# Superior Venous Access: Midline vs Ultrasound IVs, a Randomized Clinical Trial

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# 1 List of Abbreviations

| Abbreviation | Abbreviation definition |
|---|---|
| CVC | Central Venous Cather |
| DVA | Difficult Venous Access |
| IVA | Intravenous Access |
| USPGIV | Ultrasound Guided Peripheral Intravenous catheter |
| MC | Midline Catheter |
| RA | Research Assistant |

# 2 Protocol Summary

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| **Title:** | Superior Venous Access: Midline vs Ultrasound IVs, a Randomized Clinical Trial |
| **Population:** | Patients seen in the emergency department who meet criteria for DVA and study eligibility will be approached for enrollment by research staff. Inclusion criteria include: Expected inpatient admission for 72 hours or more, Age 18 or older, able to provide consent, English speaking, expected inpatient admission, two staff have looked for IV access or patient has history of requiring ultrasound guided IV. Exclusions: Prisoner, not suspected of having bacteremia, No phone number for follow up, Pregnancy, known to require long term IVA with a CVC or MC, no target vessel <1.6cm in depth, or do not have an upper extremity (left or right arm) that can accept a deep venous IV (example dialysis fistula in one arm and upper extremity deep venous thrombosis in the contralateral arm). Minimum sample size of 108, 54 in each study arm to be appropriately powered for this clinical question. It is likely we will need to enroll more than 108 after exclusions and randomization to ensure we obtain 54 in each arm. |
| **Intervention:** | Patients will be randomized to receive a standard UGPIV that is 4.88cm in length or a 10cm midline catheter. |
| **Objectives:** | Aim 1: To determine if UGPIVs have a higher failure rate than midline catheters within 72 hours of placement.<br>Aim 2: To perform a direct cost analysis of UGPIV against that of the midline catheter over the length of the hospitalization.<br>Aim 3: To determine experience and satisfaction with each device to determine patient preference. |
| **Design/Methodology:** | A convenience sample of patients will be randomized to one of two arms. The first arm will receive standard UGPIV. The second arm will receive a MC. Patients will be randomized based on pre-randomized patient enrollment packets. Patients will receive one of two venous access options either the UGPIV or the MC in the ED. Catheter survival will be assessed based on time to when a failed catheter is found to be dysfunctional or when a catheter is removed |

| | |
|---|---|
| | by hospital staff. Study personnel will review medical records and visit patients daily Monday to Friday to assess how the IV is working. They will check to make sure that catheters have not been removed and have not malfunctioned by speaking with the patient or hospital staff. |
| **Total Study Duration:** | Expected April 1, 2018 to June 30th, 2019 |
| **Subject Participation Duration:** | Patients will participate as long as they have a midline catheter or UGPIV in place, or are still hospitalized within 29 days of ED visit. The longest a patient should be in the study is 29 days as this is the length of time that a MC is approved to be utilized for prior to removal. |

# 3 Background/Rationale & Purpose

## 3.1 Background Information

Obtaining intravenous access (IVA) is the one of the most common procedures performed in the emergency department (ED). Placement of IVA allows for blood work, medical testing, and delivery of intravenous fluids and medications. IVA is a critical component to many ED visits and allows for the diagnosis and treatment of life threatening conditions. Despite the common placement of IVA, this routine procedure can be extremely challenging to perform in some patients. As many as 1 in 9 patients may be considered a difficult venous access (DVA) patient.[1] Patients who are unable to receive IVA with standard measures by palpation and visualization, may require a rescue procedure. We define a rescue procedure as requiring ultrasound guidance for peripheral IV, midline placement, or central venous catheter (CVC) placement.

The implementation of ultrasound guided peripheral IVs (UGPIV) have greatly reduced the need for placement of CVCs.[2] CVC placement can be a time consuming procedure that is associated with significant complications including infection, pneumothorax, or vascular injury. Although safer, UGPIVs are known to be associated with infiltration and have failure rates as high as 44%.[3] The use of midline catheters is a middle ground between UGPIV and CVCs. Midline catheters are associated with lower infection rates than CVCs, and midlines can remain in location for up to 29 days.[4] Midlines are however associated with their own complications including thrombosis, infection, and are more expensive than UGPIVs. It is however unclear if ED patients with DVA should receive an UGPIV or a midline catheter. We seek to compare the failure rates, cost, and patient preference for midline catheters against UGPIVs.
This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

## 3.2 Rationale and Purpose

At this time at BMC, patients in the Emergency Department setting who are DVA patients can receive a UGPIV to avoid placement of a CVC. One alternative that is not frequently being used for DVA patients

is a MC in an Emergency Department setting. Midline catheters are more timely to place, are costlier to place, and are intended to be used for up to 29 days prior to removal. UGPIV are intended to be used for up to 3 days and are less costly than MC, however may have a higher failure rate. There has never been a randomized study to compare the MC to the UGPIV in the same population. It will be important to determine if MC used in relation to UGPIV can survive longer, how it may impact cost, and how patients perceive the procedure in regards to preference. Because DVA patients are common in the emergency department this study has implications in how we approach vascular access for all DVA patients in the ED. Both the MC and the UGPIV are approved for use at Boston Medical Center for patient care. We will plan to compare our current practice of placing UGPIV to that of the MC.

# 4 Objectives

## 4.1 Study Objectives

Aim 1: To determine if UGPIVs have a higher failure rate than midline catheters within 72 hours of placement.

There are several reasons why UGPIVs may fail. UGPIVs are shorter than midline catheters, and shorter catheters may fail due to infiltration which can be a result of malposition as well as having the catheter pull out of the vessel. We suspect that by using a midline catheter with a guidewire for placement with additional catheter length placed into the vessel, midlines will be superior to UGPIVs with regards to survival time of the catheter.

**Hypothesis: Midline catheters have a lower failure rate at 72-hours compared to ultrasound guided peripheral IVs.**

Aim 2: To perform a direct cost analysis of UGPIV against that of the midline catheter.

This study will not be large enough to complete a robust cost effectiveness analysis to compare UGPIV to midline catheters. As a part of this study we will collect information including but not limited to: the number of catheters used for IVA attempts, time for placement of each device, complications, and need for additional IV access during hospitalization (MC, PIV, or CVC).

**Hypothesis: Midline catheters are a cost effective change in clinical practice due to lower complication rate and longer dwell times.**

Aim 3: To determine patient experience and satisfaction with each device to determine patient preference.

Our goal will be to compare UGPIV to MC for patient experience (including pain, satisfaction, and preference) based on survey.

**Hypothesis: Pain scores will be similar between the UGPIV and MC group, however patients will prefer the placement of the MC.**

### 4.1.1 Primary Outcome Measures

The primary outcome measure is survival of each venous access device. Time of device placement will be stamped based on placement of the IV at the time of the procedure on the ultrasound machine. Research assistants will daily visit patients Monday to Friday to determine if the IV are still in place and review medical records for overnights and weekends. As a part of hospital policy vascular access sites are flushed regularly to assess for failures and complications. Any removal of IVs should be documented in nursing notes. We will review these notes; however, we will also visit patients daily during the week to determine if the UGPIV or MC is still in place. If the device is removed the patient and the treating nurse will be asked to identify the cause of the failure (removal for patient preference, thrombosis, infiltration, completion of clinical care and no longer needed, etc). Data will be entered into REDCap. Data will also be written down by the physician placing the UGPIV as well as the MC. See attached. These will be REDcap forms that are printed and then later filled into the database to allow for physician ease. Time of device failure will be documented in REDCap when determined. It is possible that patients will be discharged with the device in place. If this is the case, we will review the medical record to determine when the device is expected to be removed and call the patient to determine when the device failed or was removed. It is however likely the patient will get all care delivered through BMC and we will know when the device fails or is removed due to returning for clinical care.

### 4.1.2 Secondary Outcome Measures

Secondary outcomes will be determined based on review of the clinical record and patient responses to a questionnaire. All procedures that are performed including placing an IV and removing an IV should be available to determine additional costs associated with IV access during the hospitalization.

Responses for each of the questions on the study questionnaire will be compared between the study groups. Appropriate statistical tests will be used for bivariate, categorical, or continuous variables.

## 5 Study Design

This is a convenience sample, randomized controlled trial to determine if the midline catheter is superior to the ultrasound guided IV with respect to survival at 72 hours. Folders will be sealed and pre-randomized using computer number randomization. Patients will be screened for enrollment in the emergency department. Patients will be considered eligible for enrollment if they are considered a difficult vascular access patient and are expected to require hospitalization after physician assessment. We have selected patients who are felt to require admission as the midline catheter is indented for longer dwell times and are attempted to screen for patients who are likely to require IV access for a minimum of two hospital nights. There will be two arms 1) those randomized to standard care with ultrasound guided IV, and 2) those randomized to receive a midline catheter. Data will be collected from the medical record into redcap as well as an enrollment log stored on the hospital G drive. These will be password protected. Data will also be stored on QPATH which is a secure software for storing medical imaging (ultrasound images). Data lastly recorded on paper sheets including consent forms will be stored in locked filing cabinets with only study personnel access. Data will be collected directly from the patient as well as from the medical record.

# 6 Potential Risks and Benefits

## 6.1 Risks

Regardless if patients are placed in the ultrasound guided IV or Midline catheter group they will be at risk of complications of these devices. Each device carries the risk of failure (malposition), pain, bleeding, infection, or thrombosis (a blood clot forming). Serious complications are extremely rare and are not expected to occur in this study. The most likely serious complication, blood stream infection may occur in 0.5/1000 catheter days for midline and 0.2/1000 catheter days for ultrasound guided IVs. It is possible that either device may be placed improperly or malfunction during its intend lifetime. Although it is expected that some devices will fail during this study it is not considered a serious complication. If a device malfunctions, it is possible that medical solutions or blood may collect in the arm. Under very rare occurrences (limited to case reports) this can result in damage to the tissue around the catheter, the need of a surgery, or threaten the survival of the limb. In order to ensure the midline catheter does not enter into the axillary vein physicians will be trained to measure from the axilla to the target location. Each device is 10cm and there is a tape measure that will be used to ensure the procedure location is at least 10cm from the axillary vein. It is possible if measured incorrectly this could result in the midline catheter extending into the axillary vein. Despite the risks listed, both devices are routinely used as a part of medical care safely and it is extremely rare to have a serious adverse event from either device.

It is mostly likely that if either device fails additional venous access may be required for medical care. If this occurs, it will be up to the medical team to determine which is the best option. One particular benefit of the midline catheter is that it may remain in use for up to 29 days while the ultrasound guided IV is used until there are signs and symptoms of phlebitis (warmth, tenderness, erythema, and or palpable cord), infiltration or a malfunctioning catheter. The site assessment guides the need for PIV replacement. The average ultrasound guided IV generally does not typically last longer than 3 to 4 days. Given the midline catheter may remain in place longer, it may be at slightly higher risk of having a clot form or developing an infection. If a clot or infection develops and is not identified and/or if left untreated it can be life threatening. In order to reduce these risks, we will follow our hospital guidelines for placement and monitoring of catheters. If any complication occurs, either the patient or their insurance will be responsible for any cost associated with a complication of the device.

Risks will be reduced by following hospital guidelines for the monitoring and care of venous access devices. There is also the risk of loss of confidentially as covered in the consent form.

## 6.2 Potential Benefits

The benefits of being in this study may be having a midline catheter placed if randomized to that study arm. The benefit of this device is that it may remain in place for up to 29 days for medical use. Patients who are randomized to this device will not be billed for its placement. If they are randomized to the standard ultrasound IV group, they will receive routine care. Being in the study may help the investigators learn whether midline catheters should be used routinely in place of ultrasound guided IVs.

### 6.3 Analysis of Risks in Relation to Benefits

Both MC as well as UGPIV are currently standardly incorporated during clinical care at Boston Medical Center. The risk to the patients are low considering these devices are currently being used for routine clinical care. Both are considered so low risk that only verbal consent is required prior to placing these devices. We will express to the patient the difference in complication rates are unknown and they could experience thrombosis, associated infection, infiltration, or failure for another reason in either study group. Specifically, since MC and UGPIV are being placed in the emergency department the patient maybe at higher risk for complication. Each device has its own associated pros and cons which is why we are performing this study to compare the two devices head to head in a single patient population. The benefit is that by comparing these devices we hope to compare failure rates, associated costs, and patient preferences to help guide future IV access for patients.

## 7 Study Subject Selection

### 7.1 Subject Inclusion Criteria

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

Patients will be screened for enrollment by the study team. The procedure resident will contact the study team by pager when a patient requires ultrasound guided IV access. It will be expected that at least two ED staff who are qualified to place a standard peripheral IV will have attempted to place vascular access prior to attempting an ultrasound guided rescue procedure. Attempted is defined as applying a tourniquet and searching for a target vessel. If no target vessel can be identified this will still count as an attempt by one staff. We have chosen not to require a minimum number of needle sticks before considering the need for ultrasound guidance as there are numerous patients in our hospital system who are well known to our providers and no longer have sites for standard IV placement, specifically our sickle cell population. We feel it would be unfair to require a set number of needle sticks when there is no reasonable expectation of success for placement of standard peripheral IV. Specifically, patients will be eligible as a difficult vascular access patient if they meet either 1) previous history of difficult vascular access requiring ultrasound guidance for IV placement or 2) have had at least two staff apply a tourniquet and search for a target vessel.

For inclusion, the general impression is that the patient will require admission, and that ED staff are unable to obtain standard peripheral IV access. We have chosen to select patients who have an impression of requiring admission to maximize the dwell time being studied. Patients will be eligible if standard IVA cannot be obtained by two qualified ER staff, and are age 18 or over. Additionally, for consent purposes the patient must speak English and be able to provide informed consent.

### 7.2 Subject Exclusion Criteria

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

Patients will be excluded from enrollment if they are prisoners, non-English speaking, known allergy to the materials used, device cannot be stabilized due to tissue or treatments, are deemed not to have capacity for informed consent, cannot provide a phone number for follow up, or do not have an upper extremity (left or right arm) that can accept a deep venous IV (example dialysis fistula in one arm and upper extremity deep venous thrombosis in the contralateral arm). We will exclude patients who are not able to consent in English as study investigators are not bilingual and unable to consent in languages other than English. Patients will be excluded if they are expected to require medication that is not approved for administration via a peripherally guided IV or midline as defined by hospital pharmacy guidelines. Patients will also be excluded if they are known to require long term access that a midline could provide. Patients will be excluded if they are known to have bacteremia or have a high suspicion of bacteremia, as we do not want to seed the midline catheter and potentially prolong the need for antibiotics. We will exclude patients with veins that are found to be greater than 1.6cm in depth (patient's body insufficient to accommodate implanted device) due to UGPIV catheters being too short. Pregnant women will be excluded as it is known that during pregnancy risk of clotting increases (documented in screening form), and we wish to avoid this with the placement of the MC. If patient does not have a vessel <1.6cm in depth in a location appropriate for a UGPIV or MC, the patient will not be eligible for enrollment and UGPIV may be placed in any location available as is already the standard of care. If UGPIV cannot successfully be placed despite all attempts and the only other option is a CVC, if study personnel are available a MC maybe placed, but will be billed to the patient at the discretion of the treating attending physician.

## 8 Study Intervention

Patients will be randomized to receive one to two devices:

Ultrasound Guided Peripheral IV: Boston Medical Center currently uses a BD Insyte Autoguard 1.88in 18-guage needle with self-retraction. Our protocol will not allow for attempting any vessel greater than 1.6cm from the skin surface for placement. The UGPIV will be placed with a Tegaderm over the probe for cleanliness. We will use sterile gel applied to the skin after a target vessel is identified. Once the vein is identified standard hospital gloves will be worn for safety and to avoid infection. Once the target vessel is identified an ultrasound image of the vessel will be captured and recorded with the patient's study ID number to allow for vessel depth and size to be measured. For both UGPIV and midline placement, operators will be instructed to attempt placement with short-axis out-of-plane technique, visualize the "vanishing target sign," and confirm catheter placement once deployed with long-axis in-plane view.[10]

BARD Powerglide Pro Midline: Boston Medical Center is currently approved and using an 18-gauge midline catheter. This midline catheter is unique in that it is a standard 10cm and does not require premeasurement or trimming of the catheter prior to placement. The physician will have measured from the axillary vein to the target needle entry location to ensure the catheter does not enter into the axillary vein. Additionally, because it is only 10cm it does not require a

confirmatory chest x-ray or EKG waveform confirmation prior to usage. The physician will wear sterile gloves, gown, mask, and cap. The patient will be prepped with cholrhexidine, and as with the UGPIV, a tourniquet will be applied to the arm to increase the vessel size. The patient will be covered with a sterile drape that comes in the midline bundle set. A sterile probe cover will be applied to the ultrasound probe and be placed onto the sterile drape. Once the target vessel is identified, an ultrasound image of the vessel will be captured and recorded with the patient's study ID number from the randomization packet to allow for vessel depth and size to be measured. The vessel will then be selected and the needle will be guided by ultrasound until venous flash is obtained. The guidewire will be advanced and then using a seldinger technique the catheter advanced into the vessel. The catheter placement will then be confirmed with a long axis view of the catheter in the vessel. The catheter will then be secured in place and a Tegaderm will be placed over the entire midline insertion site to prevent infection.

BD Insyte Autoguard will be purchased by the hospital as already done without any changes in protocol. If patients are randomized to the UGPIV arm, the will be treated as receiving standard of care and will be billed as would otherwise be the case. These devices will be stored as already done within locked drawers in the IV carts in the emergency department.

BARD Powerglide Pro Midline; Bard will supply the training devices free of charge. This will include each provider placing 5 midline catheters for training purposes on phantom models. If patients are randomized they will not be charged for the MC placement. It is already hospital operating procedures not to bill for this procedure. MC will be stored in the charge nurse office to avoid them being stolen or used for non-study patients.

Both study groups will be responsible for any complications that occur. Because MC and UGPIV are already placed for clinical care the number of complications that are expected are low as they are considered already a safe and acceptable form of patient care.

Patients will also compete a few questions as a part of a survey to determine patient preferences with each device. The survey will be administered by physicians at the time of placement.

## 9 Study Procedures

The only study visit will be the ED visit and hospitalization associated with this visit. Patient contact information including phone number and address will be obtained. The length of the study may last up to 1 month in duration.

All patients who are determined to have DVA and require UGPIV have the "procedure resident" paged to perform the study. The procedure resident will be notified when study personnel are available to consent and perform the study measures. Patients will be approached by RAs or study staff to obtain consent. They will ask the nurse if at least two staff attempted to place IV access. If the patient is a known DVA patient and cannot receive standard IV access due to known history (such as sickle cell disease, or dialysis) two staff do not need to attempt IV access. Patient must be able to consent and be

have a high likelihood of expected admission based on physician evaluation. The total study duration will last as long as the patient has an MC or PGIV in place and are hospitalized up to 29 days.

The patient will be consented by RAs or study staff physicians. Patients will be randomized based on packet assignment. Packets will contain a preassigned randomized piece of paper which will determine which device will be used. Patients may withdraw themselves from the study at any time as is already the case for clinical care by requesting their MC or UGPIV to be removed. They may also ask our staff to remove themselves from the study. Once the device is placed per hospital recommendations, the physician who placed the line will administer a brief survey to the patient regarding pain and preferences.

Research assistants will daily during the week visit patients to determine if IVs placed in the ED are still in place. Because they are RAs they will not access the failure of these devices and will require the clinical team to make these assessments based on hospital policies for daily assessments. If the patient is discharged with the midline in place, the research assistant will attempt to reach the patient by phone to determine if there are device failures or complications. They will document these within the daily assessment form used for inpatients.

# 10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

## 10.1 Definitions

The following definitions will be used in the assessment of safety:

*Adverse Event (AE)* is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

*Serious Adverse Event (SAE)* is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the 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).

*Life-threatening* means that the event places the subject at immediate risk of death from the event as it occurred.

*Unanticipated Problem* is defined as an event, experience or outcome that meets **all three** of the following criteria:

- <u>is unexpected</u>; AND

- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

*Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

*Unexpected* means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

## 10.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows: Patients will be visited daily to determine if the device placed is working. Medical records will be reviewed for off hours and weekends. Any failure or complication from the midline catheter or ultrasound guided IV will be documented within redcap. Any complication or failures will be emailed to the study investigator to review the chart and or contact the patient to severity, seriousness, relatedness, and expectedness. It is expected that both midline as well as ultrasound guided IVs will be associated with routine bleeding, pain, swelling and failure. Any complication that requires intervention by a surgical or procedural intervention will be reported. Placement of a new vascular access device will not be considered a complication. As ultrasound guided IVs as well as midline catheters are approved for use at Boston Medical Center and are considered generally safe procedures we do not expect trends that could affect subject safety.

## 10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.

- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

## 10.4 Stopping Rules

The study has no stopping rules.
There are no expected reasons a subject will be removed from the study.

It is not expected that the study will be stopped as both devices being used are currently a part of standard clinical care.

# 11 Data Handling and Record Keeping

## 11.1 Confidentiality

We will store information in ways that are secure. We will store paper files in locked filing cabinets. We will store electronic files in computer systems with password protection and encryption. All patient information will be de-identified as soon as possible with a study ID number. We do not anticipate needing to share data. We will update clinicaltrials.gov with study findings but now share individual patient data.

Patients will be enrolled using paper consent forms. Forms will be placed into locked filing cabinet in the office of the department of emergency medicine. Patients will be assigned a study ID at the time of enrollment to immediately de-identify all patient information as possible. Patient name, date of birth and MRN will be stored on the hospital G drive in a password protected file that only study staff have access to. The study monitor or other authorized representatives of the sponsor 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 subjects in this study. The clinical study site will permit access to such records.

## 11.2 Source Documents

Source data will include any clinical information in the medical record. Source data will also include images stored from the ultrasound guided procedures (UGPIV or MC). Source data will also include patient surveys. All source data will be stored in locked file cabinets or within electronic files stored on the hospital G drive as already done with other approved IRB study protocols.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

## 11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study and will only exist in electronic entry. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was

not asked, "N/D" will be recorded. If the item is not applicable to the individual case, "N/A" will be recorded. All entries will be entered electronically directly into REDcap. Only paper forms will be the patient consent form and physician scanning report form, and patient survey. All of these are supplemental forms.

### 11.4 Study Records Retention

Boston Medical Center requires that study records be retained for at least seven years after completion of the study. The BMC/BU Medical Campus IRB requires that documentation of informed consent of subjects be retained for at least three years after the study is closed, unless the IRB waived the requirement for informed consent or documentation of informed consent. These records will be saved in locked file cabinets or as retained in password protected files on department servers.

## 12 Statistical Plan

### 12.1 Study Hypotheses

The primary hypothesis is that midline catheters will be superior to ultrasound guided IVs with relation to survival time.

Secondary assessment will 1) attempt to prove that MC are superior to UGPIV with relation to cost effectiveness despite their overall higher upfront cost. 2) Patients will experience similar pain between MC and UGPIV, however will prefer the MC knowing the survival of the catheter is longer.

### 12.2 Sample Size Determination

Previous work suggests a failure rate of UGPIV of 40-44% and 5% for a small study of midlines placed in an ICU. We have therefore estimated a sample size based on a 25% difference in survival between midline catheter and UGPIV. **Based on a 25% difference in expected survival we will require 54 patients with a power of 0.8 and alpha of 0.05 assigned to each study arm (UGPIV and Midline).** Based on an expected 25% refusal rate and 30% of patients not being able to provide consent we will need to review and approach approximately 168 DVA patients. At BMC we place approximately 1600 ultrasound guided IVs per year making enrolling 54 in each arm highly feasible.

### 12.3 Statistical Methods

<u>Statistical analysis and study measures</u>

Catheter survival will be determined by how long an IV lasts prior to be being removed measured in hours. We will include failures if a patient accidently pulled out their access, thrombosis, infiltration or site bleeding, infection leading to removal, or there is too much pain reported resulting in removal. If it is known that a patient intentionally removes the IV or midline it will not be documented as a failure. We will report data based on a Kaplan Meir curve to

display catheter survival. We will use a t-test of means to compare failure rates between the two groups.

Direct Cost Analysis

A complete cost effectiveness analysis is beyond the scope of this proposal. We therefore wish to capture the direct costs and easily estimated costs associated with this change in practice. **We expect use of the midline catheter will be a cost effective change in practice.** Although more upfront costs, we expect that because the midline can dwell up to 29 days and is associated with fewer failures, it will be less expensive in the long run. We will obtain information from EPIC, as to whether a UGPIV or Midline fails. Nursing staff at BMC are required to file daily notes that include IV access type and location and daily events. We will have our study staff follow-up with patients or their medical teams to determine survival of the IV line if it cannot be determined from the medical record. If a failure occurs we will document the date and type of failure, i.e. thrombosis, infiltration, etc. We will then capture each additional IV that is placed and the associated billing from that procedure.

We additionally will capture the time spent placing each UGPIV in comparison to midline catheters. This will be accomplished by using the timestamp on the ultrasound at time of vessel identification, and then again at time of successful documentation of the catheter within the vessel. We will estimate for each failure of IV access a four-hour delay to have it replaced once hospitalized. Based on geographic cost, it is about $100 per hour for inpatient hospitalization in Massachusetts. We additionally estimate the cost for staffing to be $100 to replace a midline or UGPIV. We anticipate approximately a 5% failure in the midline group and 40% failure in the UGPIV group. We anticipate all midline failures will require repeat midline or CVC placement. We anticipate 10% of UGPIV will go on to get a CVC due to medical needs. We additionally estimate 33% of patients in the UGPIV group will require replacement during hospitalization. We anticipate one patient in the UGPIV to get a CVC and have a complication. CVC complications are reported to cost $15,000 to $50,000, however we will estimate a $30,000 cost for each complication (example pneumothorax or line infection).[12]

Cost Estimate for 54 patients in UGPIV group:
54 initial UGPIV placements (54 x $371): Projected outcomes: 5 patients progress to needing CVC (5 x $1338), 17 subsequent failures getting repeat UGPIV (17 x $371), 22 total failures at $500 in estimated cost from delays in care and staffing (22 x $500), 18 patients require additional access past 72-hour dwell time limit and get repeat UGPIV (18 x $371). One CVC complication in the group of 54 patients: (1 x 30,000). = **Total Estimate: $80,709**

Cost Estimate for 54 patients in Midline group:
54 initial midline placements (54 x $1338), 3 failures with replacement cost and staffing and hospital delays (3 x $1338 & 3 x 500), No complications expected or need for CVC. **Total Estimate: $77,766**

We have projected a slight decrease in cost for midline placement at $77,766 vs $80,807 for 54 patients in this study. Based on these values with a power of 0.8 and alpha of 0.05 using a two

tailed t-test for independent means to predict a sample size with a SD of $3,000 we will need to enroll 34 patients to adequately power our cost comparison group.

Aim 3: We will compare patient survey responses based on descriptive statistics, chi-square tests, or t tests as appropriate.

## 13 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

## 14 Literature References

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## 15 Appendix

Schedule of Events:

ER Procedure Resident Paged for Difficult Vascular Access Patient During Study Hours by Medical Teams

Patient screened for eligibility based on medical record review, discussion with medical team, and patient (screening form)

Study staff obtains informed written consent

Study packet opened and patient randomized to midline catheter or standard Ultrasound Guided IV

Study personnel places midline catheter or ultrasound guided IV based on hospital policy using appropriate techniques. Study member records image with depth measurement of patient's target vessel on ultrasound machine which then will transfer to QPATH.

Procedure documented in EPIC. If Midline placed, Midline RN care order placed by MD.

Patient completes survey about pain administered by physician and preferences after midline catheter or ultrasound guided IV

Study staff review medical record and put information into REDCap for clinical data (demographics)

Study staff put information into REDCap for patient survey

Study staff visit patient during the week, and for weekend and off hours review medical record for complications or failures of devices.

If patent is discharged without information, the patients' medical team or patient may be contacted to obtain full information regarding failure of the devices.

If a patient is discharged with a device in place for clinical use the patient will be contacted by phone after discharge to determine how the device performed after discharge. The patient will be contacted by the research assistant in the event the patient is discharged to determine if there have been any complications of failures. They will use the same data collection tool for inpatients.