APT-KIDNEY

INITIATE - Incremental hemodialysis in incident patients with end-stage kidney disease

Domain-specific Appendix

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Summary of changes

This section summarizes all changes to the domain-specific appendix after initial submission for approval.

Protocol version	Date	Major changes

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1 Protocol Summary

1.1 Synopsis

Protocol Title: Incremental hemodialysis in incident patients with end-stage kidney disease: an APT-KIDNEY platform trial domain investigating benefit of incremental twice-weekly compared with conventional thrice-weekly hemodialysis frequency in patients with incident end-stage kidney disease.

Acronym: INITIATE

Rationale: Since the 1970s, incident hemodialysis has defaulted to thrice-weekly sessions. Dialysis initiation imposes substantial physical and psychological burden. Observational data suggest that incremental twice-weekly hemodialysis may be non-inferior to conventional thrice-weekly hemodialysis care, with potential benefits in survival, quality of life, and preservation of residual kidney function.

Objectives: Within the APT-KIDNEY platform, INITIATE will assess whether twice-weekly hemodialysis is non-inferior to thrice-weekly for time to all-cause mortality within 12 months.

Design: Investigator-initiated, open-label, pragmatic, parallel-group, fixed-sample frequentist platform domain.

Inclusion and exclusion criteria: Adults (≥18 years) who commenced maintenance hemodialysis within 90 days prior to screening, with residual urine output ≥1,000 mL/24h on timed collection. Exclusions include expected life expectancy < 3 months; peritoneal dialysis > 3 months; anticipated modality change or kidney transplant planned < 3 months; and inability to consent.

Number of participants: Event-driven, E=114 primary events for ~492 participants (~246 per arm, randomized 1:1).

Interventions and comparisons: Follow-up from randomization to study end (12 months) or death.

Intervention: twice-weekly hemodialysis sessions.
Control: thrice-weekly hemodialysis sessions.

Protocol-defined recommended thresholds for escalation to thrice-weekly hemodialysis are provided, with final decisions at clinician discretion.

Outcomes:

Primary (non-inferiority): All-cause mortality at 12 months (time-to-event).

Secondary (superiority): Health-related quality of life (HRQOL) at 12 months (EQ-5D-5L index values)

Tertiary (exploratory): Major adverse cardiovascular events (MACE: non-fatal MI, non-fatal ischemic stroke, or cardiovascular (CV) death), non-fatal hemorrhagic stroke, cardiovascular mortality, loss of residual kidney function, treatment adherence, and all-cause hospitalization; hospitalization-based endpoints are derived from register linkage where approved.

Abbreviated statistics: Analyses follow intention-to-treat under a treatment-policy strategy for all intercurrent events (ICH E9 R1). Non-inferiority for all-cause mortality will be assessed using a Cox proportional hazards model; non-inferiority is concluded if the upper bound of the two-sided 95% confidence interval for the hazard ratio is ≤1.30. EQ-5D-5L index (national value sets; non-survivors weighted as dead) will be compared at 12 months with supportive mixed model for repeated measures (MMRM) across scheduled assessments; EQ VAS and dimension-level outcomes analyzed while alive with death as a terminal event. Superiority testing for EQ-5D-5L is contingent on mortality non-inferiority. Tertiary endpoints analyzed using survival and count-rate models. No planned efficacy interim analyses, prespecified IDSMC safety reviews will be performed broadly aligned with event accumulation and ad hoc as needed.

Funding: Applications with Sundhedsdonationer and Danske Regioners Medicin- og behandlingspulje.

1.2 Administrative information

1.2.1 Protocol and domain-specific appendix structure

This document is a domain-specific appendix to the APT-KIDNEY core protocol. All procedures and provisions outlined in the core protocol (version specified on the front page) apply unless explicitly stated otherwise. This appendix provides domain-specific details not covered in the core protocol and should be read in conjunction with the core protocol and applicable appendices. A preliminary statistical analysis plan (SAP) for this domain is included herein.

1.2.2 Modifications of the domain-specific appendix

Substantial modifications to this domain-specific appendix will be submitted via CTIS for authorization as substantial modifications of the APT-KIDNEY platform trial (core protocol Section 7.2) prior to implementation, except where urgent safety measures are required, with data-protection documentation updated as specified in core protocol Section 8.7.7. Non-substantial changes will be version-controlled and filed in the trial master file. If required, the participant information sheet and consent form will be updated accordingly and reauthorized. Following approval, all relevant modifications affecting this appendix or the conduct of the domain will be communicated to all principal investigators and study monitors. Approved versions of this domain-specific appendix are published in CTIS and on the APT-KIDNEY website (core protocol Section 4).

1.2.3 Domain lead, domain steering committee, and contributors

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Domain-specific appendix contributors:

The INITIATE domain-specific appendix was developed by the domain lead and members of the domain steering committee. Individual contributors and their roles are recorded in the trial master file.

1.2.4 Domain independent data and safety monitoring committee (IDSMC)

The INITIATE IDSMC will comprise a clinical trialist (chair), a clinician with expertise in hemodialysis, and a biostatistician, all independent of the sponsor and trial operations. Members will be appointed before the first inclusion and listed in the IDSMC charter.

2 Abbreviations and Definitions

APT-KIDNEY	Adaptive platform trial for kidney disease
CI	Confidence interval
CTIS	Clinical Trials Information System
CV	Cardiovascular
DSA	Domain-specific appendices
DOPPS	Dialysis Outcomes and Practice Patterns study
eCRF	Electronic case report form
EHR	Electronic health record
EQ-5D-5L	EuroQol 5-Dimension, 5-Level questionnaire
EQ-VAS	EuroQol Visual Analogue Scale
ESKD	End-stage kidney disease
EU	European Union
HR	Hazard ratio
HRQOL	Health-related Quality of life
IDSMC	Independent data and safety monitoring committee
IHDIP	Incremental Hemodialysis in Incident Patients Trial
IMP	Investigational medicinal product
INCHVETS	Incremental Hemodialysis for Veterans in the First Year of Dialysis trial
INITIATE	Incremental hemodialysis in incident patients with end-stage kidney disease
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
MMRM	Mixed model for repeated measures
PI	Principal investigator
PRIDE	Twice-weekly vs Thrice-weekly Incident hemodialysis in Elderly Patients Trial
SAE	Serious adverse event
SAP	Statistical analysis plan
SONG-HD	Standardized Outcomes in Nephrology: Hemodialysis Initiative
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR	Suspected unexpected serious adverse reaction

3 Introduction

3.1 Background

Prevalence of chronic kidney disease is increasing globally, with kidney disease expected to become the 5th leading cause of death within the next 25 years.[1] Chronic kidney disease 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 chronic kidney disease.[2,3]

3.1.1 End-stage kidney disease

Before reaching kidney failure, guidelines advocate careful planning of end-stage kidney care for all patients with estimated glomerular filtration rate <20 ml/min/1.73 m^2 or perceived risk >40% for kidney replacement therapies within two years.[4] Treatment options in patients who are not candidates for kidney transplantation include comprehensive conservative care, peritoneal dialysis, and hemodialysis. Timing and choice of treatment should be based on patient preferences, symptoms, and clinical and biochemical parameters.[4] Overall, advanced chronic kidney disease is associated with a poor prognosis, including an annual mortality exceeding 20% in patients treated with dialysis.[2,3,5] Risk of death is especially high within the first few months of dialysis initiation plausibly due to physical and psychological stress.[6–10]

3.1.2 Conventional 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. The annual incidence of patients initiating hemodialysis is around 75 per 1 million Danish residents.[11] In most patients, conventional hemodialysis is prescribed as thrice-weekly in-hospital sessions of four hours. This regimen has been standard practice since the 1970s, with treatment adequacy commonly assessed by a threshold urea clearance (Kt/V ≥1.2).[12,13] The recommendation primarily originates from two landmark randomized trials: the National Cooperative Dialysis Study (1981)[14] and the Hemodialysis study (2002).[15] However, this conventional approach was implemented without evidence from prospective studies considering individual residual kidney function, patient preferences, or clinical and biochemical symptom control.[14,15]

Subsequent trials evaluating dialysis dose and frequency have mainly compared patients without residual kidney function or assessed conventional versus more intensive regimens. While augmented schedules (longer dialysis time and/or higher frequency) have shown certain clinical benefits in randomized clinical trials,[16–19] evidence for an overall survival advantage remains inconsistent across studies.[20–23] Moreover, increased dialysis intensity has been associated with negative effects on vascular access patency and residual kidney function.[12] Recently, the applicability of this long-standing *"one-size-fits-all"* paradigm has been questioned, prompting interest in more individualized approaches such as incremental dialysis.[24–26]

3.1.3 Incremental dialysis

Incremental dialysis refers to an individualized approach in which dialysis dose and frequency are adjusted according to the patient's residual kidney function, with gradual intensification as kidney function declines.[27] In a report from Dialysis Outcomes and Practice Patterns study (DOPPS) of prevalent hemodialysis patients, <5% of patients were treated with dialysis <3 times a week across most participating countries from 2009 to 2011.[28] Suggested explanations for this limited adoption include the practical challenges of frequent monitoring of residual kidney function and urea clearance to adjust dialysis dosage, which is not part of standard clinical practice.[29,30]

Potential benefits of incremental dialysis with lower treatment frequency include:

- **Improved quality of life:** Dialysis initiation is often associated with substantial psychological burden, including stress for patients and caregivers, fatigue, interference with work or education, and lifestyle

disruption. The Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) initiative listed 'dialysis-free time' as a 'critically important' outcome for patients.[31,32]

- **Reduced health care costs:** Lower treatment frequency may reduce transport expenses, dialysis-related costs, adverse events, and medication use.[24,33–35]
- **Comparable survival:** Observational studies suggest that mortality rates are similar between incremental and conventional thrice-weekly hemodialysis.[36–40]
- **Preservation of residual kidney function:** Incremental dialysis may better preserve residual kidney function, allowing greater fluid intake, improved clearance of medium-sized molecules, less anemia and inflammation, and better blood pressure control.[25,31,36,41–43]

However, most of these potential advantages derive from observational studies, which are inherently subject to selection and indication bias. A recent systematic review and meta-analysis of 22 observational studies and two small randomized controlled trials (n ≈ 100,000) found similar mortality, while the observational studies included suggested reduced loss of residual kidney function and reduced costs in incremental dialysis, and the randomized clinical trials (feasibility trials, n=23 and n=29) suggested less hospitalization.[30,35,44] More recently, a randomized controlled trial (n=150) comparing twice- versus thrice-weekly dialysis in incident hemodialysis patients found no difference in glomerular filtration rate decline, residual kidney function, clinical outcomes, or quality of life. After a mean of 193 days, 15 patients had transitioned from twice- to thrice-weekly treatment.[45]

Green nephrology and incremental dialysis

Green nephrology refers to the integration of environmental sustainability into kidney care. Dialysis is not only resource-intensive but also associated with a considerable carbon footprint, estimated at 3.8-10.2 tons of CO_2 per dialysis patient per year.[46–49] This compares to the average annual emission of approximately 6 tons per global citizen and 13 tons per Danish resident.[50] In addition, each dialysis session may require up to 500 liters of water.[51] While modern technologies provide opportunities to reduce CO_2 emissions and water consumption, incremental dialysis may also contribute to a more sustainable and environmentally responsible nephrology practice.[52] By reducing treatment frequency at initiation and escalating as residual kidney function declines, incremental dialysis has the potential to lower session-linked emissions, water use, and consumables during the early treatment window without compromising safety. Any sustainability gains must, however, be evaluated alongside clinical outcomes and unintended offsets i.e., longer individual sessions, extra transport, or increased hospitalizations.

Clinical trials and incremental dialysis

Trials on incremental dialysis have moved beyond pilot studies into a genuinely comparative phase. An overview is provided in the table below. Feasibility has been established in two trials,[35,44] and preliminary randomized evidence from one completed randomized clinical trial in Spain (n=150) demonstrated the practicability of protocolized escalation and structured safety surveillance,[45] thus providing a template for outcomes and monitoring that later studies now follow. Currently, four (4) pragmatic randomized clinical trials are underway.[53–56] The Spanish Incremental Hemodialysis in Incident Patients (IHDIP) trial (n=152) compares an incremental start (as low as once–twice weekly, with prespecified escalation) versus immediate thrice-weekly, powered to assess mortality rate, with enrollment completed in June 2024.[56] The American Comparative Effectiveness of an individualized model of hemodialysis vs conventional hemodialysis (TwoPlus) trial (n=350) aims to compare an individualized incremental algorithm versus standard care for a primary endpoint consisting of a health-services composite (all-cause death, hospitalizations, emergency-department visits) at two years while allowing for escalation as residual kidney function and/or clinical status declines.[55] Similarly, the Incremental Hemodialysis for Veterans in the First Year of Dialysis (INCHVETS) trial (n=252) aims to compare twice- versus thrice-weekly across a pragmatic, multisite network, emphasizing health-related quality of life (HRQOL) and residual kidney function outcomes alongside safety.[53] Finally, the South Korean Twice-weekly vs Thrice-weekly Incident hemoDialysis in Elderly Patients – A Pragmatic Randomized Clinical Trial (PRIDE) (n=428) targets older incident patients with the aim of assessing whether twice-weekly initiation reduces hospitalization rates compared with conventional thrice-weekly care.[54]

In summary, the feasibility of incremental hemodialysis has been demonstrated and several heterogeneous trials with different primary outcomes are underway; however, a definitive, harmonized pragmatic randomized controlled trial is warranted to address the central safety question with adequate power; namely, whether less-frequent initiation with protocolized escalation is non-inferior with regards to survival. Concurrently, such a trial should incorporate prespecified health-related quality of life and health-system endpoints (healthcare utilization, treatment intensity, costs). Standardization of endpoint definitions, including cardiovascular components and hospitalization metrics, across studies would facilitate valid data aggregation and meta-analysis, yielding more precise estimates overall and across subgroups and care settings for the direct benefit of future guideline development.

	Incremental Hemodialysis as a Starting Way of Renal Replacement Therapy[1]	Incremental Haemodialysis in Incident Patients (IHDIP)[2]	Comparative effectiveness of an individualized model of hemodialysis vs conventional hemodialysis (TwoPlus trial)[3]	A Pragmatic Randomized Clinical Trial: Twice-weekly vs Thrice-weekly Incident hemoDialysis in Elderly Patients (PRIDE)[4]	Incremental Hemodialysis for Veterans in the First Year of Dialysis (INCHVETS)[5]
Trial registration	NCT03302546	NCT03239808	NCT05828823	NCT06141798	NCT05465044
Country	Spain	Spain	USA	South Korea	USA
Inclusion period	January 1, 2017 – December 31, 2021	March 14, 2018 – June 6, 2024	January 1, 2024 – now	November 23, 2021 – now	April 1, 2023 – now
Intervention	2 vs 3 weekly HD sessions	1 vs 3 weekly HD sessions	2 vs 3 weekly HD sessions	2 vs 3 weekly HD sessions	2 vs 3 weekly HD sessions
Inclusion criteria	- Incident hemodialysis - KrU ≥2.5 ml/min/1.73 m²	- Incident hemodialysis - KrU ≥4 ml/min/1.73 m²	- Incident hemodialysis - KrU ≥3.5 ml/min/1.73 m - Urine output ≥500 ml/24 h	- Incident hemodialysis - Urine output ≥500 ml/24 h - Age ≥60 years	- Veterans initiating hemodialysis - KrU >3 ml/min/1.73 m² - Urine output ≥500 ml/24 h
Exclusion criteria	- Anuric patients with acute kidney failure - Previous kidney transplant	- Unplanned HD initiation - Previous renal replacement therapy - Active neoplasia - Severe cardiovascular disease - Cardiorenal syndrome - Active inflammatory disease - Hepatorenal syndrome	- Serum potassium ≥5.8 mEq/L - Serum sodium ≤125 mEq/L - Serum bicarbonate ≤17mEq/L - High-volume ultrafiltration - History of non-adherence - A medical condition that would jeopardize the safety of the participant - Expected dialysis modality change within the next 6 months - Life expectancy <6 months - Pregnancy	- Left ventricular ejection fraction <40% - Liver cirrhosis - Active malignancy - Active infection	- Life expectancy <6 months - Serum potassium >6.0 mEq/L
Sample size: estimated (actual)	148 (150)	152	350	428	252
Primary outcome	Loss of kidney function	Survival	Composite of all-cause death, hospitalization, or emergency department visits	Hospitalization rate	Change in Health-Related Quality of Life (HRQOL) Physical Component Score (PCS) of SF36 questionnaire
Secondary measures	- Erythropoietin dosage - Beta-2 microglobulin concentration - Hydration and nutritional status - Concentrations of uremic toxins - Dialysis dose - Number and duration of hospital admissions - Mortality - Quality of life	- All-cause hospitalization - Residual kidney function - Anemia - Bone-mineral metabolism - Hypertrophic cardiomyopathy levels - Quality of life - Costs	- Patient- and caregiver-reported outcomes	- Dialysis related hospitalization rate - Length of hospital sta - Complication of dialysis - Mortality - Clinical Frailty Scale - Costs - Kidney Disease Quality of Life Instrument (KDQOL)	- Energy/Fatigue (SF36 HRQOL) - Dialysis Symptom Index (DSI) - Residual urine output - Kt/V - Malnutrition-Inflammation Score (MIS) - Serum level of Growth Differentiation Factor 15
Follow-up	12 months	24 months	24 months	24 months	12 months
Results	No difference in GFR decline, residual kidney function, clinical outcomes, or quality of life.				

1) Lucas MF et al., Kidney Int. Rep. 2025, S2468024925006230. + Lucas MF et al., Trials 2020, 21 (1), 206.; 2) Deira J et al., BMC Nephrol. 2019, 20 (1), 8; 3) Murea M et al., Trials 2024, 25 (1), 424; 4) Han M et al., Kidney Res. Clin. Pract. 2023; 5) VA Office of Research and Development, clinicaltrial.gov

3.2 Benefit-risk assessment and safety outcomes

3.2.1 Risk classification

INITIATE aims to evaluate the safety and benefit of incremental twice weekly hemodialysis compared with conventional thrice-weekly hemodialysis in incident patients with ESKD. Observational data and results from one RCT and two smaller feasibility studies suggest that incremental dialysis can safely be performed in incident hemodialysis patients.[30,35,44,45] Overall, the domain is expected to impose minimal additional risk or burden beyond standard of care hemodialysis. Dialysis treatment will be delivered exclusively at specialized departments by highly trained staff, entailing routine monitoring of clinical and biochemical parameters both during and between dialysis sessions, enabling timely identification and mitigation of emerging risks. As such, monitoring and safety data collection will be risk-proportionate and focused on prespecified serious safety outcomes and key safety composites, with escalation procedures as clinically indicated.

INITIATE involves no investigational medicinal product, so the low-intervention criteria concerning IMPs (Article 2(2)(3)(a) and (b) of Regulation (EU) No 536/2014) do not apply. The domain is designed to meet the remaining criterion (core protocol Section 6.3): both arms deliver standard hemodialysis in routine care with protocol-defined escalation criteria (Section 7.5), and the additional procedures, timed urine collections at 4, 8, and 12 months (using clinical collections where available) and patient-reported outcome measures, are non-invasive and pose no more than minimal additional risk or burden compared with normal clinical practice. Accordingly, INITIATE is classified as Risk level 1 (core protocol Section 10.3.2.1).

3.2.2 Domain specific safety outcomes

Serious adverse events (SAEs) are defined in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use.[59] The core outcomes and the domain-specific safety outcomes below are recorded in the eCRF as trial outcomes; other SAEs and serious adverse reactions are not recorded. Investigators do not report SAEs or serious adverse reactions to the sponsor unless they consider it warranted (core protocol Section 10.3.2.2, Risk level 1; Article 41(2) of Regulation (EU) No 536/2014).

Outcomes will be assessed every four months based on the predefined core outcome set with additional safety assessment based on domain-specific safety outcomes (shown below).

- **Life-threatening cardiac arrhythmia or cardiac arrest** as defined by ventricular fibrillation, sustained ventricular tachycardia (including torsades de pointes), resuscitated cardiac arrest, and/or bradyarrhythmia requiring temporary or permanent pacing
- **Fluid overload with respiratory compromise** as defined by acute pulmonary edema or respiratory failure requiring urgent ultrafiltration or dialysis
- **Severe hyperkalemia or life-threatening electrolyte disturbances** defined as plasma potassium >6.5 mmol/L requiring urgent dialysis or repeated (≥3) plasma potassium >6.5 mmol/L

INITIATE is a non-IMP domain (see Section 9); IMP-specific safety reporting, including SUSAR reporting, does not arise. Recorded safety outcomes are reviewed by the domain IDSMC and summarized in the annual safety report submitted via CTIS (core protocol Section 10.3.2.3), with prompt notifications as specified below.

Prompt notifications via CTIS

Individual SAEs are not routinely reported to the sponsor (see above). The platform sponsor notifies the Member States concerned via CTIS of unexpected events affecting the benefit–risk balance without undue delay and no later than 15 days after becoming aware (Article 53), and of urgent safety measures without undue delay and no later than seven days after they are taken (Article 54), as identified through the governance trigger or investigator reports below.

Governance trigger: The IDSMC identifies a material safety signal at scheduled or ad hoc review, or recommends an urgent safety measure (e.g. temporary suspension of an arm or modification of escalation criteria).

Investigators may report to the domain lead any SAE they consider relevant to participant safety; such reports are assessed by the platform sponsor against the criteria above.

Pregnancy and contraception
INITIATE does not involve systemic drug exposure; neither intervention poses teratogenic or fetotoxic risk. Accordingly, core protocol requirements related to contraception and pregnancy testing do not apply to this domain. Pregnancy will be recorded in the eCRF if reported or identified during routine clinical care. Pregnant participants will be managed according to standard obstetric nephrology practice, typically entailing intensification of hemodialysis frequency. This will be documented as clinically indicated escalation under the cross-over policy (Section 7.5) and the participant will remain in the domain for intention-to-treat follow-up.

3.2.3 Benefit/Risk Assessment

Patients receiving dialysis are managed in highly specialized units by trained healthcare professionals. They undergo frequent clinical and biochemical assessments during their regular dialysis visits. In the proposed domain, participants will attend the dialysis unit at least twice weekly, and a detailed cross-over policy and escalation criteria are available (see section 7.5). Current evidence indicates that twice-weekly hemodialysis is a safe treatment approach.[35,44,45] Accordingly, the anticipated risks for participants beyond standard of care hemodialysis are minimal and comparable between the randomization arms. The non-inferiority margin (HR=1.30) was selected to ensure that the maximum tolerable excess mortality preserves at least 50% of the estimated survival benefit of hemodialysis over conservative care (see Section 8.2.1); the domain is designed on the expectation of no difference in mortality.

4 Domain aim and objectives

Although conventional thrice-weekly dialysis has been practiced since the 1970s, treatment entails substantial burden. Observational data on tolerability, safety, and benefit of incremental dialysis in patients with end-stage kidney disease is conflicting,[24,25,31,33–43] and evidence from randomized clinical trials remains limited and inconclusive.[45] The main objective of INITIATE is to investigate whether incremental twice-weekly hemodialysis can reduce treatment burden and improve patient-reported quality of life without an unacceptable increase in mortality as compared with conventional standard-of-care thrice-weekly hemodialysis in patients with incident end-stage kidney disease.

INITIATE will test non-inferiority of twice-weekly versus thrice-weekly hemodialysis for time to all-cause mortality within 12 months; health-related quality of life at 12 months will be evaluated subsequently, with confirmatory testing contingent on demonstration of mortality non-inferiority.

5 Study design

5.1 Overall design

INITIATE is designed as an investigator-initiated, pragmatic, randomized, parallel-group, open-label domain within the APT-KIDNEY platform. INITIATE uses a fixed-sample frequentist design without adaptive features; no guiding outcome for adaptive decisions, response-adaptive randomization, interim efficacy or futility analyses, or adaptive stopping rules are specified (core protocol Sections 8.9.1.1 and 9.1). The INITIATE domain compares incremental twice-weekly versus conventional thrice-weekly hemodialysis in incident hemodialysis patients to assess non-inferiority for time to all-cause mortality within 12 months in all randomized patients. The INITIATE domain is event-driven, with recruitment continuing until the prespecified number of primary events is accrued; the final sample size and enrollment duration will therefore depend on the observed event rate. Annual incidence of maintenance hemodialysis in Denmark is ~ 600–700.[11] Assuming residual urine output ≥1,000 mL/day in 50-70% of incident patients and 70-80% meeting remaining eligibility criteria, the projected eligible and consenting population is estimated at approximately 50–115 per year after accounting for site coverage and expected consent rates. A planning assumption of n= 100 per year is within range but will be monitored during accrual. Strategies in support of recruitment including international expansion may be considered if sustained shortfalls are observed. Based on planning assumptions, enrollment (n=100/year) is expected to complete within approximately five years.

This domain-specific appendix describes all required items in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 statement[57] except those covered by the core protocol where no domain-specific adaptations were made.

5.2 Study procedures overview

Participants will be identified among incident hemodialysis patients at participating sites. Following provision of oral and written study information, eligibility will be assessed using available clinical information. After informed consent, participants will be randomized to incremental twice-weekly or conventional thrice-weekly hemodialysis. The assigned dialysis frequency strategy will be initiated as soon as feasible after randomization and continued for 12 months, with protocol-defined escalation/cross-over criteria applied as clinically indicated. Outcomes, domain-specific safety outcomes, and protocol deviations will be registered by site staff from source documentation, with registers used for verification where available. Participants will be invited to complete patient-reported outcome measures during follow-up, including the EQ-5D-5L as specified in the assessment schedule. Participants will be followed until death or 12 months after randomization, with censoring as defined in the DSA. A schematic overview of participant flow and the assessment schedule is provided in Domain Appendices 1–2.

5.3 Justification for using an open-label design

The domain will employ an open-label design, as blinding of dialysis prescription is not feasible in clinical practice. An open-label approach also enhances the trial's practical feasibility and cost-efficiency by reducing the number of dialysis sessions, thereby supporting the economic feasibility of the study while maintaining the potential for conclusive results. Furthermore, assessment of patient-reported measures of quality of life such as time spent in hospital and treatment burden would be difficult to evaluate under blinded conditions that would require participants to attend "dummy" dialysis sessions. Because open-label allocation may influence participant-reported outcomes, EQ-5D-5L will be collected through standardized digital self-completion with neutral instructions and minimal staff involvement (core protocol Section 8.6.2.2); prespecified sensitivity analyses addressing collection-method effects and differential missingness are detailed in Section 8.3.4.

5.4 Data registration

In addition to APT-KIDNEY core protocol baseline and outcome variable sets, and the defined domain-specific safety outcomes, the following variables will be collected at baseline and during follow-up:

Baseline registration
For dialysis treatment variables, baseline will reflect either the prescription at randomization or, where available, values from the most recent pre-randomization session(s).

Dialysis treatment

- Date of first maintenance hemodialysis session (dd-mmm-yyyy)
- Allocated frequency (twice (2x) weekly | thrice (3x) weekly)
- Prescribed session duration (minutes)
- Interdialytic weight gain (kilograms, mean of last three (3) sessions)

Residual kidney function

- 24-hour urine collection: date of collection, measured volume (mL), normalized 24-hour volume (mL/24h), and urine creatinine clearance (mL/min)

Kidney transplantation

- Prior kidney transplantation (Yes | No)

Follow-up registration at four (4), eight (8), and 12 months
Registration during follow-up will be performed at the platform's 4-monthly timepoints (±4 weeks), counted from the participant's first platform randomization (core protocol Section 8.9.1.1). For participants already enrolled in another domain, the platform timepoints nearest to 4, 8, and 12 months after INITIATE randomization are used. The assessment window applies to capture and verification only; event outcomes will be recorded with their actual date of occurrence from source documentation. For dialysis treatment variables, follow-up will reflect the most recent session(s). A timed urine collection will be performed at each scheduled follow-up assessment (4, 8, and 12 months). If a valid clinical collection has been performed within ±4 weeks of the scheduled timepoint, this may be used.

Dialysis treatment

- Prescribed frequency (twice (2x) weekly | thrice (3x) weekly)
- Delivered frequency (no. treatments per week, mean of last three (3) weeks)
- Prescribed session duration (minutes)
- Delivered session duration (minutes, mean of last three (3) sessions)
- Interdialytic weight gain (kilograms, mean of last three (3) sessions)

Residual kidney function

- 24-hour urine collection: date of collection, measured volume (mL), normalized 24-hour volume (mL/24h), and urine creatinine clearance (mL/min).

5.5 End of Study Definition

A participant is considered to have completed INITIATE if the participant has been followed for 12 months after randomization with adherence to the program outlined in the schedule of appointments. Study end will be defined as one year after last randomization. The end of INITIATE is defined at the date of the last appointment of the last participant. The APT-KIDNEY core protocol outlines the end of platform study definition. Handling of withdrawal from the domain and discontinuation of the assigned treatment arm is described in section 7.7.

5.6 Data sharing

Data may be shared as described in the core protocol.

6 Study Population

Patients who have recently commenced maintenance hemodialysis (within 90 days) will be recruited from dialysis centers within the APT-KIDNEY platform. Recruitment projections are described in Section 5.1

In addition to the general APT-KIDNEY eligibility criteria, the following domain-specific criteria apply.

6.1 Inclusion Criteria

- Initiation of maintenance hemodialysis ≤ 90 days prior to screening
- Residual urine output ≥1,000 mL per 24 hours on a timed urine collection

6.2 Exclusion Criteria

- Life expectancy < three (3) months
- Documented plan for shift in kidney replacement therapy within three (3) months
- Prior peritoneal dialysis for more than three (3) months

Planned shift in kidney replacement therapy refers to a documented plan at screening for transition to peritoneal dialysis, home hemodialysis (if not compatible with the allocated schedule), or kidney transplantation within three

(3) months. This includes cases where evaluation and/or work-up is at a stage where transplantation or modality change is reasonably expected within the timeframe. Routine referral or early evaluation alone is not sufficient.

Maintenance hemodialysis refers to a planned, ongoing hemodialysis programme intended as long-term kidney replacement therapy. The 90-day window is calculated from the date of the first maintenance session to the date of screening. Sessions performed solely for acute indications (e.g., acute kidney injury with expected recovery, urgent ultrafiltration, or inpatient toxin removal) without subsequent transition to maintenance hemodialysis do not qualify. The date of the first maintenance session will be recorded in the eCRF.

Residual urine output is assessed by a single timed urine collection performed within 90 days prior to screening. The collection should be performed on an interdialytic day where feasible and should span a minimum of 20 hours; the measured volume will be normalized to 24 hours (volume × 24 / collection duration in hours). If a valid collection has been performed as part of routine clinical care within the 90-day window, this may be used. A repeat collection is not required but is recommended if clinical circumstances have changed materially since the collection. The collection date and measured volume will be recorded in the eCRF.

Prior treatment with peritoneal dialysis for more than 3 months refers to a cumulative duration of maintenance peritoneal dialysis exceeding three (3) months before screening.

Patients with a previously failed kidney transplant who have transitioned to maintenance hemodialysis are eligible provided they meet all other inclusion criteria, including the residual urine output threshold. Prior transplant status will be recorded at baseline.

Participants that have previously been randomized to INITIATE may not be re-randomized in the domain.

7 Study intervention and Concomitant Therapy

7.1 Incremental dialysis (intervention)

Incremental dialysis will be prescribed as twice-weekly hemodialysis in eligible patients. Adjustments to the dialysis prescription including time per session, dialysate composition, and concomitant medications are permitted. Monitoring during and after dialysis treatment should follow common clinical practice.

Preparation and administration
Hemodialysis is delivered in specialized departments by trained personnel.

Dose adjustments
Treatment frequency will remain fixed at twice weekly unless escalation is clinically indicated. Any escalation will be documented with clinical rationale and dates, and whether temporary (including start- and end-dates) or sustained.

Intervention accountability
All treatments will be documented electronically in the patient electronic health records (EHRs).

7.2 Conventional dialysis (control)

Dialysis will be prescribed as thrice-weekly hemodialysis in accordance with standard clinical practice. Adjustments to dialysis prescription including time per session and other medical treatments are permitted.

7.3 Randomization and stratification

Participants will be randomized 1:1 using a centralized web-based eCRF system with computer-generated permuted blocks of random sizes, stratified by site, with allocation concealment maintained until assignment. Co-enrollment is permitted per the core platform protocol; compatibility rules will prevent incompatible cross-domain allocations.

7.4 Intervention period

Participants will be followed from randomization until the earliest of death or completion of the scheduled 12-month follow-up after randomization.

The primary analysis is event-driven and will use a locked database cut-off date corresponding to the next scheduled 4-monthly platform timepoint after the prespecified primary event target is reached, with administrative censoring at the earliest of the data cut date, 12 months post-randomization, emigration, or withdrawal of follow-up consent where applicable. Participants who have not yet completed 12 months at the data cut date will be censored at the cut date. A final end-of-domain analysis including complete 12-month follow-up for all participants will be reported separately.

Follow-up may continue after the primary data cut for safety surveillance and final end-of-domain reporting; data accrued after the cut will not be included in the primary analysis.

7.5 Cross-over Policy and Escalation Criteria

Participants randomized to the incremental (2×/week) arm may escalate to thrice-weekly dialysis when clinically indicated. Decisions to escalate will be at the discretion of treating clinicians. Escalations may be temporary i.e. during hospitalization or acute intercurrent illness or sustained and will be recorded with clinical rationale and dates.

To reduce inter-site variability and support consistent clinical decision-making, the following framework is provided.

Recommended thresholds for sustained escalation:

- Residual urine output declining below 500 mL/24h on a timed collection, confirmed on a repeat collection if clinically feasible.
- Persistent or recurrent symptoms attributable to inadequate dialysis (e.g., refractory nausea, pruritus, restless legs, anorexia, or fatigue) despite optimization of session duration, ultrafiltration, and medical management.

When any of the above thresholds is reached, escalation to thrice-weekly hemodialysis is recommended. Clinicians may elect to escalate before these thresholds or to continue twice-weekly with enhanced monitoring if the clinical picture supports it; in either case, the rationale will be documented.

Urgent indications for immediate escalation include:

- Severe hyperkalemia requiring urgent dialysis or associated with electrocardiographic changes.
- Acute pulmonary edema/respiratory failure or clinically significant volume overload requiring hospitalization or urgent ultrafiltration/dialysis.
- Clinically significant uremic complications requiring escalation (e.g., pericarditis, encephalopathy).

Temporary escalation is permitted during hospitalization, acute illness, perioperative periods, or other transient circumstances including severe volume overload. Participants may return to the allocated schedule once clinically stable, at clinician discretion. Escalations will be recorded in the eCRF with the date, clinical rationale, whether temporary or sustained (including start and end dates for temporary escalations), and the triggering indication (recommended threshold, urgent indication, or clinician judgement).

7.6 Continued Access to Study Intervention after the End of the Study

After study completion, dialysis prescriptions may be adjusted by the treating clinicians as deemed appropriate.

7.7 Participant Discontinuation/Withdrawal from the Study

Participants discontinuing assigned treatment will be followed for one year from randomization for intention-to-treat analyses, provided they consent to continued follow-up as documented in a designated log. If participants withdraw

consent for follow-up, no further data will be collected beyond what is permitted under applicable law / regulatory approvals.

7.8 Lost to Follow up

Reasonable efforts will be made to obtain follow-up data through EHR review and, where approved, linkage to administrative health care registers, with participant contact as needed. A participant will be considered lost to follow-up if no outcome data can be obtained for 90 days despite ≥3 documented contact attempts. Transfer to a non-participating dialysis unit does not constitute loss to follow-up.

7.9 Co-enrollment and collaboration

Participants enrolled in INITIATE are allowed to be enrolled in other domains or trials in accordance with the guiding principles described in the APT-KIDNEY core protocol.

Co-enrollment with the ASPIRE CKD domain is permitted; no biological interaction between aspirin and dialysis frequency is expected, and the interventions do not modify treatment or outcome assessment across domains.

8 Statistical Considerations

8.1 General considerations

INITIATE will use intention-to-treat analyses including all randomized participants, analyzed as assigned. A per-protocol sensitivity estimand will use a hypothetical strategy for the intercurrent event of sustained treatment crossover: the treatment effect will be estimated as if participants had adhered to their assigned frequency throughout follow-up. Operationally, participants with sustained crossover i.e. ≥3 sessions/week for >4 consecutive weeks in the twice-weekly arm, or <3 sessions/week for >4 consecutive weeks in the thrice-weekly arm, will be excluded from the per-protocol analysis set. Escalations triggered by the recommended thresholds in Section 7.5 (decline in residual urine output, persistent symptoms attributable to inadequate dialysis, and/or urgent indications for escalation) will be noted but still constitute crossover for per-protocol purposes.

Endpoint variable and summary measure will remain as specified for the primary estimand. The per-protocol analysis population will be restricted to participants without sustained crossover as defined above. The per-protocol analysis addresses whether twice-weekly hemodialysis itself is non-inferior. Because escalation is expected to occur disproportionately among higher-risk participants in the twice-weekly arm, the per-protocol set is biased toward non-inferiority and is reported as supportive only.

Unless otherwise specified, analysis conventions and reporting will follow the framework described in the APT-KIDNEY core protocol. A definitive SAP will be finalized and approved prior to database lock and prior to any unblinded analyses.

8.2 Domain endpoints

8.2.1 Primary Endpoint (Non-inferiority)

The primary outcome will be time to all-cause mortality within 12 months following randomization. Participants will be followed until death or 12 months after randomization and censored at the earliest of loss to follow-up/withdrawal of follow-up consent (where applicable), emigration, or administrative censoring at the prespecified database cut-off date as defined in section 7.4.

The primary estimand is defined as follows, in accordance with ICH E9(R1):

Population: all randomized participants (intention-to-treat).

Endpoint variable: time from randomization to death from any cause within 12 months.

Intercurrent event strategies: a treatment-policy strategy will be applied to all intercurrent events, including escalation from twice-weekly to thrice-weekly hemodialysis (or de-escalation in the control arm), kidney transplantation, switch to peritoneal dialysis, and withdrawal from dialysis. Under this strategy, all events occurring after randomization contribute to the primary analysis regardless of adherence to the assigned frequency or changes in treatment modality. This reflects the clinical question of whether a strategy of initiating hemodialysis at twice-weekly frequency, with escalation as clinically indicated, is non-inferior to conventional thrice-weekly initiation.

Summary measure: hazard ratio (twice-weekly vs. thrice-weekly) from a Cox proportional hazards model, with non-inferiority assessed as specified below.

Non-inferiority will be concluded if the upper bound of the two-sided 95% confidence interval for the hazard ratio is ≤1.30. The margin is justified using the preservation-of-effect framework in accordance with FDA and EMA noninferiority guidance.[58,59] Registry comparisons of dialysis versus conservative management in elderly ESKD estimate M1 at HR ≈ 0.4–0.6; using a conservative HR=0.55, 50% preservation on the log-HR scale yields a maximum margin of approximately 1.35, and the prespecified margin of 1.30 preserves >55%. This is consistent with the IDEAL trial, which found no survival harm from delaying dialysis initiation by approximately six months (HR 1.04, 95% CI 0.83–1.30).[60] At the planning control-arm risk of 25.5%, HR=1.30 corresponds to approximately 6.3 percentage points of excess 12-month mortality.

Prespecified supportive and sensitivity analyses will include a covariate-adjusted Cox proportional hazards model (including site and key baseline prognostic factors i.e. age, sex, diabetes, and prior cardiovascular disease). If the proportional hazards assumption is not supported, restricted mean survival time at 12 months will be reported as an alternative summary. Per-protocol analyses will be presented as supportive.

8.2.2 Secondary Endpoint (Superiority)

The secondary endpoint will be EQ-5D-5L utility index at 12 months. Index values will be derived using the applicable national value set as specified in national appendices; for Denmark, the Danish value set will be used (range −0.757 to 1.0).[61,62] Non-survivors will be assigned a utility of 0 (weighted as dead) in the primary analysis, consistent with the core protocol convention (Section 8.9.1.1). A survivor-only analysis excluding non-survivors will be reported as a prespecified secondary analysis.

The secondary estimand is the between-group difference in mean EQ-5D-5L index at 12 months (twice-weekly minus thrice-weekly) in the intention-to-treat population, using a composite strategy for death (non-survivors included at utility 0, such that the estimand captures the combined effect on survival and quality of life). All other intercurrent events (escalation, de-escalation, kidney transplantation, dialysis modality switch, and withdrawal from dialysis) will be handled using a treatment-policy strategy, consistent with the primary estimand. Treatment effect will be expressed as an adjusted mean difference from a linear model including treatment, baseline EQ-5D-5L index, and site. Superiority testing is contingent on demonstrating primary mortality non-inferiority. If non-inferiority is not demonstrated, EQ-5D-5L results will be reported descriptively with 95% confidence intervals but without formal hypothesis testing.

A supportive MMRM analysis will use EQ-5D-5L index values at 4, 8, and 12 months, including pre-death assessments from non-survivors, with an unstructured covariance matrix (simplified if needed). The primary contrast will be the 12-month treatment effect; the overall mean across visits will be reported secondarily. The primary analysis assumes missing at random; sensitivity analyses will include delta-adjusted, pattern-mixture, and tipping-point scenarios. Mandatory sensitivity analyses for open-label PRO bias are specified in Section 8.3.4.

EQ VAS and dimension-level outcomes will be analyzed as exploratory endpoints in surviving participants, with death treated as a terminal event (not imputed as VAS=0), and deaths reported alongside. Conventions follow core protocol Section 8.9.1.1.

8.2.3 Tertiary Endpoints (Supportive)

All tertiary endpoints use a treatment-policy strategy for intercurrent events and follow a superiority framework unless a non-inferiority margin is specified in the final SAP. Time-to-event endpoints use Cox models with cause-specific hazards and cumulative incidence functions where death is a competing risk. Recurrent events use negative binomial models, with Andersen–Gill as sensitivity. Days-based endpoints accrue from randomization to death or 12 months. Treatment adherence summarized descriptively by arm. Loss of residual kidney function (urine output <400 mL/24h) is interval-censored at 4, 8, and 12 months and will be analyzed using a complementary log-log model, with midpoint-imputed Cox models as sensitivity.

A list of the tertiary endpoints is shown below:

- All-cause mortality: 12-month risk, Kaplan–Meier survival at 12 months, and restricted mean survival time to 12 months
- Cardiovascular death
- Major nonfatal cardiovascular event: nonfatal myocardial infarction or nonfatal ischemic stroke
- Composite cardiovascular endpoint: major nonfatal cardiovascular event or cardiovascular death
- Nonfatal hemorrhagic stroke
- Hospitalization: time to first all-cause hospitalization; recurrent hospitalization rate
- Serious infection: time to first infection requiring hospitalization; recurrent infection rate
- Treatment adherence: proportion of follow-up on allocated dialysis frequency
- Loss of residual kidney function: time to urine output <400 mL/day
- Days alive and not hospitalized (12 months): days alive and not in inpatient hospital

Hospitalization-based endpoints (hospitalization, serious infection, and days alive and not hospitalized) are derived from register linkage where approved and are exploratory.

8.2.4 Health economic evaluation (supportive):

A supportive health economic evaluation may be conducted, using health-related quality of life measured by EQ-5D-5L and healthcare resource use including dialysis delivery, outpatient contacts, hospitalizations, and rehabilitation. Analyses may include cost and cost-effectiveness summaries i.e. cost per QALY and pragmatic workload metrics relevant to dialysis delivery including staff time or time required to deliver treatment strategies, where feasible. The objectives, perspective, costing approach, time horizon, and statistical methods for the health economic evaluation will be prespecified in a separate health economics protocol and/or SAP, and results may be reported separately from the primary clinical publication.

8.3 Overview of analyses (primary, secondary, and sensitivity)

8.3.1 Primary analysis (mortality non-inferiority)

The primary analysis will use a Cox proportional hazards model with treatment as the explanatory variable, stratified by site to allow site-specific baseline hazards. A covariate-adjusted Cox model including age, sex, diabetes, and prior cardiovascular disease will be reported as supportive, retaining site stratification where feasible; if not feasible due to sparse events, site will be modeled using fixed effects. Non-inferiority will be assessed as defined in Section 8.2.1. Proportional hazards will be assessed using standard diagnostics, including Schoenfeld residuals. If proportional hazards is not supported, restricted mean survival time through 12 months will be reported as the primary alternative summary. Time-varying effects will be explored in sensitivity analyses.

8.3.2 Secondary analysis (EQ-5D-5L superiority)

The key secondary analysis will estimate the adjusted mean between-group difference in EQ-5D-5L utility index at 12 months using a linear model including treatment, baseline EQ-5D-5L index, and site. The analysis population will include all randomized participants with a baseline EQ-5D-5L assessment, analyzed according to randomized treatment. Participants who died before 12 months will be assigned a utility of 0 at the 12-month timepoint (composite strategy), regardless of whether a post-baseline assessment was obtained. Surviving participants without a 12-month assessment will be handled under the missing-at-random assumption in the primary analysis, with sensitivity

analyses as specified in Section 8.3.4. A survivor-only analysis excluding non-survivors will be reported as a prespecified sensitivity analysis.

A supportive repeated-measures analysis will use EQ-5D index values at 4, 8, and 12 months to estimate an overall mean treatment effect across follow-up visits. Within-participant correlation will be modeled using an appropriate covariance structure; a simpler structure will be used if needed for model stability. Handling of missing data and deaths, including any analyses of EQ VAS and/or EQ-5D dimension-level outcomes, will follow Section 8.2.2.

8.3.3 Subgroup analyses (exploratory)

Exploratory subgroup analyses will be conducted for the prespecified subgroups listed below. For each subgroup, treatment effects will be summarized with hazard ratios and two-sided 95% confidence intervals, and heterogeneity assessed using treatment-by-subgroup interaction terms.

- Age (<60; 60–70; 70–80; >80 years)
- Sex (male vs female)
- Weight (<60; 60–90; >90 kg)
- Diabetes (yes vs no)
- Prior cardiovascular disease (yes vs no)
- Baseline HRQoL (EQ-5D utility <0.5; 0.5–0.7; >0.7)
- Prior kidney transplantation (yes vs no)
- Mean session duration (≤240 min vs. >240 min)

8.3.4 Sensitivity analyses

Sensitivity analyses will include: (i) per-protocol analysis (as defined in section 8.1), (ii) covariate-adjusted Cox models including site and baseline prognostic factors (age, sex, diabetes, prior cardiovascular disease), and (iii) robust standard errors clustered by site, where appropriate. Sensitivity analyses will also assess the impact of censoring/loss to follow-up and any partial or uncertain event dates using prespecified approaches detailed in the SAP.

For the secondary endpoint (EQ-5D-5L index), prespecified sensitivity analyses will include: (i) survivor-only analysis excluding non-survivors; (ii) analysis assigning non-survivors the worst observed EQ-5D-5L index value in the dataset rather than 0; (iii) tipping-point analysis in which missing EQ-5D-5L data in the twice-weekly arm are progressively shifted toward worse values; (iv) analyses adjusting for EQ-5D-5L collection method (digital vs. assisted) as a covariate, to assess potential open-label bias associated with mode of administration; and (v) assessment of differential EQ-5D-5L missingness between arms, with inverse-probability-of-response weighting and multiple imputation under a missing-not-at-random assumption if differential missingness exceeds 5 percentage points at any timepoint. Items (iv) and (v) are mandatory for open-label domains per core protocol Section 9.6.

8.4 Sample Size Determination

8.4.1 Sample size assumptions for the primary endpoint (12-month mortality)

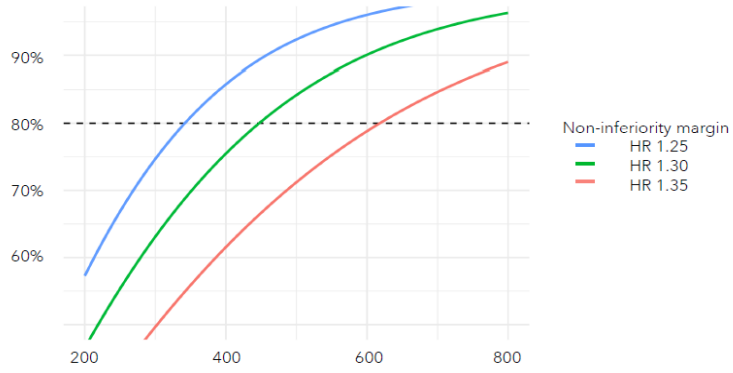
Per the non-inferiority margin and testing parameters specified in Section 8.2.1 (HR=1.30, one-sided α=0.025), with power=80%, allocation 1:1, and follow-up fixed at 12 months, the required number of primary events when the true HR=1.0 would be:

$$E=(z_{1-\alpha}+z_{1-\beta})^2/\{\ln(M)\}^2, \text{ with } z_{1-\alpha}=1.96,\ z_{1-\beta}=0.842,\ M=1.30 \Rightarrow E\approx 114 \text{ deaths.}$$

Power is ~ 80% at true HR=1.0, 63% at HR=1.10, and 53% at HR=1.15. Observational and clinical data support an assumption of no meaningful mortality difference between incremental twice-weekly and conventional thrice-weekly hemodialysis.[30,35,36,38–40,44,45] The planning value p_0=0.255 is anchored to Danish observational data in incident hemodialysis patients aged 60–90 years (2015–2023) with an estimated 12-month mortality risk of 25.5%. For planning purposes only, an exponential constant-hazard approximation was used to translate HR margins to absolute 12-month risks; the primary analysis will use a Cox model and does not rely on an exponential survival assumption. Using a control 12-month risk p_0=0.255, the expected total sample size is:

$$N \approx E/p_0 = 114/0.255 \approx 447 \ (\sim 224 \text{ per arm}).$$

Applying a 10% buffer yields a planned enrollment ≈ 492 total (~246 per arm). An overview of sample size and power relative to the non-inferiority margin is shown in the figure below:



The trial is event-driven and powered for approximately 114 deaths occurring within 12 months post-randomization. Enrollment will continue until the event target is reached or projected to be reached with enrolled participants, after which enrollment will cease. The primary analysis will use a locked data cut at the next scheduled 4-monthly platform timepoint after attainment of the event target, with administrative censoring at the earliest of the data cut date, 12 months post-randomization, emigration, or withdrawal of follow-up consent (where applicable).

Statistical analyses will be conducted in R (R Foundation for Statistical Computing) using validated, version-controlled code. The R version and key package versions used for the primary analyses will be documented in the final SAP and archived with the analysis code.

8.4.2 Sample size assumptions for the secondary endpoint (EQ-5D-5L)

Based on prior observations, a conservative variability estimate for the EQ-5D-5L utility in a population of patients with ESKD is 0.267, with minimal important differences for EQ-5D-5L utility in comparable settings estimated to be approximately 0.05–0.08.[63] With two-sided α=0.05 and 80% power, the corresponding detectable mean difference is about 0.086 with 150 evaluable participants per arm, 0.075 with 200 per arm, and 0.067 with 246 per arm, which falls within the clinically meaningful range. EQ-5D-5L is a key secondary endpoint tested for superiority at two-sided α=0.05 conditional on demonstrating primary non-inferiority; therefore, no additional alpha adjustment is required for a single gated key secondary.

8.5 Event Accrual, Enrollment Stop, and Analysis Trigger

8.5.1 Primary event definition

Primary events are deaths from any cause that occur within the first 365 days after randomization. Deaths occurring after day 365 do not contribute to the primary event target.

8.5.2 Enrollment stop rule.

Enrollment will cease when a locked database extract confirms that ≥114 primary events (deaths within 365 days of randomization) have accrued across both arms.

8.5.3 Analysis trigger

The primary analysis will be performed using a database cut-off date corresponding to the next scheduled nominal 4-month platform assessment window after the event target is reached.

9 Ethics and Dissemination

INITIATE compares two frequencies of standard hemodialysis, a medical procedure delivered using CE-marked equipment within its intended purpose. The domain involves no investigational medicinal product as defined in Article 2(2)(5) of Regulation (EU) No 536/2014 and is not a clinical investigation of a medical device; it is conducted as a non-IMP domain of the APT-KIDNEY platform trial under the Regulation (core protocol Section 7.2), with safety reporting as described in Section 3.2.2.

Patient and public perspective. Where feasible, patient perspectives will be considered to support the relevance, feasibility, and acceptability of INITIATE in routine dialysis care. Patient representatives and/or relevant patient organizations may be invited to comment on participant-facing materials and on the acceptability of participant-reported outcome collection (including EQ-5D-5L) and overall study burden. Patient-facing dissemination approaches will be considered when communicating study results.

10 Study Assessment and Monitoring

Study assessment and procedures are described in the APT-KIDNEY core protocol. Additional domain-specific assessments and procedures are summarized in the schedule of appointments.

10.1 Monitoring plan

Monitoring by the GCP-unit and central monitoring will be performed in accordance with the APT-KIDNEY core protocol.

10.2 Protocol deviations and serious breaches

Protocol violations and serious breaches will be handled as described in the core protocol.

10.3 Independent Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee (IDSMC) will oversee participant safety, trial conduct, and the overall benefit–risk balance for the INITIATE domain. The IDSMC will provide independent recommendations to the domain and platform steering committees in alignment with the APT-KIDNEY core protocol. No formal interim analyses for efficacy or futility are planned; IDSMC reviews are for safety and conduct oversight. Any unblinded comparative summaries will be used for oversight and participant protection only.

10.3.1 IDSMC Membership and independence

IDSMC composition and independence requirements follow the APT-KIDNEY core protocol. In brief, the IDSMC is multidisciplinary, independent of sponsor/investigators, and members should have no relevant conflicts of interest. The domain-specific IDSMC will be named prior to first inclusion.

10.3.2 IDSMC meetings and reports

The IDSMC will schedule monitoring and meetings as appropriate for domain progress, and will meet periodically (and at least annually), with additional ad hoc meetings as needed. For INITIATE, reviews are expected to occur periodically during accrual i.e. broadly aligned with event accumulation, without fixed interim analysis milestones.

Meetings will follow the core protocol structure. An open session focusing on operational updates and aggregate data will be followed by a closed session with participation limited to the IDSMC and designated unblinded methodological/statistical support permitting review of unblinded comparative summaries. Open and closed reports will be prepared and shared according to the core protocol.

10.3.3 IDSMC responsibilities

The IDSMC's core responsibilities will be to protect participant safety and identify emerging safety concerns, to monitor trial conduct and integrity including recruitment, adherence, cross-over patterns, and protocol deviations, and to advise as to whether risk-mitigating changes to trial conduct are warranted.

Key clinical outcomes for monitoring of INITIATE safety include:

- All-cause mortality
- Major adverse cardiovascular events (non-fatal MI, non-fatal ischemic stroke, or cardiovascular death)
- EQ-5D-5L completion rates by arm and timepoint
- Domain-specific safety outcomes as defined in section 3.2.2
- Escalation and de-escalation rates by arm, site, and triggering indication

10.3.4 Unblinding, confidentiality, and communication

INITIATE is open-label, participants and treating teams know the assigned dialysis frequency. However, interim comparative results i.e. between-group summaries, are confidential and restricted to the IDSMC and designated unblinded support staff. Communications to the sponsor/PI, investigators, and steering committees will be framed as recommendations i.e. “continue” / “modify” / “pause”, without sharing interim comparative estimates or interpretations unless urgent participant-safety actions require disclosure.

10.3.5 Interpreting signals and recommendations (harm-focused; non-binding)

Consistent with the core protocol, the IDSMC may recommend continuing, modifying, pausing, or stopping the domain (or an arm) if observed differences in safety outcomes are concerning, even without prespecified statistical rules. The IDSMC will consider the totality of evidence, including magnitude and consistency across mortality and serious safety outcomes, clinical plausibility, timing and severity of events, data quality, and operational factors including cross-over and/or escalation. All recommendations will be advisory.

If recommending cessation or a pause, the IDSMC will specify whether additional analyses including participants enrolled up to that point are needed and whether a temporary moratorium on further enrollment should apply during those analyses, as described in the core protocol.

10.3.6 IDSMC Documentation

An IDSMC Charter documenting meeting cadence, report templates, confidentiality, documentation of deliberations, and urgent communication pathways will be finalized prior to enrollment of the first participant and maintained as part of domain and platform governance. Any subsequent changes to monitoring procedures will be prospectively documented and archived.

10.4 End-point classification

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 where available. Non-fatal MACE components will be registered by site staff from source documentation, with register data used for verification. As the primary endpoint is all-cause mortality and MACE components are tertiary, central blinded adjudication is not required (core protocol Section 8.9.2).

10.4.1 End-Point Definitions

1) **All-cause mortality:** Death from any cause during follow-up.
2) **Cardiovascular death:** Death due to a cardiovascular cause (e.g., sudden death/arrhythmia, MI, stroke, heart failure/pulmonary edema, PE, aortic catastrophe, peri-procedural CV). Classification as CV death is attributed to a CV cause or non-CV causes are reasonably excluded and the presentation fits a CV cause.
3) **Non-fatal myocardial infarction (MI):** Acute MI with myocardial injury and ischemia: troponin >99th percentile with rise/fall plus ≥1 of ischemic symptoms; new ischemic ECG or new LBBB; new Q-waves; imaging showing new loss of viable myocardium/regional wall-motion abnormality; or angiographic thrombus. If troponin is unavailable, accept a discharge summary naming acute MI with consistent clinical documentation. Include Type 1–2 MI.

4) **Non-fatal ischemic stroke:** Treating-team diagnosis of acute ischemic stroke causing a new focal neurological deficit ≥24 h, or <24 h with imaging evidence of acute infarction. TIA will not be defined as stroke. Hemorrhagic transformation of an ischemic stroke will be classified in accordance with the primary mechanism as ischemic unless clinically reclassified as primarily hemorrhagic.

11 Organizational and financial aspects

11.1 Conflicts of interest

Declarations of interests are handled as described in core protocol Section 11.3.

11.2 Funders, supporters, and roles

Funders, supporters, and roles: The domain is conducted under the platform sponsor (core protocol Section 3.1). Funding has been applied for from Sundhedsdonationer and Danske Regioners Medicin- og behandlingspulje; funders have no role in design, conduct, analysis, or publication decisions.

11.3 Compensations

Sites may receive per-patient payments for screening, randomization, and follow-up visits. No participant reimbursement is planned. Participant compensation for trial-related injury is provided at platform level as specified in core protocol Section 11.4.2.

11.4 Publication and authorship considerations

Publication and authorship considerations will be in accordance with core protocol considerations.

11.5 Estimated timeline

First sites are expected to open in Q1–Q2 2027. Enrollment is expected to complete within approximately five years (planning rate approximately 100 participants per year), with 12 months of follow-up after randomization. The primary analysis is event-driven and takes place at the first platform timepoint after 114 primary events have accrued (Section 8.5).

12 Supporting Documentation

Appendix 1: Flowchart of study inclusion

Appendix 2: Schedule of appointments

Appendix 3: INITIATE Design card

13 References

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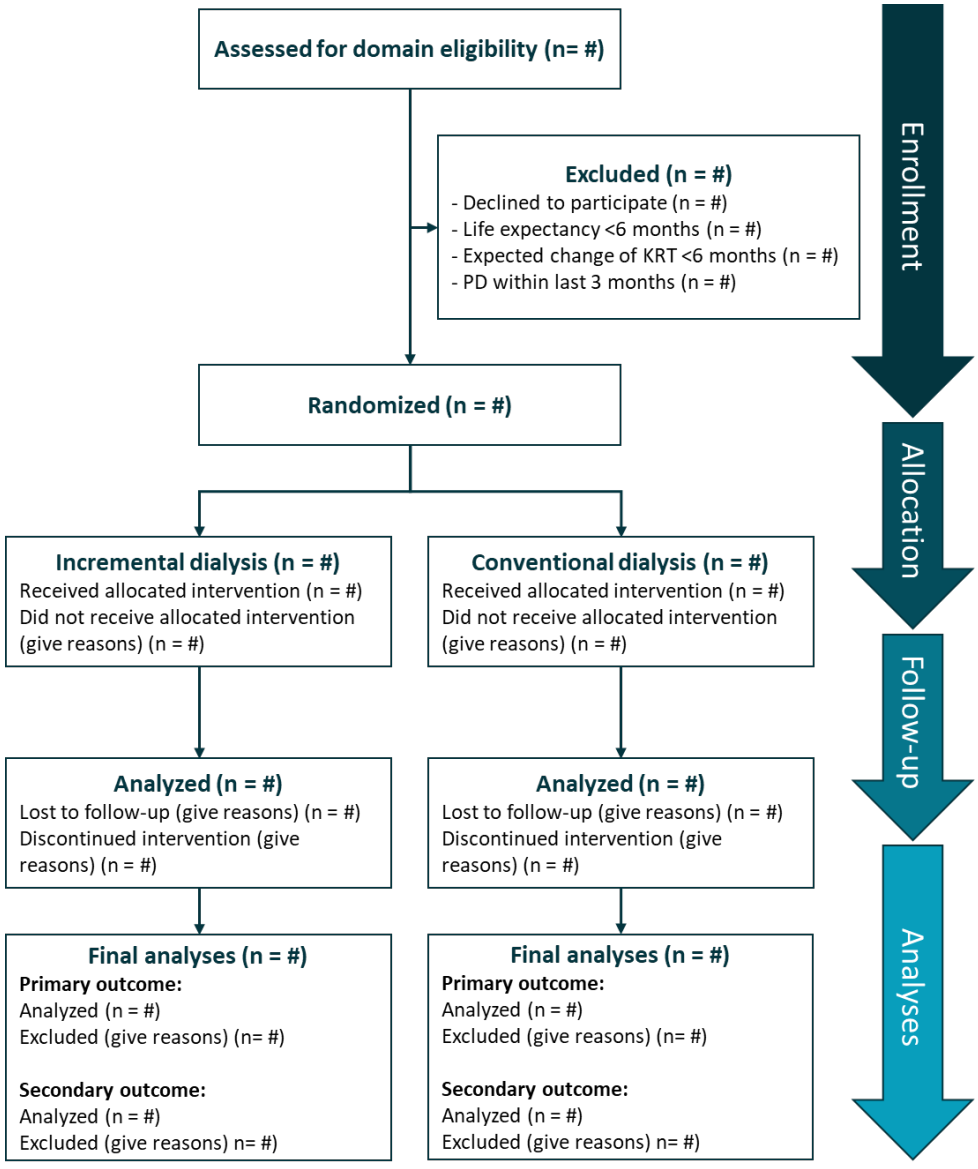
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14 Appendix 1: Flowchart of study inclusion



Inclusion flowchart
Abbreviations: KRT, kidney replacement therapy; PD, peritoneal dialysis

15 Appendix 2 Schedule of appointments

	Screening	Inclusion	4 months	8 months	12 months	End of study
Eligibility check (inclusion/exclusion)	●					
Informed consent		●				
Baseline data		●				
24-h urine collection		●	●	●	●	
HRQoL (EQ-5D-5L)		●	●	●	●	
Dialysis prescriptions		●	●	●	●	
Safety outcomes			●	●	●	●
Survival status			●	●	●	●
Discontinued allocation			●	●	●	●

Abbreviations: HRQoL, health-related quality of life;

16 Appendix 3: INITIATE Design card

Paradigm: Frequentist, fixed-sample

Primary outcome: All-cause mortality (time-to-event, 12 months)

Guiding outcome for adaptation: Not applicable (no adaptive features)

Randomization: Fixed 1:1, permuted blocks, stratified by site

Interim efficacy/futility analyses: None

Adaptive stopping/arm-dropping: None

Response-adaptive randomization: None

Decision rules: Not applicable

Maximum planned information: 114 primary events

IDSMC role: Safety and conduct oversight only