HOME RUN

Protocol 02-001

A Prospective, Multi-Center, Open-Label Assessment of Efficacy and Safety of Quanta SC+ for Home Hemodialysis

Version: 1.9

Date: 15 February 2024

US Investigational Device Exemption Application # G200362

NCT # NCT04975880

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SPONSOR SIGNATURE PAGE

Product name: Quanta SC+

Indication: Home hemodialysis

Protocol number: 02-001

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Study title: A Prospective, Observational, Multi-Center, Open-Label Assessment of Efficacy and Safety of Quanta SC+ for Home Hemodialysis

Quanta Dialysis Technologies (Sponsor)

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I agree to the conduct this study according to the procedures and instructions in this document. I understand that any changes to the protocol instituted by me or the people to whom I delegate, other than urgent changes necessary for the wellbeing of the participants, without full discussion with the Sponsor and approval of the Institutional Review Board overseeing the study will constitute a violation of the protocol and of Good Clinical Practice guidelines.

I agree to conduct the study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, Good Clinical Practice guidelines, US federal regulations, and other applicable regulations and laws. I will obtain Institutional Review Board approval and Sponsor authorization prior to performing any study assessments or interventions. I will obtain informed consent from all participants prior to performing any study assessments or interventions involving that participant, I will maintain that consent and abide by their express wishes throughout the study as they undergo further assessments or interventions. I will allow direct access to source documents and agree to audits or inspections conducted by the Sponsor, its delegates, or regulatory authorities. I will ensure that the investigational device supplied by the Sponsor are used only as described in this protocol.

Principal Investigator	Signature	Date

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1 PROTOCOL SYNOPSIS

Title	02-001: A Prospective, Observational, Multi-Center, Open-Label Assessment of Efficacy and Safety of Quanta SC+ for Home Hemodialysis
Objective	The purpose of this study is to determine non-inferiority of efficacy and safety when Quanta SC+ is used for delivery of self-care home hemodialysis, compared to a hemodialysis facility.
Efficacy Endpoint	Mean standardized weekly Kt/V greater than or equal to 2.1, using a hemodialysis prescription of 4 sessions per week for 3.5 hours per session, measured for dialysis delivered during the home portion of the study.
Safety Endpoints	**Primary Safety Endpoint** The primary safety endpoint is the adverse event (AE) rate: the number of AEs per 100 treatments occurring in the home phase of the study, compared with those occurring in the in-clinic phase. All AEs will be collected, summarized by phase of the study, and compared between the in-clinic and in-home phase of the study. Additionally, in accordance with NCT02460263 (Plumb 2020), the rate of pre-specified AEs comprising the following components: as defined by: o Serious adverse event (SAE): any SAE that resulted in death, was life-threatening, required hospitalization or prolonged existing hospitalization, required intervention to prevent permanent impairment or damage, or resulted in persistent or significant disability/incapacity. o Allergic reaction: type A, anaphylactoid or type B dialyzer reactions to dialyzer, blood tubing, or chemical disinfectant. o Blood loss: blood loss resulting in hemodynamic compromise that led to death, transfusion, or fluid resuscitation with greater than 1 liter of crystalloid IV fluids. o Hemolytic reaction: hemolytic reactions due to disinfectant exposure, dialysate temperature, mechanical failure, or other device related causes. o Infection: any infection related to hemodialysis catheter, its tunnel or exit site, arteriovenous fistula (AVF), or arteriovenous graft (AVG). o Intradialytic event: a significant clinical event such as loss of consciousness, cardiac arrest, or seizure caused by device failure. o Vascular access complication: defined as AVF or AVG clotting during the dialysis procedure, bleeding for more than 30 minutes post-dialysis for 3 consecutive sessions, difficulty with vascular access resulting in inability to initiate or complete dialysis treatments or complications related to hemodialysis catheters (not including reduced blood flow in catheter or tissue plasminogen activator (TPA) or catheter exchange). o Pyrogenic reaction: onset of objective chills (visible rigors) and fever (oral temperature greater than or equal to 37.5

	degrees Celsius) in a participant who was afebrile and who had no recorded signs or symptoms of infection before treatment. **Secondary Endpoints** <u>Safety</u> • Number of serious adverse events (SAEs) per 100 treatments occurring in the home phase of the study compared with those occurring in the in-clinic phase • Number of device-related AEs and SAEs per 100 treatments in the in-clinic portion of the study compared with those occurring in the home portion • Additional adverse events of special interest: o Individual components of the primary safety endpoint o Air in blood tubing that cannot be resolved through usual procedures. o Significantly elevated venous (>250 mmHg) or negative arterial (>100 mmHg) pressures during three (3) consecutive treatments. o Intradialytic hypotension, as defined by treatments during which hypotensive symptoms led to either lowering the ultrafiltration rate or saline administration Post-dialysis (30 minutes) systolic blood pressure <90 mmHg or systolic blood pressure >180 mmHg following two (2) consecutive treatments. The following biochemistry and hematology laboratory values will be collected and compared to target ranges from clinical practice guidelines. <u>Biochemistry:</u> assessments of pre-treatment plasma at visits C1, C2, C4, C6, C8 H2, H4, H6 and H8/withdrawal: o sodium (Na) (target range, 135-145 mEq/L) o urea (BUN) o potassium (K) (target range, 3.5-5.5 mEq/L) o creatinine (Cr) o bicarbonate (HCO3) (target range, ≥22 mEq/L) o magnesium (Mg) o phosphate (Phos) (target range, 3.5-5.5 mg/dL) o chloride (Cl) o calcium (Ca) (target range, 8.4-9.5 mg/dL) o albumin (Alb) (target range, ≥3.5 g/dL) o iron (Fe) o transferrin saturation (TS) (target range, >20%) o total protein (TP) o ferritin (Fn) (target range, >200 ng/mL) o alkaline phosphatase (ALP) o parathyroid hormone (PTH) (target range, 150-600 pg/mL) o total iron binding capacity (TIBC) o aspartate transaminase (AST) o alanine aminotransferase (ALT) <u>Hematology:</u> assessments of pre-treatment blood at visits C1, C2,

	C4, C6, C8 H2, H4, H6 and H8/withdrawal: ○ hemoglobin (Hb) ○ hematocrit (Hct) ○ white cell count (WBC) ○ platelet count (PC) ○ reticulocyte Count (RC) <u>Ultrafiltration (UF)</u> ○ Ultrafiltration volume (net fluid removal), such that the recorded value from the Quanta SC+ dialysis delivery system (DDS) is within ± 100 mL/h or ± 400 mL of set point during the treatment, based on the UF prescription. ○ Clinical utility during the home portion as measured by number of alarms pertaining to patient safety, time to resolve alarms, type of alarms ○ Reliability of delivery of prescribed treatments ○ Proportion of participants (both subjects and their care partners) who successfully complete the training program and attempts required for successful completion ○ Descriptive summary of device deficiencies Patient reported outcomes ○ Time to recovery after dialysis treatment (Lindsay RM, 2006) ○ EQ-5D-5L (Culleton BF, 2007) ○ Medical Outcomes Study (MOS) Sleep Index (Hays RD, 2005; Hays R, 1992) ○ Renal Treatment Satisfaction Questionnaire (RTSQ, Bardense 2005) ○ Zarit Burden Interview (ZBI12, Bédard 2001, completed by caregiver rather than participant) ○ Edmonton Symptom Scale (ESAS-r, Davidson SN., 2006)
Sites	8-15 sites in United States
Participants	50 participants with established kidney failure undergoing hemodialysis will be enrolled to obtain 33 evaluable participants. Participants will have been receiving hemodialysis for at least 90 days, or in the case of peritoneal patients transitioning to hemodialysis, at least 90 days. Enrollment will include participants planning for home hemodialysis, peritoneal dialysis or currently on home hemodialysis. No more than 25% of participants will be recruited from a single site.
Duration	Participants will be enrolled for up to 19 weeks.
Inclusion criteria	Candidates for participation in the study must meet all of the following inclusion criteria. It is anticipated that this population will include Medicare beneficiaries, as approximately 80% of patients currently undergoing hemodialysis are enrolled either traditional Medicare or in Medicare Advantage plans. (USRDS 2020)

	1. Provision of a written informed consent form signed by the participant 2. Age between 18 and 80 years at time of enrollment 3. A care partner must be available for training on SC+ and to be present in the home during all home hemodialysis sessions 4. Participants should be either receiving regular, facility-based hemodialysis therapy for at least 90 days, or in the case of peritoneal patients transitioning to hemodialysis, at least 90 days, or performing home dialysis (with any frequency) for at least 90 days and willing to return to facility for purpose of study, and should be clinically stable and deemed suitable for home dialysis in the opinion of the principal investigator 5. Willing to accept a dialysis prescription of 3 sessions per week, 4 hours each session or facility standard during in-clinic visits (delivered Monday, Wednesday and Friday unless otherwise approved by Sponsor) and 4 sessions, 3.5 hours each session during in-home sessions (delivered Monday, Wednesday, Friday, and Saturday unless otherwise approved by Sponsor) 6. In the opinion of the Investigator, participant has well-functioning and stable vascular access (tunneled, central venous catheter, arteriovenous fistula, or graft) that allows a blood flow of at least 300 ml/min 7. Home environment is adequate to ensure that appropriate electrical connections and water supply necessary for the use and storage of the device as assessed by Quanta prior to subject C1 visit. Also ensure that cellular signal and/or WIFI capacity is adequate. 8. Participant or care partner are capable of understanding the nature of procedures and requirements of the study protocol and of home-based hemodialysis, and are willing and capable of complying with protocol and returning to treatment center as stated in protocol 9. Participant or care partner are capable of being trained to use the machine and troubleshoot should an alarm situation occur 10. In the opinion of the treating physician, the subject is able to participate in the trial in terms of social factors and personal functioning. 11. Acceptable physical ability of the participant and/or care partner to perform the hemodialysis treatment at home 12. Financial coverage for treatment costs by Medicare, Medicaid, private insurance, or other arrangement acceptable to participant
Exclusion Criteria	1. Pregnant or trying to become pregnant (women of childbearing potential must use medically accepted contraceptive measures) 2. Predicted life expectancy of less than 12 months from the first study procedure 3. Major cardiovascular adverse event in the 3 months prior to screening 4. Fluid overload due to intractable ascites secondary to liver cirrhosis 5. Uncontrolled or unstable blood pressure (systolic BP outside the range 90 to 180 mmHg) 6. Unstable coronary artery disease

	7. New York Class III or IV heart failure, or ejection fraction less than 30% 8. Participation in other clinical studies that may interfere with the current protocol 9. Known problems with coagulation 10. Active, life-threatening, rheumatologic disease. 11. Hematocrit less than 28% at enrollment (within 30 days of enrollment) 12. Hemoglobin less than 9 g/dL at enrollment (within 30 days of enrollment) 13. Suffering from active severe infection 14. Seroreactive for hepatitis B surface antigen 15. Suffering from active malignancy with expected deteriorating course within 6–12 months 16. History of severe reactions to dialyzer membrane material 17. Expected to receive an organ transplant during the course of the study 18. Have dementia or inability to understand procedures 19. Lack an ability for self-care 20. Are non-adherent to their current dialysis treatments 21. Experience intra-dialytic hypotension defined as a decrease in systolic blood pressure of greater than or equal to 20 mmHg or a decrease in mean arterial pressure of greater than or equal to 10 mmHg provided that the decrease is associated with clinical events (symptoms) and the need for an intervention (ultrafiltration turned off, bolus of fluid) in 3 of 5 prior treatments 22. Is intolerant to heparin 23. Considered in the investigator's opinion to be clinically unstable for any other reason 24. Undergoing outpatient dialysis for the treatment of acute kidney injury (AKI)
Statistical overview	The study will be considered a success from a statistical standpoint if: 1. Both primary effectiveness variables pass their respective hypotheses, i.e., Ha0 and Hb0 below are rejected in favor of Ha1 and Hb1, respectively, and 2. The rate of adverse events per 100 treatments is not worse during the In-Home period as compared to the In-Center period. Summary statistics will be provided for all baseline characteristics and endpoints. The primary effectiveness endpoint will be tested using the Least Squares Mean from a repeated measures analysis of variance (ANOVA) model. A 95% confidence interval will be computed for the primary safety endpoint for each treatment period using the Least Squares Mean from a repeated measures GEE model. All hypothesis testing will be performed at a two-sided α=0.05 level unless otherwise specified. The primary analysis of the primary effectiveness and primary safety endpoints will be performed on all enrolled patients with available data. A sensitivity analysis will be performed for the primary

	effectiveness endpoint using multiple imputation. No imputation will be performed for the primary safety endpoint or any secondary endpoints.
US Agent (Sponsor)	QDT Inc. 71 Cherry Hill Drive, Suite 205 Beverly, MA 01915

2 SCHEDULE OF ASSESSMENTS

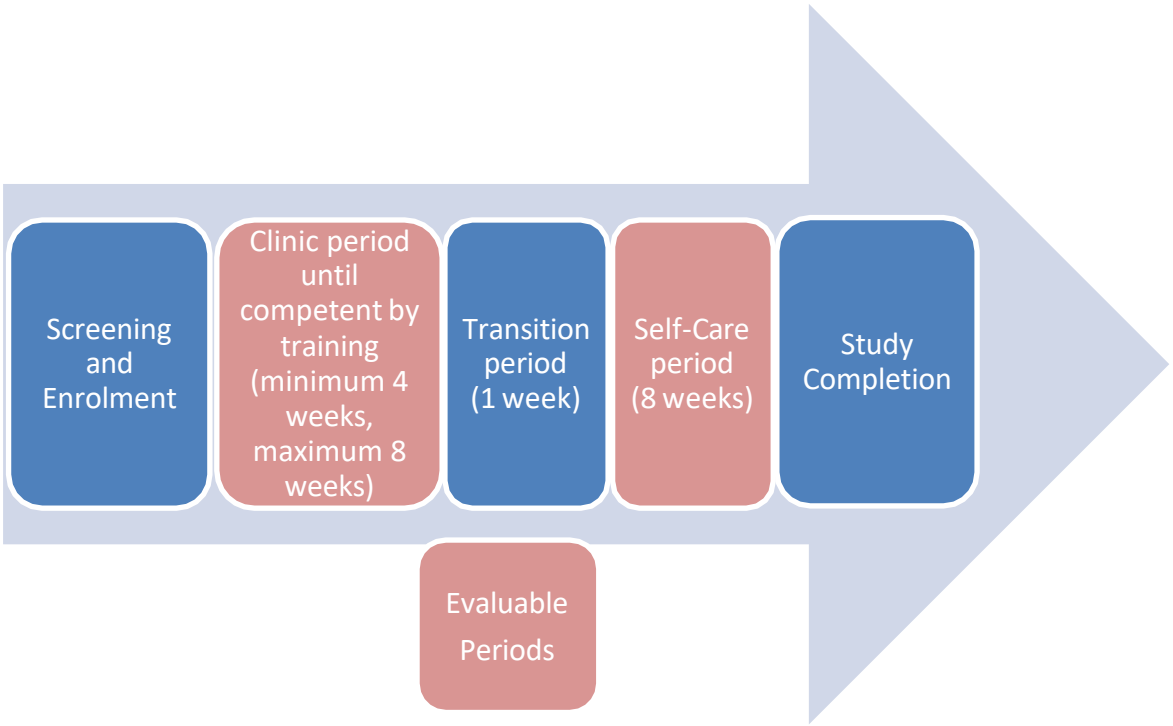
	Screening and enrollment	C1	C2	C3	C4	C5 [1]	C6 [1]	C7 [1]	C8 [1]	T	H1	H2	H3	H4	H5	H6	H7	H8	Withdrawal
Week	−2 to 0	C1	C2	C3	C4	C5	C6	C7	C8	T	H1	H2	H3	H4	H5	H6	H7	H8	
		C=in clinic T=transition at home with trained dialysis professional present H=at home																	
Informed consent, demographics	x																		
Inclusion and exclusion criteria	x																		
Medical and surgical history[2]	x																		
Disease history	x																		
Dialysis treatment history	x																		
Pregnancy Test[3]	x																		
Device training		x	x	x	x	x	x	x	x										
Physical examination		x																x	x
Vital signs		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Biochemistry, hematology[4]		x	x		x		x		x			x		x		x		x	x
Treatment adequacy[5]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Preparation of home setting		during this period																	
Training on software		during this period																	
RO water/dialysate quality[7]					x				x	x				x				x	x
Treatment with Quanta SC+[8]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Device deficiency assessment		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Treatment flowsheet										x	x	x	x	x	x	x	x	x	x
Usability[9]											x	x	x	x	x	x	x	x	x
Time to recovery after dialysis (TTR)[10]		x									x			x				x	x
EQ-5D-5L[11]		x									x							x	x
MOS Sleep Index[12]		x									x							x	x
Zarit Burden Interview (ZBI12)[13]																		x	x
Renal Treatment Satisfaction Questionnaire		x									x							x	x
Edmonton Symptom Assessment Scale (ESAS-r)[14]		x									x							x	x
Upload Clinical utility Report[15]																		x	x
Reliability[16]		monitored continuously during this period																	
Proportion of participants and caregivers successfully trained					x	x	x	x	x										
Adverse Events		collected continuously during this period																	
Concomitant Medications[17]	x	collected continuously during this period																	
Reason for withdrawal																			x
Review of HCP support & interactions[18]											x	x	x	x	x	x	x	x	x

[1] Visits C1–C4 will occur for all participants. Visits C5 through C8 will occur, week-by-week, if training competence has not yet been demonstrated. Once training competence is demonstrated, remaining clinic (C)

visits will be skipped and visits T and H1–H8 will begin.
[2] including comorbidities profile
[3] to be performed in female of childbearing potential
[4] Participant can draw their own blood during visits T and H1–H8. Blood will be analyzed for sodium (Na), urea (BUN), potassium (K), creatinine (Cr), bicarbonate (HCO3), magnesium (Mg), phosphate (Phos), chloride (Cl), calcium (Ca), albumin (Alb), iron (Fe), transferrin saturation (TS), total protein (TP), ferritin (Fn), alkaline phosphatase (ALP), parathyroid hormone (PTH), total iron binding capacity (TIBC), aspartate transaminase (AST), alanine aminotransferase (ALT), hemoglobin (Hb), hematocrit (Hct), white cell count (WBC), platelet count (PC), reticulocyte count (RC). BUN is collected immediately before and after Quanta SC+ treatment
[5] Kt/V done mid-week every week. In home setting, participants may be instructed on how to draw their own blood sample or bloodwork can be drawn by trained research staff.

[7] During device installation in-center and in-home and monthly thereafter, water/dialysate samples will be collected and tested
[8] Dialysis prescription is 3 times per week, 4 hours per session or facility standard for C1 through C4 and also C5 through C8 if required; 4 times per week, 3.5 hours per session for T and H1 through H8. Clinic visits will be Monday, Wednesdsay, and Friday (unless otherwise approved by Sponsor). In home visits will be Monday, Wednesdsay, Friday, and Saturday (unless otherwise approved by Sponsor).
[9] Participants queried: required assistance with any aspect of treatment over the prior 7 days and if so, with which of the following tasks: machine set up, clearing of alarms, machine take down, fistula/needling or catheter connection
[10] TTR is completed once after a dialysis treatment during the week of C1 – H1 – H4 and H8 or at withdrawal; not all treatments within those weeks (Lindsay 2006)
[11] Collected twice: (1) prior to first home treatment, and (2) if there have been any home treatments, then during last home treatment or withdrawal.
[12] Collected prior to first in-clinic treatment, prior to first in home treatment, prior to H5 treatment, and after last in-home treatment. Also collected prior to C5 treatment if competency training not achieved by treatment C4.
[13] Caregiver—not participant—completes ZBI. (ZBI12, Bédard 2001)
[14]Participant completes ESAS-r (Davidson SN., 2006)
[15] Number of alarms, time to resolve alarms, type of alarms
[16] Ability to deliver prescribed treatments
[17] Concomitant medication collection will be limited to the following: erythropoiesis-stimulating agents (ESAs), intravenous iron, phosphate binders, calcimimetics, and anti-hypertensive medications (ACE inhibitors, ARBs, beta blockers, calcium channel blockers, central alpha agonists, vasodilators [specifically, hydralazine and minoxidil]).
[18] HCP support and interactions are intended to be available to participants as required by the study, but not to provide additional training, support, or oversight of the dialysis procedure. Any contact outside study-driven procedures will be documented for purpose of understanding need for additional health care support.

3 PARTICIPANT FLOW CHART



4 LIST OF ABBREVIATIONS

Alb	albumin
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate transaminase
AVF	arteriovenous fistula
AVG	arteriovenous graft
BUN	blood urea nitrogen
Ca	calcium
CAP	continuous access protocol
CFU	colony forming units
CIP	clinical investigation protocol
Cl	chloride
CMS	Center for Medicare and Medicaid Services
COVID-19	coronavirus disease 2019 caused by SARS-CoV-2 virus
Cr	creatinine
CRF	case report form
DDS	Dialysis delivery system
eCRF	electronic case report form
Eq5d	Eq5d Health Questionnaire
ESKD	end-stage kidney disease
(ESAS)	Edmonton symptom assessment system (Davidson SN, 2006)
ETC	ESRD Treatment Choices
EU	endotoxin units
FAS	Full Analysis Set
FCS	fully conditional specification
FDA	Food and Drug Administration
Fe	iron
Fn	ferritin
GCP	Good Clinical Practice
Hb	hemoglobin
HCO3	bicarbonate
HCP	health care professional
Hct	hematocrit
HHD	home hemodialysis
ICH	International Council on Harmonization
IRB	institutional review board
ISO	International Standards Organization
Kt/V	standard urea clearance times time divided by volume
MDS	medical data system
Mg	magnesium
MOS	Medical Outcomes Study
Na	sodium
NFR	nephron filtration rate
PC	platelet count
Phos	phosphate
PTH	parathyroid hormone
QDT	Quanta Dialysis Technologies
RC	reticulocyte count

RO	reverse osmosis
RTSQ	Renal Treatment Satisfaction Questionnaire (Bardense 2005)
SADE	serious adverse device event
SAE	serious adverse event
SC+	SC+ dialysis delivery system
SCEC	safety and clinical events committee
spKt/V	single pool Kt/V
TIBC	total iron binding capacity
TP	total protein
TPA	tissue plasminogen activator
TS	transferrin saturation
TTR	Time to recovery
TVC	total viable count
UADE	unanticipated adverse device effect
UF	ultrafiltration
URR	urea reduction ratio
USADE	unanticipated serious adverse device event
USRDS	United State Renal Data System
WBC	white blood cell count
ZBI - 12	Zarit Burden Interview (Bédard 2001)

5 INTRODUCTION

5.1 Purpose of the Study

The purpose of this study is to determine non-inferiority in safety and efficacy when Quanta SC+ is used in the self-care home environment compared to a hemodialysis facility.

5.2 Background on the Disease

5.2.1 End Stage Kidney Disease

End stage kidney disease (ESKD) is defined by permanent and irreversible loss of kidney function, thus requiring either dialysis or a kidney transplant for continued survival. According to the United States Renal Data System (USRDS 2020), a national registry of participants with ESKD, the incidence of ESKD was 390 cases per million people in 2018, resulting in more than 131,000 patients who were newly diagnosed with ESKD. Due to the gradual aging of the United States population, the incidence rate of ESKD has steadily increased during the past decade. Between 2015 and 2030, the incidence rate of ESKD is projected to increase between 11% and 18% (McCullough 2019), although the effects of emerging pharmacologic interventions may temper this projection (Heerspink 2020). Still, considering that the US population continues to grow, it is likely that the annual number of patients who are newly diagnosed with ESKD will exceed 125,000 for the foreseeable future.

According to the USRDS (2020), the vast majority—approximately 97%—of patients who are newly diagnosed with ESKD initiate maintenance dialysis. Furthermore, despite a recent increase in the annual number of kidney transplants, partly due to the scourge of drug overdose-related deaths in the United States, transplantation does not fully satiate demand for kidney replacement therapy. In 2018, the rate of kidney transplantation among all patients undergoing dialysis was 3.6 grafts per 100 patient-years. For this reason, the majority—roughly 70%—of all ESKD patients undergo maintenance dialysis. With slightly more than 800,000 ESKD patients in the United States on June 30, 2020, a 70% share amounts to approximately 560,000 patients undergoing maintenance dialysis.

Again, according to the USRDS (2020), outcomes on dialysis remain less than ideal. In 2018, there were 175 deaths per 1000 patient-years among all patients undergoing dialysis. Although survival on dialysis steadily improved between the late 1990's and the early 2010's, there has been little further improvement since roughly 2013. The mortality rate among Medicare-enrolled dialysis patients aged ≥66 years was over two times higher than corresponding rates among similarly aged Medicare-enrolled patients with cardiovascular disease. Furthermore, according to the DOPPS Practice Monitor (bibliography has link), several intermediate parameters, including pre-dialysis blood pressure and the prevalence of hyperphosphatemia, have stagnated among contemporary dialysis patients. The composite rate of hospital admissions and observation stays in the subset of dialysis patients with Medicare fee-for-service coverage has even increased slightly during the past five years, reaching a rate of 2.0 events per patient-year in 2018.

5.2.2 Home hemodialysis

The USRDS (2020) reports that among all dialysis patients in the United States at the end of 2018, 87.2% of patients were treated with in-facility hemodialysis, 1.9% were treated with home hemodialysis, and 10.6% were treated with peritoneal dialysis. (Another 0.3% were treated with an unknown modality, according to the USRDS.) As nearly all peritoneal dialysis is delivered in the home setting, the total penetration of home dialysis was approximately 12.4% at the end of 2018. The share of home dialysis has moved upward by several percentage points during the past decade, following reform of the Medicare payment policy for outpatient dialysis in 2011. Further growth is likely in the near future, as the Centers for Medicare and Medicaid Services (CMS) has recently finalized the ESRD Treatment Choices payment model, which will mandatorily enroll outpatient dialysis facilities, nephrology practices, and dialysis patients with Medicare fee-for-service coverage in 30% of the country (Federal Register, link in bibliography). The model uses a series of payment bonuses and penalties to incentivize increased use of home dialysis and increased access to kidney transplantation.

Although home hemodialysis (HHD) is the least popular of the three dialysis modalities in the United States, HHD is an old modality (Lockridge 2020). Merrill and Scribner started HHD programs in Boston and Seattle, respectively, in 1965. During the 1970's, one-third of all dialysis patients in the United States were treated with HHD. Beginning in the early 1980's, use of HHD began to wane, and by the end of 2002, the modality had reached its nadir, with less than 1500 users across the country. However, HHD has undergone a modern renaissance, following Food and Drug Administration (FDA) clearance of the NxStage System One platform in 2005. According to the USRDS (2020), the number of HHD patients exceeded 10,000 for the first time at end of 2018.

Fundamentally, HHD achieves the same pair of objectives as in-facility hemodialysis: toxin removal and ultrafiltration (i.e., fluid removal). However, in-facility hemodialysis is largely bound by the constraints inherent in shift-based dialysis schedules. Thus, nearly all in-facility hemodialysis patients dialyze three times per week and between 180 and 270 minutes per session. In the home setting, schedule constraints do not exist. Thus, there is tremendous diversity among HHD prescriptions, with respect to frequency and duration. In the United States, variations of so-called short daily hemodialysis are typically prescribed. At one time, short daily hemodialysis was characterized by frequencies of 5 or 6 treatments per week and session duration between 150 and 180 minutes. Today, short daily hemodialysis is characterized by frequencies of 4 or 5 treatments per week and session duration between 165 and 195 minutes per session. Nonetheless, there are HHD patients in the United States who dialyze two, three, or six sessions per week. There are also HHD patients who adhere to a nocturnal schedule, which typically involves session duration between 6 and 10 hours. In other countries, including Australia, Canada, and New Zealand, prescriptions of thrice-weekly hemodialysis in the home setting are not uncommon.

There are currently three hemodialysis platforms that are cleared by the United States FDA for use in the home setting and utilized by existing dialysis patients: the Fresenius Medical Care 2008K@home, the NxStage System One (and System One S), and the Outset Tablo. Briefly, the 2008K@home machine closely resembles equipment that is typical of the facility setting, insofar as it requires an accompanying reverse osmosis system for dialysate preparation and operates an ordinary dialysate flow rate. The NxStage System One is a transportable device that uses an alternative approach for dialysate preparation, thus obviating the need for a reverse osmosis system, but it is constrained to a maximum of 60 liters of dialysate per treatment and a maximum dialysate flow rate of 300 mL/minute. The vast majority of HHD patients in the United States use the NxStage System One (or System One S). The newest device is the Outset Tablo. That machine produces dialysate on demand, unlike the NxStage System One; therefore, it is not limited to delivery of 60 liters of dialysate per treatment. However, like the NxStage System One, the Tablo operates at a maximum dialysate flow rate of 300 mL/minute. The Tablo received FDA clearance for HHD early in 2020. At this time, there is relatively little real-world evidence about the effectiveness of HHD with the device.

5.3 Device Description

The SC+ Hemodialysis System is intended for acute and chronic dialysis therapy, with or without ultrafiltration, utilizing Dialysis Quality Water (from standalone Reverse Osmosis (RO) units or a central RO ring main) to produce dialysate. The SC+ Hemodialysis system is for use in patients with arteriovenous (AV) fistula or central venous catheter access. The SC+ Hemodialysis System is also indicated for use in the home.

5.3.1 SC+ System Description

The system consists of (1) the Quanta SC+ machine, (2) a single use disposable dialysate cartridge, and (3) a sterile, single use, disposable blood tubeset.

The Quanta SC+ machine consists of (a) water and dialysate circuit (b) blood leak detector, air in blood detector, a pneumatic interface for the dialysate cartridges, a peristaltic blood pump and various other sensors. The dialysate cartridge consists of (a) conductivity monitors, (b) interfaces for pressure and temperature measurement, (c) membrane pumps to perform mixing and proportioning in order to produce dialysis fluid and the controlled removal of fluid from a patient with acute and/or chronic renal failure based on a physician's prescription. The dialysate fluid is manufactured using dialysis water purified externally by reverse osmosis that is heated to approximately 37^{o}C and subsequently de-aerated within the machine before entering the cartridge.

The Quanta SC+ blood tubeset is a single use, sterile device consisting of an arterial line, a venous line, connections to a standard dialyzer, a saline line, three pressure transducer pods integrated into a single unit, a venous drip chamber, and a line for heparin infusion.

5.3.2 Principle of Operation

The patient's blood enters the circuit through vascular access and is passed through the dialyzer before returning. The blood is circulated around the cartridge using motive force generated by a peristaltic pump. The SC+ DDS is currently suitable for use on patients for whom vascular access is via two needles through an AV fistula, graft or catheter. The SC+ DDS enables ultrafiltration to be carried out over the course of the treatment, to remove excess fluid from the patient in an accurate manner prescribed by a nephrologist. Ultrafiltration is carried out using a volumetric process in which flow rates into and out of the dialyser are equally balanced, fluid is removed between these flows. This volumetric control provides accurate and reliable fluid removal when "high flux" dialyzers are used, allowing fluid movement with little pressure differences.

5.4 Rationale for the Trial

Traditionally, the United States Food and Drug Administration has granted 510(k) clearance for a hemodialysis machine to be used in the home setting upon the completion of a crossover trial with two phases. In the first phase, the machine is used to deliver in-facility hemodialysis according to a prespecified prescription; that prescription may include details about treatment frequency, session duration, blood and dialysate flow rates, or target urea clearance. After a brief (e.g., 2-4 weeks) transitional period, during which the trial participant demonstrates capability to independently operate the machine, the machine is used to deliver home hemodialysis according to the same prespecified prescription. The trial of the machine is declared a success if patients collectively achieve either equivalence or non-inferiority, with respect to both efficacy and safety endpoints, in the home setting (relative to the facility setting).

This trial phenotype was employed to obtain 510(k) clearance of the NxStage System One and the Outset Tablo. In the former case, Kraus (2007) reported the results of a crossover trial involving 32 patients. During each phase of the trial, patients dialyzed 6 times per week. The primary efficacy endpoint was delivery of at least 90% of the prescribed fluid volume, which was defined as the sum of the dialysate and ultrafiltration volumes. The primary safety endpoint was the composite number of intradialytic and interdialytic adverse events, which were defined as any unfavorable or unintended sign, symptom, or disease temporally associated with use of the machine. Null hypothesis significance testing (with $\alpha = 0.05$) was used to assess equivalence between phases, with respect to both efficacy and safety endpoints. In the latter case, Plumb (2020) reported the results of a crossover trial involving 32 patients. This trial actually involved four phases: first, a run-in phase of one week of in-center hemodialysis; second, an in-center phase of eight weeks, during which staff managed hemodialysis; third, a transitional phase of up to four weeks, during which the patient and care partner were trained to independently operate the machine; and fourth, an in-home phase of eight weeks. During each phase, patients dialyzed 4 times per week. The primary efficacy endpoint was achievement of standardized weekly Kt/V greater than or equal to 2.1. The primary safety endpoint was the number of adverse events. Plumb (2020) did not report whether the statistical analysis assessed equivalence or non-inferiority between phases.

This trial phenotype was certainly sensible in an earlier era. When the NxStage System One was tested before 2005, home hemodialysis was a rarely utilized modality. In fact, at the end of 2002, the number of home hemodialysis patients in the United States had reached a low-water mark of less than 1500. Few dialysis facilities had practical experience with managing the modality. Furthermore, the NxStage System One was an unusual device, as it applied the therapeutic logic of peritoneal dialysis to the application of hemodialysis. Specifically, the NxStage System One used a low volume of premixed dialysate and inverted the traditional relationship between blood flow and dialysate flow rates. Many nephrologists were doubtful that this approach could achieve adequate solute clearance. During the 15 years following the initial clearance of the machine for use in the home settings, tens of thousands of patients have been performed home hemodialysis and collectively accumulated between 15 and 20 million treatments. According to a recent report from the United States Renal Data System, the number of home hemodialysis patients in the United States exceeded 10,000 for the first time at the end of 2018. Today, over 2200 Medicare-certified dialysis facilities offer home hemodialysis.

Overall, the renaissance of home hemodialysis—specifically, *intensive* (i.e., relative to conventional hemodialysis, any schedule that increases the number of treatment sessions per week and/or the number of hours per session) home hemodialysis—has been a success. A series of large cohort studies by Weinhandl and colleagues have demonstrated favorable outcomes associated with short daily home hemodialysis versus conventional in-facility hemodialysis. In the first study (Weinhandl 2012), the risk of death was 13% lower among 1873 patients dialyzing either 5 or 6 times per week

at home versus matched patients dialyzing 3 times per week in the facility. In a subsequent study (Weinhandl 2014), the risk of cardiovascular hospitalization was 11% lower among 3480 patients dialyzing either 5 or 6 times per week at home versus matched patients dialyzing 3 times per week in the facility; regarding hospitalizations for heart failure and fluid overload, the relative risk reduction was 31%. Finally, in another study (Weinhandl 2016) outcomes were assessed associated with 4201 home hemodialysis patients versus 4201 matched peritoneal dialysis patients. Home hemodialysis was associated with 20% lower risk of risk, 8% lower risk of hospitalization, and 37% lower risk of technique failure (i.e., conversion to in-facility hemodialysis); among patients who were newly diagnosed with end stage kidney disease, the modalities exhibited similar risks of death and hospitalization, but home hemodialysis was still associated with 30% lower risk of technique failure. In a large prospective cohort study, initiation of frequent home hemodialysis was associated with improvements in depressive symptoms, post-dialysis recovery time, restless legs syndrome, and sleep quality, as well as both physical and mental health-related quality of life. Despite the observational nature of all these studies, the associations in these studies are concordant with mechanistic effects that have bene identified in the Frequent Hemodialysis Network randomized clinical trials. In any case, the clinical experience of home hemodialysis in the United States is now well-characterized. The field is certainly not aided by resource-intensive studies that continue to compare outcomes with home versus in-facility hemodialysis.

In fact, with so many home hemodialysis patients in the United States and so many dialysis facilities with extensive experience in managing the modality, a reevaluation of the trial phenotype for testing new hemodialysis machines is required. To establish a more relevant phenotype, one must consider—and permit mimicry of—the usual path that a patient traverses on the way to home hemodialysis. Although home hemodialysis is sometimes prescribed to patients with incident end stage kidney disease, the practical reality is that the “average” patient who initiates home hemodialysis is an established patient undergoing hemodialysis in the facility setting. In a large cohort study (*N* = 4201, Weinhandl 2016), the mean duration of end stage kidney disease was 44.6 months at initiation of home hemodialysis. Moreover, less than 0.4% of all patients with incident end stage kidney disease in 2018 initiated home hemodialysis. From this point of view, the typical path is to move from thrice-weekly hemodialysis in the facility, where a large hemodialysis machine (which is coupled with a water treatment system) is used during sessions that are between 180 and 270 minutes, to home hemodialysis training and subsequently to home hemodialysis itself. During training, treatment frequency is immediately increased (but typically constrained to weekdays, thus permitting long interdialytic gaps spanning weekends) and the dialysate flow rate is immediately decreased (due to the specifications of the NxStage System One and the Outset Tablo), but professional staff continue to assist. Upon commencement of hemodialysis in the home setting, treatment frequency is typically maintained, but weekend treatments become commonplace, as patients are typically counseled to avoid two-days gaps in treatment. Importantly, professional staff are no longer present. The bottom line is this: the transition from in-facility treatment to home hemodialysis training to home hemodialysis itself is a series of changes to the dialysis prescription, with attendant changes in single-pool Kt/V, let alone changes in the dialysis environment, as well as medications that are indicated for the treatment anemia, hypertension, and mineral and bone disease. Nothing is entirely stable. Thus, the trial phenotype of maintaining perfect stability in the prescription represents a very artificial environment without parallel in clinical practice. Truly, the traditional trial phenotype, in which patients accumulate at least 8 weeks of treatment with a new hemodialysis machine before taking that machine to the home setting, inadvertently creates a false sense of security (relative to what can be expected after a brief course of home hemodialysis training), thereby creating a bias that favors equivalence of clinical outcomes during the in-facility and home phases.

It is certain that any hemodialysis machine that is intended to be used in the home setting must deliver adequate solute clearance, with or without ultrafiltration, and in the modern era, must be

associated with adverse event incidence that is comparable to corresponding incidence with machines already in use in the home setting. Dialysis providers are now very familiar with the NxStage System One and the application of frequent hemodialysis with low-volume dialysate. In addition, dialysis providers are now accustomed to managing home hemodialysis prescriptions with treatment frequency equal to four sessions per week, as was employed in the crossover trial that supported 510(k) clearance of the Outset Tablo. With these observations in tow, the vision of a new trial phenotype becomes clear: a trial should enroll patients who are already established in the dialysis facility and undergoing thrice-weekly hemodialysis; should proceed to a training protocol for home hemodialysis with the candidate device, but without concern for whether the prescription matches what was used in the facility setting beforehand; and should conclude in the home, where the prescription may be altered to the end of continuing to achieve adequate solute clearance, with or without ultrafiltration. If the candidate device can be used to deliver adequate dialysis in the home setting, following a successful course of home hemodialysis training, and the adverse event rate is no different than what is typical of other devices that are used in the home setting, then the device is clearly suitable for use in the home. (Nevertheless, it is important to note that in practice, patients may utilize home hemodialysis for a period, transfer to in-facility hemodialysis for another period, and subsequently return to home hemodialysis. In some cases, patients utilizing home hemodialysis transfer from one dialysis provider organization to another, but because of differences in organizational protocols, retaining is required. Ultimately, both scenarios show that patients may initiate home hemodialysis training with either distal or proximal experience with the modality. Thus, a valid trial of a candidate device may—and probably should—include some patients with home hemodialysis experience.)

Furthermore, although broader considerations about dialysis delivery may not be strictly pertinent to the 510(k) clearance process, it is important to note the recent Executive Order on Advancing American Kidney Health (White House, 2019). That policy includes ambitious goals for home dialysis growth in coming year. In support of those goals, the Centers for Medicare and Medicaid Services has launched the ESRD Treatment Choices (ETC) payment model as of January 2021. That model involves 30% of dialysis facilities and patients with Medicare fee-for-service coverage. The mechanics of the performance measures in that payment model will ultimately increase the pressure on dialysis providers to directly shift patients from in-facility hemodialysis to home dialysis—likely employing home hemodialysis. This stands in some contrast to the historical approach of growing home dialysis programs by introducing patients with advanced chronic kidney disease to peritoneal dialysis. From this point of view, it is actually critically important that a multi-phase trial that establishes the efficacy and safety of a new hemodialysis machine for use in the home setting convincingly demonstrate that stable patients can be trained in a set number of weeks, initiate treatment in the home setting, and continue to achieve adequate solute clearance. After all, adequate solute clearance is nearly universally achieved by in-facility hemodialysis patients and neither dialysis providers nor patient themselves will tolerate lack of adequacy when treatment migrates from the facility to the home.

Two other issues merit attention. First, it is important to emphasize that home hemodialysis is an attractive modality to middle-aged adults with end stage kidney disease. The lengthy (8-week) in-center phases that have characterized the crossover trials that supported 510(k) clearance of the NxStage System One and Outset Tablo are problematic, insofar as frequent hemodialysis in the facility is disruptive to patient schedules, thus creating burden that slows trial enrollment. Forgoing a lengthy in-center phase in a multi-phase trial not only will likely speed enrollment, but also will likely improve the diversity of trial subjects, thereby increasing generalizability. Second, this moment in history is truly unique, considering the risk posed by novel coronavirus disease 2019 (COVID-19). The USRDS recently reported that during the springtime peak of COVID-19, the mortality rate among dialysis patients was 37% higher than during corresponding weeks of 2017–2019. The same impact is likely to be observed during the wintertime. Although there is substantial promise of vaccination

during the first half of 2020, there is lack of clarity about the efficacy of vaccination in patients receiving dialysis, not only because these patients have been excluded from vaccination trials, but also because these patients generally exhibit immune dysfunction. It is arguably unethical to harbor patients in a facility setting any longer than is necessary during the COVID-19 pandemic. As at any other time, patients must demonstrate that can competently complete the home hemodialysis treatment before graduating from training, but at this time, patients should not be compelled to remain in the facility setting simply to satisfy a traditional study protocol.

5.5 Indication for Use

The SC+ Hemodialysis System is indicated for use in patients with acute and/or chronic renal failure, with or without ultrafiltration, in an acute or chronic care facility. Treatments must be administered under physician's prescription, by a trained person who is competent in the use of the device.

The SC+ Hemodialysis System is under experimentation in this clinical trial for home use.

5.6 Summary of Prior Experience

Quanta has conducted the following clinical investigations for the SC+ Hemodialysis System each of which are summarized below.

SC-00879	Open-Label, Single-Arm, First-in-Human, Pilot Initiation Study Report for the SC+ Hemodialysis System
SC-001232	Pilot Study (Periodic Progress Report no.1)
SC-01281	Clinical Study Report N=20 Home Patient

5.6.1 Clinical First in Human (FIH) Study SC-00879

This open-label, single-arm, first-in-human, pilot study was conducted to assess the efficacy, safety, and formative usability of the SC+ Hemodialysis system in the hemodialysis-dependent ESRD patient population. This study was performed in a hemodialysis clinic where the Quanta SC+ DDS was operated by a nurse and used to treat 6 subjects for a total of 10 dialysis sessions. The study was carried out using version 1.1.1 version of the Quanta SC+ DDS.

Key findings were as follows:

- Clinical and technical performance was demonstrated by measuring clearance (assessed using URR and Kt/V), which both exceeded therapy goals, and ultrafiltration (UF) error (assessed based on changes in patient mass), which was acceptable.
- The system performed in a safe manner at all times, with no device failures, no failures to deliver intended treatment and no adverse device events.
- Initial usability assessments revealed no major issues and reflect positive patient feedback.

In this study 6 patients were administered a total of 10 dialysis therapies. Patients were aged between 40 and 79 years.

Each therapy was performed on an outpatient basis with a target dialysis time of 240 mins (4 hours) using a bicarbonate-based dialysate at a dialysate flow rate of 500 ml/min.

The report acknowledges that the variability in the estimated UF error and error rate may be due to experimental error in the weight measurements such as estimation of fluid intake and washback volume. Washback volume was based on either full washback volume of 400 ml or counting pump

rotations if full washback was not completed. It is unclear whether the UF error and error rate is due to these experimental factors or due to the Quanta SC+ DDS.

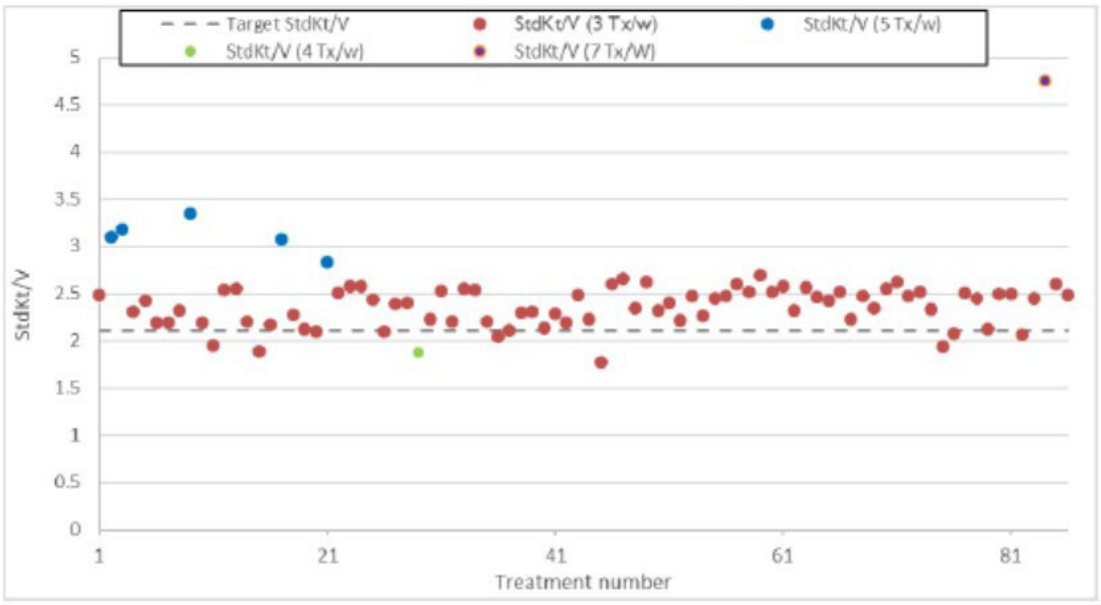
The Quanta SC+ DDS performed with acceptable clinical and technical performance in the patient population. There was no measured loss of therapy time, UF error was acceptable, no significant usability issues were noted, and there were no apparent safety issues in this subject population. Clinical performance was demonstrated by URR and Kt/V being greater than the referenced recommendations.

5.6.2 Pilot Study SC-01232

SC-01232 was a continuation of the pilot study for the Quanta SC+ DDS. It was a single-arm, prospective, multi-center, non-randomized, open-label, observational study. The objective of this study was to demonstrate safety, performance, and usability of the device in different treatment modalities within the clinical and home setting. Review of data from this study concluded that the SC+ DDS can be installed and used safely in the sponsor-led in-center and in-home modalities. The study data suggest that treatments in the clinic, supervised use modality were likely safe and effective and further trials were warranted.

A total of 660 treatments were carried out on 47 subjects across 3 centers between the start data and the data cutoff date. These treatments resulted in a 98.8% reliability rate. Individual treatments were considered successful if the patient received the full programmed dialysis session or if the session ended early but considered by the site to have provided an acceptable level of dialysis prior to session termination. Efficacy was measured by NFR error and clearance adequacy (Kt/V).

Clearance was assessed for 86 treatments based on monthly blood sampling in accordance with regular clinical practice by measuring Kt/V. See the graph below. Almost all treatments were successful, except in a small number of cases where the patient had residual renal function (and therefore would still maintain the ability to remove urea, affecting the treatment effectiveness).



Treatment number versus Kt/V

The mean urea reduction ratio (URR) for available blood data was 74.4% with a standard deviation of 7.1%.

All reported adverse event observations related to complications commonly noted during hemodialysis treatment such as hypotensive episodes. No deaths or hospitalizations were reported. Measured NFR figures showed an apparent bias due to a measurement error. One adverse device effect was reported, however the Quanta SC+ DDS safety mechanism functioned correctly and protected the patient from harm.

5.6.3 SC+ Hemodialysis Home Use Clinical Study (N=20) SC-01281

The purpose of this study was to capture information from the first 20 supervised home dialysis therapies using the Quanta SC+ DDS and to state clearly if the results suggest safety and efficacy to support further clinical use of the device in the supervised home modality.

The device was installed effectively in the home of two existing HHD patients. SC+ performed dialysis safely and effectively in the home setting: For patient HHD N1, treatment parameters using SC+ were broadly similar in in-center and in-home settings. Patient HHD N2 had no clinic treatments with SC+ prior to beginning treatments at home, this patient transferred to SC+ from a commercially available system in the home setting. The transition was straightforward without any issues and again SC+ performed dialysis safely and effectively.

5.6.4 Assessment of Efficacy

NFR calculations for treatments conducted at home appeared to indicate removal of excess fluid compared with target values. It is highly likely that the NFR error arises from the difficulty in adequately controlling and measuring the weight changes, in a clinical setting, due to the difficulty in accurately assessing patient fluid intake, washback volume, etc., This is consistent with known clinical experience and practice. It is for these reasons that the gold standard for assessing for NFR error is to do so under controlled laboratory conditions and not a clinical setting. As a further confirmatory check, the specific devices in question were returned to Quanta Dialysis Technology's laboratory to be reassessed for NFR error. Measurements indicated that the machine in question performed within specification limits and the relevant standards.

Machine B7/25 (used for subject HHD N1) had an NFR error of +29 g/hr (target fluid removal was 1 kg/h) following home treatments, machine B7/45 (used for subject HHD N2) showed an NFR error of +52 g/hr (target fluid removal was 1kg/h) following home treatments. These values being within the specified limit of ±100 g/h.

5.6.5 Assessment of Safety

There were no observed concomitant clinical signs, symptoms or Adverse Events to suggest issues with poor patient fluid management. This matter has been thoroughly discussed with, and reviewed by, the Principal Investigator at Nottingham and Quanta Dialysis Technologies MAB, who agree with the above. Therefore, the matter is not seen as clinically significant or a clinical risk. Blood data were available from a single treatment for HHD N1 which indicated effective URR For patient HHD N2 the URR values were below the recommended target of 65%; however, this patient was known to have residual renal function. Kt/V was above the recommended target threshold of 2.1 in all instances with respect to these patients.

No unexpected symptoms were observed during the home treatments, so it can be concluded that the Quanta SC+ DDS performed safely in the home setting. Progression to the supervised home modality of use is, therefore, considered appropriate.

Although the data is limited, nevertheless this study demonstrates the safety and performance of the Quanta SC+ DDS. No adverse events were identified.

5.7 Benefits and Risks

5.7.1 Benefits

The potential benefits of trial participation may be due to skills gained during the training period or the change in hemodialysis setting. With respect to skills, patients may develop proficiency at self-cannulation. Whether a patient remains on home hemodialysis or returns to in-facility hemodialysis after the completion of the study, the ability to self-cannulate will remain. Patients who can self-cannulate often report feeling a greater sense of control over their treatment and their vascular access and are less likely to experience short-term complications when moving from one dialysis facility to another, such as during travel (Brouwer 2011). With respect to hemodialysis setting, patients dialyzing at home may experience an improved sense of autonomy (Ishani 2015). The flexibility inherent in scheduling treatment at times of day that are convenient for a patient may be perceived positively by patients. Some observational studies (Marshall 2014, Nadeau-Fredette 2015, Marshall 2011) have suggested that home versus in-facility dialysis is associated with improved clinical outcomes, regardless of the details of dialysis modality and prescription.

With respect to hemodialysis intensity, the study protocol specifies a prescription of 4 sessions per week and 3.5 hours per session, or 14 hours per week, during the in-home phase. This treatment intensity compares favorably to the usual in-facility hemodialysis regimen of 3 sessions per week and a weekly total of 11 to 12 hemodialysis hours. The increase in frequency, particularly when coupled with the elimination of long interdialytic gaps, is likely to result in improved volume control, lower blood pressure, and decreasing utilization of antihypertensive medications. In the Frequent Hemodialysis Network trials (FHN Trial Group 2010, Kotanko 2015, Rocco 2011, Suri 2013), increased treatment frequency resulted in regression of left ventricular hypertrophy. In addition, with an increase in total hemodialysis hours per week is a decrease in UF rate during treatment. Lower UF rate may lower the incidence of intradialytic complications, such as hypotension, cramping, and nausea. In addition, increased treatment frequency and lower ultrafiltration rate are associated with shorter post-dialysis recovery time.

5.7.2 Risks

There are also potential risks associated with trial participation. Potential risks are associated with changes in hemodialysis intensity and setting. With respect to treatment intensity, increased frequency of hemodialysis may increase the risk of vascular access complications (Suri 2013). In the Frequent Hemodialysis Network trials, the risk of vascular access complications (including access repair, access loss, or access-related hospitalization) was significantly higher with 6 versus 3 sessions per week. Frequent hemodialysis may accelerate the loss of residual kidney function, particularly if recurrent episodes of intradialytic hypotension (possibly due to volume depletion) occur (Daugirdas 2013). Nevertheless, these data reflect effects of 6 sessions per week, not 4 sessions per week.

With respect to treatment setting, home hemodialysis presents some potential risks. In the absence of medical professionals, patients and care partners are responsible for managing all complications, including medical emergencies. Severe intradialytic hypotension, loss of consciousness, and significant blood loss (due to needle dislodgement) are all possible. Observational studies in the United States have indicated that frequent home hemodialysis is associated with increased risk of infection-related hospitalizations (Weinhandl 2015, Suri 2015), although this association may reflect

delays in reporting symptoms and initiating antibiotic therapy for vascular access infections, rather than risks inherent in the practice of home hemodialysis itself; there are no published studies that establish that the incidence of vascular access infection is higher with home versus in-facility hemodialysis. Finally, home hemodialysis may increase burden on care partners (Bennett 2015).

5.7.3 Minimization of Risks

Eligibility criteria have been selected that exclude subjects who are at a higher risk for experiencing an anticipated adverse event in order to reduce the risks to subjects who participate in this study. In addition, subjects enrolled in this study will receive their hemodialysis treatments by qualified dialysis center staff when undergoing in-facility treatments and will perform their own hemodialysis treatments after having completed device study training when performing treatments at home.

Monitoring will take place throughout the course of treatment and adverse events will be recorded in the subject's charts and on case report forms developed for the study.

6 STUDY DESIGN

This is a prospective, multi-center, two-treatment, two-period, open-label study. A dialysis prescription of 3 sessions per week, 4 hours per session, or facility standard will be provided during the in-clinic visits. A dialysis prescription of 4 sessions per week, 3.5 hours per session will be provided during home dialysis.

This study does not duplicate any current knowledge existing today on use of the SC+ Hemodialysis System in the United States.

6.1 Study Objective

The purpose of this study is to determine non-inferiority of efficacy and safety when Quanta SC+ is used for delivery of self-care home hemodialysis, compared to a hemodialysis facility.

6.2 Study Endpoints

6.2.1 Primary Safety Endpoint

The primary safety endpoint is the adverse event (AE) rate: the number of AEs per 100 treatments occurring in the home phase of the study, compared with those occurring in the in-clinic phase. All AEs will be collected, summarized by phase of the study, and compared between the in-clinic and in-home phase of the study. Additionally, in accordance with NCT02460263 (Plumb 2020), the rate of pre-specified AEs will be compared between treatment groups, with the pre-specified AEs comprising the following components:

- Serious adverse event: any adverse event that resulted in death, was life-threatening, required hospitalization or prolonged existing hospitalization, required intervention to prevent permanent impairment or damage, or resulted in persistent or significant disability/incapacity.
- Allergic reaction: type A anaphylactoid or type B dialyzer reactions to dialyzer, blood tubing, or chemical disinfectant.
- Blood loss: blood loss resulting in hemodynamic compromise that led to death, transfusion, or fluid resuscitation with greater than 1 liter of crystalloid IV fluids.
- Hemolytic Reaction: hemolytic reactions due to disinfectant exposure, dialysate temperature, mechanical failure, or other device related causes.
- Infection: any infection related to hemodialysis catheter, its tunnel or exit site, arteriovenous fistula (AVF), or arteriovenous graft (AVG).
- Intradialytic event: a significant clinical event such as loss of consciousness, cardiac arrest, or seizure caused by device failure.

- Vascular access complication: defined as AVF or AVG clotting during the dialysis procedure, bleeding for more than 30 minutes post-dialysis for 3 consecutive sessions, difficulty with vascular access resulting in inability to initiate or complete dialysis treatments or complications related to hemodialysis catheters (not including reduced blood flow in catheter or tissue plasminogen activator (TPA) or catheter exchange).
- Pyrogenic reaction: onset of objective chills (visible rigors) and fever (oral temperature greater than or equal to 37.5 degrees Celsius) in a participant who was afebrile and who had no recorded signs or symptoms of infection before treatment.

6.2.2 Secondary Endpoints

Safety:

- Number of serious adverse events (SAEs) per 100 treatments occurring in the home phase of the study, compared with those occurring in the in-clinic phase.
- Number of device-related AEs and SAEs per 100 treatments in the home phase of the study, compared with those occurring in the in-clinic phase.
- Additional adverse events of special interest:
  - Individual components of the primary safety endpoint
  - Air in blood tubing that cannot be resolved through usual procedures.
  - Significantly elevated venous (>250 mmHg) or negative arterial (>100 mmHg) pressures during three (3) consecutive treatments.
  - Intradialytic hypotension, as defined by treatments during which hypotensive symptoms led to either lowering the ultrafiltration rate or saline administration.
  - Post-dialysis (30 minutes) systolic blood pressure <90 mmHg or systolic blood pressure >180 mmHg following two (2) consecutive treatments.

The following biochemistry and hematology laboratory values will be collected and compared to target ranges from clinical practice guidelines.

Biochemistry: assessments of pre-treatment plasma at visits C1, C2, C4, C6, C8, H2, , H4, H6 and H8/Withdrawal:

- sodium (Na) (target range, 135-145 mEq/L)
- urea (BUN)
- potassium (K) (target range, 3.5-5.5 mEq/L)
- creatinine (Cr)
- bicarbonate (HCO3) (target range, ≥22 mEq/L)
- magnesium (Mg)
- phosphate (Phos) (target range, 3.5-5.5 mg/dL)
- chloride (Cl)
- calcium (Ca) (target range, 8.4-9.5 mg/dL)
- albumin (Alb) (target range, ≥3.5 g/dL)
- iron (Fe)
- transferrin saturation (TS) (target range, >20%)
- total protein (TP)
- ferritin (Fn) (target range, >200 ng/mL)
- alkaline phosphatase (ALP)
- parathyroid hormone (PTH) (target range, 150-600 pg/mL)
- total iron binding capacity (TIBC)
- aspartate transaminase (AST)
- alanine aminotransferase (ALT)

Hematology: assessments of pre-treatment blood at visits C1, C2, C4, C6, C8, H2, H4, H6 and H8/Withdrawal:

- hemoglobin (Hb)
- hematocrit (Hct)
- white cell count (WBC)
- platelet count (PC)
- reticulocyte Count (RC)

Ultrafiltration (UF)

- Ultrafiltration volume (net fluid removal), such that the recorded value from the Quanta SC+ DDS is within ± 100 mL/h or ± 400 mL of set point during the treatment, based on the UF prescription.
-

Clinical utility

- Number of alarms
- Time to resolve alarms
- Type of alarms

Reliability

- Ability to deliver prescribed treatments

Training and competence

- Proportion of subjects and caregivers completing training successfully
- Attempts required to complete training successfully

Device deficiencies

- Descriptive summary of device deficiencies reported

Patient reported outcomes

- Time to recovery after dialysis treatment (Lindsay RM, 2006)
- EQ-5D-5L (Culleton BF, 2007)
- Medical Outcomes Study (MOS) Sleep Index (Hays RD, 2005; Hays R, 1992)
- Renal Treatment Satisfaction Questionnaire (RTSQ, Bardense 2005)
- Zarit Burden Interview (ZBI12, Bédard 2001, completed by caregiver rather than participant)
- Edmonton Symptom Scale (ESAS-r, Davidson SN, 2006)

6.3 Sites

A total of 8-15 sites in United States.

6.4 Participant Population and Numbers

50 participants with established kidney failure undergoing hemodialysis will be enrolled to obtain 33 evaluable participants. Participants will have been receiving hemodialysis for at least 90 days, or in the case of peritoneal patients transitioning to hemodialysis, at least 90 days. Enrollment will include patients planning for home hemodialysis or currently on home hemodialysis or peritoneal dialysis. No more than 25% of participants will be recruited from a single site. No more than 40% of participants will be recruited who have received home hemodialysis during the 12 weeks preceding study entry.

6.5 Study Structure

Following enrollment participants will begin hemodialysis treatments on the SC+ machine on a prescription of four-hour treatments, three times per week or per facility standard for a baseline period of 4 weeks within a hemodialysis facility administered by qualified dialysis clinical staff. During this time, both patients and caregivers will undergo extensive training and competency sign off. Competency, defined as three observed treatments without intervention or request for intervention from either the participant or their caregivers, will be assessed to ensure they are safe and proficient to conduct regular treatments in the home setting. This 4 week period can be extended week by week to a maximum of 8 weeks until competency sign off is achieved. If competency signoff is not achieved after 8 weeks, the participant will be withdrawn from the study. Following this in-clinic phase, a one-week transition phase of home hemodialysis will be provided with a dialysis professional present, followed by the home hemodialysis phase (test phase) without a dialysis professional present for an additional 8 weeks. Treatments in the transition and home hemodialysis phases will be performed by the participant and caregiver, 4 times per week, 3.5 hours each treatment.

Participants will undergo standardized physical examinations by a physician at the beginning of the in-clinic treatment phase (C1) and at the end of the self-care phase (H8) and at withdrawal. Regular physical exams, biochemistry, and hematology testing will be performed as defined below.

The study will be considered complete with regard to the primary objective after the minimum evaluable participants have completed the protocol and associated procedures defined below.

7 PARTICIPANT POPULATION

7.1 Participant Enrollment

7.1.1 Informed Consent

Prior to any study-related procedures or assessments, participants or their legally authorized representatives (as appropriate) must be informed of the risks and benefits of the study and voluntarily agree to enter the study. Section 13.3 provides details of requirements of this process.

7.1.2 Participant Screening

Participants are considered enrolled in this study at the point where they or their authorized representative provide written informed consent and they are documented in the eCRF system to have successfully been screened to meet all inclusion criteria and not to meet any exclusion criteria. If potential participants fail screening at one point, yet meet all the inclusion criteria and none of the exclusion criteria at a later time, they may be re-screened at the discretion of the investigator.

7.2 Inclusion and Exclusion Criteria

7.2.1 Inclusion Criteria

Participants must meet every inclusion criterion to be eligible to enter the study.

1. Provision of a written informed consent form signed by the participant
2. Age between 18 and 80 years at time of enrollment
3. A care partner must be available for training on SC+ and to be present in the home during all home hemodialysis sessions
4. Participants should be either receiving regular, facility-based hemodialysis therapy for at least 90 days, or in the case of peritoneal patients transitioning to hemodialysis, at least 90 days, or

performing home dialysis (with any frequency) for at least 90 days and willing to return to facility for purpose of study, and should be clinically stable and deemed suitable for home dialysis in the opinion of the principal investigator
5. Willing to accept a dialysis prescription of 3 sessions per week, 4 hours each session or facility standard during in-clinic visits; 4 sessions, 3.5 hours each session during in-home sessions
6. In the opinion of the Investigator, participant has well-functioning and stable vascular access (tunneled, central venous catheter, arteriovenous fistula, or graft) that allows a blood flow of at least 300 ml/min
7. Home environment is adequate to ensure that appropriate electrical connections and water supply necessary for the use and storage of the device as assessed by Quanta prior to subject C1 visit. Also ensure that cellular signal and/or WIFI capacity is adequate.
8. Participant or care partner are capable of understanding the nature of procedures and requirements of the study protocol and of home-based hemodialysis, and are willing and capable of complying with protocol and returning to treatment center as stated in protocol
9. Participant or care partner are capable of being trained to use the machine and troubleshoot should an alarm situation occur
10. In the opinion of the treating physician, the subject is able to participate in the trial in terms of social factors and personal function.
11. Acceptable physical ability of the participant and/or care partner to perform the hemodialysis treatment at home
12. Financial coverage for treatment costs by Medicare, Medicaid, private insurance, or other arrangement acceptable to participant

7.2.2 Exclusion Criteria

Participants must not meet any exclusion criterion to be eligible to enter the study.

1. Pregnant or trying to become pregnant (women of childbearing potential must use medically accepted contraceptive measures)
2. Predicted life expectancy of less than 12 months from first study procedure
3. Major cardiovascular adverse event in the 3 months prior to screening
4. Fluid overload due to intractable ascites secondary to liver cirrhosis
5. Uncontrolled or unstable blood pressure (systolic BP outside the range 90 to 180 mmHg)
6. Unstable coronary artery disease
7. New York Class III or IV heart failure, or ejection fraction less than 30%
8. Participation in other clinical studies that may interfere with the current protocol
9. Known problems with coagulation
10. Active, life-threatening, rheumatologic disease.
11. Hematocrit less than 28% at enrollment (within 30 days of enrollment)
12. Hemoglobin less than 9 g/dL at enrollment (within 30 days of enrollment)
13. Suffering from active severe infection
14. Seroreactive for hepatitis B surface antigen
15. Suffering from active malignancy with expected deteriorating course within 6–12 months
16. History of severe reactions to dialyzer membrane material
17. Expected to receive an organ transplant during the course of the study
18. Have dementia or inability to understand procedures
19. Lack an ability for self-care
20. Are non-adherent to their current dialysis treatments
21. Experience intra-dialytic hypotension defined as a decrease in systolic blood pressure of greater than or equal to 20 mmHg or a decrease in mean arterial pressure of greater than or equal to 10 mmHg provided that the decrease is associated with clinical events (symptoms) and the need for an intervention (ultrafiltration turned off, bolus of fluid) in 3 of 5 previous treatments
22. Is intolerant to heparin

23. Considered in the investigator's opinion to be clinically unstable for any other reason
24. Undergoing outpatient dialysis for the treatment of acute kidney injury (AKI)

7.3 Duration

Participants will participate in the study for 14–19 weeks: screening and enrollment (up to 2 weeks) clinic period (minimum 4 weeks, maximum 8 weeks until training competency is achieved), a transition period (1 week), and self-care period (8 weeks).

7.4 Withdrawal

Participants are free to withdraw at any time. A participant will be automatically withdrawn if training competency is not achieved after 8 weeks of in-clinic treatment or if treatments cease with SC+ for a period of more than 7 consecutive days during the course of the study or if 8 or more (non-consecutive) treatments are missed. Data taken prior to withdrawal will be used for study analysis.

7.5 Discontinuation

Participants may be discontinued from the study at any point if, in the Investigator's opinion, it is not in the best interest of the participant to continue. Data taken prior to discontinuation will be used for study analysis.

7.6 Lost to Follow Up

Participants will be considered lost to follow up if they do not respond to telephone calls or requests to schedule or re-schedule visits after three attempts. The last attempt should be by registered letter.

8 PROCEDURES AND ASSESSMENTS

8.1 Visit Schedule

The following visits will take place during the study. During each visit the named study activities will be conducted. Further details can be found in the Study Activities section of this document. Participants will be queried for adverse events, including intra-dialytic events as appropriate, at every encounter. Also, participants will be asked to record adverse events and changes in concomitant medications continually between visits to facilitate thoroughness and maintain continuity of reporting between both in-clinic and home portions of the study. Patient reported outcome (PRO) measures will be collected via an ePro system at specified time points during the study. At the end of study, the participant care partner will be asked to complete a satisfaction questionnaire.

Concomitant medication collection will be limited to the following: erythropoiesis-stimulating agents (ESAs), intravenous iron, phosphate binders, calcimimetics, and anti-hypertensive medications (ACE inhibitors, ARBs, beta blockers, calcium channel blockers, central alpha agonists, vasodilators [specifically, hydralazine and minoxidil]).

- Scheduled visits
    - Screening and Enrolment
        - inclusion/exclusion criteria review
        - informed consent
        - demographics
        - ethnicity
        - comorbidities profile
        - medical and surgical history

- dialysis treatment history
- Pregnancy test (to be performed in female of child bearing potential)
- dialysis access
- reason for kidney failure
- device training details
- concomitant medication check
- Evaluation of home for installation requirements

- Clinic Period (weekly assessments) minimum 4 Weeks, can be extended week by week to a maximum of 8 weeks until training competence is demonstrated
  - treatment parameters established at C1 and changes captured thereafter
  - vital signs
  - concomitant medication check
  - adverse event and device deficiency assessment
  - biochemistry (weeks 1, 2, 4, and 6 and 8 if training competence not achieved by week 4, only)
  - hematology (weeks 1, 2, 4, and 6 and 8 if training competence not achieved by week 4, only)
  - blood iron content (weeks 1, 2, 4, and 6 and 8 if training competence not achieved by week 4, only)
  - treatment with Quanta SC+ (3 sessions per week, 4 hours each session or facility standard)
  - Kt/V (weekly)
  - Device deficiency assessment
  - TTR (patient assessment, C1 only)
  - EQ-5D-5L (C1 only)
  - MOS Sleep index (C1 only)
  - ESAS-r (C1 only)
  - RTSQ (C1 only)
  - RO water/dialysate quality (prior to new subject enrolling in the clinic period and then week 4 and week 8 if training competence not achieved until then)
  - Reliability (monitored continually by Quanta SC+)
  - Proportion of participants and caregivers successfully trained at some point by week 8
  - physical exam (week 1 only)
  - preparation of home setting for transition to home during this period
  - Participant and caregiver training on Quanta SC+
  - Training on ipad and associated apps
  - Training on completing the treatment flowsheet

- Transition Period (1 week) supervised by dialysis professional
  - treatment parameters as established for home treatments
  - vital signs as measured by subject during treatment
  - concomitant medication check
  - adverse event and device deficiency assessment
  - treatment with Quanta SC+ (4 sessions, 3.5 hours each session)

        - Review subject adherence to entering treatment information on the treatment flowsheet during each treatment
        - Kt/V (weekly)
        - in home visit by study team including mid-week blood collection per protocol mid-week (may be performed remotely)
        - RO water/dialysate quality (prior to T1)
        - Reliability (monitored continually by Quanta SC+)

    - Home Period (weekly assessments) (8 weeks)
        - treatment parameters
        - vital signs as measured by subject during treatment
        - concomitant medication check
        - adverse event and device deficiency assessment
        - biochemistry (weeks 2, 4, 6,8 only)
        - hematology (weeks 2, 4, 6, 8 only)
        - blood iron content (weeks 2, 4, 6, 8 only)
        - treatment with Quanta SC+ (4 sessions per week, 3.5 hours each session)
        - Review subject adherence to entering treatment information on the treatment flowsheet during each treatment
        - Kt/V (weekly)
        - RO water/dialysate quality (weeks 4 and 8)
        - physical exam (week 8 only)
        - in home visit by study team including possible mid-week blood collection per protocol mid-week if participant does not draw their own blood
        - Usability
        - Time to recovery (H1, H4 , and H8)
        - EQ-5D-5L (patient assessment at H1 and H8)
        - ESAS-r (H1 and H8)
        - MOS Sleep index (patient assessment at H1, and H8)
        - RTSQ (patient assessment at H1 and H8)
        - ZBI12 (carepartner, H8 only)
        - Clinical utility (H8 only)
        - Reliability (monitored continually by Quanta SC+)

HCP support and interactions are intended to be available to participants as required by the study, but not to provide additional training, support, or oversight of the dialysis procedure. Any contact outside study-driven procedures will be documented for purpose of understanding need for additional health care support.

- Unscheduled visits
    - Withdrawal
        - reason for withdrawal
        - physical exam
        - treatment parameters
        - vital signs
        - concomitant medication check
        - adverse event and device deficiency assessment
        - biochemistry
        - hematologyKt/V

- RO water/dialysate quality
- physical exam
- EQ-5D-5L
- MOS Sleep index
- RTSQ
- TTR
- ZBI12
- ESAS-r
- Clinical utility
- Reliability
- HCP support and interactions are intended to be available to participants as required by the study, but not to provide additional training, support, or oversight of the dialysis procedure. Any contact outside study-driven procedures will be documented for purpose of understanding need for additional health care support.
- Patient-caregiver satisfaction survey

8.2 Visit Windows

In-clinic dialysis should start within 2 weeks after enrollment.

In-clinic dialysis sessions will be provided on Monday, Wednesday, and Friday (unless otherwise approved by Sponsor). In home dialysis sessions will be provided on Monday, Wednesday, Friday, and Saturday (unless otherwise approved by Sponsor).

Blood sampling will be performed on Wednesday (unless otherwise approved by Sponsor).

In-clinic dialysis will continue for a minimum of 4 weeks, and can be extended week by week to a maximum of 8 weeks until training competency is demonstrated. Timings for scheduled in facility visits will be calculated based on the date baseline completed. Treatment should occur at least three times per week as per standard protocol within the facility. The start of the transition phase will begin only after competency sign-off and will be 4 times during 1 week. The 8 week in home dialysis phase will begin after the transition phase and will be 4 times weekly for 8 weeks. To be included in the data analysis, scheduled visits occurring after competency sign-off must occur within ±3 days of the expected time point.

8.3 Study Activities

Details of selected specific study activities are provided below.

Assessment	Details
physical exam	Heart, lungs, dialysis vascular access, and other body systems as appropriate
biochemistry	Sodium (Na), urea (BUN), potassium (K), creatinine (Cr), bicarbonate (HCO3), magnesium (Mg), phosphate (Phos), chloride (Cl), calcium (Ca), albumin (Alb), iron (Fe), transferrin saturation (TS), total protein (TP), ferritin (Fn), alkaline phosphatase (ALP), parathyroid hormone (PTH), total iron binding capacity (TIBC), aspartate transaminase (AST), alanine aminotransferase (ALT). BUN will be collected immediately before and after Quanta SC+ treatment.
hematology	Hemoglobin (Hb), hematocrit (Hct), white cell count (WBC), platelet count (PC), reticulocyte count (RC)

concomitant medication check	Change in concurrent medications, limited to the following: erythropoiesis-stimulating agents (ESAs), intravenous iron, phosphate binders, calcimimetics, and anti-hypertensive medications (ACE inhibitors, ARBs, beta blockers, calcium channel blockers, central alpha agonists, vasodilators [specifically, hydralazine and minoxidil])
device deficiency assessment	At each clinical encounter, participants will be asked about any unexpected signs or symptoms, as well as any device complaints/difficulties or alarms
treatment with Quanta SC+ DDS	During in-clinic phase, 3 sessions per week, 4 hours each session or as per clinic standard for training. During in-home phase, 4 sessions per week, 3.5 hours each session. During both phases, heparinization before and during each session if prescribed
Usability	Participants queried: required assistance with any aspect of treatment over the prior 7 days and if so, with which of the following tasks: machine set up, clearing of alarms, machine take down, fistula/needling or catheter connection
time to recovery	TTR is completed once after a dialysis treatment during the week of C1 – H1 – H4 and H8 or at withdrawal; not all treatments within those weeks. (Lindsay 2006))
treatment parameters	Review of dialysis prescription
treatment adequacy	Mid-week during each study period, determination of Kt/V
EQ-5D-5L	Quality of life assessment, patient reported
MOS sleep index	Quality of sleep assessment, patient reported
RTSQ	Renal treatment satisfaction, patient reported
ZBI12	Caregiver burden, caregiver reported (ZBI12, Bédard 2001)
ESAS-r	patient experience, patient reported (Davidson SN., 2006)
clinical utility	Number of alarms, time to resolve alarms, type of alarms. A report will be provided by Quanta at the end of treatment, either H8 or Withdrawal for the site to upload into the eCRF.
reliability	Ability to deliver prescribed treatments
proportion of participants and caregivers successfully trained	Measured by passing training competency by the end of clinic visits (no longer than 8 weeks of clinic visits)
RO water/dialysate quality	During installation prior to initiation of therapy for all participants water will be tested for culture and endotoxins and then minimum of each month
vital signs	Prior to dialysis treatment: pulse, blood pressure, temperature (oral, tympanic, temporal), and weight both before and after dialysis treatment. During dialysis treatment: pulse and blood pressure every 30 minutes
in home visit	Mid weekly visits will occur after the transitional week. Blood draw for Kt/V (bloodwork done pre and post dialysis) Also biweekly/monthly safety bloodwork and water quality testing as per study schedule. Review data entry on the treatment flowsheet and assess adherence, reinforce as required. Assessment of device-related events or adverse events. Assessment of vascular access site for any signs of infection etc. and review with participant any issues with self cannulation. Vital signs assessed by participants, dispense consumables according to supply needs. These visits will be done in person or virtually as per the standard of care at the

	research centre.
review of HCP support and interactions	HCP support and interactions are intended to be available to participants as required by the study, but not to provide additional training, support, or oversight of the dialysis procedure. Any contact outside study-driven procedures will be documented for purpose of understanding need for additional health care support.

8.3.1 Blood collection

Each participant will be required to provide approximately 120 ml or 8 tablespoons of total blood for the duration of the trial. Samples will be collected as per standard of care and analyzed in the local laboratory. Samples will be collected for chemistry, hematology, and iron as per schedule of assessments.

For post dialysis, a blood sample will be collected at the conclusion of therapy by reducing the blood pump speed to 100 ml per minute. After one minute has elapsed at that blood flow rate, then the sample will be collected according to the standard of care.

During training and during the transition week, the participant will be instructed on how to draw their own blood samples. During visits H1–H8, the participants may be instructed on how to draw their own blood sample or bloodwork can be drawn by trained research staff.

8.3.2 Heparinization

If an initial heparin bolus is prescribed for treatment, then a heparin dose will be manually delivered to the participant with a syringe through a fistula needle 5 minutes before commencement of treatment. Heparin therapy during dialysis treatment will be prescribed according to institutional practices and at the discretion of the Investigator and delivered via the dialysis bloodlines. For participants with arterial venous fistula or graft access should not receive heparin within 30 minutes of the end of treatment.

8.3.3 RO Dialysis Water and Dialysate Microbiological Quality Testing

During device installation in center and in home and monthly thereafter, water and dialysate samples will be collected and tested for total viable count (TVC) and endotoxin levels.

For dialysis water results above the action limits of 50 CFU/ml or 0.125 EU/ml the device manufacturer instructions should be followed for conducting a thermal or chemical disinfection cycle, a new sample will be drawn and new test results obtained. In addition, the Sponsor will review the culture and disinfection logs and determine if the system should be removed from use. If still above the action limit upon retesting, the device will be removed from use. Results above the maximum allowable level of <100 CFU/ml or <0.25 EU/ml may be considered a failure and the device removed from use.

For dialysate results above the action limits of 50 CFU/ml or 0.25 EU/ml a hot rinse thermal disinfection should be carried out, a new sample will be drawn and new test results obtained. In addition, the Sponsor will review the culture and disinfection logs and determine if the system should be removed from use. If still above the action limit upon retesting, the device will be removed from use. Results above the maximum allowable level of <100 CFU/ml or <0.5 EU/ml may be considered a failure and the device removed from use.

8.3.4 Treatment Flowsheet

During the course of the study, participants will utilize the treatment flowsheet to document medical device data and participant data in the home setting. Participants will be trained on how to document on the flowsheet during the clinic phase. Participants will begin documenting on the flowsheet during the transition phase and home phase. The information recorded on the flowsheet is as defined in the Informed Consent and Personal Health Information Use and Disclosure Authorization Form. The participants will be responsible for documenting on the flowsheet each time the patient receives treatment on the SC+.

8.3.5 Dialysis Supplies

The following supplies will be provided by Quanta:

- Cartridge (blood tubing set)
- Dialysis Cartridge
- Tablet for accessing applications for connected devices
- Bluetooth connected blood pressure monitor and scale

Note: All supplies will be returned to Quanta at the end of the study.

The following supplies will be provided by the investigator/ the treating center:

- Dialyzer (within specification as per user manual)
- saline
- dialysis needles
- cleaner for vascular access site
- gauze pads and tape for vascular access
- gloves, mask and safety glasses
- biohazard box and bag
- container of acid concentrate
- container of bicarbonate concentrate
- 20 cc syringe
- Heparin (per Subject's prescription) and syringe for administration
- recirculator
- cleaning supplies for machine after each treatment
- on-off kit for central venous catheter when applicable

8.3.6 Dialysis Prescription

The prescription for dialysis will include

- filter type used
- time on dialysis (180–240 min)
- blood flow rate (250–400 ml/min)
- dialysate flow rate (500 ml/min)
- dialysate Temp (35–37°C)
- Dialysate Conductivity (13.7 – 14.1 mS/cm)
- heparin dose and parameters
- ultrafiltration parameters and target weight
- acid concentrate composition
- Bicarbonate (35 mmol/L)

- blood pressure parameters for ultrafiltration

As much as possible unless medically necessary, the dialysis prescription should be kept constant during the study except for the change from 3 times per week, 4 hours per treatment during the in-clinic portion and 4 times per week, 3.5 hours per treatment during the transition and home portions. The prescription should not be changed for efficacy or other reasons unless medically indicated.

8.4 Participant Responsibilities Before, During, and After Treatment

8.4.1 Participant Responsibilities Before Treatment

Prior to treatment, participants will be responsible for:

- setting up device as per instructions,
- checking water for chlorine or chloramine (as per local protocol)
- measuring weight, blood pressure, pulse, and temperature and entering measurements on to the flowsheet,
- examining vascular access either by examining their fistula for signs of infection, thrill, bruit, aneurysms, and integrity of skin over the fistula or their central venous catheter site for any signs or symptoms of infection, and
- preparing dialysis access (catheter, fistula, or graft) using trained aseptic technique, and perform cannulation of the fistula or graft, or connection to a catheter.

8.4.2 Participant Responsibilities During Treatment

During treatment, participants will be responsible for:

- initiating dialysis and monitoring treatment according to center protocol,
- entering the treatment start time on the treatment flowsheet,
- performing blood pressure and pulse readings every 30 minutes and entering measurements on the treatment flowsheet,
- answering questions on the patient flowsheet,
- refraining from eating and drinking as much as possible, and if not possible, recording amounts of fluid and food intake under the “Medical issues – Other” section on the treatment flowsheet,
- documenting on the treatment flowsheet any details of symptoms experienced during dialysis.
- performing their own blood draws during visits H1–H8 as appropriate.

8.4.3 Participant Responsibilities After Treatment

After treatment, participants will be responsible for:

- measuring participant weight, blood pressure, pulse, and temperature and entering measurements on the treatment flowsheet, and documenting time to recovery disconnecting from dialysis treatment as instructed,
- answering question regarding general well being and treatment end time on the treatment flowsheet.
- cleaning device as instructed.

9 SAFETY

9.1 Adverse Event Definitions

Events will be classified based on the following definitions:

9.1.1 Adverse Event

Any Adverse Event is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in participants, users or other persons, whether or not related to the investigational medical device.

9.1.2 Device Related Adverse Event

Any adverse event related to the use of the medical devices listed for use in the study.

9.1.3 Serious Adverse Event/Serious Adverse Device Effect

Any Adverse Event or Device Related Adverse Event with any one or more of the following characteristics:

- Led to or could have led to death
- Led to or could have led to serious deterioration in the health of the participant, resulting in
    - a life-threatening illness or injury
    - a permanent impairment of a body structure or a body function
    - in-patient or prolonged hospitalization
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Led to or could have led to fetal distress, fetal death, or a congenital abnormality or birth defect.

9.1.4 Unanticipated Serious Adverse Device Effect

An unanticipated adverse device effect (UADE) is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants.

9.2 Adverse Event Relationship

All adverse events will be assigned an initial attribution according to the Investigator's believed primary cause. Events will be categorized by relationship to the investigational device, index procedure, concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or other.

Investigational Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the Quanta SC+ DDS.

Non-Investigational Device: It is reasonable to believe that the event is associated with an accessory device used during the study procedure and is not specific to the investigational device use

Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of dialysis independent of the use of the Quanta SC+ DDS.

Medication-Related Adverse Event: an adverse event is considered to be medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with any medications used.

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the participant's pre-existing condition and is not specific to the investigational device or index procedure or medication to address heart failure. Pre-existing conditions that are aggravated or become more severe during or after the index procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device- or index procedure-related.

Intercurrent Condition: It is reasonable to believe that the event is directly associated with an intercurrent condition/co-morbidity.

Intercurrent Intervention: It is reasonable to believe that the event is directly associated with an intercurrent intervention which was performed for reasons other than to address a device- or index procedure-related complication.

Observation/Incidental Finding: Abnormal or non-specific findings or observations that may be associated with study activities but no identifiable clinical correlation and suggests no specific pathophysiological process (such as painful access or tired). Such an event will not be considered an adverse event unless associated with clinical sequelae or requires specific intervention. When clinical sequelae occur or when the intervention required exceeds standard response for similar symptom or event, it will be reported as an adverse event.

Unknown: The adverse reaction cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.

9.3 Adverse Event Severity

The severity of adverse events will be rated according to the following scale:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; event does not generally interfere with usual activities of daily living.

Moderate: minimal, local, or noninvasive intervention may be indicated; event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

Severe: medically significant but not necessarily immediately life-threatening; hospitalization or prolongation of hospitalization indicated and may require intensive therapeutic intervention to resolve.

9.4 Adverse Events Recording and Reporting

9.4.1 All Adverse Events

All Adverse Events and Device Related Adverse Events will be recorded as part of this study beginning from first treatment with the Quanta SC+ DDS. Participants will be asked at each encounter an open-ended question such as, "How have you been feeling since your last visit?" and any events meeting an adverse event definition will be recorded. Clinic progress notes and other medical records will also be reviewed to determine if adverse events have occurred.

All adverse events (i.e., serious or non-serious, anticipated or unanticipated) must be recorded on the Adverse Event CRF by the Investigator or designee, for events of hypotension a specific eCRF should be used to ensure all details regarding event are recorded. All device deficiencies should be recorded on the device observations eCRF. The record must include the start date of the adverse event, treatment, resolution, and assessment of both the seriousness and the relationship to the investigational device.

The following criteria must also be adhered to by the Investigator:

- Completion of a separate Adverse Event form or log entries to document each event
- Completion of separate device observation form or log entries for each device observation or deficiency
- Electronic signature of forms or log entries
- On request of the sponsor, provision of any additional information related to the safety reporting of a particular event

All adverse events will be reported by the Sponsor or designee to the applicable regulatory authority at least annually or as required and to IRBs as instructed by the applicable IRB.

9.4.2 Serious Adverse Events

All serious adverse events (including SADE and USADE) should be reported by the Investigator (or designee) by submitting the Adverse Event Electronic Case Report Form to the Sponsor within 24 hours of learning of the adverse event.

The Investigator (or designee) shall provide source documents related to the serious and/or unanticipated adverse event as requested by Sponsor or their designee.

The Investigator must follow all unresolved serious adverse events until the events are resolved, the participant is lost to follow-up, the participant has withdrawn consent, or the adverse event is otherwise explained.

The Sponsor will evaluate all serious adverse events for reportability as an unanticipated adverse device effect in accordance with 21CFR812.46(b). The investigator and Sponsor will comply with reporting requirements per 21CFR812.150. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 21CFR812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests.

Study sponsor, or their designee, in cooperation with the Investigator, will assess all serious adverse events considered device-related for potential reportability to the FDA as an Unanticipated Serious Adverse Device Effect (USADE). Any unanticipated adverse events: must also be reported to the FDA, all reviewing IRBs, and participating investigators within ten (10) days of receiving notice of the serious adverse event or death, (or per local IRB requirements), and documentation of the report sent to Sponsor or their designee.

It is the responsibility of the Investigator to inform their IRB of serious adverse events as required by their IRB procedures and in conformance with applicable regulatory requirements.

In the event of a suspected device observation or deficiency, the device shall be returned to Sponsor for analysis. Instructions for returning the investigational device are included in the Study Reference Manual. The device will be replaced as appropriate.

9.4.3 Pregnancy

Pregnancy itself is not an adverse event. Participants of childbearing potential will be instructed that they must use medically acceptable birth control during the trial. Should a participant become pregnant, they will be followed to live birth or other outcome and any adverse events related to childbirth or fetal or newborn abnormalities will be recorded and followed to resolution or 30 days post birth.

9.4.4 Death of Participants

Participant death during the investigation should be reported with written documentation to Sponsor or designee within 24 hours of Investigator's knowledge of the death. The adverse event that resulted in death should be entered in the database within 24 hours and include a brief description of the relevant details of the death. The electronic Adverse Event Form must be electronically signed by the Investigator. A copy of the death records, death certificate and an autopsy report (if performed) are required to be sent to the Sponsor or designee within 10 days following the death. In addition, participant death must be reported to the IRB in accordance with IRB requirements.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Overview

Baseline characteristics will be summarized for all participants using conventional summary statistics reported as mean and standard deviation or median and interquartile range, as appropriate.

10.2 Sample Size for Primary Endpoint

10.2.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the delivery of a weekly standard Kt/V of greater than or equal to 2.1. The hypotheses are outlined in Section 10.4.1 below, and the analysis will be done in each of the In-Center period and the In-Home period. The sample size was derived based on the following assumptions:

- True treatment period mean weekly standard Kt/V is 2.5
- Standard deviation is 0.7
- One-sided α=0.025
- Within patient correlation of ρ=0.50
- AR(1) covariance structure

Using a one-sample test, a sample size of n=11 patients, each measured weekly for 8 weeks of treatment, will have >90% power to detect that the mean weekly standard Kt/V is greater than 2.1.

10.2.2 Primary Safety Endpoint

The primary safety endpoint is the adverse event (AE) rate: the number of AEs per 100 treatments occurring in the home phase of the study, compared with those occurring in the in-clinic phase. All AEs will be collected, summarized by phase of the study, and compared between the in-clinic and in-home phase of the study. Additionally, in accordance with NCT02460263 (Plumb 2020), the rate of pre-specified AEs will be compared between treatment groups, with the pre-specified AEs comprising the following components:

- Serious adverse event: any adverse event that resulted in death, was life-threatening, required hospitalization or prolonged existing hospitalization, required intervention to

prevent permanent impairment or damage, or resulted in persistent or significant disability/incapacity.
- Allergic reaction: type A anaphylactoid or type B dialyzer reactions to dialyzer, blood tubing, or chemical disinfectant.
- Blood loss: blood loss resulting in hemodynamic compromise that led to death, transfusion, or fluid resuscitation with greater than 1 liter of crystalloid IV fluids.
- Hemolytic Reaction: hemolytic reactions due to disinfectant exposure, dialysate temperature, mechanical failure, or other device related causes.
- Infection: any infection related to hemodialysis catheter, its tunnel or exit site, arteriovenous fistula (AVF), or arteriovenous graft (AVG).
- Intradialytic event: a significant clinical event such as loss of consciousness, cardiac arrest, or seizure caused by device failure.
- Vascular access complication: defined as AVF or AVG clotting during the dialysis procedure, bleeding for more than 30 minutes post-dialysis for 3 consecutive sessions, difficulty with vascular access resulting in inability to initiate or complete dialysis treatments or complications related to hemodialysis catheters (not including reduced blood flow in catheter or tissue plasminogen activator (TPA) or catheter exchange).
- Pyrogenic reaction: onset of objective chills (visible rigors) and fever (oral temperature greater than or equal to 37.5 degrees Celsius) in a participant who was afebrile and who had no recorded signs or symptoms of infection before treatment.

Due to a lack of published data on the overall AE rate, power calculations were performed using assumptions for the pre-specified AE rate per 100 treatments. A 95% confidence interval for the number of AEs per 100 dialysis treatments in each treatment period (In-Center and In-Home use) will be constructed as outlined in Section 10.4.2 below. Similarly, the 95% CI for the difference in number of AEs per 100 treatments in each treatment period will be calculated. The power calculations were done based on the following assumptions:

- $\mu_{IH} = 0.03$, the rate of AEs per dialysis treatment in-Home is 0.03
- $\mu_{IC} = 0.03$, the rate of AEs per dialysis treatment in-Center is 0.03
- $\mu_{IH} - \mu_{IC} = 0$, the difference in rate of AEs per dialysis treatment is 0
- $\sigma_{IH-IC} \leq 0.17$, the standard deviation of the difference is less than 0.17 AEs per dialysis interval
- Non-inferiority margin of 0.1 AEs per dialysis interval
- One-sided α=0.025

Using a two-sample t-test, a sample size of n=33 patients with 4 dialysis intervals per week for 8 weeks, (i.e., 33 patients with 32 treatments, for a total of 1056 treatments) would have >90% power to demonstrate the rate of AEs per 100 treatments is no more than 10% higher in the In-Home period versus the In-Center period. While the primary safety endpoint will be tested using the methods outlined in Section 10.4.2, we are confident that we are adequately powered to detect the difference once taking into account the repeated measures within participant.

To account for an expected 15% lost to follow-up rate, and an additional 2 expected death or transplant events during the 8 week In-Home phase (based on a combined rate of death and transplant of approximately 15 per 100 patient-years in a usual HHD population), a total of 50 patients will be enrolled to yield the 33 evaluable patients needed to be sufficiently powered for both the primary efficacy and primary safety endpoints.

10.3 Analysis Populations

All participants who meet all of the Inclusion and Exclusion Criteria and who start the first study treatment during the first treatment period will be considered enrolled and will be included in the

Full Analysis Set (FAS) . The primary effectiveness endpoint analysis will be based on the FAS with a supportive analysis for the Per-Protocol population (PP).

10.3.1 Full Analysis Set (FAS)

The full analysis set (FAS) for this study will include all participants who are enrolled in the study. The primary analysis set will be the FAS with no missing value imputation with a sensitivity analysis performed on the FAS with missing value imputation.

10.3.2 Per Protocol (PP) Population

The PP population will consist of all participants who are enrolled in the study, have successfully completed at least 75% of their dialysis treatments, have at least one valid value of the primary effectiveness variable and have no major protocol deviations while enrolled in the study. A successfully completed dialysis treatment is defined as one completed as prescribed by the physician. A major protocol deviation is defined as any protocol deviation that affects the soundness of the data. Participants to be excluded from the PP analysis set, and the reasons for their exclusion, will be determined and documented prior to statistical analysis. These decisions will not be outcome-data driven.

10.4 Analysis of Primary Endpoints

The study will be considered a success from a statistical standpoint if:

1. Both primary effectiveness variables pass their respective hypotheses, i.e., H_{a0} and H_{b0} below are rejected in favor of H_{a1} and H_{b1}, respectively, and
2. The rate of adverse events per 100 treatments is not worse during the In-Home period as compared to the In-Center period.

Note: The analysis of both primary endpoints will exclude the transition phase treatment sessions due to the supervision of study staff, as it is believed these treatment sessions will not represent a true in-home treatment session.

10.4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the delivery of a mean standardized weekly $K_{urea}t/V$ of greater than or equal to 2.1 in each of the in-center period and the in-home period, using hemodialysis prescriptions of 3 sessions per week and 4.0 hours per session during the in-center period and 4 sessions per week and 3.5 hours per session during the home period. The following hypotheses will be tested at a one-sided α=0.025 level of significance:

$$H_{a0}: \mu_{IC} \leq 2.1 \text{ vs. } H_{a1}: \mu_{IC} > 2.1$$

and

$$H_{b0}: \mu_{IH} \leq 2.1 \text{ vs. } H_{b1}: \mu_{IH} > 2.1$$

where μ_{IC} is the mean weekly standardized Kt/V for the in-center period and μ_{IH} is the mean weekly standardized Kt/V for the in-home period. These hypotheses will be tested using the least squares mean for the respective treatment period from a repeated measures analysis of variance (ANOVA) containing terms for participant, treatment period, and time points (weeks) and using an AR(1) covariance structure.

The weekly standardized Kt/V value will be calculated using the Leypoldt chain (2004):

$$UR = BUN_{post} / BUN_{pre},$$

$$spKtV = (-1 \times \log(UR - 0.008 * (t_{treatment} / 60))) + ((4 - 3.5 \times UR) \times (UFV / weight)),$$

$$q = (0.924 \times sp\_KtV) - (0.395 * (sp\_KtV / (t_{treatment} / 60))) + 0.056,$$

$$eKtV = \min(sp\_KtV, q),$$

$$\text{Standard Kt/V (stdKt/V)} = 168 \times (1 - \exp(-eKt/V)) / t /((1 - \exp(-t/V)) / (Kt/V) + 168 / (N \times t) - 1),$$

where BUN_{pre} = blood urea nitrogen concentration before treatment, BUN_{post} = blood urea nitrogen concentration after treatment, $t_{treatment}$ = treatment duration (in hours), UFV = ultrafiltration volume (in liters), weight = dry weight, and N = number of treatments during the week (7-day period).

Summary statistics (mean, sample size, standard deviation, minimum, maximum, and median) will be computed on the weekly standardized Kt/V values for each treatment period.

All analyses of the primary effectiveness variable will be performed on the FAS with no missing value imputation, the FAS with missing value imputation, and the PP population.

The number of prescription changes occurring during the study is expected to be low. A summary table will be provided of all prescription changes by treatment period (In-Center and In-Home).

10.4.2 Primary Safety Endpoint

The primary safety endpoint is the adverse event rate: the number of adverse events per 100 treatments occurring in the in-clinic portion of the study compared with those occurring in the home portion.

For each treatment period, a 95% confidence interval will be computed on the AE rate per 100 treatments. This confidence interval will be computed using the least squares mean for the respective treatment period from a repeated measures GEE model containing terms for participant, treatment arm and time points using a Poisson link function and AR(1) covariance structure. Additionally, to compare the AE rate between treatment periods, the difference in number of AEs between treatment periods and the associated 95% CI of the difference will be computed using the least squares means from the above GEE model. The difference in LS means will be used to test the following hypothesis at a one-sided α=0.025 level of significance:

$$H_{c0}: \mu_{IH} - \mu_{IC} \geq 0.1 \text{ vs. } H_{c1}: \mu_{IH} - \mu_{IC} < 0.1$$

If the upper bound of the 95% CI for the difference between number of AEs between treatment periods is below 10%, the AE rate for the In-Home treatment period will be considered not worse than the AE rate for the In-Center treatment period.

10.5 Interim and Final Analyses

There are no planned interim analyses. The final analysis will be performed following last participant last treatment (H8).

10.6 Analysis of Secondary Endpoints

Summary statistics (n, mean, standard deviation, median, minimum and maximum) on the raw data as well as changes from baseline will be presented by timepoint for all labs shown below. If multiple labs were performed at a given timepoint, the lab results from the date the site is basing clinical care from will be used and summarized in the analysis tables. All laboratory analysis will be performed by the local labs affiliated with the hemodialysis facility.

A summary table of abnormal lab results will also be provided. All summary statistics (n, mean, standard deviation, median, minimum and maximum) will be computed relative to the lab results

that fell outside of specified ranges on the raw data. These ranges will be determined prior to data analysis.

For the PRO secondary endpoints, descriptive tests will be performed comparing last measurement (H8 or withdrawal) and first measurement (C1). Specifically, total score for EQ-5D-5L, MOS and RTQS will be compared using a 95% CI for the difference in last measurement minus first measurement. No descriptive test will be performed for the ZBI12, as it is only collected at the last study visit (H8 or withdrawal), however descriptive statistics will be displayed for the ZBI12. Similarly, the per symptom scores on the ESAS-r will be compared using a 95% CI. Finally, for TTR, the difference in rate and corresponding 95% Clopper-Pearson CI between last measurement minus first measurement for each category (0-2 hours, 2-6 hours, 6-12 hours, 12-24 hours and >24 hours) will be shown. As these endpoints are not intended for labeling, the analysis will be descriptive in nature and therefore no type I error adjustment is required.

Estimates of secondary endpoints and differences measured between the test and control periods will be reported along with their two-sided 95% confidence intervals.

Secondary safety endpoints will be analyzed in the same manner as the primary safety endpoint, as described in Section 10.4.2.

Additionally, a table will be provided to show the number and percentage of the FAS subjects with at least one pre-specified AE by treatment period and overall for each dialysis treatment period (In-Center and In-Home), by MedDRA system organ class (SOC) and preferred term (PT). All AEs, all SAEs, and all device-related AEs will be summarized in a similar manner.

10.7 Treatment of Missing or Spurious Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. However, it is expected that some data may be missing for the primary effectiveness endpoint, Kt/V, in the FAS . As a sensitivity analysis, missing data for the primary effectiveness endpoint will be imputed.

Participants who are missing any Kt/V measurements during the In-Center or In-Home periods will be considered as “missing data participants” for the primary effectiveness endpoint. Missing Kt/V will be imputed using fully conditional specification (FCS) linear regression. Details will be provided in the statistical analysis plan.

There will be no imputation for the primary safety endpoint or any secondary endpoints.

11 MONITORING

All study monitoring activities will be managed and performed by the study Sponsor or designee. CRFs will be verified to source documents according to the monitoring plan. The number of monitoring visits and their duration will be conducted according to the monitoring plan. By verifying compliance, these activities will ensure:

- The study is conducted in accordance with the study protocol, relevant Good Clinical Practice (GCP), and International Conference on Harmonization (ICH) guidelines, as well as in conjunction with 21 CFR Part 812, 50, 54, 56 and other applicable government regulations
- Adequate protection of the rights and safety of the informed participants involved in the study by thoroughly providing accurate and complete data

- Quality and integrity of the data

The frequency and scope of periodic site visits will be determined according to the monitoring plan, but at a minimum, shall occur at least once per year. Monitoring activities may include: review of informed consent and research authorization confirmation, regulatory document review, overall investigational plan adherence, GCP and ICH compliance, facility assessment, study staff assessment, and additional study related functions that contribute to the safety of study participants and the integrity of study data.

Investigators must provide adequate time and resources to the study protocol and will be available to the study monitor or designees by telephone and in person during site visits. The Investigator will also provide the study monitor with a suitable working environment for review of study-related documents.

11.1 Responsibilities

This study is being run by Quanta Dialysis Technologies with support from North American clinics and nominated third parties.

11.2 Site Training

The study Sponsor or its designee will conduct training to the study site staff to develop a common understanding of the study objectives, clinical protocol, CRFs, study procedures, the Quanta SC+ DDS, and the informed consent process. Site initiation may include investigators, nurses and technicians, site research coordinators and Sponsor representatives, and designees. Training activities will include, but are not limited to, review of the clinical protocol including the study procedures, data collection procedures, adverse event reporting procedures, monitoring guidelines, and applicable regulatory requirements. All trained personnel will be required to sign a training log.

Teleconferences and web meetings may also be used throughout the study to train Investigators and other study personnel.

Investigators and study site personnel will not be allowed to participate in the study until they have completed appropriate study training.

12 DATA HANDLING AND RECORDKEEPING

Electronic data capture will be performed through a third party provider to ensure accuracy and completeness of data collection with integrated data safety checks, and ensure timely reporting of adverse events and serious adverse events

The Quanta Patient Registry will also be utilized during this trial to capture participant home dialysis treatment information in a consistent manner as well as to provide information regarding adequacy of data collection and ease of use.

Each participating site will maintain appropriate medical and research records for this trial, in compliance with applicable US regulations, ICH E6 section 4.9, and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the Sponsor(s), the Sponsor’s designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial.

The Investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

12.1 Data Management Procedures

Electronic Case Report Forms (eCRFs) will be used to collect all participant data during the course of the study, which are part of a database that meets 21 CFR Part 11 requirements. eCRFs must be fully completed for each participant and electronically signed by the Investigator when complete. Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study participant's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

1. Medical history/physical condition of the study participant before involvement in the study sufficient to verify protocol entry criteria.

2. Dated and signed notes on the day of entry into the study including the study Investigator, study name, participant number assigned and a statement that consent was obtained.

3. Dated and signed notes from each study participant visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).

4. Information related to adverse events.

5. Study participant's condition upon completion of or withdrawal from the study.

6. Discharge summaries/procedure reports, if applicable.

Overall data management will be the responsibility of the study Sponsor. All data will be managed in a 21 CFR Part 11-compliant database. Data edit checks will be performed and the study sites will be queried as needed to ensure completeness and consistency of study data. All above-mentioned tasks will be performed according to the Data Management Plan and Sponsor SOPs. Audits may be performed for quality assurance of procedures and data handling.

12.2 Data Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in the United States and until there are no pending or contemplated marketing applications in the United States or until at least 2 years have elapsed since the formal discontinuation of clinical development of the product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12.3 Investigator Records

Investigators will maintain complete, accurate and current study records. Records shall be maintained during the clinical study and for two years after the later of the date on which the study is terminated or completed, or the date the records are no longer required to support approval of the device. Investigator records shall include the following materials:

- ***Correspondence***: Documentation of all verbal and written correspondence with FDA, Sponsor, Sponsor Clinical Representative, the Clinical Monitor, the DMC, and other investigators regarding this clinical study or any participant enrolled therein.

- ***Participant Records***: Signed informed consent forms, copies of all completed Case Report Forms and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each participant to the device. Informed consent must comply with FDA regulations (21CFR50).

- ***Investigational Device Accountability:*** Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the protocol. The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

    - the date of receipt,
    - identification of each investigational device (batch number/serial number or unique code),
    - the expiry date,
    - the date or dates of use,
    - participant identification,
    - date on which the investigational device was returned, if applicable, and
    - the date of return of unused, expired or malfunctioning investigational devices, if applicable. This includes the SC+ device, well as dialysate cartridges and blood tube sets.

- ***Protocol***: A current copy of the protocol.

- ***Institutional Review Board (IRB) Information***: All information pertaining to IRB review and approval of this clinical study including a copy of the IRB letter approving the clinical study, a blank informed consent form approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, Part 56)/regulatory body regulations, and that the IRB approved the clinical study protocol.

- ***Investigator Agreements***: Copies of signed Investigator and Sub-Investigator Agreements with accompanying curriculum vitae.

- ***Other***: Any other records that may be required by applicable state or federal laws.

12.4 Investigator Reports

The Investigator will prepare and submit the following reports to the Sponsor and IRB as noted:

Type of Report	Prepared by Investigator For	Timeframe
Enrollment Notification eCRF	Sponsor	Within 24 hours of Informed Consent
Completion of eCRFs	Sponsor	Within 10 working days of participant visit or data collection

Type of Report	Prepared by Investigator For	Timeframe
Serious/Unanticipated Adverse Device Event eCRF	Sponsor and IRB (as required)	Within 24 hours of knowledge or as required by IRB
Participant Death	Sponsor and IRB (as required)	Within 24 hours of knowledge
Withdrawal of IRB Approval	Sponsor	Within 24 hours of knowledge
Informed Consent Not Obtained	Sponsor and IRB (as required)	Within 24 hours of knowledge or as required by IRB
Progress report	Sponsor and IRB	Annually
Final summary report	Sponsor and IRB and FDA	Within 6 months of study completion
Other reports	Sponsor and IRB and FDA	As needed

13 ETHICAL CONSIDERATIONS

13.1 Statements of Compliance

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ISO E6 R2, and 21CFR812, 50, 54, 56 and 45 CFR part 46 as applicable. The clinical investigation shall not begin until the required approval from FDA and the applicable IRB has been obtained. Any additional requirements imposed by the IRB or regulatory authority shall be followed.

13.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

13.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the participants. Consent forms describing in detail the study procedures and assessments, including possible risks and benefits, are given to the participant. Consent forms must be IRB-approved. The participant must be allowed sufficient time to review the form and discuss it as the participant desires with families, friends, or other trusted individuals. The Investigator will explain the research study to the participant and answer any questions that may arise. The participant must indicate their choice to participate in the trial is of their own free will. They must sign the informed consent document prior to any study-specific procedures or assessments, and progress notes must detail the informed consent discussion. Participants may withdraw consent at any time throughout the course of the trial. If a participant withdraws, no further study-related assessments, procedures, or data collection will occur; however, data already collected will be retained by the Sponsor and used for subsequent data analysis. A copy of the informed consent document must be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Legally authorized representatives may assist the participant in the consent process and sign the consent form for the participant as applicable law, regulations, and institutional policies allow.

Informed consent can be obtained through a supervised oral process if a participant or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective participant or their legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

If new information becomes available that can significantly affect a participant's future health and medical care, that information shall be provided to the participant(s) affected in written form. If relevant, all affected participants shall be asked to confirm their continuing informed consent in writing, repeating the informed consent process to convey the new information.

13.4 Participant Confidentiality

All participants must agree to the collection, review, and analysis of private health information by the Sponsor and its designated representatives, regulatory agencies, and other authorized entitites by completing the informed consent process prior to any data collection. Data will be pseudonymized as much as possible. The informed consent form will indicate the restrictions that will be in placed on disclosure.

The privacy of each participant and confidentiality of their information shall be preserved in reports and when publishing any data. The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the Principal Investigator or institution shall obtain permission for direct access to source documents from the participant, hospital administration and national regulatory authorities before starting the clinical investigation.

14 STUDY CONDUCT, OVERSIGHT, AND QUALITY CONTROL AND ASSURANCE

14.1 Protocol Amendments

The protocol, CRFs, informed consent form, other participant information, and other clinical investigation documents shall be amended as needed throughout the clinical investigation. A justification statement shall be included with each amended section of a document. Proposed amendments to the protocol shall be agreed upon between the Sponsor and Principal Investigator, or the coordinating investigator. The amendments to the protocol and the participant's informed consent form shall be notified to, or approved by, the IRB and regulatory authorities, as required. For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human participants or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

14.2 Termination of Study or Study Site Participation

The Sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five (5) working days. All participants already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final follow-up visit of the last enrolled participant.

The Sponsor reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Repeated failure to complete Electronic Case Report Forms, in a timely manner
- Failure to attempt to obtain Informed Consent from the legally authorized representative
- Failure to report Serious Adverse Events in a timely manner
- Loss of or unaccountable investigational device inventory
- Repeated protocol violations
- Failure to enroll an adequate number of participants

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

14.3 Publication Policy

The Sponsor will submit results to the clinicaltrials.gov registry in accordance with the International Committee of Medical Journal Editors and applicable US laws and regulations. Study results will be published regardless of the outcome as required by law. The Sponsor accepts the obligation to facilitate publication of medically important clinical data in a timely, objective, accurate, and balanced manner, regardless of the outcome of this trial. To ensure that an accurate record of the study data is presented to the public, the Sponsor understands the need to allow sufficient time, for careful preparation, analysis, interpretation, and review of study data and reports prior to their dissemination.

This trial will be registered at the National Institutes of Health National Library of Medicine's ClinicalTrials.gov website. Results from this trial will be submitted to ClinicalTrials.gov. The NCT number is pending.

All information regarding the Quanta SC+ DDS supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use the Sponsor's confidential information solely to accomplish the study and will not use such information for any other purposes without the prior written consent of the Sponsor. The Investigator shall provide the Sponsor with complete and accurate data obtained during the study. The information obtained from the clinical study will be used towards the development of the Quanta SC+ DDS and may be disclosed by the Sponsor to regulatory authorities, other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study may be presented at scientific meetings and/or published in peer reviewed scientific or medical journals. All publications and presentations must be approved in advance, at the sole discretion of the Sponsor. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. All publications and presentations must be approved in writing by the Sponsor before public disclosure.

14.4 Site and Investigator Selection

The Sponsor selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. Investigational sites will be selected using combined current assessments of site and investigator qualifications.

14.5 Investigator Responsibilities

Prior to participation in the Study, the appointed Principal Investigator at the Investigational Site must obtain written approval from the applicable IRB. This approval must be in the Principal Investigator's name and a copy sent to the Sponsor or designee along with the IRB approved Informed Consent Form, and the signed Clinical Study Agreement, prior to first shipment of the investigational device.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the signed Clinical Study Agreement, applicable regulations (including 21 CFR Parts 11, 50, 54, 56 and 812), the Declaration of Helsinki, Good Clinical Practices, any conditions of approval from the IRB or FDA, and ISO 14155;
- agree to participate in a device training program prior to study initiation, as applicable;
- provide a copy of a Financial Disclosure form that summarizes financial interest in the Sponsor. In addition, the Sponsor will be notified if disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the study;
- provide the Sponsor with curriculum vitae, information regarding previous clinical investigation experiences (including investigations or research that was terminated);
- assure that no study assessments or procedures occur until IRB approval has been obtained;
- assure that informed consent is obtained from each participant prior to enrollment, using the IRB and Sponsor approved forms;
- ensure that investigational devices are only used by approved, trained investigators in participants who meet all study inclusion criteria and no study exclusion criteria;
- supervise all testing of the device involving human participants;
- complete all eCRFs and study documentation and relevant imaging assessments, and promptly forward to the Sponsor or designee for data management;
- report all adverse events, non-medical complaints and non-compliance to Sponsor according to the protocol and regulatory requirements;
- provide all required data and agree to source document verification of study data with participant's medical records;
- allow staff of the Sponsor or designee, as well as representatives from regulatory bodies, to review, inspect and copy any documents pertaining to this clinical investigation; and
- oversee retention of required records and documents related to the investigation.

The Principal Investigator may delegate one or more of the above functions to an associate or Sub-Investigator. However, the Principal Investigator retains overall responsibility for proper conduct of the study, including obtaining and documenting participant informed consent, compliance with the

study protocol, and collection of all required data. Delegated tasks must be documented on a Delegation Log.

14.6 Protocol Deviations

An Investigator is not allowed to deviate from the Protocol if the deviation affects participant's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Under emergency circumstances, deviations from the Protocol to protect the rights, safety and well-being of human participants may proceed without prior approval of the Sponsor and the IRB. Such deviations shall be documented and reported to the Sponsor and the IRB as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study participant who does not meet all of the enrollment criteria specified in the protocol or instances where participants miss study visits without documentation. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, ISO guidelines, Good Clinical Practices, and any conditions of approval imposed by their IRB.

The protocol deviations for this protocol consist of, but not limited to, the following:

- Failure to obtain participant's informed consent prior to any study-related activities;
- Failure to conduct protocol required clinical follow-ups;
- Failure to conduct protocol required clinical follow-ups within time windows; and
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions may be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Participants enrolled at these sites will continue to be followed per the clinical protocol.

Investigators must report protocol deviations to the Sponsor by entering data into the eCRF. Any protocol deviations that affect the rights, safety or well-being of the participant or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported within 24 hours to the Sponsor and IRB if required by the IRB.

14.7 Safety and Clinical Events Committee

An independent safety and clinical events committee (SCEC) will be created, chartered, and maintained while any adverse events are being collected or participants are receiving study treatment to oversee trial safety and event handling. The SCEC will review all AEs reported in the primary study and SAEs reported in the extended treatment phase. Sponsor will continue to monitor AEs that are reported during the extended treatment phase and will report the events to applicable regulatory authorities and to IRBs as required. The SCEC will comprise three nephrologists (MDs or DOs) with experience in hemodialysis, including at least one with significant experience in home hemodialysis or peritoneal dialysis, and a human factors engineer. While the investigator will assign an initial finding of device relatedness for AEs in the primary study phase, the SCEC will review these events and will adjudicate, providing the final determination for the study record.

The human factors engineer will participate when a device related event is identified (please see Appendix). When the event is related to device or user error, the human factors engineer will initiate an investigation with the clinical site to obtain information to do a root cause analysis. Any such events will be fully reviewed by the human factors engineer and presented to the SCEC for adjudication to determine whether they are device related.

The SCEC will have authority to recommend after periodic review of data or after evaluating serious AEs that have been brought to its attention, that the trial continue with no changes, continue with changes to the protocol or other operational documents and procedures, or be suspended.

In the primary study, the SCEC will be blinded to whether events occurred during the in-clinic or home phase of the trial. They will not be told information about event dates or other information that would lead to deduction of the time the participant had been in the trial, whether the patient or caregiver or a clinic health care provider performed the treatment, the level of training the participant had received, or similar elements. AE narratives and other case information provided to the SCEC will be reviewed to ensure this information is masked. In the extended treatment phase, the SCEC will not be blinded when reviewing and adjudicating SAEs as all events would occur while the participant is at home.

15 CMS JUSTIFICATION

All people who are diagnosed with end stage renal disease (ESRD) in the United States are eligible to enroll in Medicare, regardless of age, subject to the accumulation of sufficient lifetime working credits. In the current population of patients undergoing maintenance dialysis for the treatment of ESRD, approximately 80% are enrolled in either traditional Medicare (as the primary payer of medical care) or Medicare Advantage. A substantial portion of the remainder of patients have private insurance; among these patients, Medicare is the secondary payer of health care services during the first 36 months of maintenance dialysis.

Because study participants will be enrolled from the prevalent dialysis patient population, it is expected that the vast majority of patients that are enrolled in this study will already carry Medicare coverage. Therefore, the results of this study are expected to be highly generalizable to the Medicare population.

16 EXTENDED TREATMENT PHASE

Patients who complete the HOME RUN Trial protocol will be permitted via new informed consent to remain on the SC+ in the home setting for a period not exceeding 30 months or until FDA clearance is granted for home use. The SC+ would be in use under the prescription of their treating nephrologist (i.e., site investigator) with a care partner. Following study completion, the subjects may remain enrolled in the study and undergo safety reporting as defined in Section 9 Safety. However, the subject will no longer have study visits scheduled to collect data relevant to the endpoints and scientific soundness of the study. Subjects will be instructed to report any device-related medical events or deficiencies throughout the extended treatment phase. As defined in Section 14.7, the SCEC will review all SAEs reported in this study phase and the human factors engineer will participate when a device related event is identified.

During the extended treatment phase, the assessments shown in the table below will be performed. The analysis of the primary and secondary endpoints will exclude the data collected from this extended treatment phase. At the conclusion of the extended treatment phase, all data collected during extended treatment will be summarized.

Month(s)	Follow-up Phase	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Withdrawal
Informed consent,	x	NA																		NA
Vital signs – Weekly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RO water/dialysate quality[1] - Monthly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Device deficiency assessment - Weekly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Usability[2] - Weekly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Reliability[3]		monitored continuously during this period																		x
Adverse Events		collected continuously during this period																		x
Concomitant Medications[4]		collected continuously during this period																		x
Reason for withdrawal - Weekly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Review of HCP support & interactions[5] - Monthly		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Month(s)	19	20	21	22	23	24	25	26	27	28	29	30	Withdrawal
Vital signs – Weekly	x	x	x	x	x	x	x	x	x	x	x	x	x
RO water/dialysate quality[1] - Monthly	x	x	x	x	x	x	x	x	x	x	x	x	x
Device deficiency assessment - Weekly	x	x	x	x	x	x	x	x	x	x	x	x	x
Usability[2] - Weekly	x	x	x	x	x	x	x	x	x	x	x	x	x
Reliability[3]	monitored continuously during this period												x
Adverse Events	collected continuously during this period												x
Concomitant Medications[4]	collected continuously during this period												x
Reason for withdrawal - Weekly	x	x	x	x	x	x	x	x	x	x	x	x	x
Review of HCP support & interactions[5] - Monthly	x	x	x	x	x	x	x	x	x	x	x	x	x

[1] Water/dialysate samples will be collected and tested monthly
[2]Participants queried: required assistance with any aspect of treatment over the prior 7 days and if so, with which of the following tasks: machine set up, clearing of alarms, machine take down, fistula/needling or catheter connection
[3]Ability to deliver prescribed treatments
[4]Concomitant medication collection will be limited to the following: erythropoiesis-stimulating agents (ESAs), intravenous iron, phosphate binders, calcimimetics, and anti-hypertensive medications (ACE inhibitors, ARBs, beta blockers, calcium channel blockers, central alpha agonists, vasodilators [specifically, hydralazine and minoxidil]).
[5] Collected monthly: HCP support and interactions are intended to be available to participants as required by the study, but not to provide additional training, support, or oversight of the dialysis procedure. Any contact outside study-driven procedures will be documented for purpose of understanding need for additional health care support.

17 DOCUMENT REVISION HISTORY

Issue	Date	Changes
v1	01 FEB 2021	Initial protocol
v1.1	26 May 2021	Added transition phase between clinic and home phases Added requirement for insurance coverage to inclusion criteria Added requirement for dialysis visits on specific days of the week Updated number of sites including addition of Canada Updated primary and secondary endpoints to include comparison of all AEs in-home and clinic Updated schedule of assessments and visits schedule for consistency Updated Bibliography to include references related to the additional Patient report outcomes

V1.2	14 July 2021	Removed foreign clinical site, Health Canada (HC) Updated total number of sites from 10-15 to 8-15 for US Updated Section 8.3.5 to allow for clinical sites to provide supplies per local protocols/requirements Editorial correction in Synopsis inclusion criteria (re. care partner statement) to be consistent with Section 7.2.1. Updated section 8.3.2 to standardize method of heparin delivery
V1.3	10 August 2021	Updated section 8.3.2 to add back heparin administration requirement for patients with AVF/AVG Updated section 8.3.5 to add back heparin and syringe supplies
V1.4	30 November 2021	Updated Section 2 to include pregnancy test, updated footnotes (4, 6, 9, 15) in Section 2 for clarification, Updated exclusion criteria to clarify blood work duration during enrollment, clarification updates to section 8.3.5 and 8.4.1, updated visits schedule for consistency with section 2, Clarification update to section 8.3.1, Updated Section 7.4 to increase threshold for withdrawal criteria, minor editorial corrections.
V1.5	17 January 2021	Added study name (HOME RUN), clarification updates to Inclusion/Exclusion criteria, updated albumin target range, removed specific requirement for pregnancy test from the schedule of assessment, multiple editorial corrections in visits schedule to align with Section 2, updated Section 8.3 for managing clinical utility data upload on eCRF.
V1.6	14 February 2022	Reverted changes regarding pregnancy exclusion criteria.
V1.7	14 March 2022	Updated statistical considerations for this protocol based on CMS feedback – specifically updated the Intent-to-Treat analysis population in Section 10.3.1 to the Full Analysis Set (as well as replaced ITT with FAS throughout the document). Additionally, we updated Section 10.6 to describe the analysis approach for the patient reported outcome secondary endpoints, as advised by CMS.
V1.8	13 July 2022	Updated section 1, participants- increased to 50 participants, included peritoneal dialysis patients, increased to 25% of participants to be recruited from a single site,; updated section 1, inclusion criteria- included peritoneal dialysis patients; updated section 2- removed participant portal from schedule of assessments; updated section 6.2.2, deleted (UF) 10% of expected next fluid removal per hour, based on the UF prescription; updated section 6.4, participant population and numbers- increased to 50 participants, included peritoneal dialysis patients, increased to 25% of participants to be recruited from a single site; updated section 7.2.1 Inclusion criteria-, included peritoneal dialysis; updated section 8.1, visit schedule, clinic period- removed digi health training and replaced with Training on ipad and associated apps; section 8.3.4, deleted software portal section and added treatment flowsheet section; updated section 8.3.6, Dialysis Prescription- included Dialysate Conductivity (13.7 – 14.1 mS/cm) and Bicarbonate (35 mmol/L); and updated section 10.2.2, primary safety endpoint- increased total number of patients to 50; added section 16- Extended Treatment Phase; Section 16, document revision history, became section 17;

V1.9	15 February 2024	Updated protocol synopsis- U.S. Agent (sponsor) with U.S. sponsor address; section 14.7- specified that all AEs would be reviewed and device related AEs adjudicated by the SCEC during the primary study and SAEs reported during the extended treatment phase will be reviewed and adjudicated by the SCEC, specified that the SCEC would not be blinded as to whether an SAE occurred in the home or clinic during the extended treatment phase; section 16- the time period for the extended treatment phase was increased from 18 to 30 months and the additional months were added to the schedule of assessments for the extended treatment phase; device deficiency and usability assessments were added to include months 12-30.

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APPENDIX: PROCEDURE FOR DEVICE- OR USER-RELATED ERRORS

From the beginning of the baseline period until study completion, the HF specialist will review each device error event and determine whether the event is likely to be use-related. As needed, the HF specialist will consult a Quanta systems specialist or the study site staff for input when determining whether an event is use-related or not. It is expected that some device error events might be induced by the user—for example, an alert that results from a user not opening a clamp at the appropriate time—whereas other device error events might be unrelated to user-device interactions. Device error events might be related to the SC+ system, software, hardware, or consumables, and could be encountered by study participants (e.g., patients, caregivers) as well as nurses participating in the trial. In the balance of this section, the term "study participant" is used to refer to any of the above individuals who might encounter a device error event during SC+ system use during the IDE clinical trial.

For all device error events that are definitely or likely use-related, the HF specialist will then reference a comprehensive list of critical tasks, identified based on the use-related risk analysis, to determine whether the device error event is related to a critical task or not. The list of critical tasks will be maintained in the study manual of operations and will be updated as needed to reflect any initially unanticipated critical tasks.

For each device error event related to a critical task, the following steps will be taken:

1. The HF specialist will determine what additional information is needed from the study participant to be able to analyse the root cause(s) of the error event
2. The HF specialist will engage the site coordinator or delegate to collect any additional information from the study participant, including subjective feedback regarding system use when the error event occurred and additional information regarding what might have led to the error; notably:
    - to supplement the training provided before the trial, the HF specialist will assist the site coordinator and/or delegate as needed to ensure they ask appropriate follow-up questions to facilitate unbiased and comprehensive root cause analysis
    - the HF specialist will not be in direct contact with the study participants at any time
    - the HF specialist will work closely with the site staff to ensure any HF work is performed without interfering with the primary objective of the IDE clinical trial
3. The HF specialist will review and analyse the data collected, including the event log information and subjective feedback collected during follow-up activities, to identify the root cause(s) of any use-related errors associated with critical tasks. The root cause analysis will aim to identify what, including any aspect of the SC+ user interface, home use environment, or other factor(s), contributed to the error.
4. The HF specialist will document the identified root causes in a format that will be determined by the CEC.
5. The CEC and other Quanta representatives, as appropriate, will be responsible for determining if any further risk control measures will need to be implemented.

Device error events that are deemed non-critical per the use-related risk analysis (i.e., errors related to use steps not associated with a potential for serious harm) are out of scope of the IDE clinical trial's HF activities, in line with FDA's HFE guidance for medical devices.

The following event framework is for use in approaching and categorising potential events that would require investigation by the Safety Team. It is derived from definitions defined in part by standards and in part by the Sponsor based on previous assessments, submissions and business defintions.

<u>Level 1: Protective System Performance</u> Did a device failure of its constructional or functional safety compromise a risk control measure of the Hazard Analysis?		If Yes, investigate immediately with Sponsor. If No, move to Level 2.
<u>Level 2: Essential Performance</u> In accordance with IEC 60601-2-16, did the device fail to meet the tolerances specified by the Sponsor under normal conditions: • Blood flow rate • Dialysis fluid flow rate • Net fluid removal • Dialysis time • Dialysis fluid composition • Dialysis fluid temperature		If Yes, investigate immediately with Sponsor. If No, move to Level 3.
<u>Level 3: Usability</u> Did a Use Error event occur in which the user performed a task incorrectly (i.e., not in accordance with the intended manner of use) or did not complete a necessary task? If Yes, move to Level 3a. Or Did a Close Call event occur in which the user performed or nearly performed a task incorrectly (i.e., not in accordance with the intended manner of use), but then resolved the issue prior to any harm being done without assistance. Or Did a Use Difficulty event occur in which the user struggled to some extent while	<u>Level 3a: Critical Use Error</u> Was the use error for a task required for safe and effective use of the device, or a task with a harm severity classification for the use error that is: Catastrophic: Could result in death, or serious health impacts to multiple people, or major breach of regulation. Critical: Could result in life-threatening injury that requires specialist medical intervention and/or causes long term or permanent disability.	If Yes, investigate immediately with Sponsor. If No, move to Level 3b.

completing a task (e.g., confusion, taking longer than expected, difficulty manipulating a device's components), but eventually completed the task successfully without assistance. If Yes to Close Call or Use Difficulty, this should be investigated further with the Sponsor but no harm is associated with the event.		
	<u>Level 3b: Non-Critical Use Error</u> Was the use error for a task with a harm severity classification for the use error that is: Serious: Could result in injury that requires general medical intervention and/or causes short-term disability. Minor: Could result in impaired device performance, or an injury that does not require trained medical intervention. Negligible: Could result in inconvenience or minor temporary discomfort only.	If Yes, this should be investigated further with the Sponsor, but no harm is associated with the event. If No, move to Level 4.
<u>Level 4: Reliability</u> Where a treatment or treatment setup initially fails, but can be restarted, a treatment is effectively delivered so is not discounted for purposes of the IDE. Reliability events are		If Yes, this should be investigated further with the Sponsor, but no harm is associated with the event. If No, move to Level 5.

categorised based on the following: Did the treatment duration increase ≥2.5% over the planned treatment time due to unplanned interruptions in treatment within the influence of the device? Or Was treatment or setup prevented by machine action such as a self-test failure or an alarm? (Nb. This is not a failure of the Protective System or Essential Performance.) Or Did the user identify a device defect prior to use?		
<u>Level 5: To Be Determined</u> This is the end of the event framework. If an event does not fall into any of the above levels, then it should immediately be investigated further with the Sponsor to ensure no harm is associated with the event.		