CONCORDIA Study Protocol

***Co**mparison**s** of biochemical and **c**linical **o**utcomes of hemodialysis patients t**r**eated with middle cut-off **dia**lyzers versus high-flux Hemodialysis or Hemodiafiltration*
(CONCORDIA Study)

Version: 20260101
Date: March 1, 2026

Contact Information:
Principal Investigator: Roberto Pecoits-Filho
Arbor Research Collaborative for Health

DOPPS Coordinating Center
Arbor Research Collaborative for Health
2723 S. State Street
Suite 150
Ann Arbor, MI
Phone: (734) 665-4108
DOPPS@ArborResearch.org

Table of Contents

Introduction

The mortality rate is exceedingly high among hemodialysis (HD) patients. Data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) have shown that mortality rates of HD patients are extremely high and vary across geographies (1). Demographic status and comorbid disease accounted for some but all the differences in the risk of mortality between the three continents. This variation in mortality across facilities and countries raises the possibility that differing treatment practices may contribute to the variation in outcomes (2).

Conventional HD treatment has an acceptable removal of small uremic molecules, but molecules of higher molecular weight are poorly cleared with HD compared to a native kidney, contributing to morbidity in the dialysis population. Hemodiafiltration (HDF) has a better removal of middle molecules compared to HD but is technically demanding, more expensive and requires well-functioning dialysis access to achieve high convective volumes (3). A recent large randomized controlled trial (RCT) has shown that HDF reduces the risk of all-cause mortality in 23% compared to high-flux HD (4).

Additionally, a novel class of membranes, medium cut-off (MCO) membranes, has been designed to remove middle and large middle molecules without requiring operational changes to standard HD sessions (5). The few studies published to date reported that MCO consistently removes more middles-sized molecules than high-flux HD, while results are conflicting compared to HDF (6). Studies comparing clinical outcomes between MCO and high-flux HD or HDF are lacking.

DOPPS provides a real-world representation of HD/HDF practices and can serve as a valuable “control” group for comparisons of biochemical and clinical outcomes versus patients utilizing MCO dialyzers. We plan to supply large-scale real-world evidence study among patients undergoing treatments with high flux HD, HDF and MCO to evaluate the impact of dialysis modality on clinical outcomes. We hypothesize that HD with MCO dialyzers is associated with an improvement in clinical and biochemical outcomes compared with high flux HD, and non-inferior results in comparison to HDF.

Study Objectives

Primary objective:

- Determine if MCO dialyzer (Theranova, Baxter Healthcare) use is associated with lower all-cause mortality compared to high-flux HD.

Secondary objectives:

- Determine if Theranova dialyzer use is associated with better biochemical outcomes compared to high-flux HD.
- Determine if Theranova dialyzer use is associated with non-inferior clinical and biochemical outcomes compared to HDF.
- Identify patient characteristics associated with Theranova dialyzer use.

Primary outcome (clinical):

- All-cause mortality

Secondary outcomes (clinical):

- Major Adverse Cardiovascular Events (MACE): composite of CV mortality, non-fatal stroke, non-fatal myocardial infarction, hospitalizations due to heart failure, non-fatal thromboembolic events
- Infection events including mortality due to infection and infections requiring either an infection-related hospitalization or prescription of intravenous antibiotics.
- All-cause hospitalizations

Secondary outcomes (biochemical):

- Anemia and iron reserves: hemoglobin, TSAT, ferritin; all expected to be better for Theranova than for high flux HD and similar for Theranova v. HDF.
- Mineral Bone Metabolism markers: phosphorus, calcium, PTH, and alkaline phosphatase, all expected to be better for Theranova than for high flux HD and similar for Theranova v. HDF.
- Beta 2 microglobulin, albeit limited to facilities that routinely collect this information in France (7). Feasibility of this analysis will be assessed early in the study.
- Protein energy wasting
    - Nutritional measures: Serum albumin is expected to be marginally lower for Theranova than high flux HD but this is not expected to substantially contribute to adverse clinical outcomes. Other nutritional measures may include serum creatinine and normalized protein catabolic rate (nPCR).
    - Measures of inflammation: C-reactive protein (CRP) (well-captured in DOPPS Europe and will be the primary measure of inflammation), white blood cell count, neutrophil/lymphocyte ratio, and erythropoiesis-stimulating agent (ESA) resistance.

The above measures may be reported on separately or combined into a single overall measure of protein energy wasting. We propose to start with the criteria outlined in Fouque (2008), adapting as necessary or indicated by the data.

Secondary outcomes (volume and blood pressure):

- Differences in pre- and post-dialysis systolic blood pressure: This comparison will serve as a marker of intradialytic hypotension episodes.
- Inter-dialytic weight gain
- Ultrafiltration volume

Secondary outcomes (medication use):

- Phosphate binders, ESAs, iron, anti-hypertensive medications, antibiotics, calcimimetics.
- Exploratory Outcomes
- COVID-19 hospitalization
- COVID-19 Mortality

Study Design and Methods

Synopsis

Our study will assess potential differences in outcomes comparing patients treated with HD using a Theranova dialyzer compared with patients treated with HF-HD and HDF from DOPPS. Our retrospective study design is observational rather than interventional, but we limit bias by comparing treatments suitable for the same group of patients, statistically adjusting for differences in case mix, and leveraging 'natural experiments' such as preferential uptake of devices in some but not other dialysis facilities.

Site Selection

Theranova study sites/patients:

As a basis for the projection of Theranova utilization in Europe, we contacted the DOPPS country investigators from seven European countries. The experts estimated that Theranova use in their countries ranges from <5% in most countries up to 8-13% in the UK. Furthermore, they described that Theranova utilization is generally clustered, indicating the existence of high-use facilities. For this analysis, we will create an Theranova cohort through targeted recruitment of patients from facilities not participating in DOPPS and identified as high Theranova users through communication with the sponsor and country investigators in Italy, France and the UK. A survey targeted to pre-identified sites with high utilization to assess interest and feasibility has been issued and is being collected at this time with support from DOPPS country investigators. Based on the initial results of this survey and statistical power considerations, we propose to invite 20 sites with high Theranova use, with the recognition that not all 20 may participate. Based on the early data on Theranova use in some candidate sites, we believe we can achieve an enrollment of 500-1000 Theranova-using patients across all participating sites.

Control study sites/patients (hf-HD, HDF in DOPPS):

We will construct comparison cohorts based on patients participating in the DOPPS Phase 7 in Europe. This design leverages the extensive existing infrastructure of DOPPS Europe, substantially improving study timeliness and efficiency. Also, the representativeness of DOPPS sites and patients improves the potential for external validity of the study findings.

Study Participants

All study participants, in order to be eligible for inclusion in the study, must be at least 18 years of age and receiving in-centre haemodialysis for the chronic treatment of kidney failure, i.e., end-stage renal disease (ESRD).

Inclusion Criteria

- 18 years of age or older
- Treated at an in-centre dialysis clinic
- Receiving chronic, maintenance HD

Exclusion Criteria

- Less than 18 years of age
- Treated with a home-based dialysis modality
- Receiving HD for acute kidney injury

Patient Informed Consent/Waiver of Consent

Patients participating in DOPPS (representing the control arm of the study) have already provided informed patient consent for participation in the study. Sites not participating in DOPPS will be identified based on the high utilization of Theranova dialyzers and invited to participate. Patients from these Theranova sites will be pseudonymized to the extent that patient informed consent will no longer be needed. Waiver of consent will be obtained to document this process point.

Procedures for pseudonymization

The data from the Theranova-only study sites will be pseudonymized at the centers, and Arbor Research will only receive de-identified data. To protect patient confidentiality, we will perform date-shifting and certain continuous variables that could be used to identify patients will be 'binned.'

Date-shifting: Dates of treatment, birth dates, and other important dates can be used to identify patients (e.g. through looking for an obituary for someone who died on a specific date). We will pick a random number between -180 and +180 for each patient, and shift all their relevant dates (birth dates, death dates, dates of treatment, lab dates, prescription start/end dates, hospitalization dates, etc.) by this number. This preserves the relative time between events (e.g. the time between starting to use a specific dialyzer and specific outcomes), while preventing identification through dates. Truncation will be performed as necessary to preserve confidentiality, as described in Hripcsak et al. (2016).

Binning: Patient age, for example will be binned within 5-year age groups, so a 63 year-old patient would be in the "60-64" age group. If any bins have too few patients to protect patient confidentiality, e.g. a "95-99" age group that contained only a single patient, it will be combined with surrounding bins (e.g. "90-99") until the group has at least ten patients.

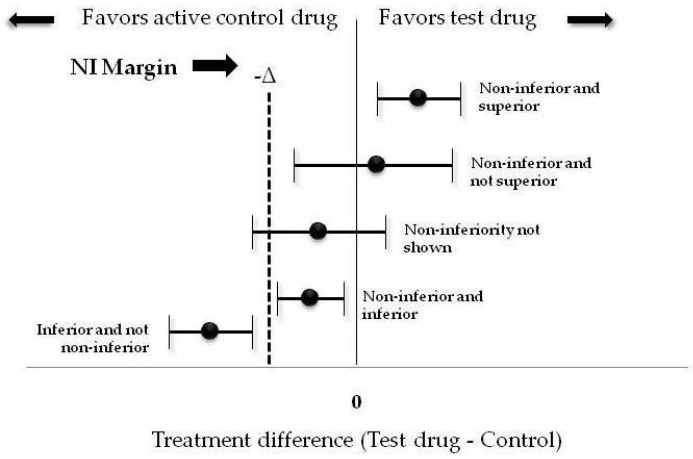
Burden to Participants

This study will not impose additional burden on patients. Any new data gathered for the Theranova study will be abstracted from medical records by study site personnel and not require interaction with patients.

Sample Size

We used the death rate in DOPPS Phase 7 among European countries as a base for estimates in that cohort. We reported 0.15 deaths/patient-year, and the rate of first hospitalizations during follow-up is 0.63 first hospitalizations/patient-year. The following assumes that patients in DOPPS 7 could be used in the matching, and that we successfully recruit non-DOPPS facilities with high Theranova use, an alpha of 0.05, and 80% power. In order to have results as soon as possible, we will ask the facilities with high Theranova use (selected as described above) to provide retrospective data on Theranova use and outcomes, which we're assuming will provide a median of 2.0 years of exposure, dependent on date of entry and censoring, since the centers started using Theranova dialyzers. We will initially assume a continuous exposure to Theranova after the initial identification of utilization and will monitor -Estimates are based on the SAS power procedure, accounting for facility-level clustering.

We will perform both superiority and non-inferiority analyses. The figure below illustrates the difference (Schumi 2011). In non-inferiority analyses, the common procedure is to select a 'margin' and demonstrate that the new treatment does not lead to clinical outcomes worse than this margin when compared to the standard treatment (8).



In the FDA guidance (Section IV, Subsection C 1 – *The Fixed Margin Approach),* a fixed margin is recommended based on the lower bound of the 95% CI from a study comparing the active control with placebo (https://www.fda.gov/media/78504/download). In our case, a placebo is not a viable choice, so we have chosen to base our comparisons on analyses that compared HDF) with the current standard treatment of high-flux HD.

The CONVINCE trial (4), a recent RCT comparing HDF vs. High-flux HD, provides an adequate basis for the non-inferiority margin, following the FDA guidance. This study found that HDF resulted in a 23% lower risk of all-cause mortality (HR: 0.77; 95% CI: 0.65 - 0.93) compared to high-flux HD. Using the upper 95% confidence bound from CONVINCE and applying it to the mortality rates in DOPPS, our study should be able to detect non-inferiority for all-cause mortality if the Theranova group death rates are lower than 13.9 per 100 patient-years. With approximately 1,000 Theranova users and 1,500 HDF patients, our study would have 80% power to detect non-inferiority comparing Theranova vs. HDF. With the same sample size, the minimally detectable hazard ratio (MDHR) comparing Theranova vs. high-flux HDF for superiority would be 0.72 at 80% power. This MDHR is consistent with the design of the CONVINCE study, which suggests our study is well-powered both for the primary objective of superiority in respect to high-flux HD and the secondary objective of noninferiority to HDF. In estimating our sample size, we assume that the effect size between high-flux HD and Theranova mirrors that of high-flux HD compared to HDF.

In a feasibility survey sent to participating countries, we found more than 1,000 patients undergoing dialysis using Theranova dialyzers in historical data. The initiation of Theranova use was > 2 years for all surveyed facilities.

Study Data

For the control group, DOPPS collects data using a common protocol and data collection instruments in all participating countries. Data are reported on study forms in a pseudonymized format. Pseudonymized means that any information about you will be linked by a number instead of your name, so that the identities of participants are not identifiable to DOPPS and remain anonymous. A Study Coordinator at each participating dialysis facility performs the majority of data collection. The retrospective data collection period will start in March 1 2026 and end in June 30, 2026. Patients on maintenance HD using Theranova dialyzers are eligible if they have available data between January 2018 and June 2026.

Data Collection Instruments

Data Collection for DOPPS Facilities (HD and HDF patients):

Per the DOPPS protocol, we will use medical record extraction and EHR extracts to obtain retrospective data on case mix details, demographics, comorbidities, and clinical outcomes for all participants. Data is already complete and fully available for DOPPS sites. Theranova facilities will collect data between March 2026 and June 2026

Data Collection for Non-DOPPS Facilities:

We will collect data for among the non-DOPPS facilities leveraging existing DOPPS procedures and infrastructure.

Subject-specific dates: Date of birth, start of ESKD, start of dialysis at this center, start of HD, recruitment dates, date of death/censoring event (transplant, transfer to another facility, etc.)

Demographics/comorbid factors: sex, comorbid factors (i.e. MQ)

Labs: serum albumin, serum creatinine, nPCR, CRP, WBC, neutrophil/lymphocyte ratio, phosphorus, calcium, PTH, and alkaline phosphatase, beta 2 microglobulin (in facilities where this is routinely collected), hemoglobin (to measure ESA resistance), and ferritin/TSAT

Dialysis treatment: Kt/V elements (BUN, duration, HDF convective volume), UF, IDWG, SBP/DBP (pre- and post-dialysis, as well as intradialytic hypotension if available), residual urine volume, dialysate sodium, vascular access type at baseline

Modality and dialyzer type: History by dialysis modality and dialyzer type (HDF, HF, Theranova, other), including start/stop dates for each

Other treatment: Medications (ESAs, hypertension control, antibiotics, phosphate binders, iron, calcimimetics) at baseline and follow up (6 months)

Hospitalizations: arrival, departure, diagnoses/treatment ICD codes

Termination events: death (including causes of death), transplant, transfer to another facility, modality change to PD, recovery.

Other:

- Frequency of collection will be monthly for labs
- Longitudinal Theranova use

Overview of Study Design Details

To be used as a control group in this study, DOPPS collects detailed data on patients' characteristics, clinical practices, and outcomes, as well as data on patient experiences and the perspectives of nephrologists. Data are collected using a common protocol across all countries. As a departure from our past DOPPS phases, the seventh phase includes a streamlined protocol that collects data every 6 months; however, key areas of focus, such as medications, hospitalizations, and mortality are collected on an event basis, and study sites are encouraged to

submit this data as the events happen. This updated study design allows the study to be flexible and responsive to the research interests of the community while capturing consistent data which permits comparison across study phases and countries.

Details of the DOPPS protocol are shown in Table 2, below.

Table 2. Study Design Details

Study Feature	
Patient Sampling	

Patient enrollment	• For DOPPS controls:
	  ○ A sample averaging 20 to 24 patients per facility, replenished every 6 months
	  ○ In Belgium, France, Germany, Italy, Spain, Sweden, and the UK (all DOPPS 7 participating countries)
	• For Theranova users (non-DOPPS facilities):
	  ○ No site minimum or maximum specified

Data Collection Frequency	
Baseline, study start	• Initial facility **CENSUS** • Enrol cross-sectional study sample
Every six months	• Update facility **CENSUS** for mortality and departures • Replenish cross-sectional study sample • Longitudinal measures (**IS**) for continuing patients • **Hospitalizations** events and procedures • Update list of **medications** per patient • Cause of death, etc. among departed sample patients (**TF**)

Data Entry and Management

Each newly participating facility will receive credentials to utilize the eCRF developed for the study using RedCap. Facilities continuing on from the preceding study phase will be able to continue to use their previously established credentials for the use of ArborLink. There are policies and procedures in place detailing the secure storage of all data, both paper (PQs) and electronic. All data are available only to authorized personnel. The

System Security Plan is kept confidential. If further details are required, for example by an ethics board, it can be provided on a case-by-case basis.

Estimated Study Duration

The DOPPS 7 study (control arm) operating period spans 2018 through 2023. Theranova facilities will include patients with available retrospective data between March 1 and June 30 2026.

Payments for Data Collection

Study sites will receive remuneration based on their performance of the protocol described above. Amounts will be offered to compensate for coordinator time and effort to abstract clinical data from medical records and input data into the study data entry system. Total payments will vary from site to site based on the number of patients enrolled and the quantity of CRFs completed. Sites will receive $750 upon submission of the first patient record, and will receive $85 for each patient record submitted thereafter. Patients will not receive compensation.

Data Processing and Reliability

Assuring the integrity of data collected in the DOPPS programs is an important activity occurring throughout the study. The first step is to run the data through quality control programs (e.g., range checks, units of measure, evaluation of non-response, etc.) when data are first received by the DCC. Once cleaned data are available for analysis, an additional standard procedure is to perform comparisons with external sources to the extent available. These external sources include, but are not limited to, published papers and registry reports. Formal data reliability studies have been performed at various time points, demonstrating a high level of data quality.

Analytical Methods

Our primary objective (Theranova superiority versus HF-HD) will be addressed using Cox models to assess associations between the treatment used with subsequent clinical outcomes. The primary approach will be an 'intent to treat' model, where modality, including Theranova use, is assessed at a point in time (preferably the first Theranova use during follow-up using the retrospective data). Statistical adjustment and, if necessary, matching will be performed to ensure that Theranova users are compared to patients who were otherwise similar. Models will be performed sequentially, including more adjustment factors with each model to illustrate the effects of each set of potential confounders. Adjustments will include country, demographics, comorbid factors, labs (see below re: serum albumin), and treatment factors. Missing data will be addressed with standard multiple imputation techniques (the MI procedure in SAS or IVEware).

The survival models will use cause-specific approaches to handle competing risks. Due to the fact that whether a patient has been hospitalized can influence the risk of future hospitalizations for that patient, analyses of MACE events or all-cause hospitalizations will be performed as time-to-first hospitalization after the measurement period. Proportional hazards assumptions will be tested using a linear interaction with follow-up. We will adjust for the clustered nature of the sampling plan through a robust sandwich estimator for the variance of our estimates. The missing-at-random assumption will be evaluated using clinical judgement for variables with substantial missing data.

Serum albumin will be added last to the sequential adjustment analyses as a supplemental model, as albumin may be either a confounder or a mediator. It is expected that Theranova use would affect clinical outcomes compared to hf-HD through two separate causal paths: improvement through greater middle-molecule clearance, and any possible effect due to reduced albumin levels. The interpretation of the supplemental model would be to assess the effect of Theranova use through the middle-molecule clearance causal pathway, excluding any effect of the reduced albumin levels. The model with and without adjustment for albumin levels would provide information clarifying the strength of the association through both causal pathways.

For objective of characteristics associated with Theranova use, patient characteristics associated with Theranova use during standard clinical practice will be evaluated by comparing means and distributions, and adjusted odds ratios will be calculated using multivariable logistic regression. Inclusion in models will consider Theranova assignment on a 'per protocol' versus 'by indication' basis. These models will adjust for facility-level clustering using a mixed model with a compound symmetry covariance structure. Patients who were randomized to Theranova use (e.g. the randomized controlled clinical trial ongoing in sites in Spain - MOTheR) will not be used for these analyses.

We expect the observational study to be confounded to some extent by treatment-by-indication bias, weakening our ability to detect improvements in patient outcomes due to Theranova. Our analyses of patient characteristics linked with Theranova use (objective 3) will help us identify the likely extent to which this is true. For example, these analyses would identify whether Theranova patients have fewer or more comorbidities than patients in the other treatment groups, and this would provide indications of possible biases in Theranova use. Focusing our sample on facilities with high Theranova use is an effective means to minimize this bias, as Theranova use would be more of a facility-wide policy than a treatment for exceptional patients.

Non-inferiority analyses will be conducted by testing if the results for patients using the Theranova dialyzer are not worse than the pre-defined margin percentage, as described above.

Sometimes, HDF patients are not able to achieve high convective volumes, often due to vascular access issues. Sensitivity analyses will be conducted where the HDF comparison population will be split into those achieving high fluid volume (20L+) and those who did not achieve these volumes. At baseline (enrolment), 77% of the European DOPPS HDF patients in phase 7 achieved 20L or more fluid volume at baseline.

Finally, infection-related endpoints will be stratified by COVID-19-related events as an exploratory analysis. Since the DOPPS 7 protocol overlapped with the COVID-19 pandemic, we decided to recruit Theranova patients covering the same period to limit calendar time bias.

Protection of Human Subjects

Compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), Public Law 104-191 and research involving human subjects under the Common Rule (45 CFR Part 46, Subpart A) is maintained. In addition to applicable laws and regulations, Arbor Research has internal policies and procedures on human subject protection including protections to help ensure the privacy of subjects and the confidentiality of information.

DOPPS is a prospective cohort study of HD subjects and facilities in multiple countries. A patient's treatment is not affected by participation in DOPPS, and there are no treatment interventions employed as part of this study. A very high level of confidentiality and security is maintained, as demonstrated throughout over 20 years of international DOPPS data collection. Patient participation in DOPPS only occurs after a patient has provided written informed consent. For further information regarding protection of human subjects, please see the Patient Informed Consent Form or contact the DCC.

A copy of the protocol, proposed informed consent form, and questionnaires are included below. These documents, along with all other necessary study materials, are submitted to the independent DOPPS IRB for written approval. A copy of the written approval of the protocol and informed consent form are on file at the DCC.

The DCC works with country investigators to submit an application and, where necessary, obtain approval from their local IRB or EC for participating in DOPPS. The country investigator is responsible for obtaining annual IRB or EC approval/renewal for the duration of the study, as needed. All data are transmitted over a secure, encrypted channel and are stored in compliance with each country's EC requirements.

To protect patient confidentiality for non-DOPPS Theranova sites, retrospective data obtained from the Theranova sites will be pseudonymized, date-shifted and certain continuous variables that could be used to identify patients will be 'binned.'

Future Directions

We can leverage this study's infrastructure to efficiently extend collection of these detailed observational data, providing a state-of-the-art resource for monitoring, analyses, and potential bioassay-based studies as Theranova use expands in the coming years. These data will substantially enhance any registry efforts to study and monitor Theranova use and outcomes. Following on previous (Weiner 2020) or ongoing but relatively small clinical trials (e.g., MOTheR, in Spain), this resource will provide accurate estimates of effect sizes, sample size needs, patient subgroups of interest, and information on use (e.g., countries/facilities/types of patients) toward the rational design of future interventional studies and an enduring real-world evidence generation program.

References

1. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States in the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 14:12:3270-3277, 2003.
2. Stirnadel-Farrant HA, Karaboyas A, Cizman B, Bieber BA, Kler L, Jones D, Cobitz AR, Robinson BM. Cardiovascular Event Rates Among Hemodialysis Patients Across Geographical Regions-A Snapshot From The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int Rep. 2019 Mar 28;4(6):864-872. doi: 10.1016/j.ekir.2019.03.016. PMID: 31194073; PMCID: PMC6551512.
3. Young EW, Goodkin DA, Mapes DL, Port FK, Keen ML, Chen K, Maroni BL, Wolfe RA, Held PJ. The Dialysis Outcomes and Practice Patterns Study (DOPPS): An international hemodialysis study. Kidney Int 57 (Suppl 74): S-74-S-81, 2000.
4. Singh AK, Carroll K, Perkovic V, Solomon S, Jha V, Johansen KL, Lopes RD, Macdougall IC, Obrador GT, Waikar SS, Wanner C, Wheeler DC, Więcek A, Blackorby A, Cizman B, Cobitz AR, Davies R, Dole J, Kler L, Meadowcroft AM, Zhu X, McMurray JJV; ASCEND-D Study Group. Daprodustat for the Treatment of Anemia in Patients Undergoing Dialysis. N Engl J Med. 2021;385(25):2325-2335. doi: 10.1056/NEJMoa2113379. PMID: 34739194.
5. Blankestijn PJ, Grooteman MP, Nube MJ, Bots ML. Clinical evidence on haemodiafiltration. *Nephrol Dial Transplant*. 2018;33(suppl_3):iii53-iii58. doi:10.1093/ndt/gfy218
6. Kanda E, Muenz D, Bieber B, Cases A, Locatelli F, Port FK, Pecoits-Filho R, Robinson BM, Perl J. Beta-2 microglobulin and all-cause mortality in the era of high-flux hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study. Clin Kidney J. 2020 Oct 27;14(5):1436-1442. doi: Weiner, Daniel E., Luke Falzon, Line Skoufos, Angelito Bernardo, Werner Beck, Mengqi Xiao, Ha Tran. Efficacy and Safety of Expanded Hemodialysis with the Theranova 400 Dialyzer. CJASN Sep 2020, 15 (9) 1310-1319;
7. Cozzolino, Mario, Lorenza Magagnoli, Paola Ciceri, Ferruccio Conte, Andrea Galassi, Effects of a medium cut-off (Theranova®) dialyser on haemodialysis patients: a prospective, cross-over study, Clinical Kidney Journal, Volume 14, Issue 1, January 2021, Pages 382–389, https://doi.org/10.1093/ckj/sfz155
8. Schumi, J., Wittes, J.T. Through the looking glass: understanding non-inferiority. Trials 12, 106 (2011). https://doi.org/10.1186/1745-6215-12-106

IRB APPROVAL

The CONCORDIA study was granted an exemption from IRB review as well as a waiver of consent by Salus IRB in the USA (Study ID: 22232). Country investigators will assist the Arbor Research team in seeking similar approvals in their corresponding countries.

QUESTIONNAIRES

Add New Patient

Add new patient			
StudyID		## {auto-generated}	
Unique Identifier		*{required}*	
Date of **first ever** dialysis	____/____/____ DD MM YYYY	Date of first haemodialysis **at this unit**	____/____/____ DD MM YYYY
Birth year:	*{dropdown 1910-2010}*	Sex:	0: Female 1: Male

Theranova history	
When did the patient start using the Baxter Theranova dialyzer for haemodialysis?	____/____/____ DD MM YYYY
Did the patient permanently stop using the Baxter Theranova dialyzer for hemodialysis and switch to another therapy (e.g., high-flux HD, HDF, PD) during the study period (January 1, 2017-December 31, 2022)?	0: No {skip rest of Theranova section} 1: Yes
Date of stop:	____/____/____ DD MM YYYY
Primary reason for stop:	1. Stopped due to clinical reasons 2. Stopped due to patient request 3. Stopped due to reimbursement/financial reasons 4. Other
What therapy did the patient switch to?	1. Haemodialysis with a high flux dialyzer 2. Haemodialysis with a non-high flux dialyzer. 3. Haemodiafiltration 4. Haemofiltration 5. Peritoneal Dialysis 6. Other
Patient status at study end	
Was the patient still on haemodialysis at your unit as of the study end (December 31, 2022)?	0. No 1. Yes {skip rest of section}
Date of LAST haemodialysis at this unit	____/____/____ DD MM YYYY
Reason for stopping haemodialysis at this unit	21: Died 23: Received kidney transplant 27: Left on holiday (vacation) for more than 6 weeks 28: Recovered renal function 29: Withdrew from dialysis 99: Did not dialyse during the study period or was entered by mistake 33a: Changed modality to peritoneal dialysis (at this unit) 33b: Changed modality to home haemodialysis (at this unit) 34: Transferred to another dialysis unit 35: Withdrew from study (still on haemodialysis at this unit) 37: Patient was lost to follow-up

I	HOSPITALISATIONS, EMERGENCY ROOM, & URGENT CARE VISITS

Please list all Hospitalisations, Emergency Room, or Urgent Care visits that occurred during the study period. A Hospitalisation is defined as admitting a patient to a hospital for a stay of one night or longer. For each visit, indicate at least one diagnosis and up to three procedures, if performed.

Date (DD/MM/YYYY)		Enter Code	Diagnoses			Procedures		
Admission or Service Date	Discharge Date	1: Inpatient Hospitalisation 2: Emergency Room or Urgent Care Visit	1	2	3	1	2	3
1. / /	/ /							
2. / /	/ /							
3. / /	/ /							
4. / /	/ /							
5. / /	/ /							
6. / /	/ /							
7. / /	/ /							
8. / /	/ /							
9. / /	/ /							
10. / /	/ /							
11. / /	/ /							
12. / /	/ /							

Date of death (if applicable)	____/____/____ DD MM YYYY

Hospitalizations

Interval Summary (IS)

C	LABORATORY DATA			
Enter the most recent lab values taken <u>during</u> the requested time intervals below. Use monthly pre-dialysis blood tests if possible.				
		Study baseline *{-6 mo to index date}*	**3 months after study baseline** *{index date to +3 mo}*	**6 months after study baseline** *{ndex date+3 mo to +6 mo}*
C-1	Date majority of measurements were taken	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY	____/____/____ MM DD YYYY
C-2	Creatinine			
C-57	Single pool, spKt/V			
C-3	Sodium			
C-4	Potassium			
C-6	Calcium			
C-7	Phosphorus			
	Albumin			
C-12	PTH			
C-25	Haemoglobin			
C-32	Transferrin saturation (TSAT)			
C-35	Ferritin			
C-38	C-reactive protein (CRP)	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done
C-41	Beta 2 microglobulin	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done	0: = 1: < 2: > 3: Below lower limit of detection 99: Not Done

	Prescription Data			
Indicate whether the patient was prescribed each medication class at of the dates indicated below				
		Study baseline *{index date}*	**+3 months after study baseline** *{index date +3 mo}*	**+6 months after study baseline** *{ndex date +6 mo}*
	Erythropoiesis-stimulating agent (ESA)	0: No 1: Yes		
	IV iron			
	Phosphate binder			

	IV vitamin D (active)			
	Oral vitamin D (active)			
	Calcimimetic			
	Anti-hypertensive agents: MRA (aldosterone antagonist) Beta blocker Calcium channel,blocker Diuretic Other			
	Angiontensin converting enzyme inhibitor (ACEi)	0: No 1: Yes		
	Angiontensin receptor blocker (ARB)			
	Mineralocorticoid receptor antagonist (MRA)			
	Diuretic			
	Other (beta blocker, calcium channel blocker, vasodilators)			

T	COVID-19	
T-3	Was the patient hospitalised for COVID-19? If yes, please enter the hospitalization in the patient's Hospitalisation Form.	O No O Yes

D	DIALYSIS PRESCRIPTION	
Enter the most recent prescribed values on or before the Reference Date for this questionnaire.		
D-22	Target post-dialysis weight (or "dry weight") as ordered:	___kg or ___lbs
D-1	Prescribed number of dialysis sessions per week.	1: 1 session/week 2: 2 sessions/week 3: 3 sessions/week 4: 3.5 sessions/week (every other day) 5: 4 sessions/week 6: 5 sessions/week 7: 6 sessions/week 8: 7 sessions/week
	Prescribed treatment time	__ __ __ hours
D-2	Prescribed blood flow rate.	__ __ __ mL/min

D-4	Prescribed dialysate sodium concentration at start of dialysis session (enter value and indicate units used).	_____	1: mmol/L 2: mEq/L
	Vascular access in use as of the reference date	1: Native arteriovenous (AV) fistula 2: Arteriovenous (AV) graft 4: Cuffed catheter (e.g., PermCath) 5: Uncuffed catheter 6: Other	
	Blood Pressure (Systolic/Diastolic) closest to reference date:	____ / ____ (pre-dialysis)	____ / ____ (post-dialysis)

Q	RESIDUAL KIDNEY FUNCTION	
Q-1	Was the patient considered anuric by the end of this reporting interval?	0: No (skip to question Q-3) 1: Yes
Q-2	If yes to Q-1, how was the anuria determined?	1: Self-reported 2: Documented 24 hour urine collection
Q-3	During this reporting interval, did the patient have a timed urine collection? If **yes** please go to question Q-4.	0: No 1: Yes
Q-3a	If **No**, indicate the estimated total urine output per day as reported by the patient at the end of this reporting interval:	0: none to <100 mL (<1/2 cup) 1: 100 to <200 mL (1/2 cup to 1 cup) 2: 200 to <500 mL (1 to 2 cups) 3: 500 to <1000 mL (2 to 4 cups) 4: ≥1000 mL (≥4 cups)
For the most recent timed urine collection:		
Q-4	Date	____/____/____ DD MM YYYY
Q-5	What was the total urine volume? (Write in the exact volume measured if known, or select a category from the choices listed.)	_____mL OR 0: 0 to 100 mL 1: 101 to 200 mL 2: 201 to 300 mL 3: 301 to 400 mL 4: 401 to 500 mL 5: 501 to 750 mL 6: 751 to 1000 mL 7: >1000 mL
For the most recent timed urine collection:		
Q-8	For how long was the urine collected?	1: 24 hours 2: 48 hours 3: Other (specify) _____

E	DIALYSIS TREATMENT SUMMARY								
During the same week the majority of measurements were taken (as reported in E-1), please indicate the date, heart rate (pulse), treatment time, and pre-dialysis and post-dialysis weight and blood pressure (sitting is preferred) for each of the dialysis sessions for that week (e.g. M,W,F or T,TH,S for three times weekly dialysis). In addition, please record the achieved treatment time for each session.									
		1st Session of the Week		**2nd Session of the Week**		**3rd Session of the Week**		**4th Session of the Week (If applicable)**	
		Date: ___/___/___		**Date: ___/___/___**		**Date: ___/___/___**		**Date: ___/___/___**	
		Pre-dialysis	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**	**Pre-dialysis**	**Post-dialysis**
E-10	Weight:	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs	1: kg 3: stone lbs
E-11	Blood Pressure (Systolic/ Diastolic):	____ / ____	____ / ____	____ / ____	____ / ____	____ / ____	____ / ____	– ___ / ____	– ___ / ____
E-13	Achieved treatment time:	__ __ __ minutes		__ __ __ minutes		__ __ __ minutes		__ __ __ minutes	

Medical Questionnaire (MQ)

C	MEDICAL HISTORY ON OR BEFORE REFERENCE DATE	
C-1	Height	_____ cm _____ inches
C-3	Primary cause of end stage kidney disease:	*{use categories/codes}*
C-9	Was the patient hospitalised in the 3 months prior to the enrolment date?	0: No 1: Yes

Coronary Heart Disease / Coronary Artery Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-10	Coronary heart disease/coronary artery disease	0: No 1: Yes
C-11	Angina	0: No 1: Yes
C-12	Myocardial infarction	0: No 1: Yes
C-13	Coronary bypass surgery	0: No 1: Yes
C-14	Percutaneous coronary intervention (coronary stent or angioplasty)	0: No 1: Yes

Other Cardiovascular Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-15	Hypertension	0: No 1: Yes
C-16	Hyperlipidaemia	0: No 1: Yes
C-17	Cardiac arrest	0: No 1: Yes
C-18	Atrial fibrillation	0: No 1: Yes
C-19	Other arrhythmia	0: No 1: Yes
C-20	Permanent pacemaker	0: No 1: Yes
C-21	Automatic implanted cardiac defibrillator (AICD)	0: No 1: Yes
C-22	Congestive heart failure	0: No 1: Yes
C-23	Pulmonary edema	0: No 1: Yes
C-24	Pericarditis	0: No 1: Yes
C-25	Valvular heart disease	0: No 1: Yes
C-26	Prosthetic heart valve (valve replacement)	0: No 1: Yes-bioprosthetic (e.g., porcine) 2: Yes-mechanical

Cerebrovascular Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer)		
C-27	Ischaemic stroke (cerebrovascular accident) with major residual neurologic deficit (e.g., weakness, impaired speech)	0: No 1: Yes
C-28	Ischaemic stroke (cerebrovascular accident) without major residual neurologic deficit	0: No 1: Yes
C-29	Transient ischaemic attack	0: No 1: Yes
C-30	Carotid endarterectomy and/or carotid stenting	0: No 1: Yes
C-77	Cerebral haemorrhage	0: No 1: Yes

Aortic or Peripheral Vascular Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-31	Peripheral vascular disease	0: No 1: Yes
C-32	Claudication (pain in legs with exertion due to peripheral vascular disease)	0: No 1: Yes
C-33	Arterial bypass surgery or percutaneous intervention (e.g., stent) for peripheral vascular disease	0: No 1: Yes
C-34	Aortic aneurysm	0: No 1: Yes
C-35	Surgical repair of aortic aneurysm	0: No 1: Yes
C-36	Extremity ulcers (e.g., ischaemic or diabetic) or gangrene of extremity	0: No 1: Yes
C-37	Amputation of digit or limb due to peripheral vascular disease	0: No 1: Yes
C-38	Recurrent cellulitis	0: No 1: Yes

Aortic or Peripheral Vascular Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-39	Calciphylaxis or calcific uraemic arteriolopathy (CUA)	0: No 1: Yes
C-40	Deep vein thrombosis	0: No 1: Yes

Diabetes on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-41	Diabetes (even if not the primary cause of end-stage renal disease)	0: No 1: Yes
C-42	Was diabetes diagnosis before age 20?	0: No 1: Yes

Gastrointestinal/Liver Disease on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-66	Gastrointestinal bleed within the past 12 months	0: No 1: Yes
C-67	Cirrhosis of the liver	0: No 1: Yes

Cancer or Blood Disorder on or before Reference Date		
Does the patient have a history of: (Choose the best answer.)		
C-68	Cancer (other than non-melanoma skin cancer)	0: No 1: Yes

Termination Form

This form should be filled out when a study patient is no longer undergoing haemodialysis at the unit.

<u>Do not</u> complete this form if a non-study patient leaves your unit.

Departure due to death or withdrawal from dialysis:				
►	A-1	Patient died on:		____/____/____ DD MM YYYY
	A-2	Place of Death (select one):		Time of death (select one):

		1: Hospital 2: Dialysis 3: Home 4: Other	A-2a	1: 10pm – 6am 2: 6am – 2pm 3: 2pm – 10pm 4: Unknown
	A-3	Primary cause of Death (from list of causes on other side)_____		
	A-4	Were there secondary causes of death?		0: No 1: Yes, specify below
	A-5	Secondary causes	1. _____ 2. _____ 3. _____ 4. _____	
	A-6a	Was haemodialysis discontinued prior to death?		0: No 1: Yes
	A-6b	If yes, discontinuation of haemodialysis occurred (select one of the following): 1: Following haemodialysis access failure 2: Following chronic failure to thrive 3: Following acute medical complication 4: Other		
	A-6c	Was discontinuation of haemodialysis after patient/family request to stop dialysis? 0: No 1: Yes 2: Unknown 3: Not applicable		
	A-7	Was patient receiving hospice/palliative care prior to death/withdrawal from dialysis?		0: No 1: Yes 2: Unknown

Departure due to reason other than death:			
►	A-8	Patient received a kidney transplant on (dd/mm/yyyy):	____/____/____
	A-9	The kidney the patient received was from (select one): 1: Cadaver 2: Living Person 3: Unknown	
►	A-10	Patient switched to peritoneal dialysis as of (dd/mm/yyyy):	____/____/____
	A-11	Note reason for switch below: 3: Patient preference 1: Haemodialysis access failure 4: Haemodynamic instability on haemodialysis 5: Other	
►	A-12	Patient switched to home haemodialysis as of (dd/mm/yyyy):	____/____/____
►	A-13	Patient transferred to another haemodialysis unit as of (dd/mm/yyyy):	____/____/____
►	A-14	Patient recovered enough renal function to come off dialysis as of (dd/mm/yyyy):	____/____/____

►	A-15	Patient refused to continue participation in the study as of (dd/mm/yyyy): ____/____/____

Causes of death

CARDIAC
23: Myocardial infarction, acute
25: Pericarditis, incl. Cardiac tamponade
26: Atherosclerotic heart disease
27: Cardiomyopathy
28: Cardiac arrhythmia
29: Cardiac arrest, cause unknown
30: Valvular heart disease
31: Pulmonary oedema due to exogenous fluid
32: Congestive Heart Failure

VASCULAR
35: Pulmonary embolus
36: Stroke - haemorrhagic
107: Stroke - ischaemic
37: Ischaemic brain damage/Anoxic encephalopathy
38: Haemorrhage from transplant site
39: Haemorrhage from vascular access
40: Haemorrhage from dialysis circuit
41: Haemorrhage from ruptured vascular aneurysm
42: Haemorrhage from surgery (not 38, 39, or 41)
43: Other haemorrhage (not 38-42, 72)
44: Mesenteric infarction/ischaemic bowel
105: Calciphylaxis

LIVER DISEASE
64: Hepatitis B
71: Hepatitis C
65: Other viral hepatitis
66: Liver-drug toxicity
67: Cirrhosis
68: Polycystic liver disease
69: Liver failure, cause unknown or other

INFECTION
47: Peritonitis (complication of peritoneal dialysis)
48: Central nervous system infection (brain abscess, meningitis, encephalitis, etc.)
49: Septicaemia due to vascular access
51: Septicaemia due to peripheral vascular disease, gangrene
52: Septicaemia, other
60: Infections, other
61: Cardiac infection (endocarditis)
62: Pulmonary infection (pneumonia, influenza)
63: Abdominal infection (peritonitis (not complication of PD), perforated bowel, diverticular disease, gallbladder)
70: Genito-urinary infection (urinary tract infection, pyelonephritis, renal abscess)
109 : COVID-19

GASTROINTESTINAL
72: Gastro-intestinal haemorrhage
73: Pancreatitis
75: Perforation of peptic ulcer
76: Perforation of bowel (not 75)

METABOLIC
24: Hyperkalaemia
77: Hypokalaemia
102: Diabetic coma
95: Acidosis

OTHER
80: Bone marrow depression
81: Cachexia/failure to thrive
82: Malignant disease, patient ever on Immunosuppressive therapy
83: Malignant disease (not 82)
84: Dementia, incl. dialysis dementia, Alzheimer's
85: Seizures
87: Chronic obstructive lung disease (COPD)
88: Complications of surgery
89: Air embolism
104: Withdrawal from dialysis/uraemia
90: Accident related to treatment
91: Accident unrelated to treatment
92: Suicide
93: Drug overdose (street drugs)
94: Drug overdose (not 92 or 93)
106: Multiple organ failure
98: Other cause of death
99: Unknown