Study Protocol and Statistical Analysis Plan

Study title: Standard vs Long IV Catheter Long-Term IV Survival Comparison

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Catheter length and IV Survival: Standard vs Long IV Catheter Long-Term IV Survival Comparison

Background/Scientific Rationale:

Patients with poor intravenous (IV) access present a daily challenge to emergency department (ED) practitioners. Placement of an ultrasound (US)-guided peripheral IV catheter in this patient population is a viable and safe option. Successful cannulation with US-guided IV occurs in more than 90% of cases compared with 25-35% with traditional IV placement in patients with difficult vascular access.[1-3] Once cannulated, however, the failure rate of IV catheters placed under ultrasound guidance is concerning compared with traditional blind IV placement. Overall failure rates after successful IV cannulation for US-guided IVs is 45-56% when compared to traditional IV placement which is 19-25%.[4-8]

Nearly all hospitalized patients need IV access for treatment. If access is lost, patients may experience treatment delays, dissatisfaction from repeat needle-sticks, and health complications if the patient's condition becomes critical. IV failure can result in a number of negative outcomes including interrupted medical therapy; painful phlebitis and reinsertions; increased hospital length of stay, morbidity and mortality from infections and/or skin necrosis from caustic medication infiltration; utilization of invasive procedures such as peripherally inserted central catheters (PICC) and central lines; and wasted medical/nursing time.[9]

Ultrasound-guided IVs are often the last recourse for IV access before resorting to more invasive procedures in patients with difficult access. Because failure rate is high, it is important to approach insertions methodically to improve survival rates. There are several characteristics of US-guided IV placement that have shown to increase catheter survival. Anatomic variations shown to increase US-guided IV longevity include placing catheters more distally in the arms and in veins that are shallow.[10] Another study determined that using a catheter over a guide-wire improves catheter longevity.[7] However, these catheters are costly, are not readily available within most EDs, and may require sterile technique.

A variable that may alter the survival of US-guided IVs that has not been studied extensively is the length of catheter that resides in the vein. Currently the general accepted rule is that an "adequate" amount of the catheter should be in the vein to avoid failure of the catheter.[11-14] However, this recommendation is only anecdotal and there has been no study to verify or quantify it. Our preliminary data focused on defining this relationship. In our study, **100% of catheters failed** in which less than 30% of the catheter was placed within the vein and **no failures** in those IVs in which at least 65% of the catheter was in the vein. All catheters in this analysis were commonly available 4.78 cm IVs. A key challenge for inserters is that achieving this quantity of catheter length in vein is impractical at the recommended angle of insertion when considering deeper target vessels. For many institutions, including ours, the 4.78 option is the longest stocked IV catheter and catheter survival is negatively impacted.

Central Hypothesis/Objectives:

We hypothesize that using an Ultra Long IV (6.35 cm) catheter increases the likelihood of ensuring a higher quantity of the catheter in the vessel lumen and leads to improved catheter longevity.

Primary Objective: Compare the IV survival between the Ultra Long IV (UL IV) (6.35 cm/20G) and the Standard Long IV (SL IV) (4.78 cm/20G) placed under US-guidance.

Function is defined as ability of catheter to flush 5 mL without resistance with or without blood sampling.

Secondary/Tertiary Objective(s):

Determine catheter survival based on vein depth.

Determine optimal cutoff length of catheter in vein for best survival profile.

Determine catheter survival based on angle of insertion.

Quantify specific etiologies related to premature catheter failure comparing UL IV to the SL IV.

Quantify overall costs associated with placement of the UL IV compared to the SL IV.

Determine overall success of placement UL IV versus SL IV.

Determine first-stick success UL IV compared to SLIV.

Determine number of attempts and time to insertion comparing UL IV to SL IV.

Safety Endpoint(s):

Compare phlebitis and thrombosis complication rates between the Ultra Long IV and the Standard Long IV.

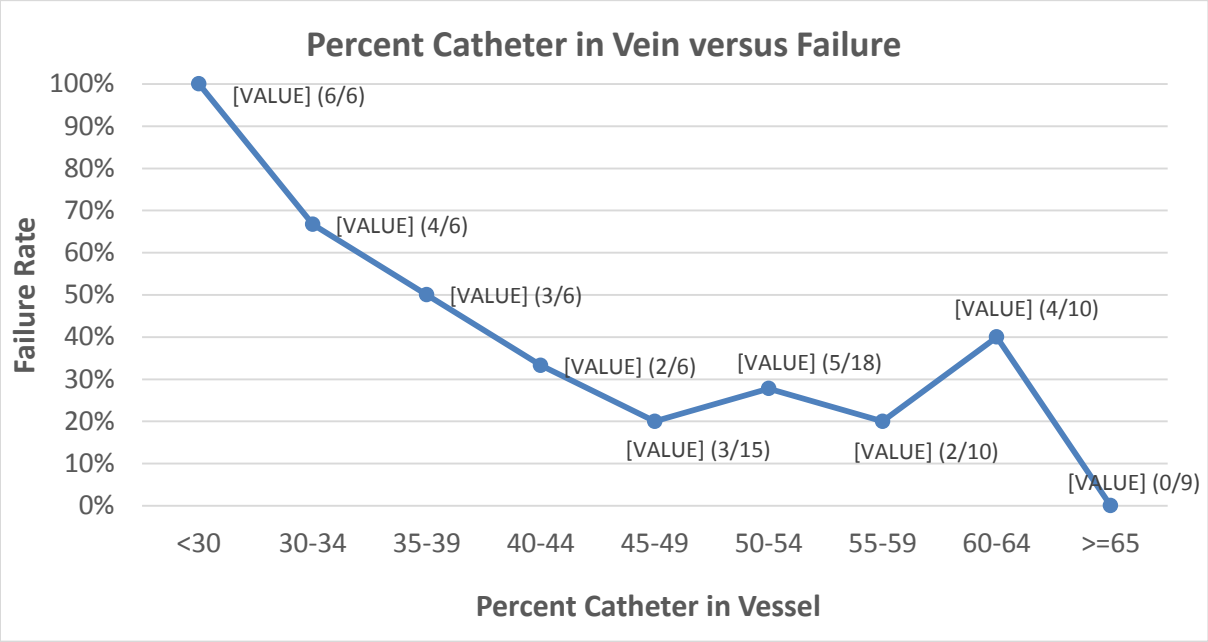
Compare infection rates for all catheters.

Study Design:

We propose a prospective, single-site, parallel, two-arm randomized investigation of catheter survival when two catheter lengths are evaluated. Specifically, experimental ultra long IV (6.35 cm/20G) will be compared with conventional standard long IV (4.78 cm/20G). The primary objective of this study is to demonstrate that there is better IV survival when the quantity of catheter residing in the vein is enhanced. Patients with functional catheters less than 24 hours duration and discharged will be excluded from the survival analysis. Exploratory secondary and tertiary objectives and adjusted multivariable analyses on the primary objective will also be conducted.

Preliminary Data:

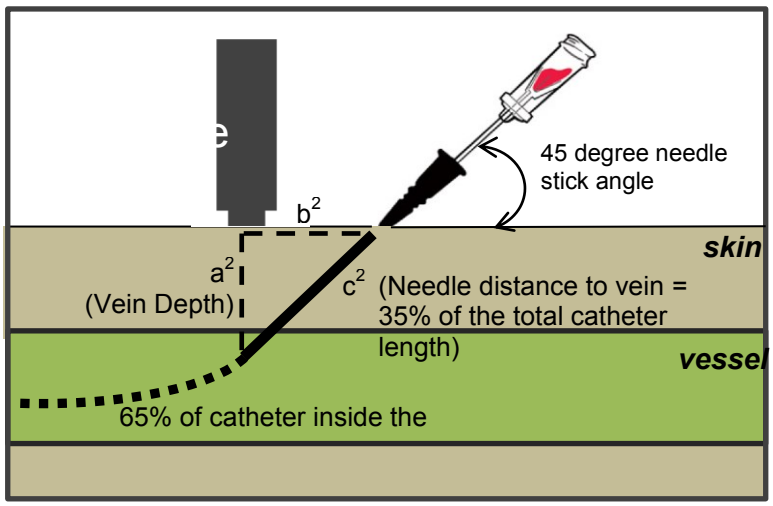
We prospectively enrolled 86 patients in our study and performed IV assessment after IV placement and within 24 hours, 48 hours, and 72 hours from time of IV placement to assess for functionality. The graph below highlights percent of the catheter in the vein as it relates to IV failure.



The table below highlights key study findings of statistical significance.

Percent catheter in vein versus longevity	**IV Functional N=57**	**IV Failed N=29**	**p-value**
Percent catheter in vein	**Survival**	**Failure**	
<30%	**0/6 (0%)**	**6/6 (100%)**	<0.0002
30-64%	48/71(67.6%)	23/71(32.3%)	
≥65%	**9/9 (100%)**	**0/9 (0%)**	

In our pilot study, **100% of catheters failed** in which less than 30% of the catheter was placed within the vein and **no catheters failed** in those IVs in which at least 65% or 3.1 cm of the catheter was in the vein. It is therefore our goal to place at least 3.1 cm of the catheter in the vessel lumen. To accomplish this task, a calculation can be performed to determine the minimum total catheter length that should be utilized to cannulate a vein at a specific depth. The figure below illustrates this calculation, which is based on the Pythagorean theorem. Given that the depth of the vein is a known variable, it is possible to determine the appropriate total catheter length required prior to starting the procedure to ensure that at least 3.1 cm of the catheter can be placed inside the vein. Based on this hypothetical model, it is possible to achieve the target catheter in vein length for depths less than or equal to 1.20 cm using the 4.78 cm option. Any depth greater than 1.20 cm would require a longer catheter. A key assumption is that inserters approach the target vein with a 45 degrees angle of insertion.



Study Population and Eligibility:

Subjects will consist of a convenience sample of emergency department patients that require US-guided IV access. Eligible patients must be greater than 18 years old, and be self-identified as a difficult stick. The patient must also recount a prior emergency room visit or hospitalization in which more than 2 attempts were required to obtain access, have a history of a rescue catheter as the result of an inability to obtain a peripheral IV, or have one of the following conditions: end-stage renal disease on hemodialysis, IV drug abuse, or sickle cell disease.

Patients are excluded if they do not meet inclusion criteria, have participated in the study prior, have already undergone an attempt at vascular access or if the enrollment process has the potential to delay their care. Study participation is voluntary and written informed consent will be obtained. See Appendix A for Eligibility Checklist.

Numerous emergency room staff members are proficient in placing ultrasound-guided IVs. This includes physicians, nurses, and technicians. Staff will be enlisted on a voluntary basis to perform insertions on a voluntary basis.

Study Procedure:

Initial Assessment

Post-consent, eligible patients will be randomly allocated to the experimental group (forearm) or the control group (upper arm) in a ratio of 1:1 via a computer-generated randomization schedule. Research staff at the Department of Biostatistics will perform concealed immediate assignment by following a block scheme. Sealed envelopes containing the randomized IV access arm will be revealed at the bedside.

After patient enrollment, the insertion nurse or physician is engaged to perform the procedure. Only providers that are credentialed in ultrasound-guided vascular access will place catheters in study subjects. Vessel depth and diameter are measured by research staff and images are saved and archived for review by the Emergency Ultrasound Director. Vessel depth is measured on the ultrasound unit from the point of contact to the middle of the vein. All catheters are 20 gauge in diameter. The research staff will direct the inserter to choose the basilic, cephalic or brachial vein at least 2 cm above the antecubital fossa. If the patient is randomized to the control group, the inserter will place the Standard Long 4.78 cm catheter. If the patient is randomized to the experimental group, the inserter will place the Ultra Long 6.35 cm IV.

Staff members are expected to attempt a minimum of 3 attempts before enlisting another provider for help. A functional IV is confirmed by extraction of 5 mL of nonpulsatile blood and low-resistance infusion of a 5 mL normal saline flush without evidence of extravasation. Other data variables collected include: inserter details, need for rescue inserter, patient pertinent medical history, vitals, age, sex, first-stick success, cannulation success or failure, vein diameter, catheter in vein longitudinal measurement, angle of insertion, number of venous access attempts, time of IV insertion, time to IV insertion, location of IV insertion, distance of IV insertion from the antecubital fossa, medications infused, ionic contrast injection for computed tomography. A venous access attempt is defined as each time the needle punctures the skin. Once the IV is secured, research staff will measure distance from the puncture or catheter insertion site to the antecubital fossa to quantify the site to antecubital measurement. See Appendix B for Data Collection Tool for insertion-related variables.

Follow-up Assessment

After initial assessment, the catheter will be assessed by the research team every 24 hours as long as the patient is hospitalized. At each follow up interval the researcher notes the date/time of evaluation and assesses for any signs and symptoms of complications and functionality of the device. A catheter is functional if the IV flushes without resistance. Catheters will be assessed daily for signs and symptoms of complications. See Appendix C for details regarding the assessment for functionality and complications. Any signs or symptoms of complications or lack of functionality will be reported to the patient's primary care team so that management of the IV catheter can be addressed.

If the catheter was identified to have any signs or symptoms of complications during follow-up assessment the date and time of observation of the complication will be documented in the data collection tool and the primary team will be notified of the complication. If the catheter was removed prior to the follow-up assessment then the IV removal time and the reason for removal will be obtained through chart review. For all catheters removed due to a complication, re-insertion attempt data will be tracked through the medical record in the nursing section for venous lines and need for reinsertion of the IV or escalation to a midline, PICC, or CVC will be noted. If the patient is discharged prior to the time of follow-up assessment then the time of discharge will be documented and the IV will be presumed functional until time of discharge unless otherwise noted in the chart.

The medication administration record will be queried for all medications given through each catheter. Vesicants/irritants that are generally given via central line or considered caustic to the vessel will be noted in both groups. Number of doses will be recorded. See Appendix D for full list of non-neoplastic vesicants/irritants.

Additional data gathered by research staff on follow-up evaluation includes: dwell time in days/hours, hospital length of stay, and number of peripheral IVs or rescue catheters for duration of stay.

Appendix E represents the data collection documentation tool for all medications.

SVT and DVT rates will be calculated based on upper extremity proven diagnosis of SVT and/or DVT in symptomatic cases. Researchers will review all study subject records in EPIC and screen for all upper extremity venous Doppler examinations. Radiology interpretations will be reviewed for findings of consistent with thrombus. This review will occur thirty days post patient discharge.

Infection rate will be tracked using confirmed blood stream infection data from epidemiology. These are cases in which line sepsis or bacteremia is confirmed by positive blood cultures.

Cost difference between approaches will be tracked. Equipment costs and personnel costs will be tracked. Number and type of IV catheters inserted/attempted will be extracted from the medical record. Supply costs will be estimated based on number of IVs attempted. Median time to successful catheter placement will serve as a baseline for estimating time needed for future reinsertions. Time will be assigned a monetary value. We will also track the number of patients from each group that require a PICC or CVC as a rescue catheter.

Sample Size and Power Analysis:

For this randomly allocated two-groups experiment, the primary outcome is catheter survival. Sample size calculation is based on primary outcome: composite or all cause premature removal due to complication of the IV catheter. Based on literatures and a new published article immediately prior to study period, we estimate sample size using the median survival time 30 hours for the 4.78 cm standard IV option. 91 subjects per group for a total sample size of 182 subjects is the minimum recommendation assuming a 10% dropout rate. This calculation

achieves power of 80% to detect a hazard ratio of 0.63 or less for line failure of the 6.35 cm ultra long IV based on log-rank test.

Statistical Analysis:

Characteristics of enrolled and eligible patients will be summarized between two arms using means [standard deviations] and medians [interquartile ranges] compared by t-tests or Wilcoxon tests for continuous variables and frequencies (percentages) compared by chi-squared tests or Fisher's exact tests for categorical variables.

Survival analysis methods (Kaplan-Meier curves, the log-rank test for continuous failure times or logistic model for discrete failure times) will be used for analyzing times to IV failure with non-failure times treated as censored. Proportions of SVT, DVT and catheter infection rates will be reported separately for each arm. Nonparametric summaries and a Wilcoxon Rank sum test will be used for the cost data. To test the effect of catheter variables on survival, we will further use Cox proportional hazard regression models for time-to-event outcomes and logistic regression models for binary outcomes. P-values of less than 0.05 will be considered statistically significant. Analysis will be conducted using SAS 9.4.

Study Site:

William Beaumont Hospital, Royal Oak (RO) campus is the proposed site for the investigation. It is a 1,100 bed major academic and referral center with Level 1 adult trauma and Level 2 pediatric trauma status. A major teaching facility, Beaumont, Royal Oak has 55 residency and fellowship programs with 454 residents and fellows. Beaumont is the exclusive clinical partner for the Oakland University William Beaumont School of Medicine. The Beaumont Research Institute was established more than 30 year ago at Royal Oak and offers research support services to clinical investigators.

The Royal Oak (RO) Emergency Center (EC) has the resources available to complete this project. This site is a tertiary care, level I trauma center with an annual ED census greater than 130,000 visits. I collaborated with nursing leadership in 2015 and implemented an ancillary staff-training program for placing US-guided IVs. Nearly forty ancillary staff members are certified in this procedure. Further, weekly logs of IVs placed under US-guidance show that an average of 10 US-guided IVs are placed daily. The RO EC has 130,000 annual visits of which many patients have difficult access. We also have 11 portable US machines with high frequency linear transducers that are ideal for vascular imaging.

Beaumont Health is Michigan's largest health care system and is the most preferred for health care in the tri-county area, according to National Research Corporation survey data. A not-for-profit organization, it was formed in 2014 by Beaumont Health System, Botsford Hospital and Oakwood Healthcare to provide patients with the benefit of greater access to extraordinary, compassionate care, no matter where they live in Southeast Michigan. Beaumont Health has total net revenue of $4.5 billion and consists of eight hospitals with 3,429 beds, 187 outpatient sites,

nearly 5,000 physicians, 38,000 employees and 3,500 volunteers. In 2017, Beaumont Health had 175,700 inpatient discharges, 17,800 births and 575,000 emergency visits.

Potential Impact:

Optimization of peripheral vascular care is a critical strategy to improve patient outcomes and reduce health care costs. Enhanced dwell times will lead to improved patient/staff satisfaction, decreased interruptions in care with shorter hospital length of stay, and decrease in complications such as thrombosis, bleeding, and infection. Over 2 billion IV catheters are used worldwide annually with less than one-third of catheters actually ending up in a patient. No other industry would accept this degree of failure in its most essential and necessary process to deliver care. In a study by Rickard et al in 2012, a patient required an average of 1.7 IV catheters per admission.[15] With a cost of approximately $35 per catheter for straightforward insertions, even a slight improvement in dwell time has the potential to save our health system millions of dollars.

References

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Appendix A: Eligibility Checklist

MRN: _____

Enrollment Date:___/___/201___ Enrollment Time: ___:___

Inclusions: **All must be "yes" or do not enroll participant**	**Yes**	**No**
Patient self-reports a history of difficult IV access		
Patient has a history of AT LEAST ONE of the following: *(indicate which patient meets)* Pt. recounts a prior emergency room visit/hospitalization when > 2 sticks required to obtain access History of a rescue catheter (such as US-guided IV, PICC line, midline, or CVC) ESRD on dialysis History of IV Drug Use History of Sickle Cell		
Patient is 18 years of age or older		

Exclusions: **All must be "no" or do not enroll participant**	**Yes**	**No**
Patient is under the age of 18 years of age		
Patient refuses to participate in the study		
Previous Inclusion in the study		
Cognitively impaired		

Form Completed by:_____(Printed name) _____(Signature)

Date:_____Time: _____

Principal Investigator:_____(Printed name) _____(Signature)

Date:_____Time: _____

Appendix B: Insertion-Related Data

Research Staff completing form (signature/date): _____

Catheter Type (circle): Ultra Long IV Standard IV

	Depth (cm)	Diameter (cm)	# Attempts	Depth (cm)	Diameter (cm)	# Attempts
	1st Venous Access point			2nd Venous Access point		
Inserter #1 ID:						
	1st Venous Access point			2nd Venous Access point		
Inserter #2 ID:						

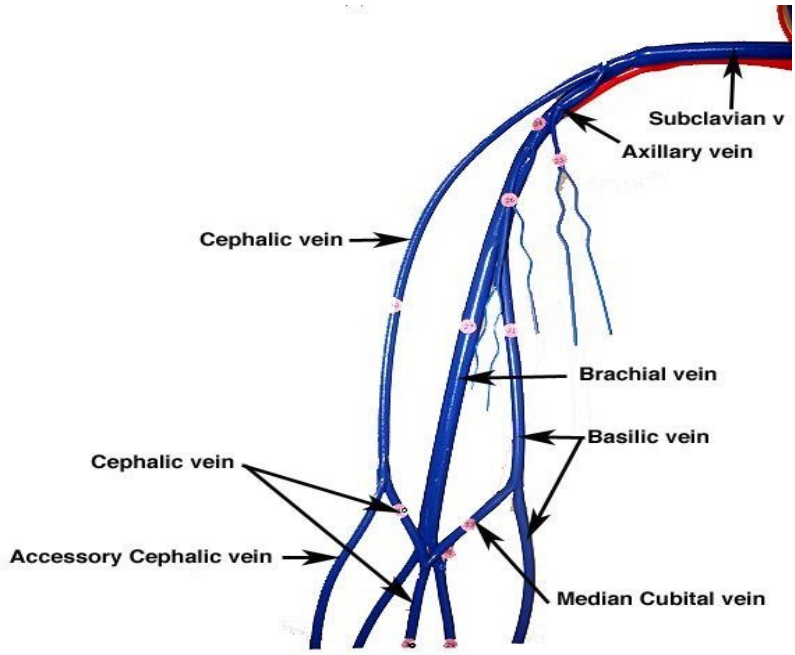
Minutes for procedure completion (time from needle to skin to dressing site): _____

Time at Completion of Insertion: _____

Initial EC Vitals: BP_____HR_____

Gender:_____ Age:_____ BMI:_____

Location of Successful Cannulation
(Mark 1/2/3 for access attempts, circle successful site): Left Right



Insertion site distance from AC fossa (cm): _____

Disposition (Circle): Observation Regular Progressive ICU Discharge

Appendix C: Functionality and Complications

Day	Functional 1: draw 2: flush 3: infusing 4: failed	Removal Time	Reason for Removal	Venous Doppler 1: + for dvt 2: + for svt 3: + for dvt/svt 4: - for both 5: none	Lab confirmed infection Y/N	Discharge <24 hrs from insertion	Replacement Access in the case of failure 1: Midline 2: PICC 3: PIV 4: US PIV 5: CVC	Research staff initials
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Reasons for Removal: (1) Completion of therapy; (2) infiltration; (3) infection; (4) dislodgement; (5) leaking; (6) pain; (7) other; (8) unknown

Post processing data

Angle of Insertion (°)	Length in vein (cm)	% Length in Vein

Signature/Date: _____

Appendix D: List of Vesicants (Red) and Irritants (Yellow)

RED LIST Well-recognized vesicants with multiple citations and reports of tissue damage upon extravasation	YELLOW LIST Vesicants associated with fewer published reports of extravasation; published drug information and infusate characteristics indicate caution and potential for tissue damage
Calcium chloride	**Acyclovir**
Calcium gluconate	**Amiodarone**
Contrast media - nonionic	**Arginine**
Dextrose concentration ≥ 12.5%	**Dextrose concentration ≥ 10% to 12.5%**
Dobutamine	**Mannitol ≥ 20%**
Dopamine	**Nafcillin**
Epinephrine	**Pentamidine**
Norepinephrine	**Pentobarbital sodium**
Parenteral nutrition solutions exceeding 900 mOsm/L	**Phenobarbital sodium**
Phenylephrine	**Potassium ≥ 60 mEq/L**
Phenytoin	**Vancomycin hydrochloride**
Promethazine	
Sodium bicarbonate	
Sodium chloride ≥ 3%	
Vasopressin	

Appendix E: Medications

Day	Medications transfused via catheter
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