APT-KIDNEY



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

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Protocol Summary

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1 Background and rationale

1.1 Advanced kidney disease and the evidence gap

Advanced kidney disease is a severe chronic condition associated with substantial morbidity, excess mortality, and reduced quality of life. The global prevalence of chronic kidney disease (CKD) is 10–15%, and CKD is predicted to become the fifth leading cause of death worldwide by 2040. Advanced CKD carries the poorest prognosis, with an annual mortality exceeding 20% in patients with end-stage kidney disease (ESKD) on dialysis, and confers markedly increased risks of cardiovascular disease, infection, and major bleeding. In Denmark, advanced kidney disease as defined by an eGFR < 30 mL/min/1.73 m^2, maintenance dialysis, or kidney transplantation affects an estimated 18,000–25,000 adults, including > 5,000 patients on dialysis or living with a functioning kidney transplant.

Despite this burden, the evidence base remains strikingly weak. Trials in nephrology have historically been small, frequently inconclusive, and often terminated early because of low recruitment and event rates. Patients with advanced CKD have been systematically excluded from larger cardiovascular trials: across more than 1,000 randomized cardiovascular trials enrolling over two million participants, more than 70% excluded patients with CKD on safety grounds, only ~3% enrolled CKD populations exclusively, and fewer than 25 reported outcomes for eGFR < 30 mL/min/1.73 m^2. Consequently, the management of advanced kidney disease continues to rely predominantly on observational data, opinion, and clinical experience rather than randomized evidence, leaving a persistent imbalance between clinical need and the evidence available to inform practice.

1.2 The platform trial solution

APT-KIDNEY addresses these gaps through an enduring, investigator-initiated adaptive platform trial designed for continuous learning to the direct benefit of patients. Where conventional stand-alone trials are restricted to two interventions built on a purpose-built infrastructure, leading to repetitive, duplicated work and inflexible designs, a platform trial uses a common core protocol focused on the disease rather than on a single intervention. Comparable interventions are nested in defined domains, each conceptually equivalent to a stand-alone trial, and new domains can be added or retired over time within one shared regulatory and logistical framework.

Management of advanced kidney disease is particularly well suited to this approach: event rates are high, therapeutic options are limited, care is concentrated at specialized hospital-based nephrology centers, and a multi-stakeholder core outcome set already exists. APT-KIDNEY is designed exclusively for low-intervention comparisons, meaning authorized treatments and care strategies used in clinical practice, with no more than minimal additional risk or burden for participants.

2 Aim and objectives

The primary objective is to establish an investigator-initiated adaptive platform trial enabling efficient and rigorous assessment of interventions in adults with advanced kidney disease (defined as eGFR < 30 mL/min/1.73 m^2 for ≥ 3 months, end-stage kidney disease (ESKD) on maintenance hemo- or peritoneal dialysis, conservative kidney

management, or kidney allograft recipient). APT-KIDNEY prioritizes 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.

3 Overall design and platform methods

3.1 Design, eligibility, and co-enrolment

APT-KIDNEY is an investigator-initiated, pragmatic, randomized, embedded, multifactorial adaptive platform trial with interventions nested in designated domains, which may be open-label or blinded.

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.

3.1.1 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

3.1.2 Exclusion criteria

- ⊙ Inability to provide free and informed consent

Participants may be enrolled concurrently in more than one domain where prespecified compatibility rules confirm the absence of biological, treatment-delivery, or outcome interactions permitting concomitant investigation of multiple questions in the same patient population.

3.2 Core outcomes

APT-KIDNEY outcomes will overall adhere to the principles and results of the global Standardized Outcomes in Nephrology (SONG) initiative. The SONG initiative was launched in 2014 with the aim of establishing a standardized set of outcomes for clinical trials in kidney disease.

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 health-related quality of life (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)

*only patients with measurable kidney or allograft function at randomization

3.3 Data capture and data sources

Primary, secondary, and safety outcomes are registered in a GCP-validated eCRF by trained trial staff from source documentation. Linkage to Danish national health registers and clinical quality databases is used, where approved, for baseline enrichment, treatment exposure and adherence, exploratory outcomes specified in the domain-specific appendices, verification of events, resource use, and minimizing loss to follow-up.

3.4 Statistical framework

Domains typically use fixed-sample or event-driven frequentist designs; adaptive features and Bayesian analysis may be used where justified, prespecified per domain according to the question and design. The primary analysis population in all domains is the intention-to-treat population, with supportive analyses assessing robustness, and primary outcomes are drawn from the shared core outcome set unless otherwise justified. Effects are reported with appropriate measures of uncertainty using models suited to the outcome type and adjusted for prespecified baseline factors. Missing data are minimized through harmonized follow-up and, where approved, register linkage, with prespecified strategies for participants who switch or discontinue treatment.

3.5 Informed consent

Written informed consent is obtained before any trial-related procedure, at platform and domain level. Consent follows an oral information interview with a qualified member of the investigating team, in person or, where approved by the ethics committee, by video, and participants are offered at least 24 hours for deliberation and may bring a companion of their choice. Consent is given digitally, by electronic signature with unambiguous identification, or on paper where digital consent is not possible or not preferred.

3.6 Safety and oversight

Safety monitoring is risk-proportionate and specified for each domain. Prespecified safety outcomes are registered in the eCRF according to each domain's risk level and reviewed by independent data and safety monitoring committees, and an annual safety report covering all domains is submitted via CTIS. In domains with an investigational medicinal product, suspected unexpected serious adverse reactions are reported to EudraVigilance.

4 Dissemination and patient involvement

Results from each domain will be published irrespective of outcome and reported in accordance with CONSORT, including the adaptive-design (CONSORT-ACE) extension where applicable. Within one year of each domain's primary analysis data cut, a summary of the results with a summary for laypersons is submitted to CTIS. Core outcomes follow the patient-prioritized SONG standards, and a patient and public representative is a member of the Platform Steering Committee.

5 Ethics

The APT-KIDNEY platform trial will be conducted in accordance with the Declaration of Helsinki (2024 revision) and the ICH E6(R3) Good Clinical Practice guideline. The sponsor is Nicholas Carlson. The trial is submitted via the Clinical Trials Information System (CTIS) for assessment by the Danish Medicines Agency and the Medical Research Ethics Committees, and new domains are added by substantial modification.

6 Funding

The APT-KIDNEY platform is funded by DKK 962,000 from Rigshospitalet's internal research funds. Domains are financed by independent grants, with planned initiation of domains dependent on funding.