Triferic AVNU infusion via Freedom Pump During Hemodialysis

Protocol Title: Triferic AVNU Infusion via Freedom Pump during Hemodialysis

An open-label clinical study to evaluate the delivery of Triferic AVNU intravenously using the Freedom Pump-20 during hemodialysis into the pre-dialyzer and post-dialyzer blood lines.

Intervention Model:

Cross-over: Participants receive alternative interventions during sequential hemodialysis treatments.

Primary Purpose:

Device Feasibility: An intervention of the Freedom Pump -20 to evaluate the feasibility of the pump to deliver Triferic AVNU into the pre-dialyzer or post-dialyzer blood lines . this study will confirm the design and operating specifications of a device in hemodialysis patients.

Study Phase: Post marketing

Study to assess feasibility of an approved device to administer an approved drug in hemodialysis patients.

Number of Arms:

2 Arms: Infusion to Pre-dialyzer and Post-dialyzer blood lines.

Masking:

No masking

Health Measurement/Observation:

The ability to deliver the full dose of Triferic AVNU during the hemodialysis procedure.

Intervention Name:

Triferic AVNU: Ferric Pyrophosphate Citrate Injection

Freedom Edge® Syringe Driver F10020

Intervention Form:

Solution for intravenous injection

Participant Sex:

Male and Female

Participant Age Range:

≥ 18 years of age,

Condition/Disease:

End-stage kidney disease on chronic hemodialysis (CKD_HDD).

Protocol Number: RMFPC-27

Amendment Number: N/A

Compound: Triferic AVNU (Ferric Pyrophosphate Citrate injection).

Brief Title:

Triferic AVNU Freedom Pump Evaluation

Study Phase: IV

Study to assess feasibility of an approved device to administer an approved drug in hemodialysis patients.

Sponsor Name: Rockwell Medical Inc

Legal Registered Address:

Freedom Pump Manufacturer:

KORU Medical Systems
24 Carpenter Road
Chester, NY 10918
USA

Tel: 1-800-624-9600

Regulatory Agency Identifier Number(s)

NDA: 212860

Approval Date: 27 March 2020

Sponsor Signatory:

I, the undersigned, have read and approve this protocol and agree on its content. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guidelines of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements.

Raymond D Pratt, MD **C**hief Development Officer	**Date**

Medical Monitor Name and Contact Information:

Raymond D Pratt, MD
Rockwell Medical Inc
30142 S Wixom Rd.
Wixom MI 48393
Tel: 248 960 9009 X405

INVESTIGATOR PROTOCOL AGREEMENT

Protocol Title: **Triferic AVNU Infusion via Freedom Pump during Hemodialysis**
Protocol Number: RMFPC-27 Version: 1.0

By my signature, I

- Confirm that my staff and I have carefully read and understand this protocol or protocol amendment and are thoroughly familiar with the appropriate use of the investigational drug described herein.
- Agree to comply with the conduct and terms of the study specified herein and with any other study conduct procedures provided by the Sponsor, Rockwell Medical.
- Agree to assume responsibility for the proper conduct of the study at this site, including complying with EMA guidelines, China Food and Drug Administration (CFDA) regulations, the International Conference on Harmonization (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable rules, regulations, and federal, state, and local laws relating to the conduct of clinical studies and the protection of human Patients.
- Agree not to implement deviations from or changes to the protocol or protocol amendments without agreement from the Sponsor and prior submission to and written approval (where required) from the Institutional Review Board (IRB) or Ethics Committee (EC), except when necessary to eliminate an immediate hazard to the Patients, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- Agree to onsite monitoring of the case report forms (CRFs) and source documents by Rockwell Medical or designee and to onsite inspection of CRFs and source documents by appropriate regulatory authorities, including but not limited to the EMA, CFDA, local governing regulatory bodies, and IRB/EC inspectors.

_____ _____
Investigator's Signature Date

_____
Print Name

Abbreviations:

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title:

Triferic AVNU Infusion via Freedom Pump During Hemodialysis

An open-label clinical study to evaluate the delivery of Triferic AVNU intravenously using the Freedom Pump-20 during hemodialysis into the pre-dialyzer and post-dialyzer blood lines.

Intervention Model:

Cross-over: Participants receive alternative interventions during sequential hemodialysis treatments.

Primary Purpose:

Device Feasibility: An intervention of the Freedom Pump -20 to evaluate the feasibility of the pump to deliver Triferic AVNU into the pre-dialyzer or post-dialyzer blood lines . this study will confirm the design and operating specifications of a device in hemodialysis patients.

Brief Title: Triferic AVNU Freedom Pump Administration

Rationale:

Triferic AVNU is approved for IV infusion direct into the pre- or post-dialyzer bloodlines over 3 to 4 hours. In the clinical trial for approval, the on-machine syringe pump was used to administer the drug. Because some HD machines do not have an on-machine syringe pump, an external pump is required to administer Triferic AVNU. This study will explore the feasibility of using an external mechanical syringe pump to deliver the approved dose of Triferic AVNU (6.75 mg Fe/4.5 mL).

Objectives and Estimands:

Objectives	Estimands
Primary	
• Time for complete infusion of 4.5 mL Triferic AVNU pre-Dialyzer and post-Dialyzer	• At 2 mL/hr infusion rate total volume to be delivered at 2.25 ± 0.3 hr
Secondary	
• Mean Δ sFe pre-Dialyzer and post-Dialyzer	• Mean ΔsFe pre-Dialyzer and post Dialyzer are equal ± 15%
• Mean TSAT Max pre-Dialyzer and post-Dialyzer	• TSAT max does not exceed 100%
Safety	

• Adverse Events	• Number of adverse events overall • Number of adverse events related to device

Overall Design:

Brief Summary:

This is an open label 6 period crossover study to examine the feasibility of using an external spring-driven infusion pump (Freedom Edge-20) to administer Triferic AVNU intravenously in the pre- and post-dialyzer blood lines in subjects undergoing chronic hemodialysis.

Study Duration: Patients will be in the study for a maximum of up to 21 days..

Treatment Duration: Treatment duration will be 6 HD sessions.

Health Measurement/Observation: The study will examine the delivery of Triferic AVNU, 4.5 ml by intravenous infusion into the pre-dialyzer and post-dialyzer blood lines using the Freedom Edge 20 pump. The time for delivery at a nominal rate of 2 mL/hr will be assessed along with the maximum sFe and TSAT achieved at the end of the infusion. Because the duration of infusion is slightly shorter than recommended in the approved product labeling, the effect on iron parameters will be compared to published data for continuous infusion over 3 hours.

Visit Frequency: Patients will be assessed at 6 consecutive HD sessions. The site of infusion (pre or post-dialyzer) will be alternated at each HD session so that at eh end of the study each patient will receive Triferic AVNU infused IV into pre-dialyzer and post-dialyzer blood lines 3 times each. A total of 10 subjects will participate in this study.

Number of Participants:

A maximum of 12 participants will be enrolled to study intervention such that approximately 10 evaluable participants complete the study.

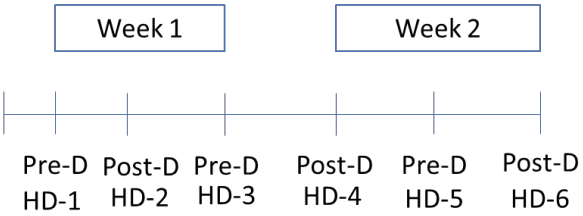
Intervention Groups and Duration:

All patients will receive Triferic AVNU at each of 6 HD sessions.

Data Monitoring/Other Committee: No

1.2. Schema

- Sequential Crossover Design
  - Pre-Dialyzer, Post Dialyzer infusion
  - 3 Rx each on alternating HD
- Measurements:
  - Time for complete infusion
  - Observed events
  - Pre-HD/Post-Infusion sFe, TSAT
  - Ease of use questionnaire for Nursing Staff
- Adverse Events
- Analysis:
  - Mean ΔsFe pre- to post infusion; Δ TSAT
  - Mean time to complete infusion



1.3. Schedule of Events (SoE)

Table 1: Schedule of Events.

Procedure	Screening (up to 7 days before Day 1)	Interventional Period (HD Days)						Follow-up (2 to7 days after last dose) or E/D = Early Discontinuation
		1	2	3	4	5	6	
Informed consent	-7							
Inclusion and exclusion criteria	X							
Demography	X							
Height and weight	X							
History of IV Fe Current medications	X							
Current medical conditions	X							
Serum pregnancy test (WOCBP only)	X							
Laboratory tests (CBC, Serum iron profile)	X							X
Vital signs (pre and post HD)	X	X	X	X	X	X	X	
Study intervention		←==========→						
Infusion Duration (min.)		X	X	X	X	X	X	
AE review		←==========→						
Administration events		←==========→						X
Adverse events		←==========→						X
Device deficiencies		←==========→						X
HD Parameters (Qb,Qd, arterial machine pressure, venous machine pressure)		←==========→						X
Iron profile: pre-Dialysis		X	X	X	X	X	X	
Iron profile: End of Infusion		X	X	X	X	X	X	

2. Introduction

Triferic AVNU (Ferric Pyrophosphate Citrate) injection for intravenous use, is the intravenous formulation of Triferic. Triferic AVNU delivers quantitatively the same amount of iron as delivered through the dialysate (6.5 mg Fe/HD). Triferic AVNU should be administered as a slow infusion into the pre-dialyzer or post-dialyzer blood line over 3 hours. Triferic is indicated for the maintenance of iron and hemoglobin in patients on chronic hemodialysis. The safety profile of Triferic AVNU is the same as Triferic for hemodialysate in that the same amount of iron is delivered with each treatment type.

2.1. Study Rationale

During the development of Triferic AVNU, the drug was delivered using the on-machine syringe pump programmed to deliver the volume of the ampule (4.5 mL) over 3 hours. Some dialysis machines do not have an integral syringe pump or the pumps are used to deliver a constant infusion of heparin. This study is designed to investigate the use of an independent spring driven syringe pump to deliver the dose of Triferic AVNU into the pre-dialyzer and post-dialyzer blood line.

2.2. Background

Triferic (Ferric Pyrophosphate Citrate) is a novel iron replacement product indicated to maintain hemoglobin concentrations in patients receiving chronic hemodialysis. Triferic in conjunction with erythropoiesis stimulating agents maintains hemoglobin by delivering the quantity of iron lost, on-average, during a hemodialysis session. Triferic delivers 100% bioavailable iron by donating its complexed iron directly to transferrin upon infusion to the blood compartment. Triferic administers approximately 6.5 mg of iron (III) with each treatment. Triferic AVNU is the intravenous presentation of Triferic. Triferic AVNU was approved in March 2020 based on a clinical equivalence study demonstrating delivery of iron intravenously matching the delivery of iron from the dialysate.

2.3. Benefit/Risk Assessment

- Triferic is approved as an iron replacement product to maintain hemoglobin and iron stores in patients receiving chronic hemodialysis when administered via the dialysate. Triferic AVNU is the intravenous presentation of Triferic and was approved by establishing that Triferic AVNU administered the same quantity or iron as the dialysate treatments. Triferic AVNU can be administered as a slow infusion over 3 to 4 hours into the pre-dialyzer or post-dialyzer blood line.
- The safety profiles of Triferic and Triferic AVNU are similar to placebo. Full prescribing information is included in the approved product labeling for both products. There are no contraindications to the use of Triferic or Triferic AVNU.
- The Freedom Edge Pump is approved for the infusion of prescribed liquid medicines. It is self-contained and can administer liquid medicines at a constant infusion rate which is determined by the flow restrictor tubing. The Freedom Edge pump is approved in the US.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of Triferic and Triferic AVNU may be found in the Package Insert (Section 9). Information and instructions for use for the Freedom Edge Pump are (IDFU) can be found in the instruction brochure (Section 10) and online at https://www.korumedical.com/products/freedomedge.

2.3.1. Benefit Assessment

Objectives for this study are to establish the ability of the Freedom Edge Pump to deliver the dose of Triferic AVNU over a period of 2 to 3 hours as a continuous infusion.

All products are approved for use in the USA

The benefits of using Triferic AVNU with the Freedom pump is to provide a maintenance dose of iron primarily in patients who dialyze on machines that use solid bicarbonate.

This study will confirm the safety of Triferic AVNU administered as a continuous infusion using the Freedom Edge pump.

2.3.2. Overall Benefit: Risk Conclusion

The benefit of this study will be to demonstrate an alternate means to dose Triferic AVNU to patients on chronic hemodialysis. Currently, the product labeling for Triferic AVNU indicates that the product is to be infused over 3 to 4 hours. In the studies leading to the approval of Triferic AVNU, on-machine syringe pump was used to control the rate of administration. Using the Freedom Edge pump, will provide a means of administration to patients whose HD machine does not have a syringe pump, or the pump is otherwise used for administration of heparin.

The risks to patients are minimal. The main risk identified is the inability to deliver the entire dose of Triferic AVNU over the 2 to 3-hour duration. The consequences of a missed dose of Triferic AVNU are minimal since only small quantities of iron are administered at each HD. Should the iron dose not be administered, patients can receive their usual dose of macromolecular iron at the next scheduled administration time.

3. Objectives

- Investigate the administration of Triferic AVNU by means of the Freedom Edge Pump
- Validate the administration rates int the pre- and post-dialyzer blood lines when using the 2 mL/hr line set.
- Investigate the maximum serum iron and TSAT concentrations.
- Investigate the useability of the Freedom Edge Pump in the setting of a dialysis unit to administer Triferic AVNU IV.

Table 2: Objectives and Estimands.

Objectives	Estimands
Primary	
• **Time for complete infusion of 4.5 mL Triferic AVNU pre-Dialyzer and post-Dialyzer**	• **At 2 mL/hr infusion rate total volume to be delivered at 2.25 ± 0.3 hr**
Secondary	
• Mean Δ sFe pre-Dialyzer and post-dialyzer	• Mean ΔsFe pre-Dialyzer and post dialyzer are equal ± 15%
• Mean TSAT Max pre-Dialyzer and post-Dialyzer	• TSAT max does not exceed 100%
Safety	•
• Adverse Events	• Number of adverse events overall • Number of adverse events related to device

4. Study Design

4.1. Overall Design

- Single site open-label repeated crossover.
- 10 subjects on chronic HD
- 3 doses of Triferic AVNU administered via Freedom Edge pump into the pre-dialyzer blood line
- 3 doses of Triferic AVNU administered via Freedom Edge pump into the post-dialyzer blood line
- Pre-dialysis and End-of-Infusion serum iron profiles at each
- Adverse events reported during each HD.
- Device issues reported with each HD.

4.2. Scientific Rationale for Study Design

- All products and devices are approved and used according to their labeling
- This study will confirm the utility of the Freedom Edge pump to administer intravenous medications during a hemodialysis session.

4.3. Justification for Dose

- The dose of Triferic AVNU (6.75 mg Fe) is the approved adult dose.
- The Freedom Edge pump is calibrated to deliver medications at various rates and is approved for such administrations.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all study visits.

4.5. Study Population

Adult age >18 years receiving chronic hemodialysis 3X/week.

4.6. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must be 18 years of age inclusive, at the time of signing the informed consent.
2. Receiving chronic hemodialysis for 3-4 hours each session 3x/week.
3. Medically stable according to the investigator opinion
4. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

4.7. Exclusion Criteria

1. Hemodynamically unstable during hemodialysis
2. Evidence of active bleeding from the GI tract.

5. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

5.1. Study Intervention(s) Administered

ARM Name	Pre-Dialyzer Infusion and Post-Dialyzer infusion
Intervention Name	FPC 6.75 mg Fe/4.5 mL pre-dialyzer blood line infusion
Type	Drug / Device
Dose Formulation	Solution
Unit Dose Strength(s)	6.75 mg Fe/4.5 mL
Dosage Level(s)	6.75 mg IV/HD
Route of Administration	IV Infusion
Use	Feasibility of administration with Freedom Edge pump
IMP and NIMP	Triferic AVNU
Sourcing	Triferic AVNU Provided by Rockwell Medical Inc. Freedom Edge pump provided by Koru Medical
Packaging and Labeling	Study Intervention will be provided in pouches. Each pouch is labeled as required for the approved product

5.1.1. Medical Devices

1. The medical device provided for use in this study are Freedom Edge pump manufactured by Koru Medical Systems, Chester NY 10918 USA.
2. Instructions for medical device use are provided in the instruction manual shipped with the device.
3. Precision flow rate tubing sets for administration rate of 2 mL/hour will be provided by the manufacturer RMS Medical Products Chester NY 10918.
4. Instructions for connecting the tubing to the syringe and the Freedom Edge pump are provided in Section 10

5. All device deficiencies (including malfunction, use error and inadequate labelling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 7.3.7) and appropriately managed by the sponsor.

5.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants who have signed an informed consent may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

5.3. Measures to Minimize Bias: Randomization and Blinding

Open-label, No blinding at site level	This is an open-label study

5.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

A record of the quantity of Triferic AVNU and the duration of infusion administered to each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

5.5. Dose Modification

No dose modifications are allowed, if a subject does not tolerate the dose, they will be discontinued from the study.

5.5.1. Retreatment Criteria

All participants entered in the study will be treated at HD # 1 to 6. Throughout the study, study intervention will be open label.

5.6. Continued Access to Study Intervention after the End of the Study

At the end of this study, subjects may continue to receive Triferic AVNU via the Freedom Edge pump at the discretion of the Investigator. Triferic AVNU will be provided by the Sponsor (Rockwell Medical Inc) until such time as the product becomes commercially available.

6. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

6.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to discontinue study intervention. If study intervention is discontinued, the participant will not remain in the study. See the schedule of events for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

6.1.1. Temporary Discontinuation

Should a subject develop symptoms of intolerability, the infusion should be immediately stopped, and a serum sample should be obtained for iron profile. The event should be reported as an adverse event. If the adverse event is mild to moderate in severity and recovery has occurred, the patient may be rechallenged at the next HD treatment

6.1.2. Rechallenge

If the adverse event leading to temporary discontinuation is mild to moderate in severity and required no intervention, the subject may be rechallenged at the next HD treatment. If the event recurs, the subject must be permanently discontinued form the study.

6.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoE. See SoE for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.3. Lost to Follow up

Not applicable for this study

7. Study Assessments and Procedures

- Study procedures and their timing are summarized in the Schedule of Events (SoE).
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoE, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Events.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 70 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

7.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the Schedule of Events.

7.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Events.

7.2.1. Physical Examinations

- A brief physical examination will include, at a minimum, assessments of the skin and cardiovascular system (BP heart rate).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.2.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed according to the site protocol at the start and end of each HD

7.2.3. Clinical Safety Laboratory Assessments

- See the Schedule of Events (Section 1.3) for the timing and frequency of laboratory sample collection

7.2.4. Pregnancy Testing

Female subjects of child-bearing potential should be tested if pregnancy is possible.

7.3. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 8.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the Triferic AVNU (see Section 0).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.3.

7.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the start of intervention] until the follow up visit at study termination at the time points specified in the Schedule of Events (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 7.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

7.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

7.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is provided in Section 7.3.3.

7.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with regulatory requirements relating to safety reporting to the regulatory authority and Institutional Review Boards (IRB).
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the package insert and will notify the IRB/IEC, if appropriate according to local requirements.

7.3.5. Pregnancy

- Details of all pregnancies will be collected after the start of study intervention and until delivery.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 3 days of learning of the [female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner)] pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 7.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study may request to continue in the study. Prior to continuation of study intervention following pregnancy, the following must occur:
    - The sponsor and the relevant IRB/IEC give written approval.
    - The participant gives signed informed consent.
    - The investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

7.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events (DREs) are common in participants with end-stage kidney failure on chronic hemodialysis and can be serious/life threatening:

- Myocardial Infarction
- Stroke
- Hypertension
- Intradialytic hypotension
- Vascular access clotting or failure

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of an SAE.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

7.3.7. Medical Device Deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device deficiency can be found in Section 8.4.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Section 7.3.7 of the protocol.

7.3.7.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such a deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Deficiency is provided in Section 8.4.

7.3.7.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

7.3.7.3. Prompt Reporting of Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.
- The Medical Device Deficiency Report Form will be sent to the sponsor by email or fax.
- The sponsor will be the contact for the receipt of device deficiency reports.

7.3.7.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

7.4. Pharmacokinetics

- Serum samples of approximately 4.5 mL will be collected for measurement of serum iron, TSAT, TIBC and Ferritin concentrations as specified in the Schedule of Events (Section 1.3)at the start of hemodialysis and at the end of the Triferic AVNU infusion.
- A maximum of 2 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the delivery of iron from Triferic AVNU using the Freedom Edge pump.

Pharmacodynamic parameters are not evaluated in this study.

7.5. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

7.6. Biomarkers

Biomarkers are not evaluated in this study.

7.7. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

7.8. Medical Resource Utilization

Medical Resource Utilization data, associated with medical encounters, will be collected by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- Number and duration of medical care encounters, for Triferic AVNU infusion using the Freedom Edge pump.
- Time to withdraw Triferic AVNU from ampule
- Time to set up Freedom Edge Pump
- Nursing time to monitor pump performance.

7.9. Statistical Hypotheses

7.10. Sample Size Determination

The sample size is empirical as this is a feasibility study.

7.11. Analysis Sets

Participant Analysis Set	***Description***
Safety	*All participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.*

7.12. Statistical Analyses

All parameters obtained will be presented as summary statistics. No hypothesis testing will be performed.

7.12.1. General Considerations

All data collected will be summarized.

7.12.2. Primary Endpoint(s)

The primary endpoint will be the change in serum iron concentration from pre-dialysis to the end of infusion.

7.12.3. Secondary Endpoint(s)

The secondary endpoints will be the change in serum iron transferrin saturation (TSAT) concentration form pre-dialysis to the end of infusion.

7.12.4. Safety Analysis

All safety analyses will be made on the Safety Population.

7.12.5. Other Analysis

The performance of the Freedom Edge pump will be assessed by questionnaire and time-and motion assessment.

8. Supporting Documentation and Operational Considerations

8.1. Regulatory, Ethical, and Study Oversight Considerations

8.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, [IDFU] and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

8.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

8.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants] will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant <End of common text>

8.1.4. Data Protection

- Participants will be assigned a unique identifier by the Investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.1.5. Committees Structure

There will be no additional committees for this study.

8.1.6. Dissemination of Clinical Study Data

The posting of company-sponsored study information and tabular study results on the US National Institutes of Health's website www.ClinTrials.gov and other publicly-accessible sites.

8.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 1 years after study completion unless local

regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

8.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 8.1.8.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

8.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the study start date.

Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

8.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

8.2. Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the central laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1: Protocol-Required Safety Laboratory Tests

Laboratory Tests	Parameters			
Clinical Chemistry[1]	Serum iron concentration (sFe)	TSAT	Ferritin	TIBC
Pregnancy testing	• Highly sensitive [Serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[3]			

Investigators must document their review of each laboratory safety report.

8.3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

8.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Definition of Unsolicited and Solicited AE
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a [participant/participant's parent(s)/LAR(s)] who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The [participants/ participant's parent(s)/LAR(s)] will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of [participant/ parental /LAR's] concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by [participant/participant's parent(s)/LAR(s)] will be collected during interview with the [participants/participant's parent(s)/LAR(s)] and by review of available medical records at the next visit. • Solicited AEs are predefined local [at the injection site] and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a suspected transmission of any infectious agent via an authorised medicinal product

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

8.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Rockwell Medical Inc..
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to Sponsor within 24 hours of receipt of the information.

8.3.4. Reporting of SAEs

SAE Reporting to Sponsor via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Medical monitor. • Medical Monitor: Contact Information Raymond D Pratt, MD Chief Development Officer Email: rpratt@rockwellmed.com Fax: 248 960 9119

8.4. AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this section are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 5.1.1 for the list of sponsor medical devices.

8.4.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom,

or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.

- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

8.4.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is an any serious adverse event that:

a. Led to death

b. Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
- A permanent impairment of a body structure or a body function.
- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Chronic disease (MDR 2017/745).

c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect

d. Is a suspected transmission of any infectious agent via a medicinal product

SADE definition

- A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of an SAE.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a serious adverse device effect that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 8.3.3).

8.4.3. Definition of Device Deficiency

Device Deficiency Definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

8.4.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE, and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Product Information in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by [X] to

elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

8.4.5. Reporting of SAEs

SAE Reporting to Sponsor via Paper Data Collection Tool

- Facsimile or email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.

8.4.6. Reporting of SADEs

SADE Reporting to Sponsor]

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.
- The sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting:

Raymond D Pratt, MD

Chief Development Officer

Email: rpratt@rockweellmed.com

Fax: 248 960 9119.

8.5. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [amendment number]:

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale

9. Triferic AVNU US PI

See attached US Package Insert

10. Freedom Edge Pump

See Attached Freedom Pump Document