therefore, it is important to educate sites and study coordinators, as well as patients' families and caregivers, of this risk and maintain constant lines of communication with patients.

Conclusion

Of the five stages of CKD, stage 5 Dialysis-Dependent CKD is by far the most complex in terms of conducting clinical trials due to the unique issues that arise when working with dialysis patients. Overcoming the complexities of developing products for Dialysis-Dependent CKD requires the right people, processes, and technology. The right people are those who possess recent, hands-on experience in dialysis and who understand the dynamic nephrology landscape. The right processes and tools should include a project management methodology that facilitates the selection of sites with a proven track records of success with enrollment and a high quality of data output. Research organizations must be familiar with the dialysis-specific clinical environment and have the necessary training programs and practices to work seamlessly within that setting to reduce variability in the trials they conduct in that setting. Finally, the right technology infrastructure can provide a repository of all of an organization's past experience in Dialysis-Dependent CKD trials, in order to capitalize on lessons learned and best practices. With these pieces in place, a research organization can optimize Dialysis-Dependent CKD trials and ensure they are completed on time and on budget.



¹ Chronic Kidney Disease (CKD) Surveillance Project. Centers for Disease Control and Prevention. Available at <https://nccd.cdc.gov/ckd>. Accessed 4/26/2016.

² Stages of Chronic Kidney Disease. Davita. Available at <https://www.davita.com/kidney-disease/overview/stages-of-kidney-disease>. Accessed 4/26/2016.

³ American Kidney Fund. Available at <http://www.kidneyfund.org/kidney-disease>. Accessed 4/26/2016.

10 Steps to Maximize Renal Disease Trial Success



Identify the right sites with research experience, involved PIs, and a focus on adequate staffing



Establish a site support function or team on either the CRO or the sponsor side focused on engagement and relationship building with the trial site



Make periodic calls to every site to discuss prescreening, screening, and enrollment of subjects



Train on study procedures beyond randomization to increase Clinical Research Coordinator confidence and engagement



Implement a monitor/co-monitor strategy to help minimize the effects of any potential turnover among CRAs



Ensure each site coordinator is well acquainted with the monitor/ co-monitor and Clinical Team Manager responsible for their site



Consider adding ex-US venues such as Western, Eastern, and Central Europe to provide access to additional patient populations in venues where the standard of care is similar to the US



Use communication tools, such as monthly newsletters, to commend high enrollers and discuss best practices



Initiate the main site and then bring on the satellites after performance and staff bandwidth is demonstrated



Keep the data collection process simple to maximize compliance

About the Authors



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Ms. Finnegan is the President of Biorasi's Divisional Operations. Her more than 25-year career in the biologics and healthcare industry began as a consultant to large pharmaceutical companies on product development and manufacturing. She then became the founder and CEO of the biologics industry's first contract manufacturing organization. As leader of all Biorasi Divisional Operations, Ms. Finnegan develops and fosters the growth of therapeutic area specialists and targeted therapeutic specialty divisions, including CNS, haematology/oncology, immunology, psychology/neurology, nephrology, endocrinology, dermatology, and ophthalmology.



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As the Director of Biorasi's Client Solutions group, Mr. Bowden oversees the design, development, and optimization of sponsor programs and leads Biorasi's proposal development team across all therapeutic and geographical areas. His focus is on the optimization of US and global clinical trial development in the areas of innovative small molecules, biosimilars, and cell-based therapies, and he co-developed a division with a concentration on indications in the areas of CNS, oncology, and endocrinology. Previously, as a project manager, he led multiple projects in the areas of chronic kidney disease, schizophrenia, and Parkinson's disease.



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