APT-KIDNEY



The **A**daptive **P**latform **T**rial for **Kidney** Disease

CORE PROTOCOL

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Summary of changes

This section summarizes all changes to the core protocol after initial submission for approval.

Protocol version	Date	Major changes

Contents

1 Protocol Summary....5
1.1 Synopsis....5
2 Abbreviations and definitions....6
3 Administrative information....7
3.1 Sponsor and Platform Steering Committee....7
3.2 Coordinating and methodological centers....7
3.3 Investigators and clinical trial sites....8
3.4 Protocol contributors....8
4 Core protocol – an overview....8
4.1 Core protocol....8
4.2 Appendices....8
5 Trial Objectives....8
5.1 Aims and objectives....8
6 Background....9
6.1 Evidence and clinical trials in advanced kidney disease....9
6.1.1 Advanced kidney disease (eGFR < 30 ml/min/1.73m^2)....9
6.1.2 End-stage kidney disease....10
6.1.3 Kidney transplantation....12
6.2 Adaptive platform trials....13
6.3 Low-intervention trials....13
6.4 Rationale and ethical considerations....14
7 Trial conduct....14
7.1 General considerations....14
7.2 Regulatory approval and oversight....15
7.3 Protocol deviations and serious breaches....15
7.4 End of trial and results reporting....15
8 Platform Trial Design....16
8.1 General design....16
8.2 APT-KIDNEY Eligibility criteria....16
8.2.1 Inclusion criteria....16
8.2.2 Exclusion criteria....16
8.3 Domains and interventions....16
8.3.1 APT-KIDNEY and co-enrollment....17
8.3.2 Interventions....17
8.4 Trial sites and personnel....18
8.4.1 Trial sites....18
8.4.2 Trial personnel....18

8.5 Screening and informed consent....18
8.5.1 Screening....18
8.5.2 Informed consent....18
8.6 Randomization and allocation concealment....19
8.6.1 Randomization....19
8.6.2 Allocation concealment and blinding....20
8.7 Trial data....20
8.7.1 General considerations....20
8.7.2 eCRF interfaces....21
8.7.3 Data sources....21
8.7.4 Core variables....21
8.7.5 Data quality and monitoring....22
8.7.6 Biological samples....23
8.7.7 Data protection and privacy....23
8.8 Trial Follow-up....24
8.8.1 Follow-up....24
8.8.2 Discontinuation and participant withdrawal....24
8.9 Trial outcomes....24
8.9.1 Core outcomes....24
8.9.2 End-point adjudication....26
9 Statistics....26
9.1 Overall principles....26
9.2 Statistical framework....26
9.2.1 Analysis populations and sets....26
9.2.2 Outcomes, estimands, and guiding outcome....26
9.2.3 Models and covariate adjustment....27
9.3 Randomization and co-enrollment....27
9.4 Adaptive analyses, decision rules, and simulation....27
9.5 Multiplicity and error control....27
9.6 Missing data, intercurrent events, and sensitivity analyses....28
9.7 Final analyses, reporting, and reproducibility....28
10 Trial Safety....28
10.1 Pregnancy and contraception....28
10.2 Trial risk assessment....28
10.3 Safety management....28
10.3.1 Adverse events and reactions....29
10.3.2 Registration and reporting of safety outcomes....29
10.4 Independent Data and Safety Monitoring Committees....32

10.4.1 Adaptive analyses and methods....32
10.4.2 IDSMC sessions and recommendations....32
10.5 Data confidentiality and sharing....32
10.6 Trial conduct integrity....33
11 Organizational Framework....33
11.1 Governance....33
11.2 Funders and roles....34
11.3 Conflicts of interest....35
11.4 Compensation and insurance....35
11.4.1 Site compensation....35
11.4.2 Participant compensation and insurance....35
12 Publication and dissemination....35
12.1 Dissemination....35
12.2 Authorship and contributorship....35
12.2.1 Standards....35
12.2.2 Manuscript types....35
12.2.3 Committees....35
12.2.4 Group authorship....35
12.2.5 Order/guarantor....36
12.2.6 Review....36
13 References....37
Appendix I. SPIRIT reporting checklist....48
Appendix II. Core variable specification....53
Appendix III: Common serious adverse events in patients with advanced kidney disease....55

1 Protocol Summary

1.1 Synopsis

Protocol title: The Adaptive Platform Trial for Kidney Disease

Acronym: APT-KIDNEY

Background: Randomized clinical trials (RCTs) are essential for evaluating intervention effects but are often challenged by regulatory and logistical burdens, high costs, and extended timelines. To address these challenges, the 'Adaptive Platform Trial for Kidney Disease' (APT-KIDNEY) will establish an investigator-initiated platform trial built on a unified regulatory, contractual, and operational framework. The platform emphasizes adaptive, cost-efficient methodology, data capture supported by linkage to electronic health records and administrative registers, and stakeholder engagement.

Objectives: The primary objective of APT-KIDNEY is to establish an adaptive platform trial for evaluation of multiple interventions in patients with advanced kidney disease as defined in the study population.

Study design: APT-KIDNEY is a pragmatic, randomized, embedded, multifactorial, adaptive platform trial with interventions organized into domains, designed exclusively for low-intervention comparisons. Domains may be open-label or blinded and will be able to use response-adaptive randomization, adaptive stopping and arm-dropping, and adaptive enrichment to enhance efficiency and relevance where applicable.

Study population: Adults (≥18 years) eligible for ≥1 domain with advanced kidney disease as defined by: (i) eGFR < 30 mL/min/1.73 m^2 for ≥3 months; (ii) ESKD on hemo- or peritoneal dialysis; (iii) ESKD on conservative kidney management; or (iv) recipient of a kidney allograft. Key exclusions include inability to provide informed consent; domain-specific exclusions may apply, but eligibility cannot be broadened beyond the core protocol.

Trial outcomes: Core outcomes will be all-cause mortality, major adverse cardiovascular events (nonfatal myocardial infarction, nonfatal ischemic stroke, or cardiovascular death), health-related quality of life (EQ-5D-5L), and, for participants with measurable kidney or allograft function, kidney disease progression.

Abbreviated methods: APT-KIDNEY will permit domains to use frequentist and/or Bayesian methods. Primary analyses will target prespecified primary estimands and be conducted using the full analysis set. Prespecified sensitivity analyses will assess robustness to alternative strategies for intercurrent events and missing data, including per-protocol and as-treated supportive analyses. Outcomes are analyzed with generalized linear/mixed models and time-to-event methods with covariate adjustment. Frequentist analyses will be fixed-sample or group-sequential; results will be reported with 95% CIs and p-values, and Bayesian analyses will report posterior effects with 95% credible intervals and posterior probabilities. Bayesian domains will primarily use neutral, mildly skeptical priors. Multiplicity will be controlled at the domain level by a prespecified hierarchy: primary comparisons will precede secondary outcomes. Advanced adaptive domains will be evaluated by simulation to quantify operating characteristics, including power and Type I error, and the impact of outcome delays and missing data.

Perspectives: APT-KIDNEY will establish an enduring, investigator-led platform for pragmatic, embedded nephrology trials, reducing start-up time and administrative burden through a shared regulatory and operational framework. Using standardized core outcomes, supported by linkage to electronic health records and national registers, it will generate faster, comparable, practice-relevant evidence across multiple interventions.

2 Abbreviations and definitions

AE	Adverse event
AR	Adverse reaction
API	Application programming interface
APT-KIDNEY	Adaptive platform trial for kidney disease
ASR	Annual safety report
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CKM	Conservative kidney management
CTIS	Clinical trials information system
CTR	Clinical Trials Regulation
CONSORT	Consolidated standards of reporting trials statement
DSA(s)	Domain-specific appendice(s)
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EPR	Electronic patient records
EQ-5D-5L	EuroQol 5-Dimension, 5-Level questionnaire
EQ-VAS	EuroQol Visual Analogue Scale
ESKD	End-stage kidney disease
EU	European Union
EU CT number	European union clinical trial number
GCP	Good clinical practice
HRQOL	Health related quality of life
ICH-GCP	International Council for Harmonization on Good Clinical Practice
ICMJE	International committee for medical journal editors
IDSMC	Independent Data and Safety Monitoring Committee
IMP	Investigational Medicinal Product
INCEPT	Intensive Care Platform Trial
ITT	Intention to treat
KDIGO	Kidney Disease: Improving Global Outcomes
KRT	Kidney replacement therapy
KTx	Kidney transplantation
LAB	Clinical laboratory information register
LVEF	Left ventricular ejection fraction
MACE	Major adverse cardiovascular event
NPR	National patient register
NRDT	Danish Registry on Regular Dialysis and Transplantation
PI	Principal investigator
PROM	Patient-reported outcome measures
PTH	Parathyroid hormone
RCT	Randomized clinical trial
RRT	Renal replacement therapy
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of product characteristics
SONG	Standardized outcomes in nephrology
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischemic attack
Tx	Transplantation
UACR	Urine albumin-creatinine ratio
WHO	World Health Organization

3 Administrative information

3.1 Sponsor and Platform Steering Committee

APT-KIDNEY Sponsor
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APT-KIDNEY has a single sponsor for the platform and all domains, referred to in this protocol as the platform sponsor. The platform sponsor holds overall responsibility for APT-KIDNEY and platform domains, as defined by responsibilities related to the core protocol, the CTIS platform application, and all platform- and domain-level regulatory obligations, including domain-specific regulatory submissions, investigational medicinal product (IMP) accountability (where applicable), and safety reporting. Domain leads will hold responsibility for the scientific and operational conduct of the domain under the authority delegated by the sponsor. Where a domain is led from another institution, the delegated responsibilities and any country-specific arrangements will be defined in a written agreement prior to domain activation. The platform sponsor retains the right to pause or close any domain where delegated obligations are not met.

APT-KIDNEY Platform Steering Committee
The APT-KIDNEY Platform Steering Committee provides overall scientific and operational governance of the platform. Its composition, including representation of the coordinating centre, participating sites and countries, domain leads, the platform statistician, and patient/public representation, together with voting and participation rules, is specified in Section 11.1. Domain leads (or their delegates) with a conflict of interest in relation to other domains or general platform management (such as partnerships with industry or commercial actors) will hold an advisory, non-voting role. Platform Steering Committee membership is published on the APT-KIDNEY website.

3.2 Coordinating and methodological centers

Key persons at the coordinating and methodological centers are listed on the APT-KIDNEY website.

Central coordinating center
Department of Nephrology and Endocrinology
Copenhagen University Hospital – Rigshospitalet
Blegdamsvej 9, 2100
Copenhagen E, Denmark

Data management center
Department of Nephrology and Endocrinology
Copenhagen University Hospital – Rigshospitalet
Blegdamsvej 9, 2100
Copenhagen E, Denmark

Advisory structures and independent data and safety monitoring committees
Advisory structures supporting the Platform and Domain Steering Committees, such as an advisory board or research panels, are described in the Platform Governance Charter (Section 11.1).

An Independent Data and Safety Monitoring Committee (IDSMC) is established for each domain (Section 10.4), with scope specified in the relevant DSA.

Patient and public involvement
The APT-KIDNEY platform aims to incorporate patient perspectives to support relevance, feasibility, and acceptability of participant-facing procedures. Domain teams are encouraged to seek patient review of participant-facing materials (including participant information sheets and questionnaires) and to engage patient research partners and/or relevant patient organizations to provide input on perceived burden, visit schedules, and dissemination planning. All

domains will describe patient and public involvement activities undertaken (or planned) in the domain-specific appendices (DSAs).

3.3 Investigators and clinical trial sites

A list of all investigators (including all national and local investigators) and clinical trial sites will be available with the registration in the Clinical Trials Information System (CTIS) prior to initiation of APT-KIDNEY and subsequently continuously updated by the platform steering committee. An overview of the participating sites in each domain will be available and continuously updated at the APT-KIDNEY website.

3.4 Protocol contributors

The core protocol was developed by members of the APT-KIDNEY Platform Steering Committee. Individual contributors and their roles are recorded in the trial master file.

4 Core protocol – an overview

Approved versions of the core protocol and appendices are published in CTIS and on the APT-KIDNEY website. A manuscript describing the rationale and key design features will be submitted to a peer-reviewed, international medical journal.

4.1 Core protocol

This core protocol describes the overarching methodological and organizational aspects of the APT-KIDNEY platform trial. In several sections, the protocol includes multiple methodological options; different choices and combinations thereof will be chosen for specific domains on the platform as described in DSAs.

APT-KIDNEY's linkage to electronic patient records and administrative health care registers will be implemented iteratively, as interfaces are developed, validated, and approved, and is used as specified in Section 8.7.1.

4.2 Appendices

The DSAs provide information on background, rational, specific interventions, and methodological specifics related to the domain. Local and national appendices provide details on any adaptions to the APT-KIDNEY protocol relevant in specific regions or countries. Additional appendices may be added if relevant.

The APT-KIDNEY core protocol document encompasses three (3) appendices:

i. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting checklist[1]
ii. APT-KIDNEY core variable specification
iii. Common serious adverse events in patients with advanced kidney disease

5 Trial Objectives

5.1 Aims and objectives

The primary objective of the APT-KIDNEY research program is to establish an investigator-initiated adaptive platform trial to facilitate efficient and rigorous assessment of interventions in patients with advanced kidney disease, i.e. eGFR < 30 mL/min/1.73 m^2 for ≥ 3 months, end-stage kidney disease on maintenance hemo- or peritoneal dialysis, conservative kidney management, or kidney allograft recipient. APT-KIDNEY will be established as a broad platform trial with a common regulatory and logistical framework, prioritizing shared protocols and contracts, adaptive and cost-efficient methodology, stakeholder involvement, and data capture supported by linkage to electronic patient records and administrative health care registers. APT-KIDNEY is designed exclusively for low-intervention comparisons (Section 6.3).

The APT-KIDNEY core protocol describes central platform trial features and methods and outlines the framework for preparing domains in which specific interventions are compared. Domains are conceptually comparable to stand-alone trials running on the platform. Domain-specific appendices (DSAs) will describe specific interventions, methodological approaches, allocation and randomization schemes, outcome selection, adaptation rules, and statistical analysis plans. In addition, the APT-KIDNEY research program aims to develop tools and guidance to facilitate nephrology research using a similar platform trial framework, in alignment with the recommendations of the World Health Organization (WHO).[2] The rationale for the platform trial approach is described in Section 6.4.

6 Background

Advanced kidney disease is a severe chronic condition associated with increased risks of adverse outcomes. Despite life-sustaining treatments such as dialysis and transplantation, patients experience a high burden of treatment-related complications, hospitalizations, comorbidity, and reduced quality of life. While therapies aim to prolong life and manage symptoms, evidence remains limited.[3]

Clinical trials are essential to validly assess the effects of different treatments.[2] However, conventional stand-alone clinical trials are typically restricted to comparisons of two distinct interventions based on a purpose-built infrastructure.[3–5] As such, trial design is often inflexible both in terms of participant requirements (leading to increased risks of inconclusive results), and in terms of trial logistics and infrastructure (leading to repetitive and duplicated work and resource use).

APT-KIDNEY aims to address key evidence-gaps in management of advanced kidney disease through an enduring, adaptable research platform designed for continuous learning to the direct benefit of patients. Based on a platform trial structure, APT-KIDNEY enables open-ended continuous assessment of both present and future interventions, with potential for increasing participant and stakeholder involvement based on a common trial framework.

6.1 Evidence and clinical trials in advanced kidney disease

The sections below summarize areas of clinical uncertainty identified by the APT-KIDNEY collaboration.

6.1.1 Advanced kidney disease (eGFR < 30 ml/min/1.73m^2)

Global prevalence of chronic kidney disease (CKD) is reported to be 10-15%[6,7] with prevalence growing and CKD predicted to become the fifth leading cause of death by 2040.[8] CKD is associated with substantial morbidity, excess mortality, and reduced quality of life, even in the early stages, and the majority of patients die before reaching advanced CKD.[9,10] Advanced CKD continues to be associated with the poorest prognosis, including an annual mortality risk exceeding 20% in patients with ESKD on dialysis.[9–11] Furthermore, ESKD also confers increased risk of cardiovascular disease, infection, major bleeding, and fractures consequent to the combination of kidney dysfunction and prevalence of concomitant diseases such as diabetes, hypertension, and dyslipidemia.[9,10]

The number of randomized controlled trials conducted focusing on patients with kidney disease has historically been comparably limited[12], with trials generally small (62% of trials conducted between 2007 and 2010 included <100 participants)[13], and often inconclusive or terminated early due to low rates of inclusion and events.[14] Furthermore, patients with CKD and especially ESKD have been systematically excluded of from larger trials, with advanced CKD excluded from >75% of multicenter trials investigating management of cardiovascular disease.[15,16] Several possible explanations for this have been suggested. CKD is often a 'silent' disease leading to delayed recognition of significance on both individual and societal levels. Trial conduct, interpretation, and generalizability are also complicated by both altered pharmacokinetics and marked population heterogeneity, leading to increased variability of observed treatment effects. Furthermore, clinical trials in advanced CKD, particularly ESKD, have overwhelmingly been industry-funded and inconclusive (or negative) throughout the past two decades,[14,17] with plausible limiting effects on funding opportunities for investigator-initiated trials in non-profitable medications.

Based on systematic reviews with meta-analyses of >1,000 randomized cardiovascular trials enrolling over 2 million participants, >70% excluded patients with CKD on safety grounds; only ~150 trials (≈15%) reported results for patients with CKD, and a mere 34 (≈3%) trials enrolled CKD populations exclusively, with fewer than 25 reporting outcomes for eGFR <30 mL/min/1.73 m^2. Notably, this reporting proportion has not improved over the past two decades, with presented CKD data often limited to composite endpoints within heterogeneous strata, and 'CKD' subgroups predominantly represented by eGFR >60 mL/min/1.73 m^2, indicative of minimal renal impairment and limiting applicability to advanced CKD.[18] In general, a prevalent lack of adequately powered randomized clinical trials in nephrology has led to an imbalance between clinical needs of patients with kidney disease and evidence to support and inform clinical practice.[19] Although management of CKD has been enriched by a number of large clinical trials in recent years (plausibly due to regulatory updates in acceptable surrogate markers),[20,21] implementation remains challenging, and applicability in advanced kidney disease continues to be uncertain.

6.1.2 End-stage kidney disease

Guidelines advocate careful planning of end-stage kidney care for all patients with eGFR < 30 ml/min/1.73 m^2 or perceived risk >40% for kidney replacement therapies within two years.[22] Planning is, however, uncertain due to the substantial imprecision for estimation of residual kidney function in advanced kidney disease. Where transplantation is a treatment option, pre-emptive transplantation (before dialysis initiation) is preferred where feasible, and timely referral for transplant evaluation is recommended 6 to 12 months before anticipated dialysis initiation.[23] For patients without pre-emptive transplantation as an option, or awaiting transplantation, both randomized data from the Initiating Dialysis Early and Late (IDEAL) trial and observational data have overall failed to demonstrate survival benefit attributable to early initiation of kidney replacement therapies i.e. dialysis initiation at a higher eGFR.[24–27] As such, identifying the appropriate time for initiation of dialysis continues to be a multifactorial decision, and according to KDIGO, decision to initiate treatment should be based on symptoms, signs, and patient preferences together with clinical and biochemical parameters.[22]

6.1.2.1 Hemodialysis

Hemodialysis is a kidney replacement therapy form in which solutes and water are removed from the blood by diffusion, convection, and ultrafiltration. Components of the hemodialysis system include a vascular access (arterio-venous fistula, arterio-venous graft, or central venous catheter), a fiber membrane (dialyzer), dialysate solution with different concentrations of solutes, and a dialysis machine. There is no international guideline on overall management of hemodialysis. Standard prescription of hemodialysis is three weekly sessions of four hours to obtain a sufficient clearance as estimated by Kt/V≥1.2 ((Kt/V = (clearance [ml/min] x time [min]) / total body water [ml]).[28,29] However, several central issues of hemodialysis management are being debated:

Frequency and duration of hemodialysis

The recommendation of thrice weekly dialysis schedules to obtain a Kt/V of ≥1.2 is primarily based on two randomized trials, the National Cooperative Dialysis Study (1981)[30] and the Hemodialysis (HEMO) study (2002).[31] Augmented schedules (longer dialysis time and/or higher frequency) have been demonstrated to have some clinical benefit in RCTs[32–35], while reports on overall benefit on mortality from observational studies and trials are inconsistent[36–39], and potential harm to vascular access and residual function should be considered.[28] On the other hand, incremental dialysis has been demonstrated to be non-inferior to the thrice weekly regimen, at least in observational studies.[40–42]

Hemodialysis vs. hemodiafiltration

Due to the potential for removal of middle-sized molecules during the dialysis session, hemodiafiltration has been suggested to be superior to high-flux hemodialysis.[43] This hypothesis was tested in four previous randomized trials.[44–47] However, due to methodological shortcomings, a high degree of heterogeneity, and diverging benefit on survival, no clear benefit of hemodiafiltration was demonstrated. The recent Comparison of high-dose-HDF with high-flux HD (CONVINCE) trial[48] was, however, able to demonstrate a clear benefit on survival in patients treated with hemodiafiltration, although benefit and feasibility might be restricted to certain patient groups.[43]

Composition of dialysate

In advanced CKD, the progressive loss of kidney function often results in fluid and electrolyte imbalances such as fluid overload, hyperkalemia, hypocalcemia, hyperphosphatemia, and metabolic acidosis. Management strategies comprise nutritional counseling, pharmacological therapy, and adjustment of dialysate composition. Nevertheless, high-quality evidence to define optimal dialysate concentrations remains limited.[28,49]

Management of cardiovascular disease

More than 50% of deaths in patients treated with dialysis can be attributed to cardiovascular disease.[50] As such, cardiovascular mortality in these patients is 10-30 times higher than in general populations.[51] Suggested explanations include underdiagnosis, due to atypical symptoms[52,53], and undertreatment, due to patient frailty[54], insufficient evidence[15,16], and, possibly, clinical inertia.[55,56] As such, unanswered questions include primary and secondary treatment of acute coronary syndrome[57–62], oral anticoagulation in atrial fibrillation[63–66], and blood pressure targets.[22]

6.1.2.2 Peritoneal dialysis

Peritoneal dialysis is a kidney replacement therapy in which a special dialysis fluid is infused into the abdominal cavity, using the peritoneal membrane as a natural filter to remove waste products and excess fluid from the blood. In observational studies, peritoneal dialysis has been associated with clinical outcomes and survival at least comparable

to hemodialysis,[67] with potential benefit on survival in incident dialysis patients starting on peritoneal dialysis observed in The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) trial.[68] Treatment can be guided by the 2020 International Society for Peritoneal Dialysis guideline[69], while different aspects of the treatment should be considered:

Dialysis modality: Continuous ambulatory peritoneal dialysis or automated peritoneal dialysis
Comparable outcomes have been demonstrated in patients treated with continuous ambulatory- or automated peritoneal dialysis as initial peritoneal dialysis modality.[70,71] However, the distribution of modality choice differs substantially across countries, as highlighted by the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS).[72] When selecting modality, factors such as the patient's lifestyle and available resources, residual kidney function, and the ability to achieve a weekly Kt/V >1.7 with adequate symptom control should be taken into account.[67,69]

Dialysis solution and preservation of residual kidney function
According to current evidence, including a Cochrane review,[73] the Balance in Australian and New Zealand peritoneal dialysis patients (balANZ) trial[74], and several systematic reviews[73,75,76], 'biocompatible' dialysis solutions with normalization of pH, reduction of glucose degradation products, and a bicarbonate and/or lactate buffer appear superior to conventional solutions. Benefit appears both at a cellular level[67] and at the patient level, particularly with preservation of residual kidney function[73–76], while benefit on rate of peritonitis, death, and adverse events remains uncertain.[73] Furthermore, guidelines emphasize that hypertonic glucose dialysis solutions should be avoided due to their potential harmful effects on membrane function, body weight, glycemic control, gastric emptying, and hemodynamic stability.[67,69]

Prevention of peritonitis
Peritonitis is a common, yet rarely (<5%) fatal, complication of peritoneal dialysis, which can result in technique failure and conversion to long-term dialysis.[77] Prophylactic antibiotics are recommended prior to catheter insertion based on evidence from randomized trials[78], while there seems to be no benefit associated with catheter placement technique.[79] Additionally, hypokalemia has repeatedly been observed to be associated with increased risk of peritonitis in observational data,[80] with supplemental potassium possibly associated with reduced risk based on a single multicenter randomized trial.[81] However, uncertainties remain, with no clear evidence available indicative of whether increased risk is associated with modality[71,82] or solute composition.[83]

6.1.2.3 Comprehensive conservative care

Comprehensive conservative care is a holistic patient-centered approach focused on symptom management, quality of life, and supportive care for patients who do not pursue or are not candidates for dialysis or transplantation.[84] Despite the complexity of treating patients with advanced CKD and, potentially, patient preferences[85,86], conservative care is underutilized in CKD compared with other chronic diseases[85,87], while overall benefit of dialysis compared with conservative care remains controversial, especially in elderly patients with a low performance status.[88–91]

In previous studies, patients with advanced CKD have identified symptom assessment and management as a top priority.[92,93] A summary from a KDIGO controversies conference on supportive care reported sufficient evidence on uremic pruritus, sleep disturbance, restless legs syndrome, pain and depression in CKD to give specific recommendations for treatment of these symptoms, primarily based on observational studies and extrapolation of results from non-CKD populations, but reported insufficient evidence to give recommendations on treatment of various gastro-intestinal symptoms, although quite common.[84]

6.1.3 Kidney transplantation

Kidney transplantation is associated with significantly lower mortality and substantially better quality of life.[94] A meta-analysis of observational studies confirmed the survival benefit of transplantation.[95] Cost-effectiveness analyses from Sweden further demonstrated that kidney transplantation becomes cost-saving within 2–3 years despite higher costs during the first year after transplantation.[96] Currently, approximately 3,500-4,000 patients in Denmark live with a functioning kidney transplant.[97] However, access to kidney transplantation remains constrained by inadequate organ donor availability, compounded by a median graft survival of only 10–15 years.[98] Consequently, many patients require multiple consecutive transplantations.

Despite marked improvements in short-term graft survival and reductions in acute rejection, long-term graft outcomes have not substantially improved.[98,99] Improving long-term outcomes through optimized treatment strategies and

follow-up organization has therefore been identified as a critical unmet clinical need.[100] This need is further underscored by the generally low quality of evidence underpinning current practice, with more than half of recommendations in the 2010 KDIGO guidelines based on low-level evidence.[101]

Key outcomes for kidney transplant trials include mortality, graft survival, kidney function decline (defined analogously to CKD progression outcomes such as decline in eGFR, initiation of dialysis, and/or death), major adverse cardiovascular events (MACE), and patient-reported outcome measures (PROMs).[102]

6.1.3.1 Optimal blood pressure management in kidney transplant recipients

Hypertension affects 50–90% of kidney transplant recipients and is associated with cardiovascular disease and graft loss.[103] No randomized controlled trials have established the optimal antihypertensive regimen in kidney transplanted populations,[104] and the available evidence remains insufficient to guide treatment decisions.[103] The optimal antihypertensive regimen, including the role of renin–angiotensin system blockade, therefore remains uncertain. Major antihypertensive drug classes are in widespread but non-standardized use in this population, making this an area amenable to pragmatic low-intervention comparisons within existing clinical infrastructure.

6.1.3.2 Immunosuppression optimization

The UK Kidney Transplant Priority Setting Partnership identified optimization of immunosuppression, including improved monitoring, regimen selection, and personalization, as key research priorities.[105] Open questions include the relative effectiveness of alternative follow-up programs, monitoring strategies, and visit frequencies, and the differential dosing or combinations of standard immunosuppressive therapies in balancing graft survival against treatment-related adverse effects.

6.1.3.3 Cardiovascular and metabolic management

Cardiovascular disease is a major cause of graft loss and death in kidney transplant recipients,[106] yet interventions to minimize cardiovascular risk in transplanted populations remain poorly studied. Despite pathophysiological mechanisms unique to transplantation, including chronic immune activation and the countervailing effects of immunosuppressive therapy,[107] recommendations for cardiovascular risk management are largely extrapolated from non-transplanted patient populations.[108] As such, key areas including lipid-lowering therapy, glycemic and metabolic control, management of hyperuricemia, correction of metabolic acidosis, sodium-glucose cotransporter 2 inhibitors, and non-steroidal mineralocorticoid receptor antagonists remain principally unexplored in kidney transplanted patients.

6.1.3.4 Patient-reported outcomes and supportive care

Life participation, defined as the ability to engage in meaningful daily activities, has been identified as critically important by kidney transplant recipients. Nonetheless, life participation remains broadly underreported as demonstrated in a recent review of > 30 trials.[109] In addition, evidence for the effectiveness of educational interventions for kidney transplant recipients remains limited,[110] and the effects of interventions such as prebiotics, erythropoiesis-stimulating agents, exercise programs, nutritional recommendations, patient education, and restrictions on daily activities following surgical procedures remain uncertain.[110]

6.2 Adaptive platform trials

Adaptive trials use results from pre-defined interim analyses of data to modify the ongoing trial.[111] All adaptions are implemented according to well-defined and pre-specified statutes to ensure trial integrity and validity of results.[111,112] Conventional RCTs may include limited adaptivity through prespecified group-sequential designs with interim analyses and stopping rules. More complex adaptive designs extend this by allowing additional, prespecified adaptations including response-adaptive randomization, arm dropping, enrichment, and are increasingly used. Adaptive platform trials enable these features within a flexible framework to evaluate multiple interventions over time.[113]

Adaptive trials may use several adaptive features, including adaptive stopping and arm-dropping (early termination of arms or the trial based on interim results), response-adaptive randomization (shifting allocation toward better-performing interventions based on accumulating outcome data), and adaptive enrichment (refining the target population based on observed treatment-sensitive subgroups). These features may confer ethical and efficiency benefits,[5,114–116] but require prespecified rules, simulation-based evaluation of operating characteristics, and operational safeguards to maintain trial integrity and validity. [111,112,117] The methodological framework for adaptive features in APT-KIDNEY is described in Sections 8.6 and 9.

Furthermore, adaptive platform trials provide possible solutions for challenges associated with conventional RCTs,[118] and are increasingly being introduced across medical specialties,[113,118] including nephrology.[119] Adaptive platform trials permit continuance of adaptive trials beyond singular interventions through the use of a core protocol focusing on diseases or conditions as opposed to specific interventions.[112,120] In APT-KIDNEY the population will be broad, encompassing all patients with advanced kidney disease irrespective of management, with nesting of comparable interventions or intervention groups in defined domains which are conceptually comparable to distinctive conventional RCTs. Based on perpetual design structure, APT-KIDNEY will enable ongoing introduction of novel domains to the platform, permitting reutilization of the trial framework across multiple interventions. The specific rationale for applying this approach in advanced kidney disease is described in Section 6.4.

6.3 Low-intervention trials

Low-intervention trials are crucial for assessing standard management and interventions based on a perspective of optimizing existing standards of care in frameworks contributory to public health and evidence-based medicine. APT-KIDNEY is designed exclusively for low-intervention comparisons, given the distinct paucity of evidence from clinical trials for existing management of advanced kidney disease.

A low-intervention trial is a regulatory term denoting use of authorized investigational medicinal products either in accordance with the summary of product characteristics (SmPC) or off-label with evidence-based support from published scientific evidence on safety and efficacy, and only minimal additional risk or burden imposed on the trial participants. Unless treatment guidelines of the SmPC are followed completely, or specific guidelines are referred, low-intervention trials require specific justification to ensure compliance with defined legislative and regulatory requirements:[121]

a) Investigational medicinal products, excluding placebos, are already authorized.

and

b) Investigational medicinal products are used in accordance with the SmPC *or* use is evidence-based i.e. supported by published scientific evidence on safety and efficacy

and

c) Any additional diagnostic or monitoring procedures pose only minimal additional risk or burden to the safety of the trial subjects compared to normal clinical practice in any concerned member state

All domains are designed to fulfil these criteria, and each DSA provides the domain-specific justification against them. For domains that do not involve an IMP, the criteria concerning IMPs do not apply, and the justification addresses the criterion of minimal additional risk or burden compared with normal clinical practice.

With implementation in January 2022, the EU Clinical Trials Regulation (EU 536/2014) governs clinical trials of medicinal products for human use in the European Union, including the introduction of the 'low-intervention trial' classification. In APT-KIDNEY, the low-intervention design reflects the scientific and ethical basis of the platform: comparisons of authorized treatments and care strategies used in clinical practice, with no more than minimal additional risk or burden compared with normal clinical practice. Formal classification as a low-intervention clinical trial is not requested, as risk-proportionate procedures for safety management, monitoring, and IMP handling follow from the risk assessment of each domain (Section 10.3.2).

6.4 Rationale and ethical considerations

Evidence-based medicine in nephrology remains suboptimal, with broad and persistent exclusion of patients with moderate to advanced kidney disease from randomized clinical trials.[122,123] Consequently, evidence-gaps remain. Motivation for the APT-KIDNEY platform trial is based on perceived benefit attributable to adaptive platform trials in terms of increased efficiency, particularly for pragmatic comparisons of treatments used in clinical practice. Evidence supporting specific management of advanced kidney disease continues to be predominantly reliant on observational data, opinion and experience rather than RCTs.

A number of specific considerations support the platform trial rationale. Platform trials enable reutilizing trial infrastructure across multiple interventions leading to reduction in costs overall, and logistical burden compared with

multiple stand-alone trials, with platform trials demonstrated to be associated with a 20-60% reduction in trial costs compared with conventional stand-alone clinical trials.[124] Management of advanced kidney disease is particularly well-suited for platform trial research due to a number of key parameters related to event rates, limited therapeutic options, broad use of hospital-based care including both dialysis and kidney transplantation concentrated at specialized nephrology centers, and the pre-existence of a defined multi-stakeholder core outcome sets adaptable for platform research.[125] Additionally, a platform trial allows enrichment through linkage with national health care registers where approved, in Denmark via the Danish Health Data Authority, with plausible benefit for trial logistics, quality, and validity.

Platform trials also hold the potential for direct benefit to trial participants, with utilization of adaptive features such as early dropping of inferior arms and response-adaptive randomization impacting participant allocation leading to possible accelerated implementation of beneficial effects.[112,113,126] Furthermore, employment of adaptive stopping rules may mitigate risk of sample size miscalculation lending positive impact on trial costs and durations.[111]

Of note, the concurrent enrollment of participants to multiple domains permit cross-domain standardization of trial procedures and data collection leading to more efficient and nimble assessment of interactions and outcomes.[127] Additionally, the continuous disposition of platform trials permits ongoing updates on trial interventions, with a possibility of adding emerging interventions within the existing framework.[128]

Finally, the development of a more lasting research framework enables greater engagement and involvement of stakeholders compared with stand-alone trials, with benefit on trial relevancy and transparency and plausibly dissemination.

7 Trial conduct

7.1 General considerations

The APT-KIDNEY core protocol describes all required items as denoted in Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement.[129] The core protocol and relevant appendices, including domain-specific amendments, will be submitted via CTIS for authorization by the competent authorities and ethics committees of the Member States concerned before enrollment commences and prior to the addition of specific domains to the platform (Section 7.2). APT-KIDNEY will comply with Regulation (EU) No 536/2014, the Declaration of Helsinki,[130] the WHO guidance for best practices for clinical trials,[2] the International Council for Harmonization on Good Clinical Practice (ICH-GCP),[131] the General Data Protection Regulation, and all applicable national laws including the Danish Data Protection Act. All trial conduct is overseen by the Platform Steering Committee, domain leads, and the domain IDSMCs. The guiding principles of the APT-KIDNEY protocol have been designed based on the practical and regulatory experiences from the Intensive Care Platform Trial (INCEPT) Research Programme and related platform trial groups, particularly with respect to the adaptive analysis framework (Section 10.4.1).[132]

7.2 Regulatory approval and oversight

APT-KIDNEY is submitted, authorized, and maintained as a single clinical trial in the European Union Clinical Trials Information System (CTIS) under Regulation (EU) No 536/2014, with one sponsor (Section 3.1) and one EU CT number. The trial is constituted as a clinical trial under Regulation (EU) No 536/2014 by virtue of its investigational medicinal product (IMP) domain(s); should no IMP domain remain active or authorized, the platform sponsor will agree the continued regulatory pathway for the platform with the competent authorities. All domains, including domains that do not involve an IMP (non-IMP domains), form part of the trial and are submitted, assessed, authorized, and overseen through CTIS under the same procedures by the competent authorities and ethics committees of the Member States concerned (in Denmark, the Danish Medicines Agency and the Medical Research Ethics Committees). New domains, and amendments to existing domains, are introduced as substantial modifications, providing a uniform point of regulatory access, assessment, registration, and transparency across the platform.

The provisions of Regulation (EU) No 536/2014 apply to the trial as a whole, irrespective of domain classification, including informed consent (Article 29), notifications of the start, temporary halt, early termination, and end of the trial and submission of results (Articles 36 to 38), annual safety reporting (Article 43), notifications of serious breaches, unexpected events, and urgent safety measures (Articles 52 to 54), and archiving of the trial master file (Article 58). Provisions that by definition concern an IMP, including IMP accountability and labeling, reference safety information, and expedited reporting of suspected unexpected serious adverse reactions (SUSARs) to EudraVigilance

within 7 days for fatal or life-threatening cases and 15 days for other cases, apply to IMP domains only. The classification of each domain and the corresponding safety framework are specified in the relevant DSA.

This common regulatory model provides a single, coherent application, assessment, and governance record for the platform, with uniform participant protection and oversight across domains.

Domain sequencing within the platform will be planned by the Platform Steering Committee with consideration of regulatory constraints applicable to platform trial applications, including CTIS architecture.

7.3 Protocol deviations and serious breaches

Protocol deviations: A protocol deviation is any departure from the approved core protocol or DSA. Assessment windows and permitted treatment changes are defined in the DSAs. Minor deviations are handled as data queries through automated checks in the eCRF as part of risk-based monitoring. Investigators report deviations that may affect participant safety or rights or the reliability of key data to the platform sponsor for assessment without undue delay, including whether they constitute a serious breach. Protocol deviations are summarized annually for the Platform Steering Committee and in the final report of each domain.

Serious breach: A serious breach is defined as any breach of Regulation (EU) No 536/2014 or of the currently applicable version of the protocol, including the core protocol and all DSAs, that is likely to significantly affect the safety and rights of a participant or the reliability and robustness of the trial data.[121] In case of any serious breach, the platform sponsor will notify the competent authorities via CTIS without undue delay and within seven days of becoming aware of the breach. For participating countries outside the EU, serious breaches will be reported in accordance with applicable national legislation.

7.4 End of trial and results reporting

The end of each domain is defined in the relevant DSA. The primary analysis of each domain constitutes an intermediate data analysis within the meaning of Article 37(8) of Regulation (EU) No 536/2014; a summary of the domain results, accompanied by a summary for laypersons, will be submitted via CTIS within one year of the domain's primary analysis data cut. The end of APT-KIDNEY is defined as the date of the last data collection for the last participant in the last active domain, following a Platform Steering Committee decision to close the platform, and will be notified via CTIS within 15 days in each Member State concerned.

8 Platform Trial Design

8.1 General design

The APT-KIDNEY trial is an investigator-initiated, pragmatic, randomized, embedded, multifactorial adaptive platform trial with interventions nested in designated domains. Domains can be open-label or blinded. APT-KIDNEY is designed exclusively for low-intervention comparisons (Section 6.3) and permits features including adaptive stopping and arm-dropping, response-adaptive randomization, and adaptive enrichment, with design and analyses accounting for secular trends and other time-varying confounding.

8.2 APT-KIDNEY Eligibility criteria

The overall core eligibility criteria shown below apply to APT-KIDNEY in general, and by extension to all domains on the platform. Domains may apply secondary domain-specific eligibility criteria to restrict the domain-specific study population. Domains may not broaden eligibility criteria beyond the overall core eligibility criteria. Domain-specific eligibility criteria will apply collectively to all arms in the domain.

8.2.1 Inclusion criteria

- ⊙ Advanced kidney disease as defined by: (i) eGFR < 30 ml/min/1.73m2 ≥ 3 months; (ii) ESKD on maintenance dialysis; (iii) ESKD on conservative kidney management; or (iv) kidney allograft recipient
- ⊙ Age ≥ 18 years
- ⊙ Eligibility for ≥ 1 (one) active domain

Domain-specific eligibility criteria in the DSAs will specify which of the eligible populations are included in the relevant domain, with any further restrictions. Domains may restrict but may not broaden eligibility beyond the core inclusion criteria above.

8.2.2 Exclusion criteria

- ⊙ Inability to provide free and informed consent

Patients previously included in APT-KIDNEY may be re-included for randomization to new domains in which they have not yet previously been randomized. Re-inclusion to a new domain requires domain-level consent. Platform-level consent is renewed only where the platform participant information has been substantially modified since the participant's original consent.

8.3 Domains and interventions

All interventions to be investigated in APT-KIDNEY will be nested in domains comprising intervention arms comparable to conventional stand-alone trials.[112] Although interventions will be mutually exclusive, the individual interventions may comprise combinations of drugs or doses of drugs. APT-KIDNEY is designed exclusively for low-intervention comparisons (Section 6.3) and will be used only to assess authorized investigational medicinal products as defined in Article 2(2)(9) of Regulation (EU) No 536/2014. Participation in domains will require domain-specific informed consent analogous to inclusion in a conventional stand-alone clinical trial. While the overall methodology is described in the APT-KIDNEY core protocol, the specific intervention and methodological approach will be related in DSAs including detailed descriptions covering the domain-specific allocation and randomization schemes, outcome selection and prioritization, adaption rules, and statistical analysis plans. Core outcomes common to all domains are defined in Section 8.9.1.1. Primary outcome(s) in domains should, as a guiding principle, be drawn from the core outcome list unless justified in the DSA.

All DSAs will require approval by the APT-KIDNEY Platform Steering Committee and authorization via CTIS (Section 7.2). Prioritization and development of domains and domain-specific protocols will incorporate input from key stakeholders where applicable. All domains will have a domain lead responsible for the conduct and management of the domain. A Domain Steering Committee may be established where the scale of the domain warrants it, as specified in the DSA. There is no specified limit on the number of possible active domains on APT-KIDNEY, the Platform Steering Committee will however continuously evaluate the sustainability of the number of domains active on APT-KIDNEY.

8.3.1 APT-KIDNEY and co-enrollment

APT-KIDNEY will allow concurrent enrollment of participants in multiple domains. Co-enrollment across domains will not be permitted where it would compromise enrollment, protocol adherence, or outcome assessment in either domain through interactions between the interventions, their delivery, or their measurement. Assessment of co-enrollment appropriateness will be performed for each pair of domains before co-enrollment between them opens, in collaboration between the Platform and Domain Steering Committees, based on the guiding principles defined below.[133–135]

- ⊙ **Biological interaction:** Interventions must not biologically interact in ways that confound either domain's analysis. If interaction cannot be ruled out, exposure shifts induced by randomization must not exceed those under routine care, in either direction
- ⊙ **Protocol compliance:** Co-enrollment should not impair protocol compliance or routine clinical care in either domain
- ⊙ **Allocation balance:** Allocation of interventions in Domain B should be balanced between groups in Domain A and vice versa
- ⊙ **Treatment modifications:** Protocol-mandated requirements or restrictions in Domain B should not modify intervention delivery in Domain A, and vice versa
- ⊙ **Outcome interaction:** Treatment effects in Domain A on shared outcomes should not be modified by allocation in Domain B (i.e. absence of treatment-by-treatment interaction on outcomes shared between domains), and vice versa

- **Clinical decision:** Protocol-driven data collection in Domain B should not influence clinical decisions affecting Domain A interventions, care, or outcomes, and vice versa
- **Adverse events** Adverse event procedures (including monitoring, reporting, and any resulting protocol modifications) in Domain B should not affect conduct or unblinding in Domain A, and vice versa

Where co-enrollment would otherwise be excluded under the principles above, the Platform and Domain Steering Committees may permit it where the resulting interaction itself constitutes a scientifically and ethically justified question, i.e. where a domain is specifically designed to assess interaction with another domain's intervention. Participation in APT-KIDNEY does not preclude co-enrollment in other non-related trials; this is assessed at the discretion of the Domain Steering Committee. Statistical handling of co-enrollment is described in Section 9.3.

8.3.2 Interventions

The intervention arms will be specified in each DSA. The DSA will provide details as to the comparisons, i.e., whether all intervention arms will be compared simultaneously or if one intervention arm will be applied as common control with separate, pairwise comparisons. Dependent on the domain, analyses may use (i) a common control with prespecified pairwise comparisons to each intervention, and/or (ii) an initial omnibus comparison across arms when sample size is limited, followed by prespecified pairwise comparisons as applicable. The current format of APT-KIDNEY does not support arm-adding or staggered entry within domains. As such, the perpetual design of APT-KIDNEY is contingent on continuously adding and closing domains, with the possibility of new domains assessing similar or identical interventions with new interventions following closure of a specific domain.

For domains involving IMPs, the platform sponsor holds overall responsibility for IMP accountability in accordance with Regulation (EU) No 536/2014, with operational implementation delegated to the domain lead as specified in the DSA. Two IMP supply models are anticipated. In prescription-based domains, participants will receive IMPs through standard clinical prescribing and commercial pharmacy dispensing; in such domains, IMP-specific manufacturing, importation, labeling, and packaging obligations do not apply, and the domain lead's delegated responsibility is limited to ensuring that the prescription strategy is implemented as specified in the DSA. In supply-based domains, the domain lead will be responsible, under the platform sponsor's accountability, for IMP sourcing, labeling, storage, and distribution, including any manufacturing, importation, or qualified person certification requirements; procedures will be detailed in the DSA and, where required, in pharmacy-specific agreements. The applicable supply model and associated responsibilities will be specified in each DSA.

8.4 Trial sites and personnel

8.4.1 Trial sites

Trial sites in APT-KIDNEY will be departments of nephrology and dialysis satellites in Denmark and other participating countries. Trial sites may opt to only actively participate in selected domains. Trial sites participating in the domain will permit inclusion into all active arms in each domain they are participating in. Trial sites will be listed in the CTIS registration and on the trial website. No trial site will be activated until the following platform-level requirements are confirmed: applicable regulatory and ethics approvals; compliant compensation or insurance arrangements (see Section 11.4); a signed site agreement; a designated principal investigator and sufficient trained research staff; documented role-proportionate training of personnel performing trial-specific tasks (Section 8.4.2); operational access to the eCRF system; and, where applicable, confirmed IMP supply arrangements. Domain-specific activation requirements will be defined in the DSAs. Fulfilment of all activation criteria will be documented by the coordinating center prior to first participant enrollment at each site.

8.4.2 Trial personnel

Clinical staff providing care for included trial participants will overall be eligible to care for and deliver trial interventions to participants unless specifically restricted in the DSAs. Personnel performing trial-specific tasks (screening, informed consent, eligibility assessment, randomization, and eCRF data entry) will be trained in trial procedures and GCP proportionate to their role, in accordance with ICH E6(R3). Clinical staff delivering interventions

as part of routine care require training in the relevant domain procedures only.[131] Screening of participants to domains will be performed by trained trial staff. Similarly, the oral information interview and informed consent will be conducted by members of the investigating team who are appropriately qualified under national requirements and delegated this task by the site principal investigator, with in-depth knowledge of the APT-KIDNEY trial including relevant domains. Participating trial sites will receive oral and written instructions detailing trial procedures and training.

8.5 Screening and informed consent

8.5.1 Screening

Screening for APT-KIDNEY will be performed by trained trial staff at participating sites, who will identify potential participants fulfilling the core inclusion criteria among patients under the care of their department and through referrals from other departments, in accordance with national rules on access to health records for recruitment. Following initial screening for platform eligibility, patients will be screened for inclusion to all active domains providing fulfilment of the domain-specific inclusion criteria. APT-KIDNEY permits continuous reassessment of patients who do not fulfil domain-specific inclusion criteria for currently active domains at initial screening. Domain-specific flowcharts illustrating screening and inclusion procedures will be provided in the DSA.

8.5.2 Informed consent

Eligible patients will be approached by members of the investigating team in accordance with this protocol and Article 29 of Regulation (EU) No 536/2014, with national adaptations as needed. Participant information will be modular i.e. a general section describing APT-KIDNEY, followed by domain-specific information sheets for the domains for which the patient is eligible.

The oral information interview will take place in an undisturbed setting, in person or, where approved by the ethics committee, by video-based communication allowing individual, direct, and simultaneous dialogue. Before the interview, potential participants will be informed of their right to bring a family member, friend, or other companion of their choice. The information will cover the trial, its potential benefits and harms, and the processing of personal data, including linkage with electronic patient records and national health registers.

Participants will be offered at least 24 hours for deliberation and may take more time or waive this period. They will be informed that participation is voluntary, that declining has no consequences for their care, and that consent may be withdrawn at any time, in any form, and without giving a reason.

APT-KIDNEY aims to obtain consent digitally, by electronic signature using a technique that ensures unambiguous identification of the signatory in accordance with national requirements; where digital consent is not possible or not preferred, consent will be signed on paper. The formats are equivalent and may be combined, including for platform-level and domain-level consent of the same participant. In either format, consent will be dated and signed by the participant and by the person who conducted the oral information interview, and the participant will receive a copy. Digital consent will use a validated system with an audit trail and version control of participant materials, and consent documentation in either format will be available for monitoring, audit, and inspection. Where a participant is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness.

No trial-related procedures will be performed before written informed consent is obtained. Randomization will follow consent without undue delay, with eligibility confirmed at randomization; DSAs may specify a maximum interval where the domain requires one.

8.6 Randomization and allocation concealment

8.6.1 Randomization

Randomization in APT-KIDNEY will be performed using an electronic randomizer. Randomization will be defined at the domain level and described in each DSA. Where co-enrollment across domains is permitted, allocation will be coordinated to ensure compatible treatment combinations and preserve interpretability; where co-enrollment is not permitted, participants will be randomized only within eligible domains per the prespecified rules. The randomization schemes will be described in detail for each domain in the DSA.

On a general note, domains will initially use balanced allocation unless the DSA prespecifies enrichment and/or response-adaptive randomization. In multi-arm domains with a common control, allocation will be balanced by default but may be unbalanced if justified by the planned testing approach and power considerations, as specified in the DSA.[136] Domains using fixed randomization will address stratification and blocking approach in the DSA. If applicable, permuted blocks of varying sizes will be default, with block size and allocation ratios remaining undisclosed to ensure concealment. In domains using response-adaptive randomization, allocation will initially be stratified on site and as specified in the DSAs, with possible transition to simple randomization without stratification or blocks following burn-in.

The use of fixed versus response-adaptive randomization will be prespecified in each DSA based on statistical and practical considerations. For domains using response-adaptive randomization, allocation will be updated at prespecified interim looks using model-based probabilities of intervention benefit i.e. posterior probabilities of superiority, with prespecified constraints to maintain minimum and maximum allocation to each arm and to avoid abrupt early shifts including burn-in and probability softening. Design choices and operating characteristics will be evaluated by simulation as described in Section 9.4, and all response-adaptive randomization details will be specified in the DSA.

8.6.2 Allocation concealment and blinding

8.6.2.1 Allocation concealment

APT-KIDNEY will employ full allocation concealment in all domains, including domains that are otherwise unblinded. Allocation concealment refers to preventing prediction or knowledge of the upcoming treatment assignment prior to randomization (i.e., pre-randomization concealment). Randomization will be implemented via a secure, centralized randomization system, and the randomization algorithm will be accessible only to designated trial statisticians and system administrators not involved in screening or enrollment.

For domains that are unblinded after assignment, randomization details that could enable prediction including block sizes (and any variability thereof), allocation ratios, and any stratification or minimization parameters, will be concealed from all clinical staff and trial personnel involved in screening, enrollment, and randomization. Any updates to allocation probabilities during the trial (i.e. due to adaptive features) will not be disclosed to site staff or personnel involved in participant inclusion and routine outcome registration.

In domains using response-adaptive randomization, the magnitude and/or frequency of adaptive updates may be restricted in unblinded domains to reduce the risk of operational bias and to avoid prematurely influencing equipoise through perceived shifts in allocation probabilities.

8.6.2.2 Blinding

Use and level of blinding will be determined separately for each domain and will be described in the DSA. Where feasible, blinding and use of placebo may mitigate bias and better isolate treatment effects; however, in an adaptive platform trial, blinding may introduce additional complexity, including the potential need for multiple (and evolving) placebos, with associated increased regulatory burden, cost and logistical demand. Considering the pragmatic design of APT-KIDNEY, including its restriction to low-intervention comparisons, and the limited and uncertain evidence for benefit of blinding on mortality outcomes (including the uncertain association between blinding and mortality in RCTs),[137] unblinded or partially blinded domains with rigorous allocation concealment and blinded outcome assessment where relevant will be considered appropriate options.

Where a domain includes assessor-administered outcomes susceptible to assessment bias (e.g. cognitive function or symptom evaluation), the DSA will specify whether and how outcome assessors are blinded. For PROs including EQ-5D-5L, full blinding will not be possible in open-label domains; bias will therefore be mitigated through standardized self-completion (preferably electronic), neutral instructions, pre-specified assessment time points, minimal staff involvement, centralized scoring where feasible, and pre-specified sensitivity analyses.

Where domains are blinded, procedures for emergency unblinding for urgent treatment or safety reasons, will be specified in the DSA, including documentation requirements and safeguards to preserve trial integrity.

Designated statisticians supporting the IDSMCs will be unblinded to allocation and comparative interim results; access for other trial personnel is restricted as described in Section 10.5.

8.7 Trial data

8.7.1 General considerations

Outcome and safety data are registered in the eCRF by trained site staff from source documentation. Linkage to electronic patient records and to administrative and clinical registers is used, where approved and validated, for baseline enrichment, treatment exposure and adherence, exploratory outcomes specified in the DSAs, independent verification, resource use, and minimizing loss to follow-up. Data sources are described in Section 8.7.3.

The APT-KIDNEY eCRF will be a purpose-built, GCP-compliant electronic data capture system hosted by the region operating the platform sponsor's institution within its framework for sensitive healthcare data, using secure connections between users, systems, and the trial database. The eCRF will support data entry by trained trial staff, domain-specific data dictionaries built on a shared core variable set, validation rules and branching logic, registration of informed consent, patient-reported outcome capture, role-based access, and ICH-GCP E6(R3)–compliant audit trails.

Following completion of a domain, finalized datasets and essential documents will be archived in a secure, access-controlled environment, with access limited to the platform sponsor, domain leads, and authorized delegates. All trial records, including domain-specific records, will be retained for at least 25 years after the end of the trial (Section 7.4), in accordance with Article 58 of Regulation (EU) No 536/2014, or longer where other applicable law requires.

8.7.2 eCRF interfaces

The eCRF comprises the interfaces listed below.

Interface	Function
Screening	Assessment of eligibility, and registration of informed consent and key variables
Randomization	Centralized eCRF randomization with allocation and stratification variables.
Data registration	Registration of descriptive and outcome variables
Administration	Quality control including monitoring of missingness and summary statistics; Extraction of aggregate metadata i.e. site-specific screening and exclusion data
Participant	Registration of patient-reported outcome measures
Monitoring	Read-only access to trial data for monitoring supportive of GCP queries.

The eCRF will support real-time validation against predefined variable and value limits and data standardization to support quality control of data entry.

8.7.3 Data sources

Data sources and the availability of register linkage vary between countries; sources for sites outside Denmark will be specified when such sites are added. In Denmark, data sources comprise the regional electronic patient records; national administrative health care registers, including the Central Person Register, the Danish National Patient Register, the Clinical Laboratory Information Register, the Register of Pharmaceutical Sales, the National Hospital Medication Register, the Danish Pathology Register, and the Cause of Death Register;[138–140] and national clinical quality databases, including the NRDT.[141] Use of register and database data requires the applicable approvals, in Denmark from the Danish Health Data Authority for national health registers and from the Danish Clinical Quality Program (RKKP) for clinical quality databases such as the NRDT, and is limited to the purposes specified in Section 8.7.1.

8.7.4 Core variables

A limited set of core variables is recorded for all participants in APT-KIDNEY, supplemented by domain-specific variables defined in the DSAs. The core set is intentionally restricted to essential variables. Full definitions, coding, units, source, and timing are specified in the core variable specification detailed in Appendix II.

8.7.4.1 Screening and baseline variables

Screening and baseline variables are recorded prior to or on the randomization date; baseline values refer to the most recent value available at that point. For participants randomized in a subsequent domain, only variables specified in the DSA are re-recorded; register-derived variables are refreshed automatically against the domain randomization date.

Screening variables

- Participant identifier
- Trial site
- Eligibility confirmation (in- and exclusion criteria)
- Informed consent date (DD/MMM/YYYY)
- Randomization date (DD/MMM/YYYY)

Baseline variables

- Date of birth (DD/MMM/YYYY)
- Sex (Male | Female)
- Weight (most recent, kilograms)
- Height (centimeters)
- CKD category
- eGFR (most recent, mL/min/1.73m^2; if not on dialysis)
- UACR (most recent, mg/g or mg/mmol; if not on dialysis)
- Primary kidney disease
- Systolic and diastolic blood pressure (most recent, mmHg)
- Comorbidities
    - Hypertension (Yes | No)
    - Diabetes (Yes | No)
    - Ischemic heart disease (Yes | No)
    - Heart failure (Yes | No, LVEF % if applicable)
    - Thromboembolic disease incl. stroke / TIA (Yes | No)
    - Peripheral vascular disease (Yes | No)
    - Prior major limb amputation (Yes | No)
- Clinical frailty scale (Rockwood Frailty scale, version 2.0)[142,143]
- Participant-reported HRQOL (EQ-5D-5L including EQ-VAS)[144,145]
- Laboratory work-up (most recent; register-derived where available)
- Medications

CKD: Chronic kidney disease. CKM: Conservative kidney management. HRQOL: Health related quality of life. KRT: Kidney replacement therapy. TIA: Transient ischemic attack.

Baseline variables are registered in the eCRF from source documentation and may be enriched or verified through register linkage where available (Section 8.7.1).

8.7.4.2 Follow-up variables

Resource-use and other follow-up variables are captured at platform level through automated register linkage during follow-up, where available. Resource-use variables, combined with the EQ-5D-5L outcome, constitute a platform-level dataset sufficient for cost-utility and cost-effectiveness analyses without domain-specific specification of resource-use variables. Country-specific register sources (non-Danish) will be detailed in national appendices.

Core outcome variables i.e. all-cause mortality, major adverse cardiovascular events, and repeated participant-reported HRQOLs, and, for participants with measurable kidney or allograft function, kidney disease progression, will be captured at platform level during follow-up as specified in Section 8.9.1.1. Domain-specific safety and outcome variables will be defined in the respective DSAs.

8.7.4.3 Other variables

Core safety variables, including serious adverse events, will be captured and reported under the risk-proportionate framework specified in Section 10.3; the common-SAE reference list is provided in Appendix III. Domain-specific safety and feasibility variables will be defined in the DSAs.

8.7.5 Data quality and monitoring

Data will be registered in the eCRF by trained trial staff from source documentation (Section 8.7.1). Data quality will be ensured through integrated validation rules, including hard limits preventing entry of impossible values and soft limits flagging outliers for review. Data completeness and summary measures will be monitored at the site and domain level through standardized eCRF reports.

A risk-based quality management framework will govern monitoring across the platform. Critical-to-quality factors at the platform level include: accuracy of eligibility confirmation and informed consent documentation; fidelity of

randomization and allocation concealment; completeness and timeliness of primary and guiding outcome data; and compliance with safety reporting timelines. Site and domain performance against these factors is assessed through central review of eCRF data, which may include central statistical monitoring, with targeted remote or on-site verification where prespecified thresholds are exceeded. Routine source data verification will not be performed; SDV will be risk-directed, focusing on consent, eligibility, the primary outcome, and safety-critical variables. A single monitoring plan, developed with the GCP unit affiliated with the primary site prior to first participant enrollment, defines indicators, thresholds, escalation procedures, and SDV scope, with domain-specific annexes where required. Domain-specific risks and mitigations will be summarized in each DSA. Trial investigators, GCP units, and competent authorities will have access to participant files including EPRs for quality control and monitoring as required.

8.7.6 Biological samples

Samples collected in APT-KIDNEY domains are analyzed as routine clinical samples and are not stored for the trial unless a DSA specifies otherwise. A domain proposing storage of biological samples for research will describe the samples, storage arrangements, consent, and applicable approvals in its DSA, introduced by substantial modification (Section 7.2).

8.7.7 Data protection and privacy

8.7.7.1 Legal framework and basis for processing

Processing of personal data in APT-KIDNEY will comply with Regulation (EU) 2016/679 (GDPR), the Danish Data Protection Act (Act No. 502 of 23 May 2018, as consolidated), and applicable national data-protection legislation in participating countries. The data-protection provisions of the Clinical Trials Regulation (EU) No 536/2014 apply concurrently across all domains. Informed consent for trial participation is an ethical and procedural requirement; it does not constitute the legal basis for data processing within the meaning of the GDPR.[146]

The legal bases for processing are: for ordinary personal data, GDPR Article 6(1)(e) (task carried out in the public interest), as further specified in the Danish Health Act and equivalent national legislation; for special categories of personal data including health data, GDPR Article 9(2)(j) (scientific research purposes), subject to appropriate safeguards in accordance with Article 89(1) and, in Denmark, Section 10 of the Danish Data Protection Act. Processing of the Danish civil registration number for participant identification and register linkage will be performed under Section 11(1) of the Danish Data Protection Act. For countries outside Denmark, the applicable national legal bases will be documented in the relevant national appendices prior to site activation.

8.7.7.2 Data controllership

The region operating Copenhagen University Hospital Rigshospitalet, the platform sponsor's institution, is data controller for platform-level data, and its data protection officer advises on the processing. Controllership arrangements with participating sites, including any joint controllership under GDPR Article 26, and data processing agreements under Article 28 are established in writing before data processing begins and documented in the trial master file. The participant information identifies the data controller and the data protection officer.

8.7.7.3 Data protection impact assessment

A data protection impact assessment under GDPR Article 35 will be completed before data processing begins and updated when processing changes materially.

8.7.7.4 Safeguards, security, and cross-border transfers

Trial data are entered in the eCRF, and other trial data are stored in access-logged files at the responsible department. Personal data will be pseudonymized at the earliest feasible point, with direct identifiers stored separately and accessible only to authorized personnel for register linkage, safety reporting, and regulatory compliance. Technical and organizational security measures follow the regional framework for sensitive healthcare data of the region operating the platform sponsor's institution and are documented in the DPIA (Section 8.7.7.3).

Within the EEA, data transfers between sites and the coordinating center are governed by the arrangements in Section 8.7.7.2. If the platform expands to countries outside the EEA, transfers will comply with GDPR Chapter V using the appropriate mechanism (adequacy decision, standard contractual clauses, or other approved mechanisms), with transfer impact assessments conducted where required. Transfer arrangements will be specified in national appendices prior to non-EEA site activation.

8.7.7.5 Participant rights and oversight

Participants will be informed of the processing of their personal data including purposes, legal basis, recipients, retention periods, and their rights under GDPR Articles 13–22 as part of the informed consent procedure (Section 8.5.2). The participant information will specify that trial consent and the legal basis for data processing are distinct and will describe any limitations on data-subject rights applied under GDPR Article 89(2) and national implementing legislation. If applicable, the data protection officer designated by Copenhagen University Hospital Rigshospitalet will provide oversight of platform-level data-protection compliance and will be consulted on the DPIA, processing agreements, and material changes to data processing activities. Local DPO oversight at participating sites will follow applicable national requirements.

8.8 Trial Follow-up

8.8.1 Follow-up

Follow-up in APT-KIDNEY will be conducted as part of routine clinical care. No trial-specific follow-up visits, additional investigations, or participant contacts are required, unless explicitly stated in the DSAs.

Outcome and safety data, including domain-specific safety outcomes, are registered in the eCRF by trained site staff from source documentation, with contact to responsible clinicians only if required for clarification. Patient-reported outcome measures are collected directly from participants, electronically or on paper. Register linkage is used only for the purposes specified in Section 8.7.1.

8.8.2 Discontinuation and participant withdrawal

Discontinuation of study treatment and participant withdrawal from APT-KIDNEY will be conducted in accordance with Regulation (EU) No 536/2014, the Danish Act on Clinical Trials of Medicinal Products, applicable guidance from the Danish Medicines Agency and the Medical Research Ethics Committees,[147] the EU GDPR and Danish Data Protection Act (Act No. 502 of 23 May 2018), and ICH-GCP (E6[R3]).[148] Modifications will as necessary be detailed in national appendices where applicable.

8.8.2.1 Discontinuation or withdrawal

Participants may withdraw consent to take part in the platform trial at any time, without providing a reason and with no impact on their ongoing or future treatment. Withdrawal may apply to the entire platform or to one or more specific domains; we will explicitly confirm which option the participant intends. To minimize missing data, participants who discontinue the intervention will be asked for permission to continue follow-up and collection of outcome and safety data.

Participants may also be discontinued and/or withdrawn by the site investigator if the participant experiences intolerable, serious safety events suspected to be related to a trial intervention, if discontinuation is deemed to be in the participant's best interest, or if active therapy is withdrawn. If any of these events result in discontinuation of interventions, data collection and follow-up will continue, and the participant will remain in the intention-to-treat (ITT) population. Wherever feasible, discontinuation will apply only to the relevant intervention-specific domain(s), with participation continuing in other domains and the platform as a whole.

8.8.2.2 Transfer to non-participating center

Participants will generally discontinue interventions allocated in APT-KIDNEY following transfer to non-participating centers, unless explicitly stated in the DSAs. If participants are retransferred to a participating center within the intervention period, the allocated intervention(s) may be resumed. Patients transferring from participating to non-participating centers will be followed through central registers, EPRs, and via remote modalities as appropriate.

8.8.2.3 Lost to follow-up

Participants will be considered lost to follow-up if no further trial data can be obtained despite reasonable, documented efforts, and in the absence of withdrawal of consent for follow-up. Data will be analyzed according to the ITT principle. Where approved, register linkage may be used to minimize missing data (Section 8.7.1).

8.9 Trial outcomes

8.9.1 Core outcomes

Trial outcomes in APT-KIDNEY are multidimensional. Core outcomes will be collected and reported for all participants in all domains. Outcome variables are defined as data occurring after randomization. APT-KIDNEY outcomes will overall adhere to the principles and results of the global Standardized Outcomes in Nephrology (SONG) initiative.[149] The SONG initiative was launched in 2014 with the aim of establishing a standardized set of outcomes for clinical trials in kidney disease. Based on a comprehensive approach entailing consensus building across key stakeholders including patients, caregivers, and health professionals, the SONG initiative has currently generated seven (7) core outcome sets spanning differing kidney populations.[150] SONG outcomes sets have been developed based on a principle of feasible implementation in target population trials. Of note, all outcome sets include at least one (1) PROM. Overall, the SONG core outcome sets reflect shared priorities of > 10.000 patients, caregivers and health professionals from 79 countries,[151] and use is in alignment with recommendations of both the United States Food and Drug Administration[152], the European Medicines Agency[153], and Kidney Disease: Improving Global Outcomes (KDIGO).[154] Based on the broad inclusion of all patients with advanced kidney disease as defined in Section 8.2.1, APT-KIDNEY core outcomes will be defined based on the SONG outcomes set published for hemodialysis, peritoneal dialysis, kidney transplantation, and CKD.[151] Any deviation from the prespecified core outcome measurement set related to implementation, data registration, or trial feasibility will entail careful consideration and deliberation by the Platform Steering Committee following discussion with all relevant stakeholders.

8.9.1.1 Core outcome variables

Core outcomes are listed below; domain-specific outcomes will be defined in the DSAs. Follow-up is assessed at 4-monthly timepoints (±4 weeks) from the participant's first platform randomization. For participants co-enrolled in later domains, each domain's scheduled assessments use the nearest platform timepoint; event outcomes use actual event dates.

Core outcomes to be defined as follows:

Death	Any death irrespective of cause
Cardiovascular event	Any major adverse cardiovascular event as defined by; nonfatal myocardial infarction; nonfatal ischemic stroke; and/or cardiovascular death
Patient-reported HRQOL	Standardized HRQOL as defined by EQ-5D-5L, including EQ-VAS
Kidney disease progression	Sustained ≥40% decline in eGFR from baseline (confirmed at ≥4 weeks), initiation of maintenance kidney replacement therapy, or allograft loss (return to chronic dialysis or retransplantation)

Kidney disease progression will apply to participants with measurable kidney or allograft function at randomization (CKD not on KRT; kidney transplant recipients); participants on maintenance dialysis do not contribute. The outcome will be defined as the first occurrence of any component, with death treated as a competing event. Domains may restrict but not broaden the component definitions; any deviation will be specified and justified in the DSA.

Primary outcome(s) in each domain should, as a guiding principle, be drawn from the core outcome list unless a domain-specific justification is provided in the DSA. In domains employing adaptive design, a single guiding outcome from the core outcome list must be specified in the DSA. Prioritization of additional outcomes will be specified in the DSA.

EQ-5D-5L will preferentially be collected through digital self-completion pathways (web-based and/or app-based solutions) using standardized, neutrally framed instructions without staff involvement. Alternative collection methods may be used where digital access is not feasible, with the method documented and accounted for in analyses. The EQ-5D-5L collection method (digital or analog self-completion or telephone/interviewer-assisted) will be recorded in the eCRF at each assessment as a core follow-up variable. PROMs will be analyzed using applicable national EQ-5D value sets specified in national and local appendices; if unavailable, the Platform Steering Committee and national investigator(s) will select the most appropriate value set, defaulting to the Danish value set, prior to country

initiation.[155] The EQ-5D index will be the primary PROM, with non-survivors assigned the dead/worst value (weighted as dead) and survivor-only analyses as secondary.[156,157] EQ VAS and dimension-level outcomes will by default be based on assessments obtained while alive, with death treated as a distinct terminal event. Any deviation from these defaults will be specified and justified in the DSAs.

8.9.2 End-point adjudication

Events will be ascertained by site staff from source documentation, with national register data used for verification where available. Patient-reported HRQOL will not require adjudication. Cause of death (cardiovascular or non-cardiovascular) will be classified by site staff from source documentation, with verification against the Danish Register of Causes of Death (or national equivalent) where available. Domains in which MACE or cardiovascular death is the primary or guiding outcome will specify in the DSA whether central blinded adjudication is required, and the procedure for it.

9 Statistics

9.1 Overall principles

APT-KIDNEY is a pragmatic, investigator-initiated adaptive platform trial with interventions grouped into domains. Each domain prespecifies its design and analysis in the DSA, including a domain-specific statistical analysis plan and a one-page design card summarizing the paradigm, guiding outcome (if any), interim looks (if any), decision rules, and maximum planned information. Domains will typically use fixed-sample or event-driven frequentist designs. Adaptive features, such as early stopping, arm-dropping, or response-adaptive randomization, and Bayesian analysis may be used where they offer a clear advantage, subject to the requirements in Sections 9.2 to 9.6.

9.2 Statistical framework

The platform supports both Bayesian and frequentist paradigms, with statistical approach detailed in the DSAs.

By default, domains use a frequentist analysis with a single primary analysis at the prespecified sample size or event count, without formal interim efficacy or futility analyses. Where a domain plans interim analyses, the DSA specifies a group-sequential design, including timing, decision boundaries, and control of the Type I error and power. Where a domain uses a Bayesian design, the DSA specifies the priors and the decision rules, including posterior probability thresholds. As a guiding principle, primary analyses use neutral or mildly skeptical priors, with prespecified sensitivity priors. Operating characteristics, including false-positive risk, power, bias, and precision, are evaluated by simulation (Section 9.4), and computational reliability is documented with prior-predictive checks and MCMC diagnostics against predefined criteria.[158]

9.2.1 Analysis populations and sets

The primary analysis population will be the intention-to-treat (ITT) population (all randomized participants analyzed according to assigned intervention). Per-protocol and as-treated populations may be used in prespecified sensitivity analyses where relevant (as-treated: participants analyzed according to intervention actually received), with definitions and eligibility criteria specified in the DSAs.

9.2.2 Outcomes, estimands, and guiding outcome

Primary outcomes for domains should, in principle, be selected from the APT-KIDNEY core outcome set (Section 8.9.1). For each domain, the primary estimand, corresponding to the primary outcome, will be defined in accordance with ICH E9 (R1), specifying population, endpoint variable, intercurrent event strategy, and summary measure. In adaptive domains, the guiding outcome for adaptive decisions will by default match the primary estimand; alternative guiding outcomes will be justified in the DSAs and should be highly correlated with the primary outcome or estimand.

EQ-5D index, EQ VAS, and dimension-level outcomes will be analyzed in accordance with the conventions specified in Section 8.9.1.1, using the applicable national value set. For longitudinal EQ-5D index outcomes, the default primary analysis will compare groups at a single prespecified timepoint, with optional adjustment for baseline values and stratification factors to improve precision. A default supportive analysis will use mixed models for repeated measures across scheduled visits using all observed data. Alternative summaries may include average utility over follow-up, weighted by the time between assessments. All deviations from the default approach, including methods for handling missing data, will be prespecified and justified in the DSAs.

9.2.3 Models and covariate adjustment

On a general level, all effect estimates will be reported with an appropriate measure of uncertainty, using two-sided 95% confidence intervals for frequentist analyses and 95% credible intervals for Bayesian analyses, unless otherwise specified. Where applicable, posterior probabilities for clinically meaningful effects will be reported for Bayesian analyses. Effects will be summarized on appropriate scales, and reference categories, transformations, and covariate adjustment sets will be prespecified in the DSAs.

Analyses will use standard regression models appropriate to outcome type, with covariate adjustment prespecified in the DSAs. Time-to-event outcomes will use standard survival models; key model assumptions will be assessed and alternative summaries used where appropriate. Where time-related changes or staggered activation occur within a domain, analyses will adjust for calendar time and prioritize concurrent controls; any inclusion of non-concurrent controls will be prespecified and justified in the DSAs. Borrowing across periods/strata may be used only if prespecified with appropriate robustness checks. Borrowing across domains will not be performed unless explicitly prespecified and justified in a DSA. Prespecified subgroup analyses are exploratory unless multiplicity control is prespecified.

9.3 Randomization and co-enrollment

Domains use fixed randomization unless the DSA specifies response-adaptive randomization, which follows prespecified rules with safeguards for stability, equipoise, and estimability, including bounds on allocation probabilities and limits on changes per look, with more conservative settings in open-label domains where appropriate. Multi-arm domains may use a shared control with prespecified pairwise comparisons. Stratification factors used at randomization are included in the primary analysis models.

Participants may be enrolled in more than one domain where the domains have been assessed as compatible (Section 8.3.1). The randomization system enforces the compatibility rules, and where domains are incompatible, a prespecified rule determines which domain is offered. Randomization in a domain is stratified by allocation in any domain in which the participant is already enrolled, where feasible, and primary analyses adjust for allocation in other domains where specified in the DSA. In domains using response-adaptive randomization, allocation safeguards are applied within these strata.

9.4 Adaptive analyses, decision rules, and simulation

Interim analyses are optional. Where planned, the DSA prespecifies the information thresholds that trigger them, such as accrual or event counts, a burn-in period before any adaptation, and the decision rules, including margins, probability or error thresholds, and their priority. Interim analyses use locked data cut-offs with prespecified data-management and quality-control steps. Bayesian domains use posterior probabilities for superiority, inferiority, and equivalence or non-inferiority, and predictive probabilities for futility; frequentist domains use group-sequential methods (Section 9.2).

Recruitment may continue while an interim analysis is prepared. Decisions are implemented after IDSMC review, and interim results are available only to the IDSMC and an independent statistical group.

Adaptive domains are evaluated by simulation before activation to assess power at the minimally important effect and false-positive risk under the null, across plausible scenarios that include domain-relevant sensitivity scenarios such as delayed outcomes or time trends. Each DSA specifies the maximum planned information and any interim schedule. Simulation outputs and code are archived in the trial master file before the first participant is enrolled in the domain.

9.5 Multiplicity and error control

Multiplicity is controlled within each domain for the primary outcome, across arms and interim analyses; other outcomes follow a prespecified hierarchy or are supportive or exploratory. Frequentist domains control the family-wise Type I error, for example by group-sequential error spending or closed testing, allowing for correlation where arms share a control. Bayesian domains calibrate posterior thresholds by simulation (Section 9.4). Conclusions are drawn at the domain level; any borrowing or shared controls across domains require safeguards specified in the DSA.

9.6 Missing data, intercurrent events, and sensitivity analyses

Primary analyses follow the intercurrent-event strategies of the estimand. Missing data are minimized through harmonized follow-up and, where approved, register linkage. Where appropriate, primary analyses use likelihood-

based models with all observed data under a missing-at-random assumption, with sensitivity analyses under prespecified departures from that assumption and in other analysis sets, as specified in the DSAs. EQ-5D outcomes follow the conventions in Section 8.9.1.1, including survivor-only analyses and alternative missingness assumptions as sensitivity analyses. In open-label domains, sensitivity analyses of patient-reported outcomes adjust for collection method and assess differential missingness between arms.

9.7 Final analyses, reporting, and reproducibility

Final analyses are conducted after database lock for the domain, following the DSA and any IDSMC recommendations. Results are reported according to CONSORT, including the CONSORT-ACE extension where applicable,[159] stating the estimands, adaptation rules, interim analyses, and any deviations. In adaptive domains, a ledger of interim analyses, decisions, data cut-offs, and implementation dates is archived with the final report. Shared data structures and eCRF standards support consistent analyses across domains and integration of core outcomes at platform level.

Analyses use validated, version-controlled code in R, Stan, or equivalent software. Code, simulation scripts, and outputs are archived in a secure repository with an audit trail and frozen at database lock; for adaptive domains, simulation and interim analysis code are additionally frozen before the first participant is enrolled (Section 9.4). Where a domain has interim analyses, the DSA identifies the independent statistical group that prepares the interim outputs.

10 Trial Safety

10.1 Pregnancy and contraception

Domains involving systemic exposure to potentially teratogenic or fetotoxic agents will specify requirements for contraception and pregnancy testing in the DSA, in accordance with the recommendations of the Clinical Trials Coordination Group under the Heads of Medicines Agencies.[160] Pregnancies identified during participation are recorded in the eCRF and managed according to clinical practice, as specified in the DSA.

10.2 Trial risk assessment

APT-KIDNEY is designed exclusively for low-intervention comparisons, so intervention-related risks to participants are low; risks specific to each intervention are assessed in the DSAs. The main risks to the trial itself are operational and methodological.

Domains may be underpowered or less representative if recruitment is lower than expected, sample sizes are misestimated, or eligibility criteria are too restrictive. Domain leads therefore set sample sizes and eligibility criteria with statistical input, and each DSA prespecifies power and Type I error or, for adaptive domains, simulated operating characteristics (Section 9). Only departments with sufficient nephrology and research expertise are approved as sites; activation follows the requirements in Section 8.4.1, and monitoring follows the risk-based plan in Section 8.7.5. Shared infrastructure, procedures, data elements, and core outcomes reduce start-up costs, duplication, and data collection burden, and site payments are governed by site agreements (Section 11.4).

Adaptive features are used only where methodologically justified. Their risks are managed through burn-in periods, neutral or mildly skeptical priors, simulation reflecting expected accrual and follow-up, and restrictions on response-adaptive randomization in open-label domains (Sections 9.3 and 9.4). Comparisons use concurrent controls; any use of non-concurrent controls is prespecified and justified in the DSA (Section 9.2.3).

10.3 Safety management

Safety management follows Regulation (EU) No 536/2014.[161] Domains without an investigational medicinal product may adapt the procedures, as specified in the DSA.

10.3.1 Adverse events and reactions

All definitions have been adapted from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use to fit both domains assessing pharmacological and non-pharmacological interventions used in APT-KIDNEY.[162]

Adverse event (AE)
Any undesirable medical event occurring to a participant during a clinical trial, which does not necessarily have a causal relationship with an intervention.

Adverse reaction (AR)
An unintended and noxious response to an intervention occurring when normally used.

Serious adverse event (SAE)
Any AE that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Serious adverse reaction (SAR)
Any SAE assessed to be related to the intervention. SARs are specified in the DSA for each intervention; for investigational medicinal products, they are based on the reference safety information in the SmPC and may include additional clinically relevant events.

Suspected unexpected serious adverse reaction (SUSAR)
A serious adverse reaction whose nature, severity, or outcome is not consistent with the reference safety information. Causality is assessed by the investigator.

10.3.2 Registration and reporting of safety outcomes

10.3.2.1 Risk-proportionate approach

APT-KIDNEY participants are routinely followed in local nephrology departments with close clinical and biochemical monitoring, and safety events are managed according to usual clinical practice. Safety data are recorded according to each domain's risk level, as specified below and in the DSA. References to the domain lead receiving or handling safety reports denote operational steps under the platform sponsor's delegated authority; statutory reporting obligations rest with the platform sponsor.

APT-KIDNEY will employ a risk-proportionate approach for recording and monitoring of safety outcomes in accordance with Regulation (EU) No 536/2014 and recommendations of the Danish Medicines Agency.[161,163] Given that advanced kidney disease carries a high comorbidity burden with frequent symptoms and hospitalizations, the safety framework will distinguish between expected, disease-related events and events that may plausibly be intervention-related. Given the risk profile of the low-intervention comparisons in APT-KIDNEY and the participant adverse event burden, all domains in APT-KIDNEY will be exempt from reporting AEs and ARs unless specifically noted in the DSAs. SAEs and SARs are recorded as specified for the domain's risk level and in the DSA, with investigator assessment of seriousness, severity, and causality using standard terminology. In IMP domains, SUSARs will be reported to EudraVigilance within regulatory timelines (seven (7) days for fatal or life-threatening, 15 days for others); annual safety reports covering all domains will be submitted via CTIS.

Safety is overseen through routine nephrology follow-up, risk-based monitoring with targeted source data verification of safety-critical fields, and annual review of safety data across domains.

All domains will perform an independent assessment of risk (and benefit) in accordance with the risk definitions outlined in the Danish Medicines Agency's guidance paper and the recommendations advocated in the European commission expert group for risk proportionate approaches in clinical trials.[161,163] Risk levels determine risk-adapted safety management and are distinct from the low-intervention design of the platform (Section 6.3), which applies to all domains irrespective of risk level.

Risk level 1, low risk

Classification: The following requirements apply:

- Investigational medicinal product(s) hold marketing authorization(s) and use is in accordance with the SmPC *or* off-label use is evidence-based with published safety and efficacy data
- Additional diagnostics or monitoring impose only minimal additional risk or burden
- Intervention(s) are comparable with standard care

General considerations: Risk-adapted adverse event management is generally justifiable, and SAE and SAR recording may be limited under a protocol-defined, risk-adapted monitoring plan supported by documented risk assessment. SUSARs are the only mandatory external expedited reports: all SUSARs must be notified to the domain lead within 24 hours of site awareness. The platform sponsor reports SUSARs to EudraVigilance within regulatory timelines and includes them in the annual safety report.

Considerations applicable to APT-KIDNEY: Domains will provide a domain-specific, risk-adapted adverse event monitoring and management assessment. Routine registration of SARs is not required; however, specific clinically

relevant SARs defined in the DSA may be registered and included in the annual safety reports and final domain reports.

Risk level 2, intermediate risk

Classification: The following requirements apply:

- Investigational medicinal product(s) hold marketing authorization(s) but use is off-label
- The intervention(s) does not substantially deviate from standard care and the safety profile is expected to be comparable
- The safety profile(s) of the investigational medicinal product(s) is robust

General considerations: Prespecified SAEs and SARs described in the SmPC may be exempt from immediate investigator notification when justified in the protocol and supported by risk assessment; all such events are still recorded, reviewed by the IDSMC, and included in the annual safety reports. All non-specified or concerning SAEs and SARs must be notified to the domain lead within 24 hours. The platform sponsor reports SUSARs to EudraVigilance within 7 days for fatal or life-threatening cases and within 15 days for other cases, and includes them in the annual safety report.

Considerations applicable to APT-KIDNEY: Off-label use in risk level 2 domains must be evidence-based and supported by published scientific evidence on safety and efficacy (Section 6.3). In intermediate-risk comparisons, domain-specific protocols will include a risk assessment and, where applicable, define a prespecified list of SAEs and known SARs exempt from immediate notification within 24 hours. All SAEs and SARs will be included in annual safety reports and final domain reports.

Risk level 3, high risk

Classification: *One or more* of the following requirements apply:

- The investigational medicinal product(s) does not hold prior marketing authorization
- The intervention(s) is previously untested or substantially deviating from standard care
- Evidence related to safety and efficacy of the intervention(s) and/or investigational medicinal product(s) is limited or insufficient
- The investigational medicinal product is authorized but subject to restricted reporting requirements or additional monitoring

General considerations: Thorough adverse event management is required to safeguard participant safety and characterize the safety profile. All SAEs and SARs, and any other events defined in the protocol, must be notified to the domain lead within 24 hours; any deviation from full recording or immediate notification must be explicitly justified in the protocol on the basis of a prespecified risk assessment. The platform sponsor reports SUSARs to EudraVigilance within 7 days for fatal or life-threatening cases and within 15 days for other cases and includes them in the annual safety report.

Considerations applicable to APT-KIDNEY: Comparisons meeting one or more of these criteria fall outside the low-intervention design of the platform (Section 6.3) and are not permitted in APT-KIDNEY.

10.3.2.2 Risk-adapted safety management

	Risk level 1 = “Low”	Risk level 2 = “Medium”	Risk level 3 = “High”
Recording of adverse events			
Is risk-adaptation for AE recording possible?	YES — AE recording can be exempted	YES[1] — AE recording can be exempted	NO[2] — all AEs must be recorded
Is risk-adaptation for SAE recording possible?	YES — SAE recording can be exempted	YES[1] — Predefined SAEs can be exempted	NO[2] — all SAEs must be recorded

Is risk-adaptation for SAR recording possible?	YES — only SUSARs must be recorded	YES[1] — Predefined SARs can be exempted	NO[2] — all SARs must be recorded
Reporting of serious adverse events from investigator to sponsor			
Is risk-adaptation for SAE reporting to sponsor possible?	YES — SAE reporting can be exempted	YES[1] — immediate SAE reporting can be exempted, but must be reported to the ASR	NO[2] — all SAEs must be reported immediately to sponsor
Is risk-adaptation for SAR reporting to sponsor possible?	YES — only SUSARs must be reported immediately to sponsor	YES[1] — predefined SARs can be exempted from immediate reporting, but be included in the ASR	NO[2] — all SARs must be reported immediately to sponsor
Sponsor's reporting obligations			
SUSAR reporting	Reported to EudraVigilance database[3]	Reported to EudraVigilance database[3]	Reported to EudraVigilance database[3]
Annual safety report (ASR)	Submitted via CTIS[4]	Submitted via CTIS[4]	Submitted via CTIS[4]

(adapted from the Danish Medicines Agency)[164]

[1] Must always be justified based on the trial-specific risk assessment.

[2] Generally not possible, unless robust justification provided.

[3] IMP domains only. SUSAR reporting does not arise in non-IMP domains, as a SUSAR by definition concerns an investigational medicinal product.

[4] Submitted via CTIS for all domains. For non-IMP domains, the content follows the domain-specific safety reporting plan described in the DSA.

10.3.2.3 Outcome and safety registration

Safety outcomes will be reported by the investigators to the domain lead(s) in accordance with the risk assessment outlined above, unless otherwise stated in the DSAs. To ensure unbiased registration, SARs presumed to be causally related to the interventions will be prespecified and reported for all intervention arms, unless specified otherwise in the DSAs. Potential SUSARs will be reported to the domain lead(s) (or delegate(s)) within 24 hours. For fatal and/or life-threatening SUSARs, the domain lead will inform all participating sites in the domain and the platform sponsor without delay; the platform sponsor will report to EudraVigilance within seven (7) days of becoming aware, with any relevant follow-up information reported without undue delay. For all other SUSARs, the platform sponsor will report to EudraVigilance within fifteen (15) days of becoming aware. The operational reporting procedure, including any service provider used by the platform sponsor, is documented in the trial master file.

The annual safety report covers all domains and includes, for each domain, a description of the plan for registration and reporting of safety outcomes and a pooled summary of prespecified safety outcomes across all sites; where arm-level summaries are required, these are prepared by the independent statistician (Section 9.4). The report will follow the template required by the competent authorities, which for trials conducted only in Denmark is the template of the Danish GCP units and for multinational trials the Heads of Medicines Agencies – Clinical Trials Coordination Group template, and will be submitted via CTIS. For domains that do not involve IMPs (non-IMP domains), the report will summarize the safety data specified in the domain-specific safety reporting plan defined in the DSA.

10.4 Independent Data and Safety Monitoring Committees

An IDSMC will be established for each domain. Domains with adaptive features, blinding, or risk level 2 classification are reviewed at intervals specified in the DSA; other domains are reviewed at least annually. Each IDSMC is multidisciplinary, chaired by a clinical trialist, and includes a biostatistician and a clinician with expertise in the domain. Members must have no relevant conflicts of interest; trial investigators, the platform sponsor, domain leads, staff involved in the conduct of APT-KIDNEY, and individuals with regulatory responsibilities for the domain interventions cannot be members. Scope, membership, and meeting cadence are specified in the DSA and the IDSMC charter.

Each IDSMC will schedule and plan monitoring and meetings for its domain as appropriate. IDSMCs will have access to strictly confidential unblinded data on benefit and harm of interventions, and at minimum provide an annual written recommendation to the Platform- and Domain Steering Committees regarding the continued conduct of the domain. Platform- and Domain steering committees will be responsible for evaluating, accepting or rejecting IDSMC recommendations, and implementing modification to the core and domain-specific protocols and trial conduct based on the IDSMC recommendation, without prejudice to the responsibilities of the platform sponsor (Section 3.1). Platform and domain-specific steering committees, and IDSMCs may schedule supplementary monitoring and data analyses as appropriate.

10.4.1 Adaptive analyses and methods

For domains using adaptive features, the IDSMC receives the prespecified decision rules, a simulated example dataset, and the analysis code before the first participant is enrolled. Interim analyses are produced by the independent statistical group defined in the DSA (Section 9.4), and the IDSMC may request access to data and code for verification. The adaptive framework builds on the INCEPT platform trial (Section 7.1).[132]

10.4.2 IDSMC sessions and recommendations

IDSMC meetings comprise an open session, which domain leads and steering committee members may attend, and a closed session restricted to the IDSMC and a designated unblinded statistician. Comparative data by arm are presented only in closed reports, which are shared only with the IDSMC until the final analysis of the domain is complete. The IDSMC may recommend pausing or stopping a domain or arm if observed differences in safety outcomes are concerning, even in the absence of prespecified rules. The content and timing of open and closed reports, and the procedures for recommendations, are specified in the IDSMC charter.

10.5 Data confidentiality and sharing

Trial data are held in the platform eCRF, with access to full domain datasets restricted to the domain lead and designated methodological and statistical staff responsible for data cleaning, verification, and analyses; sites have access only to their own data. Staff with dataset access do not contact participants or influence enrollment, allocation, or outcome assessment. Interim comparative results are confidential to the IDSMC and the independent statistical group until the final analysis of the domain (Section 10.4.2).

The broader trial organization including steering committees, investigators, clinical and research staff, participants, and families will be notified only if a domain or arm is stopped, with a brief reason provided. Detailed information will be withheld until completion of follow-up for the primary and guiding outcomes. Disclosure practices for blinded domains will be specified in the DSAs. Recommendations and decisions of the IDSMC and platform and domain steering committees will be communicated in writing. Copenhagen University Hospital Rigshospitalet, as the platform sponsor's institution, holds intellectual property and stewardship of the combined platform dataset on behalf of the Platform Steering Committee; participating sites retain ownership of their site-level source data. Data sharing will follow applicable data protection law and a data-sharing policy maintained by the Platform Steering Committee; external access requires approval by the relevant Domain Steering Committee and, for pooled or cross-domain data, the Platform Steering Committee. Participants will be informed of potential data sharing in the participant information, and analysis code may be shared on request with approval from the domain steering committee.

10.6 Trial conduct integrity

In open-label domains, bias is limited by objective, clinically meaningful endpoints, standardized outcome assessment, and blinded adjudication where prespecified. Prespecified stopping rules are applied as specified in the DSA, and the

IDSMC may also recommend stopping for other reasons, such as external evidence or safety concerns. Confidentiality of interim results follows Section 10.5.

11 Organizational Framework

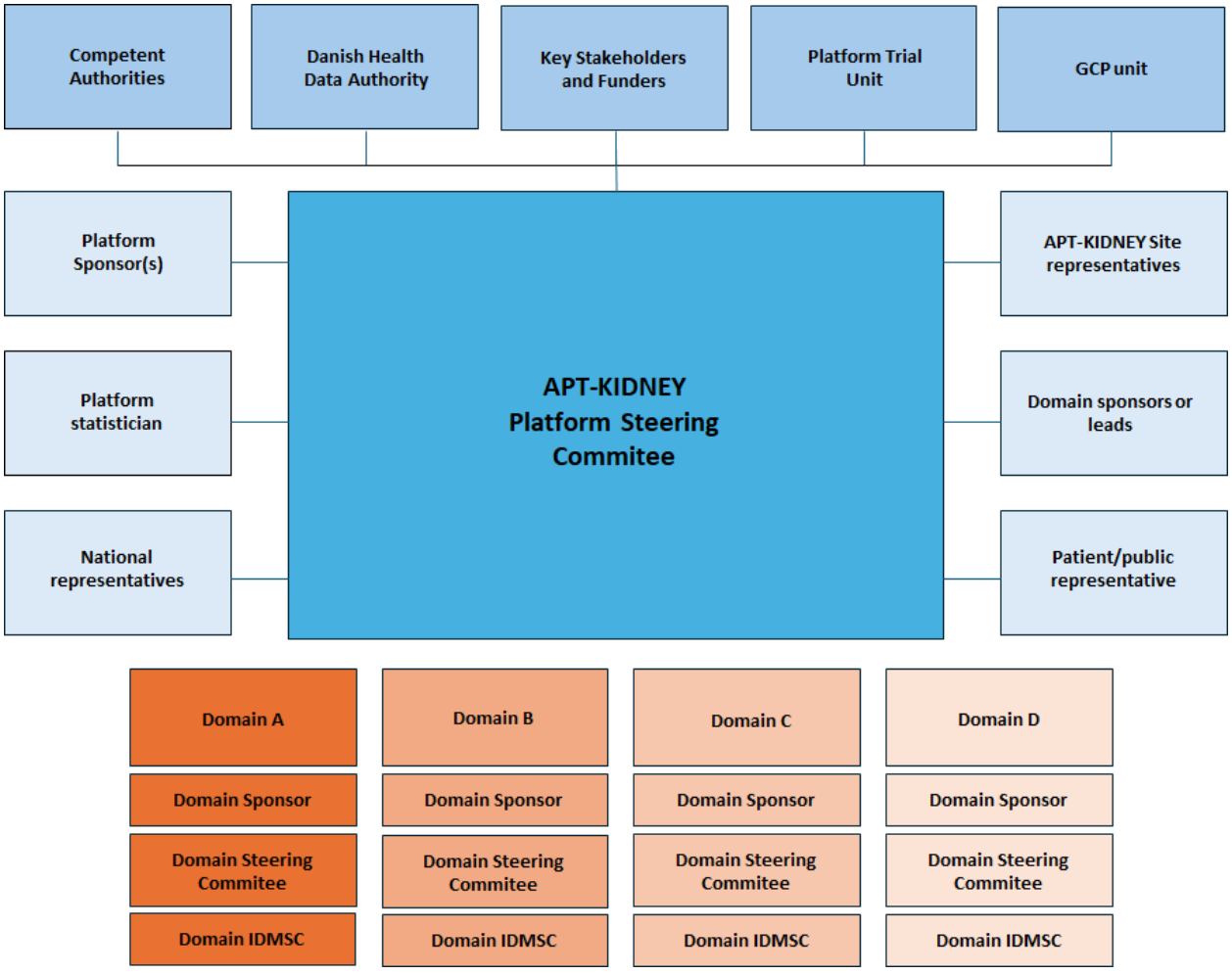
11.1 Governance

APT-KIDNEY is a multi-site national platform trial with planned expansion to compatible sites within and beyond the EU. A founding principle of APT-KIDNEY is that all participating sites contribute as equal partners, collectively shaping and owning the direction of the platform and its core protocol. Platform-level decisions are made collectively through the Platform Steering Committee. The Committee is chaired by the Coordinating Investigator, appointed by the platform sponsor, who convenes the Committee, sets the agenda, and is accountable for execution of its decisions. Decisions of the Platform Steering Committee are without prejudice to the responsibilities of the platform sponsor under Regulation (EU) No 536/2014 (Section 3.1).

Voting membership of the Platform Steering Committee comprises one representative from each active participating site, the Coordinating Investigator, and one patient/public representative; domain leads and national representatives of non-Danish participating countries attend in a non-voting advisory capacity. Voting rights, observer status, quorum, and related procedures are specified in the Platform Governance Charter.

Each domain operates under a domain lead, with a Domain Steering Committee where established and an IDSMC independent of the sponsor and trial operations. Each participating site appoints a Principal Investigator and research team and may contribute to one or more domains. Principal Investigators may concomitantly serve as site representatives on the Platform Steering Committee.

An overview of the platform framework is provided below:



A Platform Governance Charter, maintained separately, specifies operational governance procedures, including the chair's role and succession, voting procedures and quorum, representation, financial responsibilities, and budget oversight, and is reviewed annually by the Platform Steering Committee.

Annual platform reporting, including the summary of protocol deviations (Section 7.3), the cross-domain safety review (Section 10.3.2.1), and review of the Platform Governance Charter, is consolidated in a single annual platform report prepared alongside the annual safety report.

Lifecycle and version control. Domains and the DSAs may be created, approved, activated, amended, and retired throughout the platform lifecycle under Platform Steering Committee governance. Activation requires Platform Steering Committee and regulatory approvals. A central register will list current and historical versions of the core and domain-specific protocols including effective dates and status.

Collaboration. APT-KIDNEY will formalize a research collaboration among participating and contributing sites in Denmark and abroad.

11.2 Funders and roles

The APT-KIDNEY platform is currently funded by DKK 962,000 in internal research funds from Copenhagen University Hospital Rigshospitalet.

APT-KIDNEY will seek additional support to sustain the platform and to resource specific domains. Platform infrastructure (core protocol governance, coordinating and methodological centers, central eCRF and data management, and platform-level monitoring) is funded centrally through institutional support and competitive grants. Individual domains are responsible for securing their own funding, including site compensation as specified in §11.4.1. A platform-overhead model addressing whether and how domains contribute to platform infrastructure costs will be defined in the Platform Governance Charter (§11.1). All domains aim to be investigator-initiated; investigators must have no financial interest in study outcomes; funders will play no part in study design, trial operations, data access or analysis, interpretation of results, or decisions regarding submission or publication; and all support received will be transparently disclosed.

11.3 Conflicts of interest

Declarations of interests from the platform sponsor, protocol contributors, and members of the Platform and Domain Steering Committees are collected before appointment, updated when circumstances change, and filed in the trial master file; a summary is published on the APT-KIDNEY website. Any conflicts arising during the trial will be managed by the Platform Steering Committee and, if necessary, the platform sponsor, which may include restricting roles or replacing the individuals involved.

11.4 Compensation and insurance

11.4.1 Site compensation

Each domain will provide a financial plan outlining site compensation. Compensation models should account for participants enrolled across multiple domains and should permit ongoing updates pending approval by the APT-KIDNEY Platform Steering Committee and relevant institutional review including financial and legal oversight.

11.4.2 Participant compensation and insurance

Compensation for trial-related injury is provided in accordance with Article 76 of Regulation (EU) No 536/2014. All participants in Denmark will be covered in accordance with Danish law as determined in the *Lov om klage- og erstatningsadgang inden for sundhedsvæsenet*.[165] Activation of trial sites in non-Danish countries will be contingent on confirmation and documentation of compliant compensation or insurance arrangements in the relevant national or local appendix prior to enrollment of the first participant at that site.

12 Publication and dissemination

12.1 Dissemination

Domain results will be submitted to international peer-reviewed medical journals regardless of outcome. The APT-KIDNEY website will host publication lists and plain-language summaries. Key findings may also be communicated to relevant media.

12.2 Authorship and contributorship

12.2.1 Standards

Authorship follows ICMJE criteria. All authors must approve the final manuscripts and accept accountability.

12.2.2 Manuscript types

- Domain manuscripts: led by a domain writing committee drawn from that domain investigators; platform-level methods/statistics contributors included if they meet ICMJE criteria.
- Platform/methods manuscripts: led by a platform writing committee appointed by the platform steering committee

12.2.3 Committees

Membership on the platform and/or domain steering committees does not confer authorship per se. Members who make qualifying contributions (i.e. design, analysis, substantial drafting/revision) will be awarded co-authorship, others will be acknowledged by name and role. IDSMC members are generally acknowledged only (to preserve independence) unless their contribution meets authorship criteria and does not compromise oversight.

12.2.4 Group authorship

Publications may use group authorship ("APT-KIDNEY Investigators") with a public roster and contributorship appendix.

12.2.5 Order/guarantor

First/last/corresponding author(s) and guarantor(s) are designated by the relevant writing committee using pre-specified, transparent criteria (e.g., intellectual contribution, enrollment, data quality).

12.2.6 Review

Drafts undergo platform steering committee statistical and methodology review for accuracy; funders have no publication approval rights. Preprints are permitted.

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Appendix I. SPIRIT reporting checklist

Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement

Reference: Chan A-W, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomized trials. BMJ 2025;389:e081477.

The table below maps each SPIRIT 2025 checklist item to the corresponding section(s) of the APT-KIDNEY core protocol (version 1.22, 21-10-2026). Items addressed primarily in domain-specific appendices (DSAs) are noted in the Comment column. The SPIRIT 2025 participant timeline figure will be provided per domain in the DSAs.

No.	SPIRIT 2025 checklist item	Protocol section(s)	Comment
Administrative information			
1a	Title stating trial design, population, and interventions, with identification as a protocol	Title page	States adaptive platform trial design, advanced kidney disease population, multi-domain interventions; identified as protocol with version details.
1b	Structured summary including WHO Trial Registration Data Set items	1.1 Synopsis	Background, objectives, design, population, outcomes, methods, perspectives; registration numbers on title page
2	Protocol version and date; list of changes	Title page; Summary of changes	Version denoted; change-log table provided
3a	Names, affiliations, and roles of protocol contributors	3.4 Protocol contributors	Developed by members of the Platform Steering Committee; individual contributors and roles recorded in the trial master file
3b	Name and contact information for trial sponsor	3.1 Sponsor	Platform sponsor with contact details; domain lead model described
3c	Role of sponsor and funders in design, conduct, analysis, and reporting	11.2 Funders and roles	Funders excluded from design, conduct, analysis, interpretation, and publication
3d	Composition, roles, responsibilities of coordinating site, steering committee, IDSMC, data management	3.2 Coord. centers; 10.4 IDSMC; 11.1 Implementation	Coordinating center, IDSMCs, steering committees described; advisory structures in the governance charter; independence requirements specified
Open science			
4	Trial registry name, identifying number, registration date	Title page	EU CT 2026-527443-17-00; ClinicalTrials.gov NCT07595952; WHO UTN: U1111-1331-7534

5	Where protocol and statistical analysis plan can be accessed	4.1 Core protocol; 9.1 Overall principles	Protocol on APT-KIDNEY website; DSAs include domain-specific SAPs
6	Data sharing plan	10.5 Data confidentiality and sharing	Data sharing according to the data-sharing policy maintained by the Platform Steering Committee and applicable data protection law
7a	Sources of funding and other support	11.2 Funders and roles	Rigshospitalet internal funds (DKK 962,000) for the platform; domains to be funded by independent grants; all disclosed
7b	Conflicts of interest for PIs and steering committee members	11.3 Conflicts of interest	Declarations held in the trial master file and published on the website; management procedures specified
8	Dissemination policy	12.1 Dissemination; 12.2 Authorship	Domain results summaries in CTIS within one year of each primary analysis; peer-reviewed publication regardless of outcome; plain-language summaries; ICMJE criteria
Introduction			
9a	Scientific background and rationale including summary of relevant studies	6.1 Evidence in advanced CKD; 6.4 Rationale	CKD/ESKD epidemiology, HD, PD, conservative care evidence gaps; platform trial rationale
9b	Explanation for choice of comparator	8.3.2 Interventions; 6.3 Low-intervention trials	Low-intervention comparisons; comparator strategy per domain in DSAs
10	Specific objectives related to benefits and harms	5.1 Aims and objectives	Adaptive platform for interventions in eGFR <30, ESKD on dialysis or conservative care, or kidney allograft recipients
Methods: Patient and public involvement, trial design			
11	Patient or public involvement in design, conduct, and reporting	3.2 Patient and public involvement	Patient review of materials and patient partners encouraged; PPI in DSAs; patient representative on steering committee
12	Trial design: type, allocation ratio, framework	8.1 General design; 8.6.1 Randomization	Pragmatic, randomized, embedded, multifactorial adaptive platform; open-label or blinded; balanced allocation default; Bayesian or frequentist
Methods: Participants, interventions, and outcomes			
13	Trial setting and locations	8.4.1 Trial sites; 3.3 Investigators	Nephrology departments and dialysis satellites, Denmark and other countries; listed in CTIS and on website
14a	Eligibility criteria for participants	8.2.1 Inclusion; 8.2.2 Exclusion	eGFR <30 for ≥3 months, ESKD on dialysis or conservative kidney management, or kidney allograft recipient; age ≥18; eligible for ≥1 domain.
14b	Eligibility criteria for	8.4.1 Trial sites;	Site activation checklist (approvals, insurance, GCP, PI, eCRF,

	sites and individuals delivering interventions	8.4.2 Personnel	IMP supply); staff eligible unless DSA-restricted
15a	Intervention and comparator with replication details	8.3.2 Interventions	Domains detail arms, comparisons, IMP supply model; designed exclusively for low-intervention comparisons; DSA specifies all details
15b	Criteria for discontinuing or modifying allocated intervention	8.8.2 Discontinuation and withdrawal	Participant withdrawal at any time; investigator discontinuation for safety; domain vs. platform scope distinguished
15c	Strategies to improve adherence; monitoring procedures	8.7.5 Data quality and monitoring	Risk-based monitoring; central statistical monitoring; risk-directed SDV; adherence per DSA
15d	Concomitant care permitted or prohibited	8.3.2 Interventions	Deferred to DSAs; co-enrollment rules (Section 8.3.1) address inter-domain interactions
16	Primary and secondary outcomes with measurement details	8.9.1 Core outcomes; 9.2.2 Estimands	Core: all-cause mortality, MACE, EQ-5D-5L, kidney disease progression; 4-monthly follow-up; estimands per ICH E9(R1) in DSAs
17	How harms are defined and assessed	10.3.1 AE definitions; 10.3.2 Reporting	ICH E2A definitions; 3-tier risk-proportionate framework; common SAEs in Appendix III
18	Participant timeline (SPIRIT figure recommended)	8.5 Consent; 8.8.1 Follow-up; 8.9.1.1 Outcomes	Screening, consent, and randomization without undue delay; 4-monthly windows. SPIRIT figure provided per domain in DSAs
19	Sample size determination	9.4 Adaptive analyses and simulation; 10.2 Trial risk assessment	Domain-specific; adaptive domains: simulation; fixed domains: conventional. Specified in DSAs
20	Recruitment strategies	8.5.1 Screening; 10.2 Trial risk assessment	Screening at participating nephrology departments; continuous reassessment; broad eligibility
Methods: Assignment of interventions			
21a	Who generates allocation sequence and method	8.6.1 Randomization	Electronic randomizer; accessible only to designated statisticians and system administrators
21b	Type of randomization and stratification	8.6.1 Randomization; 9.3 Schemes	Fixed (permuted blocks) or RAR; stratification on site + DSA-specified factors; RAR burn-in, softening, bounds
22	Allocation concealment	8.6.2.1 Allocation concealment	Centralized electronic system; block sizes/ratios/stratification concealed; RAR updates restricted

	mechanism		in open-label domains
23	Implementation: access to allocation sequence	8.6.1; 8.6.2.1	Algorithm restricted to statisticians/administrators; site staff excluded from prediction-enabling information
24a	Who will be blinded after assignment	8.6.2.2 Blinding	Domain-specific; statisticians and IDSMCs always unblinded; outcome assessors blinded where applicable
24b	How blinding will be achieved	8.6.2.2 Blinding	Per DSA; role separation, restricted access, standardized scripts; digital self-completion for PROMs in open-label domains
24c	Circumstances for unblinding	8.6.2.2 Blinding	Emergency procedures per DSA with documentation and integrity safeguards
Methods: Data collection, management, and analysis			
25a	Data collection plans and instruments	8.7.1-8.7.3 Data; 8.7.4 Variables	Hybrid eCRF; EQ-5D-5L; Rockwood frailty scale; Danish registers; EPR integration; validation rules
25b	Participant retention and complete follow-up	8.8.1 Follow-up; 8.8.2 Discontinuation	Register linkage; routine care follow-up; permission for ongoing data collection if intervention discontinued; ITT
26	Data management: entry, coding, security, storage	8.7.1 General; 8.7.5 Quality	GCP-validated regional eCRF hosting; validation rules; duplicate entry; standardization; 25-year archiving after the end of the trial
27a	Statistical methods for primary/secondary outcomes	9.2 Framework; 9.2.3 Models	Bayesian or frequentist per domain; regression/survival models; covariate adjustment; priors; CIs/CrIs
27b	Analysis populations	9.2.1 Populations	Primary: ITT; per-protocol and as-treated as prespecified sensitivity analyses per DSA
27c	Missing data handling	9.6 Missing data	Likelihood-based under MAR; sensitivity with departures from MAR; harmonized follow-up and register linkage minimize missingness
27d	Additional analyses (subgroup, sensitivity)	9.4 Adaptive; 9.6 Sensitivity	Subgroups exploratory unless multiplicity-controlled; mandatory open-label PROM sensitivity analyses
Methods: Monitoring			
28a	DMC composition, role, independence	10.4 IDSMC	Domain-specific IDSMCs; multidisciplinary; independent; COI forms; charter referenced
28b	Interim analyses and stopping guidelines	9.4 Adaptive rules; 10.4.2 Sessions	Prespecified in DSAs; information thresholds; burn-in; binding rules; IDSMC may stop for non-statistical reasons

29	Trial monitoring frequency and procedures	8.7.5 Monitoring	Risk-based; central statistical monitoring; risk-directed SDV; platform + domain monitoring plans; GCP unit
Ethics			
30	Research ethics approval plans	7.2 Regulatory approval	All domains via CTIS under EU CTR 536/2014
31	Plans for communicating protocol modifications	7.2; 11.1 Implementation	Substantial modifications via CTIS; version control register; DSA lifecycle governance
32a	Who will obtain informed consent and how	8.5.2 Informed consent	Trained investigators; modular materials; oral information in person or by live video where approved; 24-hour deliberation minimum; written consent before procedures, digital or on paper
32b	Additional consent for ancillary data/specimen use	8.7.6 Biological samples; 8.7.7 Data protection	No sample storage unless specified in a DSA; data processing purposes and rights communicated at consent
33	Confidentiality of personal information	8.7.7 Data protection; 10.5 Confidentiality	GDPR-compliant; pseudonymization; DPIA; controllership model; Art. 28 agreements; rights under Art. 13-22
34	Ancillary and post-trial care; compensation for harm	11.4 Compensation and insurance	Danish law coverage; non-Danish insurance confirmed before activation; routine nephrology follow-up continues

Abbreviations: CKD, chronic kidney disease; COI, conflict of interest; CrI, credible interval; CTR, Clinical Trials Regulation; CTIS, Clinical Trials Information System; DSA, domain-specific appendix; eCRF, electronic case report form; EPR, electronic patient record; ESKD, end-stage kidney disease; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GCP, good clinical practice; GDPR, General Data Protection Regulation; HD, haemodialysis; HRQOL, health-related quality of life; ICH, International Council for Harmonisation; IDSMC, independent data and safety monitoring committee; IMP, investigational medicinal product; ITT, intention-to-treat; MACE, major adverse cardiovascular event; MAR, missing at random; PD, peritoneal dialysis; PI, principal investigator; PPI, patient and public involvement; PROM, patient-reported outcome measure; RAR, response-adaptive randomization; SAP, statistical analysis plan; SDV, source data verification.

Appendix II. Core variable specification

This appendix specifies the type, coding, units, source, and timing of the core variables listed in Section 8.7.4. Domain-specific variables are defined in the relevant domain-specific appendices (DSAs).

Source — **R**: register / electronic patient record (EPR) linkage where available; **M**: manual eCRF entry; **R/M**: linkage preferred, manual entry where linkage is unavailable. Country-specific register sources are identified in the relevant national appendix.

Screening variables

Variable	Type / coding	Source	Notes
Participant identifier	Alphanumeric	M	Platform-level ID
Trial site	Site code	M	
Eligibility confirmation	Inclusion / exclusion criteria met (Yes | No, per criterion)	M	
Informed consent	Date (DD/MMM/YYYY)	M	
Randomization date	Date (DD/MMM/YYYY)	M	Domain-specific where applicable

Screening variables to be recorded prior to randomization date. Variables liable to change between domain inclusions are re-recorded against the relevant domain randomization date.

Baseline variables

Variable	Type / coding	Unit	Source	Notes
Date of birth	Date (DD/MMM/YYYY)	—	R/M	
Sex	Male | Female	—	R/M	
Weight	Numeric	kg	R/M	
Height	Numeric	cm	R/M	
CKD category	CKD not on KRT | Hemodialysis | Peritoneal dialysis | CKM | Kidney transplant recipient	—	R/M	Incl. date of dialysis initiation or transplantation
eGFR	Numeric	mL/min/1.73m^2	R/M	Most recent; if not on dialysis
UACR	Numeric	mg/g or mg/mmol	R/M	Most recent; if not on dialysis
Primary kidney disease	Diabetes | Hypertension | Glomerulonephritis | Hereditary | Other | Unknown	—	R/M	
Blood pressure	Systolic / diastolic	mmHg	R/M	
Hypertension	Yes | No	—	R/M	

Variable	Type / coding	Unit	Source	Notes
Diabetes	Yes | No	—	R/M	
Ischemic heart disease	Yes | No	—	R/M	
Heart failure	Yes | No; LVEF % if applicable	—	R/M	
Thromboembolic disease incl. stroke / TIA	Yes | No	—	R/M	
Peripheral vascular disease	Yes | No	—	R/M	
Prior major limb amputation	Yes | No	—	R/M	
Clinical Frailty Scale	Rockwood CFS v2.0 (1–9)	—	M	Ref. [143,144]
HRQOL	EQ-5D-5L incl. EQ-VAS	—	M	Ref. [145,146]

Baseline variables will be recorded as the most recent value prior to or on the randomization date.

Baseline laboratory panel

Analyte	Unit	Source	Notes
Hemoglobin	mmol/L	R	
Creatinine	µmol/L	R	
Urea	mmol/L	R	
Potassium	mmol/L	R	
Sodium	mmol/L	R	
Bicarbonate or total-CO_2	mmol/L	R	
Albumin	g/L	R	
HbA1c	mmol/mol	R	If diabetes
Ionized calcium	mmol/L	R	
Phosphate	mmol/L	R	
Parathyroid hormone	pmol/L	R	
Alkaline phosphatase	U/L	R	

Baseline laboratory values are obtained by linkage to the Clinical Laboratory Information Register (or national equivalent) as the most recent value prior to or on the randomization date. Manual eCRF entry is not required unless specified in a DSA.

Baseline medications

Drug class	Source	Notes
Antihypertensives	R/M	
Antithrombotics / anticoagulants	R/M	
Antidiabetics	R/M	
Diuretics	R/M	

Drug class	Source	Notes
Immunosuppressive agents	R/M	

Baseline medication is recorded by drug class (yes/no) at randomization; individual drug and dose are recorded only where specified in a DSA.

Resource-use variables

Variable	Source	Notes
Hospitalizations	R	Incl. admission and discharge dates, diagnoses, department and hospital.
Dialysis sessions	R	Incl. modality, dates, department, and hospital
In-hospital procedures	R	Incl. procedure codes, and dates.
Outpatient contacts	R	Incl. dates, diagnoses, department, and hospital.
Prescription medication	R	Incl. dates, ATC code, and dose, where available.

For platform-level, health economic evaluation. Resource-use variables to be recorded during follow-up, where available.

Other follow-up variables

Variable	Source	Notes
Laboratory panel	R	Incl. NPU codes, values, units, dates, and reference intervals
Hospital-administered medication	R	Incl. ATC code, dose, and administration
Pathology results	R	Incl. SNOMED codes and dates
Causes of death	R	Incl. date of death and diagnoses

Other follow-up variables are obtained by linkage to administrative registers during follow-up, where approved, in support of verification of outcomes and cross-domain resource-use analyses. Outcome and safety variables are registered in the eCRF by trained trial staff (Section 8.7.1).

Abbreviations

ATC, Anatomical Therapeutic Chemical classification; CFS, Clinical Frailty Scale; CKD, chronic kidney disease; CKM, conservative kidney management; eCRF, electronic case report form; EPR, electronic patient record; HRQOL, health-related quality of life; KRT, kidney replacement therapy; LVEF, left ventricular ejection fraction; NPU, Nomenclature for Properties and Units; PROM, patient-reported outcome measure; SNOMED, Systematized Nomenclature of Medicine; TIA, transient ischemic attack; UACR, urine albumin-to-creatinine ratio.

Appendix III: Common serious adverse events in patients with advanced kidney disease

Purpose

This appendix provides a non-exhaustive reference list of serious adverse events (SAEs) commonly observed in patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2) and ESKD on dialysis or conservative care. The list is intended to assist investigators, site staff, and members of the IDSMCs in distinguishing expected disease-related events from events that may be plausibly related to a trial intervention.

Context

Advanced kidney disease is characterized by a high comorbidity burden and frequent hospitalizations. In ESKD populations, annual hospitalization rates exceed one admission per patient-year, and cardiovascular disease and infection together account for approximately 70–80% of all-cause mortality. Patients on hemodialysis are additionally exposed to procedure-related hemodynamic stress and vascular access complications, while peritoneal dialysis patients face catheter-related infections and peritonitis. Many events listed below will occur at high background rates regardless of any intervention being studied.

Use within APT-KIDNEY

APT-KIDNEY employs a risk-proportionate safety framework (Section 10.3.2). For low-risk (level 1) domains, SAE recording may be limited to protocol-defined events based on documented risk analyses. For intermediate-risk (level 2) domains, more comprehensive recording and reporting obligations apply (see Section 10.3.2.2). DSAs will specify which SAEs from the list below (and any additional domain-specific events) require active capture, and which warrant expedited reporting. This appendix does not replace the domain-specific risk assessment but serves as a common reference framework across all domains.

The table is organized by organ system. For each SAE, the typical clinical context in the target population and its relevance to APT-KIDNEY safety assessment are provided. Investigators should assess causality on a case-by-case basis using their clinical judgement and the criteria specified in the relevant DSA.

References: Go AS et al. N Engl J Med 2004;351:1296–1305; Sarnak MJ et al. J Am Coll Cardiol 2019;74:1823–1838; KDIGO 2024 Clinical Practice Guideline for CKD. Kidney Int 2024;105(4S):S117–S314; USRDS 2017 Annual Data Report. Am J Kidney Dis 2018;71(3 Suppl 1):A7.

Serious adverse event	Typical clinical context	Relevance to APT-KIDNEY safety assessment
Cardiovascular		
Acute myocardial infarction (STEMI/NSTEMI)	High CV burden; accelerated atherosclerosis; coronary calcification; dialysis-related haemodynamic stress	Core outcome (MACE component); expected background rate high in ESKD
Acute heart failure / pulmonary oedema	Volume overload between dialysis sessions; diastolic dysfunction; uraemic cardiomyopathy	Common cause of hospitalization; may be influenced by dialysis prescription domains
Ischaemic stroke	Atrial fibrillation; vascular calcification; anticoagulation challenges in CKD	Core outcome (MACE component); atrial fibrillation management domains may affect rates
Haemorrhagic stroke	Uraemic platelet dysfunction; anticoagulation; hypertension	Distinguish from ischaemic stroke in adjudication; anticoagulation domains relevant
Sudden cardiac death / cardiac arrest	QT prolongation; electrolyte shifts (K+, Ca2+); LVH; myocardial fibrosis	High background incidence on haemodialysis; electrolyte management relevant
Arrhythmias requiring hospitalization	Hyperkalaemia; rapid electrolyte shifts during dialysis; AF, VT	May be influenced by dialysate composition or dialysis schedule domains
Peripheral arterial events (critical limb ischaemia, amputation)	Diabetes; medial arterial calcification; peripheral vascular disease	Expected in high-risk subpopulations; document for safety monitoring

Venous thromboembolism (DVT / PE)	Immobility; central venous catheters; nephrotic-range proteinuria	Access-related VTE particularly relevant in dialysis domains
Infections		
Bacteraemia / sepsis	Central venous catheters; uraemic immunosuppression; vascular access infections	Leading cause of non-CV mortality in dialysis; access-related infections common
Vascular access infection (AVF/AVG/catheter)	Biofilm; skin colonization; repeated needling	Directly relevant to dialysis modality and access management domains
Peritonitis (PD patients)	Touch contamination; exit-site infections; biofilm on PD catheter	Key safety outcome in peritoneal dialysis domains; defined per ISPD criteria
Pneumonia	Impaired immune function; fluid overload; elderly population	Common cause of hospitalization; seasonal variation expected
Urinary tract infection / urosepsis	Residual urine; urinary tract abnormalities; immunocompromise	More common in non-dialysis CKD and PD patients with residual function
COVID-19 or other respiratory viral infection requiring hospitalization	Impaired vaccine response; immunosenescence; congregate dialysis settings	Background rates fluctuate seasonally; monitor for temporal trends
Renal and/or metabolic		
Acute kidney injury (on CKD) requiring emergency dialysis initiation	Nephrotoxins; contrast; infection; hypovolaemia	Expected progression event; timing of dialysis initiation relevant to conservative care domains
Severe hyperkalaemia (K+ >6.5 mmol/L) requiring hospitalization	Missed dialysis; dietary indiscretion; RAAS inhibitors; metabolic acidosis	Common in advanced CKD/ESKD; may be influenced by dialysate K+ or medication domains
Severe metabolic acidosis requiring hospitalization	Progressive CKD; inadequate dialysis; intercurrent illness	May reflect dialysis adequacy; relevant to dialysis prescription domains
Symptomatic fluid overload requiring hospitalization	Interdialytic weight gain; non-adherence; inadequate ultrafiltration	Frequent in haemodialysis; influenced by dialysis schedule and prescription
Severe hypoglycaemia (in diabetic patients)	Reduced renal gluconeogenesis; reduced insulin clearance; malnutrition	Background event in diabetic ESKD population; medication adjustment domains
Severe hypocalcaemia or hypercalcaemia	CKD-MBD; vitamin D disorders; calcimimetics; phosphate binders	Relevant to mineral bone disease management; dialysate calcium domains

Dialysis access and procedure-related		
Vascular access thrombosis (AVF/AVG)	Stenosis; hypercoagulability; low flow	Expected complication; access surveillance may differ between domains
Vascular access haemorrhage	Aneurysm; repeated cannulation; anticoagulation	May require hospitalization or surgical intervention
Intradialytic hypotension requiring hospitalization	Excessive ultrafiltration; autonomic dysfunction; cardiac dysfunction	Directly relevant to dialysis schedule and ultrafiltration rate domains
PD catheter malfunction or migration requiring intervention	Omental wrapping; fibrin obstruction; catheter displacement	Expected in PD population; may require surgical revision
PD-related hydrothorax	Pleuroperitoneal communication; increased intraperitoneal pressure	Uncommon but serious; may require PD cessation and modality change
Air embolism	Rare dialysis circuit complication	Very rare; immediate reporting required
Gastrointestinal		
Upper or lower GI haemorrhage	Uraemic gastritis; AV malformations; anticoagulation; NSAID use	Common in CKD/ESKD; anticoagulation domains directly relevant
Mesenteric ischaemia	Atherosclerosis; intradialytic hypotension; AF with embolism	Rare but high mortality; dialysis haemodynamic stress may contribute
Acute pancreatitis	Hypercalcaemia; medications; hypertriglyceridaemia	Background event; document for safety monitoring
Intestinal obstruction or perforation	Constipation (phosphate binders, fluid restriction); PD-related adhesions	Phosphate binder and PD domains relevant
Hematological		
Severe anaemia requiring transfusion (Hb <70 g/L)	EPO resistance; iron deficiency; chronic inflammation; blood loss	Expected in ESKD; ESA management domains may influence rates
Major bleeding event (non-GI)	Uraemic platelet dysfunction; anticoagulation; invasive procedures	Anticoagulation domains directly relevant; document site and severity
Musculoskeletal		
Fracture (vertebral, hip, or other)	CKD-mineral bone disorder; secondary hyperparathyroidism; frailty; falls	High background rate; mineral bone disease interventions may modify risk
Calciphylaxis	Hyperphosphataemia; vitamin K deficiency; warfarin use; obesity	Rare but severe; relevant to anticoagulation and mineral metabolism domains

Neurological		
Seizures	Uraemic encephalopathy; dialysis disequilibrium; electrolyte disturbance	Background event; may occur during or after dialysis initiation
Falls with injury requiring hospitalization	Frailty; postural hypotension; intradialytic hypotension; polypharmacy	Expected in elderly CKD/ESKD population; dialysis schedule domains relevant
Malignancy		
New cancer diagnosis	Immunosenescence; uraemia-associated immune dysfunction; long-term dialysis exposure	Background event; expected given age and comorbidity profile of population
Cancer-related hospitalization or death	Progression of pre-existing or new malignancy	Document for comprehensive safety reporting
Other		
Surgical procedures under general anaesthesia	Vascular access revision; transplant surgery; other elective/emergency surgery	Common in ESKD population; perioperative risk elevated
Death from any cause	Multifactorial: CV, infection, malignancy, withdrawal from dialysis	Core outcome; all deaths documented regardless of perceived causality

Abbreviations: AF, atrial fibrillation; AV, arteriovenous; AVF, arteriovenous fistula; AVG, arteriovenous graft; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral and bone disorder; CV, cardiovascular; DVT, deep vein thrombosis; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; ESKD, end-stage kidney disease; GI, gastrointestinal; Hb, haemoglobin; ISPD, International Society for Peritoneal Dialysis; K+, potassium; LVH, left ventricular hypertrophy; MACE, major adverse cardiovascular event; NSTEMI, non-ST-elevation myocardial infarction; PD, peritoneal dialysis; PE, pulmonary embolism; RAAS, renin–angiotensin–aldosterone system; STEMI, ST-elevation myocardial infarction; VT, ventricular tachycardia.

Note: This list is not exhaustive. Domain-specific appendices may define additional SAEs relevant to the specific interventions under study. All SAE definitions follow ICH E2A criteria (Section 10.3.1 of the core protocol).