Get your renal impairment study enrolled

Balancing the needs of patients and developers in protocol design to optimize enrollment and data integrity

As drug development progresses, regulators require a clear understanding of how products are metabolized in the human body and the risks associated with compounds that may linger in critical organs. Where human absorption, metabolism, and excretion (hAME) studies raise concerns, renal impairment studies are used to generate the necessary supporting data. These studies are particularly challenging to recruit for, especially for individuals with severe conditions. Making informed decisions about the design of protocols is essential, as overly restrictive protocols can quickly narrow the patient population.

This article outlines an effective decision-making process during protocol design to successfully enroll participants and maintain the progression of drug development. Based on our extensive experience conducting renal impairment studies, our insights and recommendations are grounded in a proven track record and deep understanding of the complexities involved in these trials, and what it takes to complete them.

Fortrea has conducted 80 Phase I renal impairment studies—approximately half of those in the last five years.

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Addressing challenges in renal impairment trials

Clinical trials focused on renal impairment present significant challenges, including complex site selection decisions, patient recruitment and stringent equipment requirements. These factors impact sponsors, patients and sites necessitating a comprehensive, well-coordinated approach to trial execution. Here, we explore specific examples to understand how these challenges are addressed within the realm of renal impairment research.

Clinically, **we define chronic kidney disease by GFR and stage**

Glomerular Filtration Rate (GFR)	Stage *IF* present for >3 months	Kidney function (or loss of)	Kidney % working National Kidney Foundation
≥90	1	Normal kidney *function* (but may have kidney *damage* seen on urinalysis or imaging)	90 - 100%
89–60	2	Mild	89 - 60%
59–30	3a • 3b	Mild - Moderate • Moderate - Severe	59 - 45% • 44 - 30%
29–15 (lowest prevalence)	4	Severe *Note the difference from the **FDA guidance doc on pharmacokinetics** (PK) in patients with impaired renal function	29 - 15%
<15	5	End stage kidney disease (ESKD) not yet on dialysis or with a transplant	Less than 15%

https://www.kidney.org/atoz/content/gfr

Patient availability and overlooked factors that impact success

Renal impairment studies require careful consideration of patient availability and overlooked factors that can significantly impact success. These factors include the complexities of patient recruitment, the implications of inclusion and exclusion criteria, and the management of comorbidities and concurrent medications. Let's examine each in greater detail.

Patient recruitment challenges

Recruiting patients with renal impairment, particularly those with severe conditions, is challenging due to the limited pool of eligible individuals and their reluctance to participate in clinical trials. Patients with severe renal impairment (GFR < 30 mL/min/1.73 m^2) are often less likely to volunteer for studies due to the risk—and fear—of exacerbating their condition and going through a burdensome trial experience. This makes it crucial to design protocols that are inclusive yet stringent enough to meet scientific and regulatory standards.[1] Studies have shown that improving patient recruitment and retention involves addressing patient concerns early, providing comprehensive information and reducing the burden of trial participation.[2]

Inclusion and exclusion criteria

Balancing the inclusion and exclusion criteria is essential to ensure an adequate patient pool while maintaining scientific rigor. For instance, overly restrictive criteria can exclude many potential participants. A common pitfall is the exclusion of patients on cytochrome P-450 (CYP) inhibitors and inducers; excluding all CYP inhibitor levels can make recruitment nearly impossible. Allowing at least weak inhibitors and inducers can significantly expand the pool of eligible patients without compromising the study's integrity. This flexibility is crucial for managing the recruitment of severe renal impairment patients, who are often on multiple medications to manage their condition. Flexibility in criteria has been shown to enhance recruitment rates without sacrificing data quality.[3]

Management of comorbidities and concurrent medications

Patients with renal impairment frequently have comorbid conditions such as hypertension, diabetes and hyperparathyroidism, requiring a complex regimen of medications. Additionally, managing lab abnormalities such as elevated phosphorus and anemia is critical. Designing protocols that accommodate these medications and conditions is vital for successful recruitment and retention. For example, antihypertensives, phosphate binders and SGLT2 inhibitors are commonly used in this population. Recognizing and incorporating the management of these comorbidities into the study design helps in creating a more inclusive and practical protocol.

Patient tolerability

Ensuring patient tolerability is crucial for both recruitment and retention in renal impairment studies. Patients with renal impairment often have multiple comorbidities and are on numerous medications, which can complicate trial participation and impact their willingness to enroll.

Clinical protocol development considerations

The clinical protocol must be designed to minimize the burden on participants while ensuring the collection of high-quality data. This includes considerations for dosing schedules, the number and frequency of study visits, and the overall duration of the study.

For example, a typical Phase I renal impairment study might involve a 6-day in-house stay with one follow-up visit approximately one week later. This is much more appealing to patients than protocols with numerous outpatient visits, especially if outpatient visits continue for many months. This is because participants are paid significantly more for in-house stays versus outpatient visits. Reducing patient burden is a key factor in maintaining high recruitment and retention rates.[1]

Flexibility in dosing and monitoring

Given the altered drug metabolism in patients with renal impairment, flexible dosing schedules and close monitoring are essential. This helps in managing potential adverse effects and ensures that the investigational product (IP) is well tolerated. For instance, accommodating the higher blood pressure often seen in these patients and adjusting doses accordingly can improve patient comfort and compliance.[3] The Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network emphasized the importance of flexible and adaptive trial designs to improve patient enrollment and retention.[4]

Minimizing logistical burdens

Reducing the logistical burdens on patients, such as travel requirements and frequent hospital visits, is important for maintaining high recruitment and retention rates. Providing support for travel and scheduling flexibility can significantly enhance patient participation and reduce dropout rates.

FDA guidance and regulatory considerations

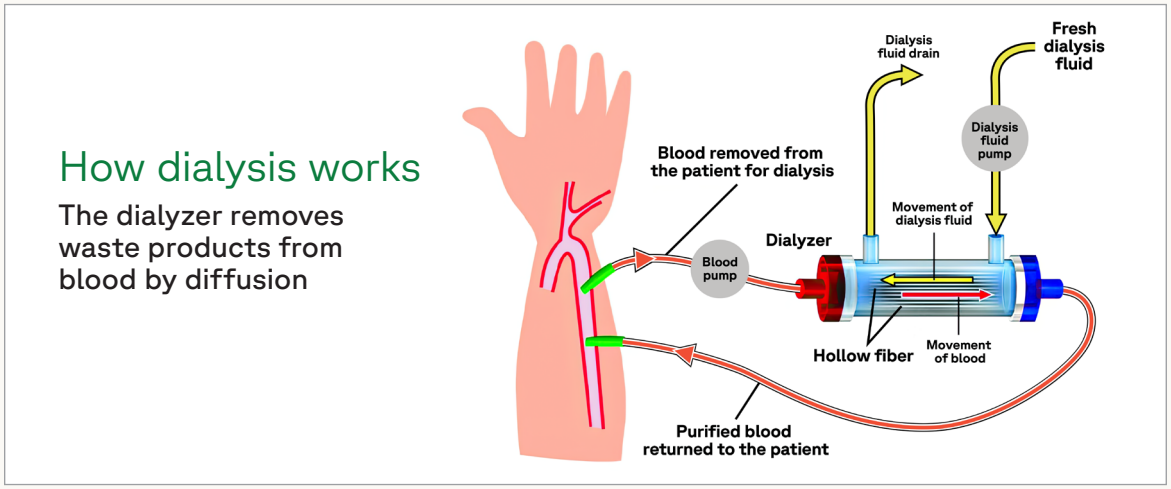
Navigating the regulatory landscape for renal impairment studies can be complex, with specific guidelines that must be adhered to ensure compliance and data integrity. The FDA provides detailed guidance on the design, conduct and analysis of pharmacokinetic studies in patients with impaired renal function.[1]

Early inclusion of renal impairment studies

The recent FDA guidance emphasizes the importance of performing renal impairment studies early in drug development to obtain appropriate dosing recommendations for renally impaired patients in Phase III trials. This proactive approach helps in identifying potential issues early and allows for adjustments in dosing and study design.[1]

Use of hemodialysis patients

The guidance also highlights the utility of including hemodialysis (HD) patients as substitutes for severe non-dialysis patients when appropriate. HD patients are often easier to recruit and provide valuable pharmacokinetic data, especially when the investigational product is likely to be administered to HD patients in clinical practice. For example, HD patients can be used effectively when the drug's half-life is less than 72 hours, as they are more available and compliant compared to non-dialysis patients with severe renal impairment.[1] For a "Reduced PK Study," it is proposed to compare the exposure of a drug/active metabolite between a control group and a renally compromised group, as many feel it is not feasible to recruit ESRD patients not yet on dialysis.[2]



https://www.researchgate.net/figure/The-procedure-of-hemodialysis-A-patient-is-connected-to-a-dialysis-machine-and-their_fig1_358158607

Considerations for age and comorbidities

The FDA's guidance on enhancing the diversity of clinical trial populations advises against restricting age in renal impairment studies. This aligns with the goal of obtaining comprehensive data across different patient demographics to ensure the drug's efficacy and safety in a real-world setting. Additionally, the inclusion criteria should account for common comorbidities and the use of concomitant medications to reflect the patient population accurately.[1] Studies have shown that patients with renal impairment often have prolonged QT intervals, which necessitates careful monitoring and adjustment of treatments to prevent adverse outcomes.[5]

Patient matching approaches and our preferred method

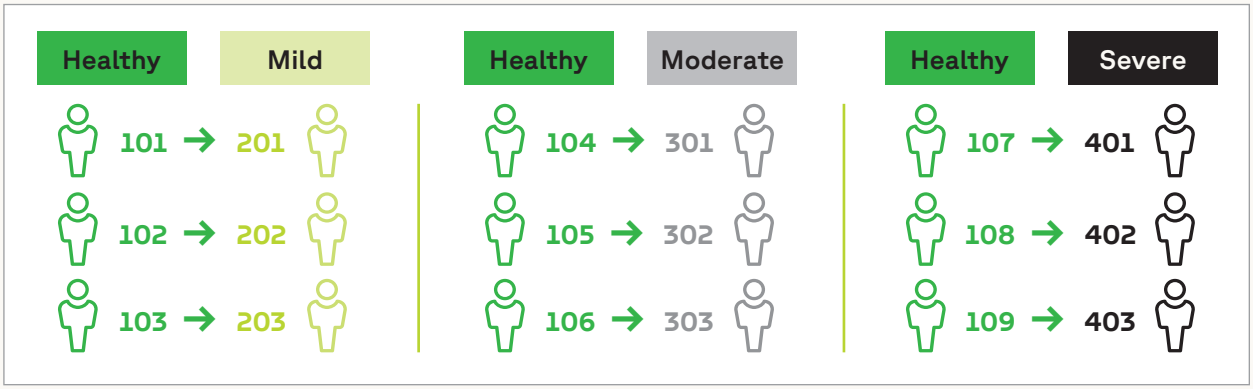
Accurate patient matching is critical for the success of renal impairment studies. Three main approaches are commonly used, each with its advantages and challenges. Our preferred method, **1-to-many matching**, combines the strengths of the other methods while offering better flexibility and efficiency.

Option A: Traditional 1-to-1 matching

Description: Each impaired participant is matched with one healthy control participant based on gender, age (±10 years) and BMI (±20%)

- Advantages:
  - Most powerful statistically
  - Direct comparison between matched pairs
- Disadvantages:
  - Most expensive
  - Requires a large number of healthy control participants

Figure 1: Traditional 1-to-1 matching



Option B: Mean matching

Description: Impaired participants are matched to healthy controls based on the mean age and BMI of the impaired group, with healthy controls falling within the specified range (age ±10 years, BMI ±20%)

- Advantages:
  - Less expensive than 1:1 matching
  - Requires fewer healthy control participants than other two methods
- Disadvantages:
  - Less statistically powerful than 1:1 and 1:many matching
  - Potential for significant age and BMI gaps between impaired participants and healthy matches

Figure 2: Mean matching

Group by gender within each impairment class. Calculate the mean age and BMI and match age +/- 10 years and BMI +/- 15-20%. Enroll similar number of healthy males to impaired males, healthy females to impaired females.

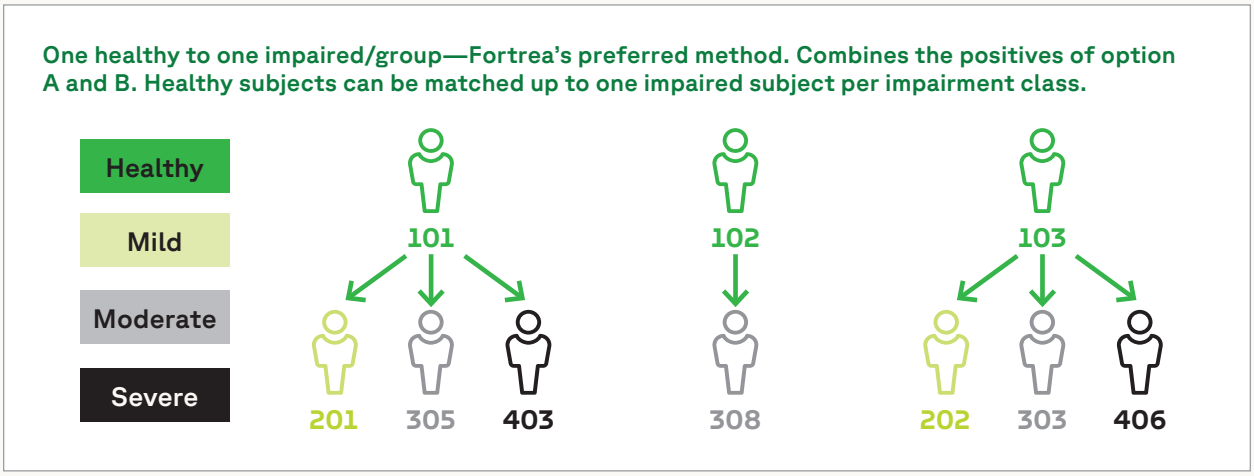
Option C: 1-to-many matching (Fortrea's preferred method)

Description: A single healthy control participant can be matched to multiple impaired participants across different impairment classes (mild, moderate, severe), but no more than 1 impaired participant per class, based on gender, age (±10 years) and BMI (±20%)

- Advantages:
  - Combines statistical power and efficiency
  - More flexible and cost-effective than 1:1 matching
  - Reduces the number of healthy control participants needed compared to 1:1 matching
- Disadvantages:
  - Requires careful protocol design to ensure valid comparisons

TIP: Use the term "approximate" in protocols to allow flexibility in matching criteria, accommodating slight deviations in age and BMI to improve recruitment feasibility

Figure 3: 1-to-many matching



Conclusion

Designing renal impairment study protocols requires a balance between scientific rigor and practical feasibility. By addressing the challenges of patient availability, patient tolerability and adhering to regulatory guidance, sponsors can optimize their study designs to enhance recruitment and data integrity. The breadth of insights gained both from the literature and through our extensive experience in conducting renal impairment studies highlight the importance of flexible, patient-centered approaches to recruitment and protocol design. The FDA's guidance on enhancing diversity in clinical trials also underscores the need to include diverse patient populations, including those with comorbidities and varying ages, to ensure comprehensive and applicable data.[6]

Our extensive experience in conducting renal impairment studies positions us as a leading partner in navigating these complexities and ensuring the successful execution of your clinical trial.

Contact us today to learn how Fortrea can enhance and simplify your clinical renal impairment study.

See how we can help.

Together, exceptional is possible

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