Confirmatory Study to Assess the V Needle in End-Stage Renal Disease Patients During In-Clinic Hemodialysis

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Confirmatory Study to Assess the V Needle in End-Stage Renal Disease Patients during In-Clinic Hemodialysis: Clinic-SAVER Study

APPROVALS

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Clinic-SAVER Study

1 Protocol Synopsis

1.1 PROTOCOL SUMMARY

In patients undergoing hemodialysis for the treatment of end-stage renal disease, Venous Needle Dislodgement (VND) is a rare, but potentially fatal situation in which the needle delivering a patient's blood back to the body after filtration by a dialysis machine becomes inadvertently disconnected from the patient. Hemotek Medical Inc. has developed the V Needle, a venous needle return that is designed to reduce patient risk from exsanguination-related injury or death. This clinical study will serve as a confirmatory study to gain FDA marketing clearance of the Hemotek V Needle system in the clinical setting. During this study, we will determine the ability of the V Needle to successfully deliver appropriate hemodialysis therapy per the facility's guidelines. It will also be used to determine if the V Needle triggers false blood alarms under normal operating conditions. This study will also be used to demonstrate the V Needle meets effective usability criteria. Rates of adverse events and ability to complete the hemodialysis session will be compared to the rates recorded using commercially available devices during the hemodialysis sessions prior to the use of the Hemotek V Needle.

This study is a prospective, multi-center, single-arm study with subjects acting as their own control designed to confirm the safety, performance, and usability of the V Needle, a new safety needle for use during in-clinic hemodialysis that is designed to automatically generate a partial occlusion of the internal fluid path and trigger the hemodialysis machine to alarm and shut off if a complete dislodgement of the venous needle from the arm inadvertently occurs.

The study is an open-label, non-randomized, single arm, multi-center trial with subject's serving as their own control. For the first three (3) control sessions, subjects will undergo usual hemodialysis sessions with a commercially available device. For the remaining six (6) sessions, subjects will be cannulated with a V Needle in place of a usual venous line AV fistula set.

The hemodialysis sessions will be conducted in the clinic. Subjects will be observed by a clinician for the duration of each session. Clinicians will monitor the session for any abnormal disruptions, therapy interruptions, and/or adverse events, including hemolysis, due to V Needle presence. All machine blood alarms, therapy interruptions, and/or partial or complete needle dislodgements will be recorded and immediately corrected. A clinician will perform cannulation.

Cannulation site and surrounding tissue will be examined by the nurse and assessed for any locally induced trauma before and after treatment.

A survey will be completed by the clinicians and patients to assess usability, comfort, and feelings of safety of the V Needle.

After the first five (5) patients will be enrolled, and data through the last visit of the fifth patient is available, this data will be submitted to the FDA while study enrollment and visits continue. No Hemotek Medical V Needle treatments will occur until after FDA has reviewed the data from the first 5 patients and allows the study to proceed. Data will also be submitted to the FDA after the tenth patient completes their last visit and data is available. After the tenth patient, study

enrollment and visits can continue, but no Hemotek Medical V Needle treatments will occur on the final 5-10 patients until the FDA allows the study to proceed. After FDA has found the data for the first 10 patients acceptable, the rest of the study can continue until the end.

1.2 STUDY TITLE

Confirmatory **S**tudy to **A**ssess the **V** Needle in **E**nd-Stage **R**enal Disease Patients during in-clinic hemodialysis: **Clinic-SAVER Study**

1.3 STUDY DESCRIPTION:

This study is a prospective, multi-center, single-arm study with subjects acting as their own control designed to confirm the safety, performance, and usability of the V Needle, a new safety needle for use during in-clinic hemodialysis that is designed to automatically generate a partial occlusion of the internal fluid path and trigger the hemodialysis machine to alarm and shut off if a complete dislodgement of the venous needle from the arm inadvertently occurs.

1.4 STUDY OBJECTIVES

The study is designed to confirm the safety, performance, and usability of the Hemotek V Needle A.V. Fistula Set for temporary cannulation for hemodialysis in the treatment of end-stage renal disease patients in the clinical setting.

1.5 CLINICAL PHASE

This study is a confirmatory study designed to provide clinical evidence for use in obtaining marketing clearance, i.e. 510(k) clearance, for the Hemotek device.

1.6 INDICATIONS FOR USE

The Hemotek V Needle A.V. Fistula Set is intended for temporary cannulation to vascular access for extracorporeal blood treatment for hemodialysis. This device is intended for single use only. The anti-needlestick safety feature aids in prevention of needle stick injuries when removing and discarding the needle after dialysis. The device also has an integrated safety mechanism that is designed to automatically generate a partial occlusion of the internal fluid path and trigger the hemodialysis machine to alarm and shut off if a complete dislodgement of the venous needle from the arm inadvertently occurs.

1.7 STUDY DEVICE

The Hemotek V Needle A.V. Fistula Set is a set that includes a needle used to access the vasculature during hemodialysis. The V Needle incorporates both a detection system that is designed to detect when the venous needle becomes completely dislodged from the patient's arm

and an internal mechanism that is designed to occlude the flow of blood through the needle in the dislodged state. The induced flow occlusion is designed to generate a change in the venous line pressure such that the hemodialysis machine will automatically alarm and halt further pumping. The V Needle used in this study will have a sharp cannula tip with an anti-stick needle guard.

1.8 STUDY RATIONALE

In patients undergoing hemodialysis for the treatment of end-stage renal disease, Venous Needle Dislodgement (VND) is a rare, but potentially fatal situation in which the needle delivering a patient's blood back to the body after filtration by a dialysis machine becomes inadvertently disconnected from the patient. The use of the V Needle as a venous needle return is designed to significantly reduce patient risk from exsanguination-related injury or death. This clinical study will serve to confirm safety, performance, and usability of the device during appropriate hemodialysis therapy. During this study, the safety and performance of the V Needle during delivery of appropriate hemodialysis therapy will be tested. The study will also assess the number of false blood alarms observed under normal operating conditions and the V Needle's usability. V Needle rates of adverse events and ability to complete the hemodialysis session will be compared to the rates recorded using standard available needle sets during hemodialysis sessions prior to the use of the Hemotek V Needle.

1.9 STUDY POPULATION

Adult men and women with end-stage renal disease undergoing chronic hemodialysis with a mature AV fistula or graft in the arm.

1.10 CLINICAL SITES

Between 2 and 4 centers

1.11 NUMBER OF SUBJECTS

Between 15 and 20 subjects (at least 87 test sessions required)

1.12 STUDY DURATION

The study will be conducted over a maximum of nine (9) dialysis sessions (first three (3) are controls) for each patient. Typically, a patient will have three sessions in one week so that the study will last three (3) weeks per patient. Each session usually lasts around three hours. Any adverse events that are reported after the study session (e.g., a hematoma in the days following the session) will also be catalogued and reported. Adverse events will be recorded up until the next dialysis treatment or for one week following the last session if no additional sessions are planned.

1.13 INCLUSION CRITERIA

1. Subjects with end-stage renal disease receiving chronic hemodialysis in a clinical setting.
2. Subjects must be able to receive hemodialysis with the Hemotek 15-gauge, 1 inch length V Needle, with 12 inch tubing.
3. Age greater than 18 years old at screening.
4. Vascular access via a mature arteriovenous (AV) fistula or graft in the arm and determined to be adequate for a chronic hemodialysis therapy.
5. AV fistula has already been demonstrated to adequately permit one or more hemodialysis sessions.
6. Subject prescribed blood flow rates between 200 ml/min and 450 ml/min
7. In women with child-bearing potential, negative urine or serum pregnancy test at Screening.
8. Subject able to communicate effectively with investigative staff, competent and willing to give written informed consent, and able to comply with entire study procedures.
9. Hemoglobin ≥9 g/dL (consistent with KDOQI guidelines)
10. Normal platelet count (≥150,000 /mm3)
11. International Normalized Ratio (INR) ≤ 1.5

1.14 EXCLUSION CRITERIA

1. Subjects receiving chronic hemodialysis with a vascular catheter.
2. Subjects with vascular access that is determined by the clinician to be unacceptable for a hemodialysis procedure.
3. Patients with a bleeding diathesis
4. Patients receiving anti-coagulants
5. Previous vascular access surgery (≤30 days from study entry) or planned access surgery
6. Known hypersensitivity to any imaging agents (e.g., contrast) that may be required during the study period
7. Patients with confirmed vasculitis
8. Vascular access infection or systemic active infection within 30 days of study entry
9. Life expectancy less than 12 months
10. Planned renal transplantation or planned conversion to peritoneal dialysis
11. Subjects with any condition determined by the investigator that precludes them from safely participating in the study.
12. Female participants at the time of consent to the study cannot be breastfeeding or pregnant.

1.15 PRIMARY SAFETY MEASURE

Rate of serious adverse device events (SADEs)

1.16 ADDITIONAL SAFETY MEASURES

- Rate of adverse events (AEs)

- Rate of serious adverse events (SAEs)
- Rate of adverse device events (ADEs)
- Rate of adverse procedure events (APEs)
- Rate of serious adverse procedure events (SAPEs)

1.17 PRIMARY PERFORMANCE MEASURES

Percentage of successful hemodialysis sessions with the Hemotek device.

1.18 SECONDARY PERFORMANCE MEASURES

No powered secondary performance measures are planned.

1.19 ADDITIONAL PERFORMANCE MEASURES

- Machine alarm rate (blood alarms only) during hemodialysis therapy, including false alarms and relationship of alarm to venous needle
- Changes to blood flow rate setting during therapy sessions and relationship to venous needle
- Venous, transmembrane, and/or arterial pressure measurements
- Patient survey including ratings for venous needle comfort and feelings of safety (V Needle only)
- Clinician survey, evaluating the following items:
    - use of the device according to the instructions for use (IFU)
    - ability to properly cannulate
    - ability to objectively see flashback
    - confirmation that the footplate is fully depressed (V Needle only)
    - feelings regarding patient risk (V Needle only)
- Achieved treatment time
- Achieved blood flow rate
- Ability to cannulate fistula
- Episodes of partial or complete needle dislodgment

1.20 STUDY DESIGN

The study is an open-label, non-randomized, single arm, multi-center trial with subject's serving as their own control. For the first three (3) control sessions, subjects will undergo usual hemodialysis sessions with a commercially available device. For the remaining six (6) sessions, subjects will be cannulated with a V Needle in place of a usual venous line AV fistula set.

The hemodialysis sessions will be conducted in the clinic. Subjects will be observed by a clinician for the duration of each session. Clinicians will monitor the session for any abnormal disruptions, therapy interruptions, and/or adverse events, including hemolysis, due to V Needle presence. All machine blood alarms, therapy interruptions, and/or partial or complete needle

dislodgements will be recorded and immediately corrected. Clinicians will be responsible for identifying adverse events as they occur and will activate established facility emergency response plans if necessary. A clinician will perform cannulation.

Cannulation site and surrounding tissue will be examined by the nurse and assessed for any locally induced trauma before and after treatment.

A survey will be completed by the clinicians and patients to assess usability, comfort, and feelings of safety of the V Needle.

1.21 SAMPLE SIZE JUSTIFICATION

The sample size was determined to compare the rate of successful treatments between hemodialysis sessions with the test needle compared to the control needle.

The hypothesis test for the primary performance measure is defined as follows:

$$H_0: p_T - p_C \leq -\delta$$

$$H_1: p_T - p_C > -\delta$$

where p_T is the probability of a successful hemodialysis treatment session with the V Needle (test), p_C is the probability of a successful hemodialysis treatment session with a commercially available device (control), and δ is the non-inferiority margin.

This sample size estimation is based on the following assumptions:

- The expected success rate for both devices is 98%
- The expected difference between the test and control treatment groups is 0%
- There is a test-to-control sampling ratio of 2:1
- A non-inferiority margin of 8% (δ = 0.08)
- Use of a one-sided Farrington-Manning Score Test with 85% power and at a one-sided 2.5% significance level

Based on these assumptions, a statistically powered sample size of 87 test (V Needle) sessions is required for the primary endpoint[1,2].

The total sample size is therefore determined to be 108 test sessions with 18 subjects required to account for 20% attrition and/or any of the 6 V Needle sessions being missed.

The primary performance analysis will test the non-inferiority hypothesis as a difference of proportions between the test and control groups using a one-sided Farrington-Manning Score Test at a significance level of α=0.025.

[1] Chow, S.C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC. Boca Raton, Florida.

[2] Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.

Additionally, the primary performance measure will be analyzed on the subject-level (utilizing a non-inferiority margin of 0.05) by testing the difference in mean success rates per subject across treatment groups using a one-sided paired t-test at a significance level of α=0.025.

1.22 STUDY TIMELINE

Month 0: Site identification and IRB approvals; study start-up and training

Month 2: First patient enrolled

Month 5: Last patient enrolled

Month 6: Data analysis

Month 7: Completion of study report

1.23 SCHEDULE OF ACTIVITIES (SOA)

Table 1: Schedule of Activities

	Enrollment Visit	Control Dialysis Sessions (Visit 1-3)	Test Dialysis Sessions (Visit 4-9)	Final Study Visit (7-10 days after Visit 9)
Informed Consent	X			
Inclusion/Exclusion	X			
Demographics	X			
Medical History Form	X			
Vital Signs	X			
Adverse Event Form	X	X	X	X
Therapy Assessment Form, including the following: • **Treatment success/failure** • **Blood alarms** • **Flow rates** • **Prescribed treatment time** • **Achieved treatment time** • **Prescribed blood flow rate** • **Achieved blood flow rate** • **Ability to cannulate fistula**		X	X	
Patient Survey			X	
Clinician Survey		X	X	

1.24 STUDY PARTICIPANT DURATION

It is expected that the visits will occur at sequential dialysis sessions such that the patient participation is limited to an enrollment visit and then approximately three (3) weeks of follow-up visits. No windows are provided for these visits, but the entire sequence shall occur within 40 days from the baseline visit.

2 Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Investigator Name (please print):

_____

Investigator Signature:

_____

Date:

_____

3 Introduction

3.1 Study Rationale

In patients undergoing hemodialysis for the treatment of end-stage renal disease, Venous Needle Dislodgement (VND) is a rare, but potentially fatal situation in which the needle delivering a patient's blood back to the body after filtration by a dialysis machine becomes inadvertently disconnected from the patient. Hemotek Medical Inc. has developed the V Needle, a venous needle return that is designed to reduce patient risk from exsanguination-related injury or death. This clinical study will serve as a confirmatory study to gain FDA marketing clearance of the Hemotek V Needle system in the clinical setting. During this study, we will determine the ability of the V Needle to successfully deliver appropriate hemodialysis therapy per the facility's guidelines. It will also be used to determine if the V Needle triggers false blood alarms under normal operating conditions. This study will also be used to demonstrate the V Needle meets effective usability criteria. Rates of adverse events and ability to complete the hemodialysis session will be compared to the rates recorded using commercially available devices during the hemodialysis sessions prior to the use of the Hemotek V Needle.

3.2 Background

Every week in the US, more than 500,000 patients collectively undergo >1,500,000 dialysis sessions which is equivalent to > 70,000,000 dialysis sessions per year, each about 3 hours long. A potentially devastating complication of hemodialysis is venous needle dislodgement (VND) whereby the needle returning blood into a patient's body accidently becomes withdrawn from the arm. If undetected, the blood loss quickly becomes injurious or, worse, can lead to death.

A device that aims to detect VND, but does not disrupt the flow of the dialysis machine, is the RedSense device. The device uses an optical sensor to activate a light and sound alarm when a VND is detected. For this device, the alarm functioned correctly in 92.5% of tests, and after device modification, the device operated in 97.2% of tests[3].

While the RedSense device can trigger an alarm when a VND occurs, there is no single, inexpensive and easy-to-use method that can both detect VND and immediately shut down the flow of blood through the needle. To address this glaring need in the dialysis marketplace, Hemotek has developed the V Needle, a single-use disposable needle with built-in VND protection. It has an elegant mechanical mechanism that is designed to automatically occlude the flow of blood during dislodgement and trigger the dialysis machine pump to shut down.

[3] Ahlmen et al., 2008. "A new safety device for hemodialysis" Hemodialysis International 2008; 12:264–267.

3.3 Risk/Benefit Assessment

3.3.1 Known Potential Risks

Risks related to the study and/or device are expected to be the same as those risks for patients undergoing hemodialysis. Due to the design of the V Needle, very slight increases in certain risks are potentially possible but are not expected.

The potential risks specifically associated with the V Needle are as follows:

- Improper needle function, leading to machine false alarms or changes to dialysis blood flow rate or pressure
- Difficulty inserting the needle into the veins (cannulation)
- Slightly increased risk of blood loss and/or air embolism

The risks associated with all AV fistula sets are as follows:

- Air in the tubing/blood vessels, which could result in blockage and reduced blood flow in that vessel or other vessels in the body
- Allergic responses to the device materials, such as swelling, itchiness, or inflammation of the skin
- Small particles released into the blood vessels, which could result in blockage and reduced blood flow in that vessel or other vessels in the body
- Improper function of the device, leading to delay in therapy
- Infection
- Breakdown of blood cells due to unstable blood flow (hemolysis), which can lead fatigue, dizziness, and headaches
- Blood loss
- Blood leaks into surrounding tissue, leading to swelling and/or pain (infiltration, when the needle tip is placed into the body but not directly into the blood vessel)
- Injury from sharp needle

3.3.2 Known Potential Benefits

The primary benefit for participation in the study is to have access to a new device that can potentially detect VND. Additionally, future patients may benefit from this potentially life-saving device, and the knowledge gained about the device and study design in this study are required first steps in bringing the device to market.

3.3.3 Assessment of Potential Risks and Benefits

The risks to study subjects beyond those normally associated with hemodialysis are due to the slight force from the footplate on the access site and the presence of the flexible membrane inside the V Needle. There may be a slightly increased risk of blood loss and/or air embolism, but based on laboratory testing and subject matter expert input, these harms are not expected to occur more frequently than in usual dialysis sessions. Due to the potentially improved safety profile through the use of the device and potential for bringing a potentially life-saving device to market, the value of the knowledge gained through this study are judged to outweigh the risks incurred by study participation.

4 Objectives and Endpoints

The study is designed to confirm the safety, performance, and usability of the Hemotek V Needle A.V. Fistula Set for temporary cannulation for hemodialysis in the treatment of end-stage renal disease patients in the clinical setting.

Because the objective of the study is confirmation of safety, performance, and usability, a number of endpoints are collected to ensure that the safety, performance, and usability of the device can be evaluated.

4.1 PRIMARY SAFETY MEASURE

Rate of serious adverse device events (SADEs)

4.2 ADDITIONAL SAFETY MEASURES

- Rate of adverse events (AEs)
- Rate of serious adverse events (SAEs)
- Rate of adverse device events (ADEs)
- Rate of adverse procedure events (APEs)
- Rate of serious adverse procedure events (SAPEs)

4.3 PRIMARY PERFORMANCE MEASURES

Percentage of successful hemodialysis sessions with the Hemotek device.

4.4 ADDITIONAL PERFORMANCE MEASURES

- Machine alarm rate (blood alarms only) during hemodialysis therapy, including false alarms and relationship of alarm to venous needle
- Changes to blood flow rate setting during therapy sessions and relationship to venous needle
- Venous, transmembrane, and/or arterial pressure measurements
- Patient survey including ratings for venous needle comfort and feelings of safety (V Needle only)
- Clinician survey, evaluating the following items:
    - use of the device according to the instructions for use (IFU)
    - ability to properly cannulate
    - ability to objectively see flashback
    - confirmation that the footplate is fully depressed (V Needle only)
    - feelings regarding patient risk (V Needle only)
- Achieved treatment time
- Achieved blood flow rate
- Ability to cannulate fistula

- Episodes of partial or complete needle dislodgment

5 Study Design

5.1 Overall Design

This study is a prospective, multi-center, single-arm study with subjects acting as their own control designed to confirm the safety, performance, and usability of the V Needle, a new safety needle for use during in-clinic hemodialysis that is designed to automatically generate a partial occlusion of the internal fluid path and trigger the hemodialysis machine to alarm and shut off if a complete dislodgement of the venous needle from the arm inadvertently occurs.

For the first three (3) control sessions, consenting subjects will undergo usual hemodialysis sessions with a commercially available device. For the remaining six (6) test sessions, subjects will be cannulated with a V Needle in place of a usual venous line AV fistula set.

The hemodialysis sessions will be conducted in the clinic. Subjects will be observed by a clinician for the duration of each session. Clinicians will monitor the session for any abnormal disruptions, therapy interruptions, and/or adverse events, including hemolysis, due to V Needle presence. All machine blood alarms, therapy interruptions, and/or partial or complete needle dislodgements will be recorded and immediately corrected. Clinicians will be responsible for identifying adverse events as they occur and will activate established facility emergency response plans if necessary. A clinician will perform cannulation.

Cannulation site and surrounding tissue will be examined by the nurse and assessed for any locally induced trauma before and after treatment.

A survey will be completed by the users to assess usability of the V Needle.

After the first five (5) patients will be enrolled, and data through the last visit of the fifth patient is available, this data will be submitted to the FDA while study enrollment and visits continue. No Hemotek Medical V Needle treatments will occur until after FDA has reviewed the data from the first 5 patients and allows the study to proceed. Data will also be submitted to the FDA after the tenth patient completes their last visit and data is available. After the tenth patient, study enrollment and visits can continue, but no Hemotek Medical V Needle treatments will occur on the final 5-10 patients until the FDA allows the study to proceed. After FDA has found the data for the first 10 patients acceptable, the rest of the study can continue until the end.

At least two different clinicians will evaluate the device for each patient and for each needle for that patient (test and control) to minimize the bias associated with the same clinician evaluating all of the sessions for a given subject.

5.2 Scientific Rationale for Study Design

The study is designed to confirm the safety, performance, and usability of the V Needle, a new medical device. The device will be tested by comparing the ability to successfully complete hemodialysis sessions to commercially available devices as determined by a clinician.

Additionally, the rates of adverse events will be compared to rates measured using commercially available devices, providing a comparator with data collected under similar circumstances and in the same patient population.

5.3 End of Study Definition

A participant is considered to have completed the study if they have completed all follow-up visits. It is expected that 15 subjects will undergo 9 treatments each. In the event that some of these patients do not complete the full set of treatments, additional subjects (up to 20 total) will be recruited until 87 V Needle treatments are completed and all patients have completed their study visits.

After the first five (5) patients will be enrolled, and data through the last visit of the fifth patient is available, this data will be submitted to the FDA while study enrollment and visits continue. No Hemotek Medical V Needle treatments will occur until after FDA has reviewed the data from the first 5 patients and allows the study to proceed. Data will also be submitted to the FDA after the tenth patient completes their last visit and data is available. After the tenth patient, study enrollment and visits can continue, but no Hemotek Medical V Needle treatments will occur on the final 5-10 patients until the FDA allows the study to proceed. After FDA has found the data for the first 10 patients acceptable, the rest of the study can continue until the end.

If there are any deaths or three SADEs during the study device period that require medical or surgical intervention, study enrollment and further visits will be stopped, and an assessment (in conjunction with the DSMB and FDA) will be enacted.

6 Study Population

6.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Subjects with end-stage renal disease receiving chronic hemodialysis in a clinical setting.
2. Subjects must be able to receive hemodialysis with the Hemotek 15-gauge, 1 inch length V Needle, with 12 inch tubing.
3. Age greater than 18 years old at screening.
4. Vascular access via a mature arteriovenous (AV) fistula or graft in the arm and determined to be adequate for a chronic hemodialysis therapy.
5. AV fistula has already been demonstrated to adequately permit one or more hemodialysis sessions.
6. Subject prescribed blood flow rates between 200 ml/min and 450 ml/min
7. In women with child-bearing potential, negative urine or serum pregnancy test at Screening.
8. Subject able to communicate effectively with investigative staff, competent and willing to give written informed consent, and able to comply with entire study procedures.
9. Hemoglobin ≥9 g/dL (consistent with KDOQI guidelines)

10. Normal platelet count (≥150,000 /mm3)
11. International Normalized Ratio (INR) ≤ 1.5

6.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subjects receiving chronic hemodialysis with a vascular catheter.
2. Subjects with vascular access that is determined by the clinician to be unacceptable for a hemodialysis procedure.
3. Patients with a bleeding diathesis
4. Patients receiving anti-coagulants
5. Previous vascular access surgery (≤30 days from study entry) or planned access surgery
6. Known hypersensitivity to any imaging agents (e.g., contrast) that may be required during the study period
7. Patients with confirmed vasculitis
8. Vascular access infection or systemic active infection within 30 days of study entry
9. Life expectancy less than 12 months
10. Planned renal transplantation or planned conversion to peritoneal dialysis
11. Subjects with any condition determined by the investigator that precludes them from safely participating in the study.
12. Female participants at the time of consent to the study cannot be breastfeeding or pregnant.

6.3 Screen Failures

Individuals who sign informed consent, but are then discovered to not meet the inclusion and exclusion criteria and/or who do not complete the Control Dialysis Sessions will be considered screen failures. These subjects will not be included in the subject count. Information about the subject's demography, screen failure details, eligibility criteria, and any adverse events that occur prior to screen failure will be collected. Subjects who are screen failures may be rescreened if deemed appropriate (e.g., they need to allow their fistula to mature). Rescreened subjects should be assigned their original patient number.

6.4 Strategies for Recruitment and Retention

Subjects will be recruited from the study center's regular pool of patients undergoing hemodialysis. Due to the number of subjects required for this study, additional advertising and/or recruitment methods should not be required.

Additionally, because each patient is expected to complete the study in approximately one month, no exceptional retention methods will be used. A payment (via check) in an amount of $50 per visit will be provided to the subjects to cover the subjects' additional time and/or expenses at the completion of the final visit.

7 Study Intervention

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

The Hemotek V Needle A.V. Fistula Set is intended for temporary cannulation (non-implanted) to vascular access for extracorporeal blood treatment for hemodialysis. Please refer to device labeling for additional information. The device is intended for single use only. The device also has an integrated safety mechanism that is designed to automatically occlude the internal fluid path and trigger the hemodialysis machine to alarm and shut off if a complete dislodgement of the venous needle from the arm inadvertently occurs.

For the clinical studies, the Hemotek 15-gauge, 1 inch length, with 12 inch tubing, V Needle Sharp configuration will be used. Devices will be packaged individually, and a clamp will be used.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Acquisition and accountability

The devices will be hand-delivered to the investigative site. Product that is not immediately in use will be stored in a locked cabinet. Expired or unused product will be retrieved by the sponsor.

7.2.2 Formulation, Appearance, Packaging, and Labeling

The device will be provided with appropriate packing and labeling, including a clear indication of the expiration date of the product. The device will be provided sterile.

7.2.3 Product Storage and Stability

The storage requirements will be indicated by the device packaging and labeling. The devices are single use. The expiration date of the device will be clearly indicated on the device.

7.2.4 Preparation

Refer to the device's instruction for use for appropriate administration of the device.

7.3 Measures to Minimize Bias: Randomization and Blinding

The study is not randomized or blinded. Control sessions measuring the rates of adverse events and successful therapy sessions is included to provide a within-subject comparator to these rates for the V Needle. To minimize bias, subjects will be considered and asked to enroll in the study sequentially to the extent possible to ensure that no unconscious bias of patient selection occurs. The study will be conducted at multiple centers to ensure that outcomes are able to be generalized across different clinics.

At least two different clinicians will evaluate the device for each patient and for each needle for that patient (test and control) to minimize the bias associated with the same clinician evaluating all of the sessions for a given subject.

7.4 Study Intervention Compliance

Adherence to the study protocol will be accomplished by the direct supervision of the study clinicians and review of the clinical data by study monitors.

8 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

Discontinuation from one study visit does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

8.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request.

A patient who is no longer active in the study, due either to patient choice or physician recommendation, will be classified as a "Withdrawal." All completed case report forms up to the point of withdrawal must be completed.

After a patient has been withdrawn from the study or after a patient has withdrawn his/her consent, for whatever reason, additional data may no longer be collected after the point of withdrawal. All open adverse events should be closed or documented as chronic. Data collected up to the point of patient withdrawal may be used for analysis. The sponsor will not actively collect any information on subjects who have been withdrawn from the study. However, all post-withdrawal adverse events of which the sponsor is notified will be recorded in the patient file.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Study Completion Form (CRF).

8.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for any scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and/or written communication). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 Study Assessments and Procedures

This section describes the study assessments and procedures. Refer to Table 1 for a list of the data to be collected at each visit. Study staff will check for AEs at each visit and fill out an AE form as necessary.

9.1 Efficacy Assessments

9.1.1 Enrollment

At the enrollment visit, the informed consent document and inclusion/exclusion criteria will be assessed and entered into the Inclusion/Exclusion Case Report Form. Multiple visits to complete the screening and obtain appropriate informed consent are allowed. Demographics and medical history will be collected, as well as vital signs (height, weight, blood pressure, heart rate, respiration, and temperature).

9.1.2 Control Dialysis Sessions

The assessment of the ability to successfully complete the session will be determined by the clinician and recorded on the Therapy Assessment Case Report Form (CRF). The actual treatment time will also be recorded. Adverse events will be recorded on an Adverse Event Case Report Form. Photos of the cannulation may be taken.

Additional performance measures include the following:

- Machine alarm rate (blood alarms only) during hemodialysis therapy, including false alarms and relationship of alarm to venous needle
- Changes to blood flow rate setting during therapy sessions and relationship to venous needle
- Venous, transmembrane, and/or arterial pressure measurements
- Clinician survey, evaluating the following items:
    - use of the device according to the instructions for use (IFU)
    - ability to properly cannulate
    - ability to objectively see flashback
- Achieved treatment time
- Achieved blood flow rate
- Ability to cannulate fistula
- Episodes of partial or complete needle dislodgment

In the event that the venous needle becomes 1) completely dislodged, or 2) partially dislodged and the venous pressure increases by more than 40 mm Hg indicating some disruption of the fluid flow, the event should be recorded on the therapy assessment and AE CRFs and appropriate laboratory tests (including CBC, plasma hemoglobin concentration, serum electrolytes) shall be obtained.

Patients shall be monitored for symptoms of hemolysis; if hemolysis is suspected, an AE form should be completed and appropriate laboratory tests (including CBC, plasma hemoglobin concentration, serum electrolytes) shall be obtained.

9.1.3 Test Dialysis Sessions

The assessment of the ability to successfully complete the session will be determined by the clinician and recorded on the Therapy Assessment Case Report Form (CRF). The actual treatment time will also be recorded. Adverse events will be recorded on an Adverse Event Case Report Form. Photos of the cannulation may be taken.

Additional performance measures include the following:

- Machine alarm rate (blood alarms only) during hemodialysis therapy, including false alarms and relationship of alarm to venous needle
- Changes to blood flow rate setting during therapy sessions and relationship to venous needle
- Venous, transmembrane, and/or arterial pressure measurements
- Patient survey including ratings for venous needle comfort and feelings of safety (V Needle only)
- Clinician survey, evaluating the following items:
    - use of the device according to the instructions for use (IFU)
    - ability to properly cannulate
    - ability to objectively see flashback
    - confirmation that the footplate is fully depressed (V Needle only)
    - feelings regarding patient risk (V Needle only)
- Achieved treatment time
- Achieved blood flow rate
- Ability to cannulate fistula
- Episodes of partial or complete needle dislodgment

In the event that the venous needle becomes 1) completely dislodged, or 2) partially dislodged and the venous pressure increases by more than 40 mm Hg (above last recorded venous pressure measurement) indicating some disruption of the fluid flow, the event should be recorded on the therapy assessment and AE CRFs and appropriate laboratory tests (including CBC, plasma hemoglobin concentration, serum electrolytes) shall be obtained.

Patients shall be monitored for symptoms of hemolysis; if hemolysis is suspected, an AE form should be completed and appropriate laboratory tests (including CBC, plasma hemoglobin concentration, serum electrolytes) shall be obtained.

9.1.4 Final Study Visit

7-10 days after the last study visit, subjects will be contacted by phone or will be interviewed at their usual hemodialysis session to ensure no additional AEs have occurred.

9.2 Safety and Other Assessments

9.2.1 Adverse Event Definitions

Adverse event forms will be filled out whenever an adverse event occurs within the reportable period. Definitions of the adverse event categories can be found below. Adverse events will be categorized according to a medical dictionary created by the sponsor and approved by the Data Safety Monitoring Board (DSMB) for reporting purposes.

Adverse Event (AE)	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 investigation medical device. Note: Pain and/or bleeding that is to be expected due to hemodialysis during the intervention are not considered untoward events and should not be recorded as adverse events. Likewise, minimal bruising, pain, and/or bleeding in the days following the procedure shall not be considered untoward and not considered an AE. In contrast, any pain, bruising, or bleeding that is considered by the clinician to be unusual in magnitude or duration shall be considered an AE.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. Note: this definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Adverse Procedure Effect (APE)	Adverse event related to the therapeutic procedure for the investigational medical device.
Device Deficiencies (DD)	Any inadequacy in the identity, quality, durability, reliability, safety, or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
Serious Adverse Event (SAE)	Any adverse event that led to any of the following: • death • serious deterioration in the health of the participant that either resulted in: ▪ a life-threatening illness or injury, ▪ a permanent impairment of a body structure or a body function,

	▪ hospitalization or prolongation of patient hospitalization, ▪ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, ▪ chronic disease • fetal distress, fetal death or a congenital physical or mental impairment or birth defect Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan (CIP), without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Procedure Effect (SAPE)	An adverse procedure effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

9.2.2 AE and Device Deficiency Documentation

All AEs will be monitored for all participants, from the time of signing consent through to the final study visit. All AEs, including SAEs, must be detailed in the source documents and reported in a timely manner to the Sponsor by completing an AE page in the CRF. Each unique event must be documented separately.

AEs can be based upon subject report, questionnaires, medical reports or other medical examinations. AEs should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit. For each medical diagnosis or sign and/or symptoms the Investigator will provide information on dates (onset/resolution), severity, relationship to the medical device, action(s) taken and outcome.

Any AEs should be followed until the event is resolved (with or without sequelae). If an event is ongoing at the time of study completion or termination, the participant will be followed until resolution or Investigator determination that the subject's condition is stable. Documentation of stabilization must be recorded in the participant's source documents. If the Investigator learns of any SAE at any time after a participant has been discharged from the study, and he/she considers

the event reasonably related to the study device and/or study procedure, the Investigator will record the occurrence in the subject 's source documents and promptly notify the Sponsor.

If adverse events occur, the first concern will be the safety of the subject. Appropriate medical intervention will be made as soon as possible. Treatment of any AEs is at the sole discretion of the Investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the CRF.

All device deficiencies, including serious incidents (a device deficiency that might have led to a SADE if a) suitable action had not been taken, b) intervention had not been made, c) if circumstances had been less fortunate), shall be documented throughout the study in the source documents and appropriately reported on a device deficiency page of the CRF.

9.2.3 Reporting of events

AEs must be reported to the Sponsor or designee by the Investigator immediately but no later than 3 calendar days after investigation site study personnel's awareness of the event of the following:

i. SAE,
ii. SADE,
iii. SAPE,
iv. USADE,
v. Device deficiency (DD) that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate,
vi. New findings in relation to any event mentioned to in points i) to v).

Notification should be made by completion of the AE form in the CRF and by contacting by phone and/or by email the sponsor or designee.

As additional information becomes available, the event should be updated in the CRF and provided to the sponsor or designee.

Non-serious AEs should be reported at the next routine contact.

9.2.4 AE and DD information and Classification

The Investigator will classify each AE and DD according to the Adverse Event Form. If the AE is serious or the Investigator feels that the device contributed in any way to the AE, the Investigator must report the event to the Sponsor and the EC, if applicable, as per above. It is the Investigators responsibility to assess the intensity of, as well as determine the causality and potential relationship of the event to the study device or procedure. The Sponsor may ask for further clarification and information to support the AE classification. If sufficient questions arise, the Sponsor may ask the DSMB to adjudicate the classification. The Sponsor may assess the potential relationship to the device or procedure differently than the Investigator; in that case, both conclusions will be collected and reported, if applicable.

The following information will be collected for any event occurring during the course of this investigation:

- Date of event onset,

- In case of SAE, SADE, SAPE, USADE, DD that might have led to a SAE in other circumstances: classification of the event (death - life-threatening illness or injury - permanent impairment/chronic disease – hospitalization - medical or surgical intervention - fetal distress, fetal death or congenital physical or mental or birth defect)
- Description of the event
- Action / treatment / patient outcome
- Intensity of the event (mild, moderate, severe)
- Relationship to procedure (not related, possible, definite)
- Relationship to study device (not related, possible, definite)
- Event status (resolved, resolved with sequelae, ongoing, death)

9.2.5 Emergency contact details for reporting reportable events

Sponsor and designee contact details for reporting reportable events are detailed in the study contacts at the beginning of the present clinical investigation plan.

9.2.6 Safety Monitoring

Safety oversight will be under the direction of a Data Safety Monitoring Board (DSMB). The DSMB shall be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSBM will operate under the rules of an approved charter that will be written by the sponsor and reviewed and approved by the DSMB.

The DSMB will be responsible for initial review of all events reported as serious. Further information may be sought from the investigational site. Events will be reviewed to check relatedness and seriousness to enable appropriate reporting to the ethics and regulatory bodies, as well as take any appropriate action with regards to study continuation.

The DSMB will include at least two physicians who have experience with hemodialysis and vascular access and one statistician.

9.2.7 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related.

Note: Pain and/or bleeding that is to be expected due to hemodialysis during the intervention are not considered untoward events and should not be recorded as adverse events. Likewise, minimal bruising, pain, and/or bleeding in the days following the procedure shall not be considered untoward and not considered an AE. In contrast, any pain, bruising, or bleeding that is considered by the clinician to be unusual in magnitude or duration shall be considered an AE.

9.2.8 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or

surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2.9 Classification of an Adverse Event

9.2.10 Severity of Event

The following guidelines will be used to describe severity of AEs:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities. For cannulation injuries, An injury that may result in bleeding, infiltration, and swelling that may be treated with conservative measures such as ice and rest for 1 to 2 days; cannulation can be reattempted for the next dialysis session. The access should be successfully recannulated with 2 needles in ≤7 days.2 Even a minor cannulation injury may require the use of a temporary catheter.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning. For cannulation injuries, an injury that results in significant bleeding, infiltration, and swelling that requires recovery for >7 days.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". For cannulation injuries, an injury that results in significant bleeding complications that requires one of the following: blood transfusion, emergency department visit, hospitalization, or endovascular or surgical intervention.

9.2.11 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study device/procedure assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – The AE is known to occur with the study device/procedure, or it is known that the study device/procedure caused the AE.
- **Possibly Related** -- The AE is could have occurred due to the study device/procedure, there is a reasonable possibility that the study device/procedure caused the AE, or there is a temporal relationship between the study device/procedure and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study device/procedure and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study device/procedure caused the event, there is no temporal relationship between the study device/procedure and event onset, or an alternate etiology has been established.

9.2.12 Expectedness

The Data Safety Monitoring Board (DSMB) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.2.13 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study clinicians will record all reportable events with start dates occurring any time after informed consent is obtained until 7 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

10 Statistical Considerations

10.1 Statistical Hypotheses

10.1.1 Sample Size

The sample size was determined to compare the rate of successful treatments between hemodialysis sessions with the test needle compared to the control needle.

The hypothesis test for the primary performance measure is defined as follows:

$$H_0: p_T - p_C \leq -\delta$$

$$H_1: p_T - p_C > -\delta$$

where p_T is the probability of a successful hemodialysis treatment session with the V Needle (test), p_C is the probability of a successful hemodialysis treatment session with a commercially available device (control), and δ is the non-inferiority margin.

This sample size estimation is based on the following assumptions:

- The expected success rate for both devices is 98%
- The expected difference between the test and control treatment groups is 0%
- There is a test-to-control sampling ratio of 2:1
- A non-inferiority margin of 8% (δ = 0.08)
- Use of a one-sided Farrington-Manning Score Test with 85% power and at a one-sided 2.5% significance level

Based on these assumptions, a statistically powered sample size of 87 test (V Needle) sessions is required for the primary endpoint[4,5].

The total sample size is therefore determined to be 108 test sessions with 18 subjects required to account for 20% attrition and/or any of the 6 V Needle sessions being missed.

The primary performance analysis will test the non-inferiority hypothesis as a difference of proportions between the test and control groups using a one-sided Farrington-Manning Score Test at a significance level of α=0.025.

Additionally, the primary performance measure will be analyzed on the subject-level (utilizing a non-inferiority margin of 0.05) by testing the difference in mean success rates per subject across treatment groups using a one-sided paired t-test at a significance level of α=0.025.

10.1.2 Primary Hypothesis

The primary performance goal for this study is that the Hemotek device will provide successful hemodialysis treatment at a rate non-inferior to that of the commercially available devices. The rate of successful treatment will be computed as the number of successful session completions of V Needle, as determined by the clinician, divided by the total number of sessions attempted.

To determine whether a dialysis session was successful, clinicians will be asked "Was dialysis session incomplete because of a vascular access issue?" If the answer is "No," this indicates that the dialysis session completed successfully or was stopped for reasons that were not related to the vascular access (e.g., patient illness, etc.).

The null hypothesis is that the difference between the rates of successfully completed hemodialysis sessions for the test and control groups is less than or equal to the non-inferiority margin (indicating inferior success rate). Rejection of the null hypothesis indicates the observed data supports the alternative hypothesis that the difference between the rates of successfully completed hemodialysis session for the test and control groups is at least the non-inferiority margin (indicating non-inferior success rate).

The hypothesis test for the primary analysis are defined as follows:

$$H_0: p_T - p_C \leq -\delta$$

$$H_1: p_T - p_C > -\delta$$

where p_T is the probability of a successful hemodialysis treatment session with the V Needle (test), p_C is the probability of a successful hemodialysis treatment session with a commercially available device (control), and δ is the non-inferiority margin.

[4] Chow, S.C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research, Second Edition. Chapman & Hall/CRC. Boca Raton, Florida.

[5] Farrington, C. P. and Manning, G. 1990. 'Test Statistics and Sample Size Formulae for Comparative Binomial Trials with Null Hypothesis of Non-Zero Risk Difference or Non-Unity Relative Risk.' Statistics in Medicine, Vol. 9, pages 1447-1454.

10.2 Populations for Analyses

Subjects will be analyzed by gender, demographics, and by site to ensure that results are consistent across these variables.

10.3 Statistical Analyses

10.3.1 Performance Endpoint Analysis

Although not a randomized study, each subject dialysis session will be performed using either the test needle or a control needle. The sites are instructed to perform 3 control sessions first and then 6 test sessions per enrolled subject, and in the case that a site deviates from this order, performance measure will be analyzed based on the needle used. Assuming there will be a 20% rate of attrition/drop-out, the remaining 18 subjects would contribute 108 test and 54 control sessions. Data will be pooled by session type (test vs. control) from all sites (no by-site analyses are planned).

The primary performance analysis will test the non-inferiority hypothesis as a difference of proportions between the test and control groups using a one-sided Farrington-Manning Score Test at a significance level of α=0.025.

Additionally, the primary performance measure will be analyzed on the subject-level (utilizing a non-inferiority margin of 0.05) by testing the difference in mean success rates per subject across treatment groups using a one-sided paired t-test at a significance level of α=0.025.

10.3.2 Safety Endpoint Analysis

The incidence rates of adverse events (including those listed under the primary and secondary safety endpoints) will be calculated as the number of events per number of treatments as well as tallied per subject. Adverse event rates will be summarized with 95% exact binomial confidence bounds for both the investigational and control groups.

The adverse events of each group will also all be stratified by their (1) seriousness, (2) severity, (3) relatedness to device, (4) relatedness to procedure, and (5) anticipated status.

Any events with onsets occurring between sessions will be associated with the group representing the device used at the last session.

10.3.3 Usability and Additional Measures

The results from the clinician and patient surveys (formatted on ordinal scaling) will each be summarized using the 5-point Likert scoring system (e.g., 5=strongly agree, 4=agree, 3=neither agree or disagree, 2=disagree, 1=strongly disagree) to represent user responses on a symmetric range, with overall item scores to represent usability measures. The usability of the V Needle will be assessed from the clinician and patient survey scores submitted for the needle device used at the end of each session. This will be done using a Mann-Whitney-Wilcoxon (MWW) test, which will assess differences in mean ranks of clinician/patient survey scores given to the V Needle and control devices, as applicable.

10.3.4 Alarm categories and definitions

The following definitions are used for dialysis machine alarms:

True Alarm: Alarm was appropriate because clinician action was required beyond resetting the alarm (e.g., venous needle dislodgement, significant needle movement, infiltration, tape failure), and/or V Needle footplate opened appropriately.

False Alarm: No clinician action was required beyond resetting the alarm, and/or V Needle footplate opened inappropriately.

The following definitions will be used for the footplate opening:

Appropriate footplate opening: Footplate opening due to a VND or infiltration and/or needle movement, tape failure, or other condition that can potentially lead to a VND or infiltration.

Inappropriate footplate opening: Footplate opening that is not due to a VND or infiltration and/or needle movement, tape failure, or other condition that can potentially lead to a VND or infiltration

10.4 Other Statisical Considerations

10.4.1 General/Summary Metrics

Simple descriptive statistics will be displayed for all relevant variables collected under the study, and be presented on the session-level (between-subject), with the exception of the additional analysis of the primary performance measure which will be done on the individual-level (within-subject).

Continuous variables will display number of observations/counts measured, mean, standard deviation, median, min/max, Q1/Q3, and 95% confidence intervals where appropriate; categorical variables will display frequency counts and percentages.

These variables will include but are not limited to the following:

- Subject demographics (including age, gender, weight, height, etc.)
- Medical history characteristics (including concomitant medication, duration in which subject was diagnosed with renal disease, any concurrent ailmnets, etc.)

Unless otherwise specified, all p-values will be considered significant at α=0.05 if tests are two-sided and α=0.025 if tests are one-sided.

10.4.2 Handling of Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. All analyses will be based on available data only; no imputation for missing data is planned.

11 Regulatory, Ethical, and Study Oversight Considerations

11.1 Informed Consent Process

11.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

11.1.2 Consent Procedures and Documentation

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. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. 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.

11.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

11.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or medical device company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the study sponsor.

11.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored with the sponsor or with a clinical research organization retained by the sponsor. No biological samples will be retained.

11.5 Safety Oversight

Safety oversight will be under the direction of Data Safety Monitoring Board (DSMB), which will consist of at least two clinicians and one statistician. The DSMB shall be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will operate under the rules of an approved charter that will be written by the sponsor and reviewed and approved by the DSMB.

11.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the sponsor or a clinical research organization. The sponsor will be provided copies of monitoring reports within 7 days of visit. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

11.7 Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring 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.

The sponsor and/or the sponsor's representatives may be present during study visits to ensure that the device is appropriately administered and that the data is correctly collected. The sponsor and/or their representative will not practice medicine and will not interact with the subjects outside the clinician's supervision.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data will either be entered into an electronic case report form or collected in paper binders and transmitted via a scanner for collection, input into a central database, and analysis. Clinical data (including adverse events

(AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into study database. No data that could be used to identify a patient will be transmitted.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. 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.

11.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All protocol deviations must be addressed in study source documents. Serious protocol deviations, which include misuses of the investigational device or deviations that endanger the study objectives, must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the Standard Operating Procedures.

11.10 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be

registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the sponsor.

11.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the medical device industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIDDK has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

12 Abbreviations

AE	Adverse Event
AV	Arteriovenous
CFR	Code of Federal Regulations
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
KDIGO	Kidney Disease Improving Global Outcomes
MedDRA	Medical Dictionary for Regulatory Activities

MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VND	Venous Needle Dislodgment

REVISION HISTORY

Rev	**Summary of Changes**	**Justification for Changes**
A	None	Initial Release
B	Added requirements for a staged study throughout the protocol. Updated inclusion and exclusion criteria. Updated the Schedule of activities (SOA) table. Updates to the risk-benefit assessment section. Added a requirement for at least two different clinicians to evaluate the device for each patient. Added requirements for actions related to SADEs. Added requirements for the the Final Study Visit. Added additional requirements for the DSMB. Added additional performance measures.	All Rev B updates were made based on requirements agreed on between Hemotek Medical and the FDA during the interactive IDE submission review. Rev B represents the FDA IDE approved version as of June 23rd, 2022.

C	Added requirements for patient hemolysis testing throughout the protocol under specified conditions. Updated a clerical error with the numbering within the exclusion criteria. Added episodes of partial and complete needle dislodgment to the additional performance measures. Added the expected success rate for both devices (98%). This was inadvertently not added to Rev A.	Rev C updates were made to satisfy specific requirements specified in the "Study Design Considerations" section of the FDA IDE approval letter dated, June 23rd, 2022.
D	Changed patient stipend to $50 payment per visit.	Requested by study site.
E	Updated exclusion criteria lists, reimbursement approach (removed gift card) and clarified statistical sample size justification language	Updates were made based on suggested 'Additional Considerations' list from FDA IDE, IDE supplement and first 5-day notice responses