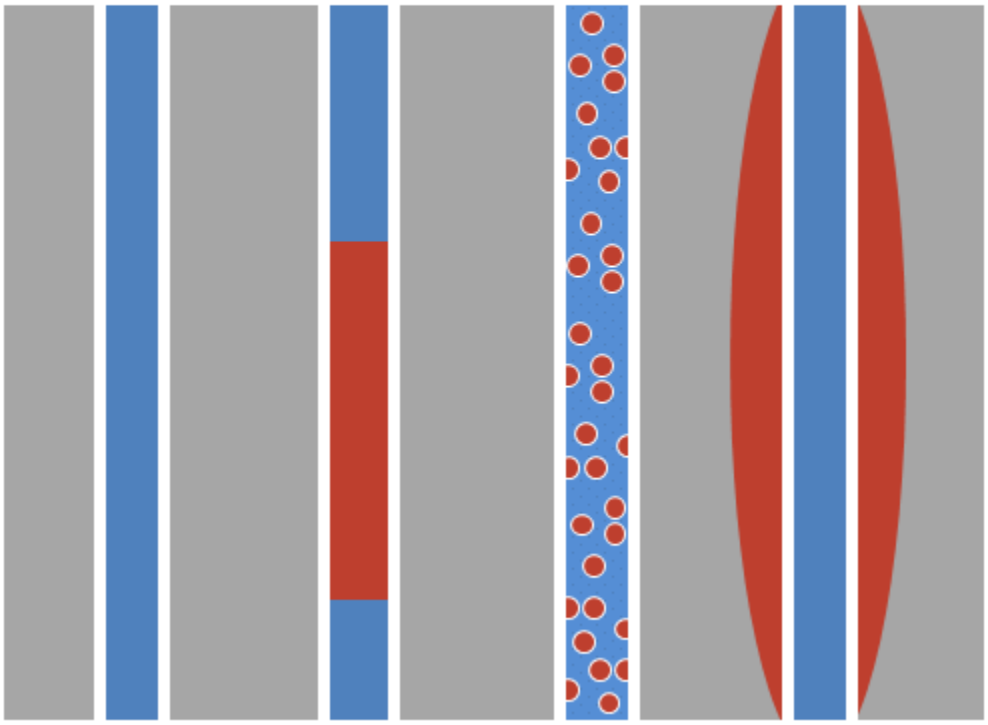
Operations Manual

Evaluation of **P**eripherally **I**nserted **C**atheter **C**omplications in **CF** Patients

PICC–CF



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A. Welcome and Introduction

BACK

You are about to participate in a study that, we believe, will provide valuable information to the CF community. Thank you for joining the team!

According to data from the U.S. CF Foundation Patient Registry, more than 25% of children and 40% of adults were treated with intravenous antibiotics for pulmonary exacerbations in 2016. This translated to 20,286 care episodes and nearly 300,000 catheter-days of risk exposure.

Case series have identified important complications of peripherally inserted central catheters (PICCs) and totally implantable venous access devices in patients such as deep venous thrombosis and central line associated bloodstream infection, central venous stenosis, and other types of mechanical dysfunction. The incidence of PICC-associated DVT in CF patients ranges from 2 to 8%. In contrast to patients with other diseases who usually undergo PICC placement for a single treatment, CF patients often require repeated instrumentation over many years. This fundamental difference in how PICCs are employed confounds extrapolation of findings from studies in non-CF populations to CF patients. Catheter-related complications may delay completion of therapy and expose patients to repeated vascular access procedures and risks associated with systemic anticoagulation in cases of thrombosis. Furthermore, devastating complications, such as central venous stenosis may discourage patients from subsequently accepting IV antibiotics. Therefore, it is critically important to identify patient- and device-related attributes associated with increased likelihood of complications and to devise strategies to mitigate these risks.

Proposed risk factors in CF patients fall into several broad categories. First are *catheter-related factors*: larger catheter size, number of catheter lumens, and catheter composition. Second are *patient factors*: lung function, nutritional status, respiratory flora, diabetes status, thrombophilia; and number of previously placed or guidewire-exchanged catheters. Third are *catheter-management factors*: insertion technique and site selection, inpatient versus outpatient care, anticoagulant use, blood sampling practices, line flushing solutions , frequency of dressing changes, and duration of line use. We hypothesize that the rate of PICC and midline vascular complications among CF patients is associated with specific patient level and line level factors as well as with line insertion and management practices. To date, no multicenter trial has prospectively studied PICC and midline catheter-associated complications in adult and pediatric CF patients. If we meet our targets, this will also be the largest study of PICC and midline complications conducted in the CF population.

B. Site Principal Investigator List and Contact Information

BACK

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C. Study Design

BACK

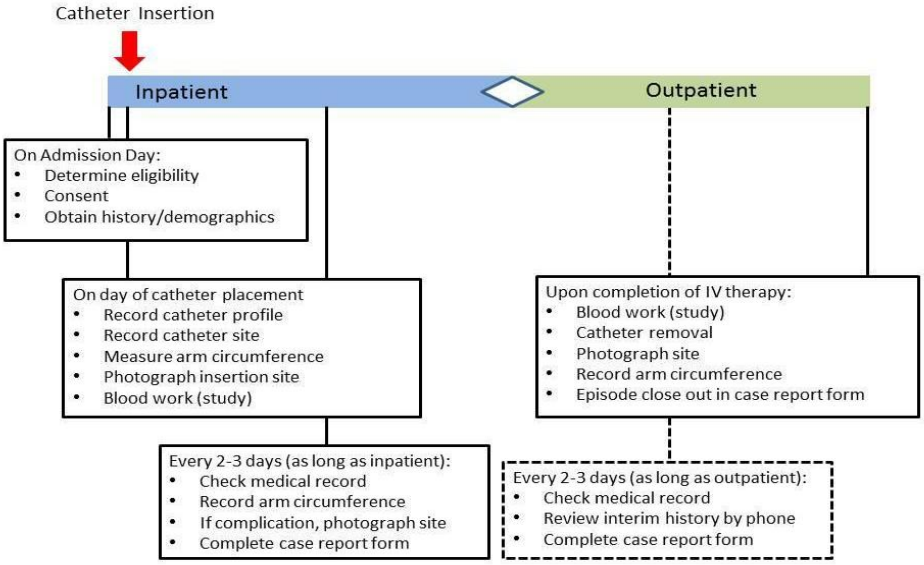
Study Design This is a multicenter, prospective surveillance study to evaluate risk factors that predict vascular complications of PICCs and midline catheters. Both adult and pediatric patients with CF who receive care at participating centers will be eligible for participation. Each participant will be assessed for a number of study variables while being treated with IV antibiotics via a PICC or midline for pulmonary exacerbation. Assessments will be performed according to a prescribed schedule of events. Antibiotic selection and treatment duration, however, will be determined and overseen by the local CF team. Patients will potentially be seen for multiple episodes of care during the study period if additional treatment(s) with IV therapy is/are prescribed following treatment of the initial pulmonary exacerbation.

Study Population and Recruitment. Participants will be recruited from the population of CF patients who receive longitudinal care at 10 CF Centers (Maine Medical Center, University of Vermont, Dartmouth-Hitchcock Medical Center, Columbia University Medical Center, University of Kansas Medical Center, Johns Hopkins Hospital, Medical University of South Carolina, University of Michigan Medical Center, Cleveland Clinic, and Children's Hospital Colorado). Patients will be screened and enrolled at the time of hospitalization for PICC or midline placement. Patients who have a PICC or midline placed at the hospital but who then have the remainder of therapy in the home setting will be eligible to participate. To reach our enrollment goal, we plan to study 335 patients per year over a 30 month period. In order to maintain appropriate representation of all centers, maximum enrollment per center will be 50 patients per year. This cap may be exceeded in the event that a previously enrolled patient has a subsequent PICC or midline placed in the same calendar year. One of the study goals is to look at the association of repeated PICC placement with the occurrence of complications, so we do not want gaps in follow up.

Screening and Enrollment. See the list of inclusion and exclusion criteria. The rationale for some of the exclusion criteria is self-evident. However, one deserves additional explanation. We have elected not to study TIVADs, since the period of observation of this project is relatively short compared to the average "lifespan" of these devices. It would therefore be difficult to achieve adequate power to study complication risk factors in a 3 year study, even in a multicenter trial. Based on the finding that anticoagulation at prophylactic or treatment doses may increase the risk of complications and since there is no standardized regimen for anticoagulation in this patient population with indwelling lines, patients who are chronically anticoagulated will be excluded at screening. However, patients who have a vascular complication after enrollment in the study and receive treatment as determined by their primary care team will be permitted to continue in the study. It should be emphasized that this study is not designed as an interventional trial to test the safety and efficacy of anticoagulation but could lay the groundwork for such an investigation.

Study Event Workflow

Potential study participants will undergo informed consent/assent on the day of catheter insertion. Additional tasks and procedures in the protocol are summarized in the figure and table.



Workflow diagram of PICC assessments during a pulmonary exacerbation. Inpatient assessments will be done every 48-72 hours. Likewise, outpatient assessments (dashed lines) will be done every 48-72 hours via phone interview. The white diamond denotes variable duration of inpatient (blue segment) and home IV (green segment) phases of therapy.

Schedule of Events

Task/Procedure	Visit 1 Day 1	Visit 2 Day 3 (+/-1 D)	Visit 3 Day 5 (+/-1 D)	Visit 4 Day 7 (+/-1 D)	Visit 5 Day 9 (+/-1 D)	Visit 6 Day 11 (+/-1 D)	Visit 7 Day 14 (+/-1 D)
Informed Consent	X						
Obtain Demographics	X						
Obtain Relevant History	X						
Akron PES	X						
Line insertion details	X						
Confirm catheter details	X						X
CBC, INR (hospital)	X						
CRP, D-dimer (study)	X						X
Picture of insertion site	X	(X)	(X)	(X)	(X)	(X)	X
Line Management Survey		X**	X**	X**	X**	X**	X
Measure Arm Circumference	X	X*	X*	X*	X*	X*	X
Evaluation for Complications		X**	X**	X**	X**	X**	X
Review line removal							X

Notes: (X)-Optional event based on signs/symptoms of the patient. X*-Patients who receive in-hospital will have arm circumference measured at each visit X**-Patients who receive in-hospital care will have face-to-face follow-up evaluations. Those who are treated at home will have a check-in by phone call

D. Investigator Roles and Responsibilities

BACK

Each site investigator is responsible for oversight of local enrollment and research activities. Each investigator should be sure to:

- Review the Operations Manual
- Have a working understanding of the study protocol
- Regularly visit the study website for updates and to read the quarterly newsletter
- Participate in conference calls, webinars and study group meetings
- Know the local annual enrollment target and communicate with the coordinating center if there are difficulties related to enrollment
- Oversee the work of the research coordinator with respect to data collection and entry into the REDCap registry
- Communicate with the coordinating center should there be difficulties related to data collection or entry
- Oversee maintenance of all local regulatory documents including study binders, IRB submissions and renewals

E. Research Coordinator Roles and Responsibilities

BACK

Research coordinators (RCs) play pivotal roles in this study and are keys to its success. We are asking each RC to maintain close lines of communication with his/her site PI and the study coordinating center. We want each RC to inform the study coordinating center and collaborators at other sites about any difficulties (and successes!) he/she encounters as the study progresses. The study leads will ensure that multiple lines of communication are available, including the PICC-CF website blog, e-mail and phone lists, and a conference call schedule. We will now break down RC duties in detail. Please refer to the Schedule of Events for additional information.

Pre-Visit Planning

- Identify study candidate. Most study subjects will be enrolled at the time of a clinic visit when their provider determines that the subject needs to be admitted to the hospital for treatment of pulmonary exacerbation. In these cases, it would be ideal for the RC to be "embedded" in the clinic so that he/she knows exactly which patient(s) is/are being admitted and can determine whether inclusion criteria are met. Other strategies that could maximize enrollment chances at your center include having the RC scan upcoming clinic rosters and/or attend weekly clinical team meetings.
- Establish line of communication with the vascular access team to be sure that study activities do not unduly interfere with the workflow of catheter placement while ensuring appropriate data capture.

Task List: Initial Visit (Day 1)

- **Obtain informed consent or assent**. Informed consent or assent should be obtained from subjects prior to data acquisition. In the Library section of the study website, we have included examples of the informed consent forms (ICFs) and assent forms required by Dartmouth-Hitchcock Medical Center for reference. RCs should create ICFs according to requirements of their local institutional review boards, but the ICFs uploaded to the study website may serve as templates. RCs should give subjects ample time to review ICFs or assent forms. RCs should answer questions about the study protocol and/or involve the site PI in this process.
- **Provide subject and/or parent with copy of signed ICF or assent form**.
- **Securely store signed ICF or assent form**. RCs should assemble a study binder for subjects enrolled in the study into which printed documents like the ICFs and assent forms would be stored. Individual ICFs and assent forms should also be scanned and uploaded to the REDCap registry
- **Determine Akron Pulmonary Exacerbation Score (PES)**. Although there continues to be no uniformly-accepted definition of pulmonary exacerbation, we want to incorporate a reasonable definition into this study in order to characterize our study population at the time of catheter placement.
- **Ensure that D-dimer and CRP samples are drawn and specimens processed**
- **Complete REDCap Registry forms**. Completion of the forms associated with the initial visit, including review of historical details and obtaining consent/assent is estimated to take approximately 3 hours. Please account for this time.
- As long as **inclusion/exclusion** criteria have been carefully reviewed prior to participant enrollment, additional historical details can be obtained/revised over the course of the study episode until the catheter is removed.
- **Provide patient stipend**

Task List: Subsequent Visits (every 2 days)

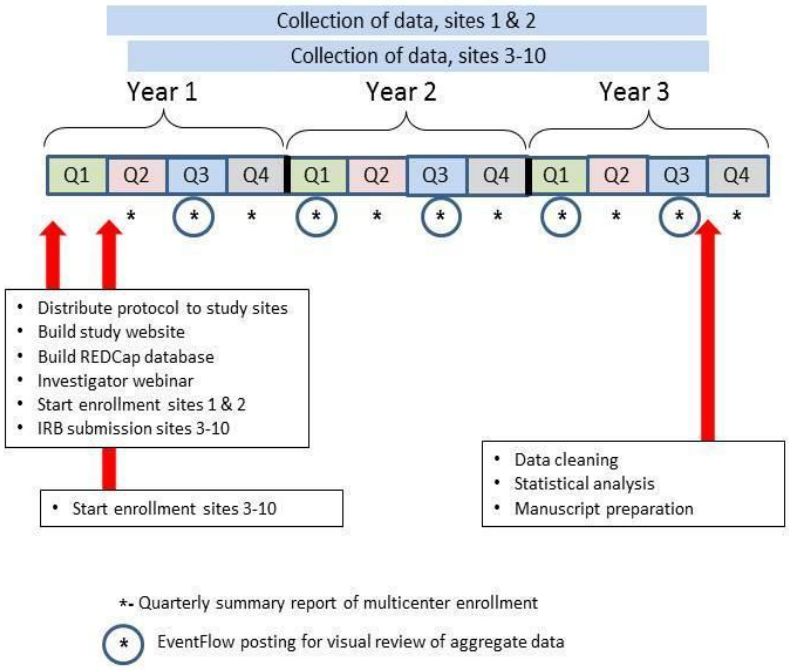
- **Complete REDCap Registry forms**. Completion of the forms associated with the subsequent visits is estimated to take approximately 20 minutes. Please account for this time.
- Additional historical details can be obtained/revised over the course of the study episode until the catheter is removed.

Task List: Final Visit (usually Day 14)

- **Complete REDCap Registry forms**. Completion of the forms associated with the subsequent visits is estimated to take approximately 20 minutes. Please account for this time.
- **Ensure that D-dimer and CRP samples are drawn and specimens processed**
- **Ensure that the intravenous catheter is removed** (depending on the institution, the catheter may be removed by another individual)
- **Provide patient stipend**

F. Study Timelines and Benchmarks

BACK



G. Screening and Patient Capture

BACK

NOTE: This may be done ahead of patient enrollment by the research coordinator and clinical team by reviewing the program's patient panel.

G.1. Main eligibility points for screening (see Research Plan for detailed **inclusion** criteria)

- ≥ 6 years of age
- Gets IV therapy through PICC or midline catheters
- Ability and willingness to give verbal assent/consent
- Ability to communicate with pertinent staff
- Ability to understand and willingness to comply with requirements of the study (allow repeated assessment of the catheter site

G.2. Main exclusion points for screening (see Research Plan for detailed **exclusion** criteria)

- < 6 years of age
- Has a TIVAD or receives IV therapy through simple peripheral catheters
- Taking anticoagulant medication (e.g., warfarin, heparin or NOAC). (NOTE: if following study entry, the patient develops a vascular complication for which the clinical team opts to anticoagulate, the patient should remain in the study for future care episodes)

G.3. Identify potentially eligible patients prior to IV catheter placement (this will be a site specific protocol). Possible options include:

- Research coordinator checks preadmission/admission list in Epic
- Develop a pathway for research coordinator-clinical team communication regarding plans for treating a pulmonary exacerbation

H. Obtaining Assent/Consent

BACK

NOTE: **Consent for participation should occur prior to catheter insertion**

H.1. Preparation for consent process

- Assign **subject ID number** to the assent/consent form
- Communicate with the vascular access team to alert them of a potential study participant
- Communicate with the vascular access team to let them know about drawing study blood samples from the catheter at the time of insertion
- Provide appropriate tubes to the vascular access team for the blood samples

H.2. Timing of assent/consent process

- Best to coordinate this with the timing of consent for the vascular access procedure though documents can be signed prior to the date of catheter insertion, if placement will be delayed
- Provide ample time to answer questions and be sure to explain that aside from obtaining the blood samples, this study will not change the treatment plan for the pulmonary exacerbation

H.3. Supplementary information (refer to Research Plan for details)

- After obtaining assent/consent verify demographic details from PortCF. Please obtain the following demographic elements whether the patient agrees to participate or not and enter in REDCap database:
    - Age
    - Sex
    - Genotype
    - FEV1% predicted
    - BMI or BMI percentile (as appropriate for age)
    - Diabetes status
    - Sputum culture results (last 12 months)
- After obtaining assent/consent obtain the following historical details from the medical record and enter in REDCap database:
    - Number of prior PICCs and/or midline catheters
    - History of difficult catheter placement
    - Prior history of venous thrombosis
    - History of thrombophilia
    - Family history of thrombophilia
    - Oral contraceptive use

I. Initial visit with catheter insertion

BACK

NOTE: **Consent for participation should occur prior to catheter insertion**

I.1. Visit Checklist

- ☐ Consent/Assent form
- ☐ White subject label
- ☐ Tube for **D-dimer** sample
- ☐ Tube for **C-reactive** protein sample
- ☐ Device for photography of catheter site
- ☐ Patient Stipend

I.2. Record information related to hospital admission

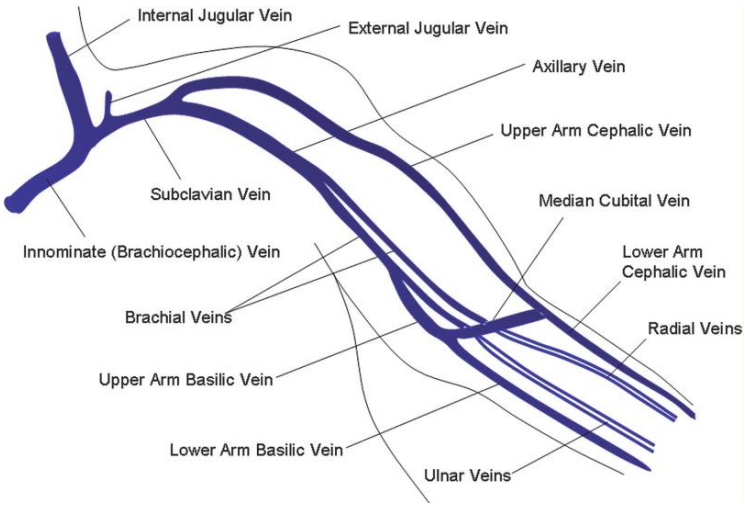
- Enter **subject number** into REDCap database
- Record whether admission is emergency admission or elective in the REDCap database
- Record **Akron Pulmonary Exacerbation Score** in the REDCap database
- Record choice of antibiotic and mode of delivery in the REDCap database

I.3. Timing of assent/consent process

- Best to coordinate this with the timing of consent for the vascular access procedure though documents can be signed prior to the date of catheter insertion, if placement will be delayed
- Provide ample time to answer questions and be sure to explain that aside from obtaining the blood samples, this study will not change the treatment plan for the pulmonary exacerbation

I.4. Record information related to catheter placement

- Record venue of insertion (e.g., bedside, procedure room or IR) in the REDCap database
- Record whether sedation was administered in the REDCap database
- Record type of local anesthetic in the REDCap database
- Record type of skin preparation in the REDCap database
- Record insertion information in the REDCap database (e.g., **vessel accessed**, size, guidance, number of needle passes and ease of floating the guidewire)



- Record catheter information in the REDCap database (e.g., catheter type and brand, French size, number of lumens, exit length)
- Record position confirmation and patency information in the REDCap database

I.5. Blood for D-dimer

Blue top tube

- Fill tube according to local clinical laboratory directions and process in local clinical laboratory
- Record D-dimer level for initial visit in REDCap database

I.6. Blood for C-reactive protein (CRP)

Green Top and Gold Top serum separator tubes

- Fill serum separator tube according to local clinical laboratory directions and process in local clinical laboratory
- Record CRP value for initial visit in REDCap database

I.7. Additional clinical lab results

- Record CBC and INR values from the clinical record in appropriate cells in the REDCap database.
- Acceptable results dates would be from within 1 month of placement of the catheter through the end of treatment.

I.8. Photography of the catheter site

- Apply white study code label with the patient ID near the catheter entry site in the field of view of the photograph (the study label has subject number on it and provides white color for post-process white-balance)
- Take picture using Epitomyze™ Capture feature with an iPad or iPhone equipped with the app
- The photo will automatically upload to the Epitomyze™ Cloud. Rename the image file as the participant ID using the format: XX-YYYYYY-ZZ_mm_dd_yyyy (patient ID followed by the date)
- Give first stipend to study participant. If using Nimblify, please follow instructions for use.

J. Subsequent Visits

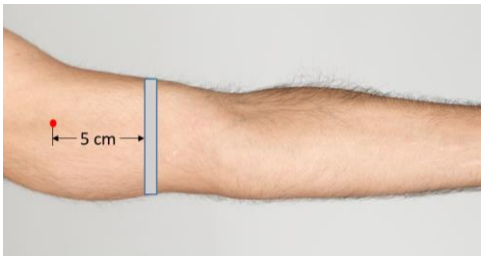
BACK

J.1. Visit Checklist

- ☐ White subject label
- ☐ Measuring tape
- ☐ Device for photography of catheter site

J.2. Complete report forms for interim visits every 2 days.

- If study participant remains in hospital record the presence or absence of signs and symptoms in the REDCap database
- If the study participant is receiving treatment at home, record the presence or absence of signs and symptoms by patient report via telephone call in the REDCap database
- Measure the arm circumference 5 cm distal to the catheter insertion site and record in the REDCap database.



J.3. Photography of the catheter site – Only if there is complaint of discomfort or visible change associated with the catheter.

- Apply white study code label with the patient ID near the catheter entry site in the field of view of the photograph (the study label has subject number on it and provides white color for post-process white-balance)
- Take picture using Epitomyze™ Capture feature with an iPad or iPhone equipped with the app
- The photo will automatically upload to the Epitomyze™ Cloud. Rename the image file as the participant ID using the format: XX-YYYYYY-ZZ_mm_dd_yyyy (patient ID followed by the date)

J.4. Complete "Call your pain" scale and catheter patency questions in the REDCap database

J.5. Use Adverse Event Worksheet and Diagnostic Calculator to determine the presence of complications and enter the following in the REDCap database:

- Venue of complication
- Type of complication (DVT, phlebitis, or CLABSI)
- If DVT by Constans score, record if confirmed by ultrasound or venogram
- Treatment, if any

J.6. Collect catheter care data (e.g., lumens used, flushing solution, etc.) and enter in the REDCap database

K. Final visit with catheter removal

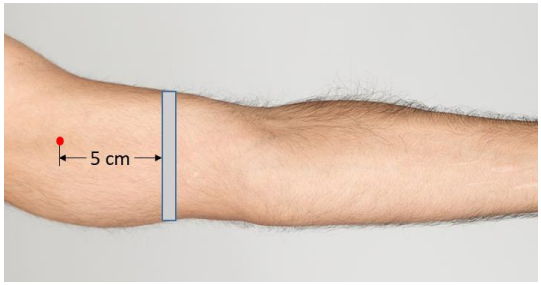
BACK

K.1. Visit Checklist

- ☐ White subject label
- ☐ Tube for D-dimer sample
- ☐ Tube for C-reactive protein sample
- ☐ Device for photography of catheter site
- ☐ Tape Measure
- ☐ Patient Stipend

K.2. Complete report forms for the final study visit.

- If study participant remains in hospital record the presence or absence of signs and symptoms in the REDCap database
- If the study participant is receiving treatment at home, record the presence or absence of signs and symptoms by patient report via telephone call in the REDCap database
- Measure the arm circumference 5 cm distal to the catheter insertion site and record in the REDCap database.



K.3. Photography of the catheter site – Only if there is complaint of discomfort or visible change associated with the catheter.

- Apply white study code label with the patient ID near the catheter entry site in the field of view of the photograph (the study label has subject number on it and provides white color for post-process white-balance)
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- The photo will automatically upload to the Epitomyze™ Cloud. Rename the image file as the participant ID using the format: XX-YYYYYY-ZZ_mm_dd_yyyy (patient ID followed by the date)

K.4. Complete “Call your pain” scale and catheter patency questions in the REDCap database

K.5. Use Adverse Event Worksheet and Diagnostic Calculator to determine the presence of complications and enter the following in the REDCap database:

- Venue of complication
- Type of complication (DVT, phlebitis, or CLABSI)
- If DVT by Constans score, record if confirmed by ultrasound or venogram
- Treatment if any

K.6. Collect catheter care data (e.g., lumens used, flushing solution, etc.) and enter in the REDCap database

K.7. Blood for D-dimer

Blue top tube

- Fill tube according to local clinical laboratory directions and process in local clinical laboratory
- Record D-dimer level for initial visit in REDCap database

K.8. Blood for C-reactive protein (CRP)

Green Top and Gold Top serum separator tubes

- Fill serum separator tube according to local clinical laboratory directions and process in local clinical laboratory
- Record CRP value for initial visit in REDCap database

K.9. Remove catheter

K.10 Give second stipend to study participant. If using Nimblify, please follow instructions for use.

L. Study Website

BACK

The PICC-CF website url is www.picccf.org and it contains the following information and resources:

- Patient-facing and investigator-facing content about the purpose and design of the study
- Link to the ClinicalTrials.gov study listing
- Research portal to the REDCap database
- Links to study resources such as the Operations Manual, REDCap instruction manual, and Epitomzye™ manual
- Overall enrollment numbers and enrollment numbers by site
- Map with study site locations
- Links to study newsletters
- Calendar of events such as group meetings and conference calls
- Constant Contact® page for questions or comments

M. Appendix

BACK

Inclusion and Exclusion Criteria

Inclusion criteria include the following:

- All ethnic groups
- Females and males
- 6 years of age and above (in order to perform spirometry on all study participants)
- Undergoing treatment for PEx with IV antibiotics via hospital-placed PICC or midline catheter
- Ability to communicate with pertinent staff.
- Ability to understand and willingness to comply with the requirements of the trial (allow repeated assessment of the catheter insertion site, photographs of the site, extremity measurement and face-to-face assessment on the day of line removal).
- Ability and willingness to give verbal consent (with the assistance of a parent or guardian, if appropriate) or assent (for pediatric patients)
- Diagnosis of cystic fibrosis consisting of both:
    - sweat sodium or chloride > 60 mEq/L by the pilocarpine iontophoresis method or cystic fibrosis genotype (homozygous for CFTR mutation or compound heterozygous for CFTR mutations)
    - clinical manifestations of cystic fibrosis

Exclusion criteria include the following:

- < 6 years of age
- Has a TIVAD or receives IV therapy through simple peripheral catheters
- Taking anticoagulant medication (e.g., warfarin, heparin or NOAC). (NOTE: if following study entry, the patient develops a vascular complication for which the clinical team opts to anticoagulate, the patient should remain in the study for future care episodes)

Assignment of Participant ID number

Participant ID numbers will be built with three components: study site number, random number, and episode number.

The center numbers will be as follows:

01: Cleveland Clinic
02: Colorado Children's
03: Columbia
04: Dartmouth
05: Johns Hopkins
06: Maine Medical Center
07: Medical University of South Carolina
08: University of Kansas Medical Center
09: University of Michigan
10: University of Vermont

Each center will receive a file with 300 random numbers to be used in building the middle segment of the ID number for each participant. Simply use the numbers in the table given to your site in sequential order for each NEW study participant.

The third part of the numbering convention includes the episode number. For the first pulmonary exacerbation care episode the participant ID will be completed with 01. If there is a second care episode for that participant during the study, then the ID will be completed with 02, and so on. To print easy-to-read labels (especially in photographs), use Calibri Font size 24.

Participant numbering algorithm

Center ID-Random Participant Number-Encounter Number

Example 02-437891-01

Participant from Center 2, assigned random number 437891, first care episode

Label printing instructions for Avery style 5160 labels can be found at:

https://support.office.com/client/en-us/videoplayer/embed/RE1XiXw?pid=ocpVideo0-innerdiv-oneplayer&jsapi=true&postJsllMsg=true&maskLevel=20&market=en-us

Akron Pulmonary Exacerbation Score (PES) Tool

Systemic Symptoms/Signs:

1. Fevers > 38C (100.4 F) in the prior 2 weeks?
   No = 0 Yes = 1
2. Malaise or fatigue in the prior 2 weeks?
   No = 0 Yes = 1
3. Any increased or new school or work absenteeism in the prior 2 weeks?
   No = 0 Yes = 2
4. Anorexia or poor appetite in the prior 2 weeks?
   No = 0 Yes = 1
5. Wt. Loss (≥ 5%) or poor wt. gain compared to last clinic visit (or in the last 3mo.)
   No = 0 Yes = 2

SUM OF SYSTEMIC SYMPTOM SCORES: _____

Pulmonary Symptoms/Signs:

1. Increased cough (frequency, duration or intensity) for ≥1 week?
   None = 0 Mild = 1 Significant = 2
2. Major change in sputum (new onset, increased, change in consistency) or change in chest congestion for ≥1 week?
   None = 0 Mild = 1 Significant = 2
3. Increased DOE or SOB at rest?
   No = 0 Yes = 2
4. Change in chest exam (wheezes, crackles, rhonchi, decreased air entry) or Increased WOB or Respiratory Rate?
   No = 0 Yes = 2

SUM OF PULMONARY SYMPTOM SCORES: _____

Objective Measurements:

1. Decrease in FEV1 (compared to highest value of the prior six months 6 months)?
   < 10% = 0 ≥ 10% = 3 ≥ 15% = 5
2. New Chest Radiographic Abnormality?
   None = 0 Increased air trapping, mucus plugging or bronchiectasis = 1 New atelectasis or infiltrate = 2 Pneumothorax = 5
3. Hemoptysis ?
   None = 0 Streaked = 3 Increased or new onset = 5
4. Decreased SaO_2 from baseline (compared to the highest value of the prior 6 months)?
   < 4% change = 0 ≥ 4% decrease = 2 ≥ 10% decrease = 5

SUM OF OBJECTIVE MEASUREMENT SCORES: _____
TOTAL PULMONARY EXACERBATION SCORE: _____

***All symptoms/signs/measurements will be compared to the patient's most recent baseline (within the previous 3 months) or as noted below.**
**If a patient has Systemic findings they must also have at least 1 finding from either the Pulmonary or Objective Measurement categories to have a PE. (i.e. a pulmonary exacerbation will not be present with Systemic symptoms alone).

Nimblify information for patients who desire payment by prepaid card:

Nimblify Participant Payments
Cardholder Information

Your Nimblify card is a reloadable prepaid card and will be active when you receive it. You can start using the card immediately for purchases. It is free to use your card at the point of sale, such as a store, restaurant, or hotel.

Do not throw this card away after use.
Each time you get a payment more money will be added to the card.

Preauthorized merchant holds
Like any debit card, your transaction might be declined even when there's enough money on your card for the purchase amount. Some merchants (such as restaurants, hotels, gas stations, and rental car agencies) require a preauthorized hold for an amount *greater* than the transaction amount to cover gratuities or incidental expenses. After the final payment is received, this hold will be removed. If the purchase amount *plus* the preauthorized hold is greater than the card balance, the purchase will be declined.

Account registration
If you're going to receive multiple payments on your card, consider setting up a free Nimblify account at nimblify.paylution.com. Registering your card has many benefits. Most importantly, it allows you to withdraw money at an ATM and increases your balance limit.

Benefits of an account

Create a Nimblify account if you want to:
- Withdraw money at an ATM
- Request cash back on a store purchase
- Check your card balance online for free

How do I create an account?
If you provided an email address when you received your card, check your email for a message with the subject line "Welcome *your name* to Nimblify". Click the link in the email, and follow the instructions to create an account and a PIN. From there, you can check your balance at any time. Can't find the email? Check your junk mail. If you still can't find it, go to https://nimblify.paylution.com, and click Resend Activation Email.

Keep it free!

- Ask for cash back on your purchases instead of using ATMs
- Check your balance for free online, at nimblify.paylution.com
- Use your card at least once every 90 days to stay active

ATM fees
It is free to use your card for purchases. Using an ATM is subject to the following charges:

Common card fees	
ATM withdrawal - in the United States - internationally	 $1.50 $3.50
ATM balance inquiry	$0.25
ATM decline	$0.25
Inactivity for more than 90 days	$3.00/month

You can read the complete list of additional, less common fees in the cardholder agreement at nimblify.paylution.com.

Lost or stolen card
If your card is lost or stolen, contact the research site that issued you the card directly to request a replacement. This is the fastest and easiest way to replace your card.

If you lose your card outside of regular business hours, call Account-holder Services at 1-855-316-5166 to deactivate the card immediately. You will still have to contact the research site for a replacement card during normal business hours.

Still have questions?
For more information about your Nimblify card, visit nimblify.paylution.com or call Account-holder Services at 1-855-316-5166.

Nimblify information for patients who desire payment by check or bank deposit:

Set up your Nimblify account: Bank deposit or paper checks

We use Nimblify, a secure online funds transfer system, to process your payments. As you participate in the study, we pay money into your Nimblify account.

You must set up your Nimblify account in order to receive payment. To do so, follow the instructions in this document.

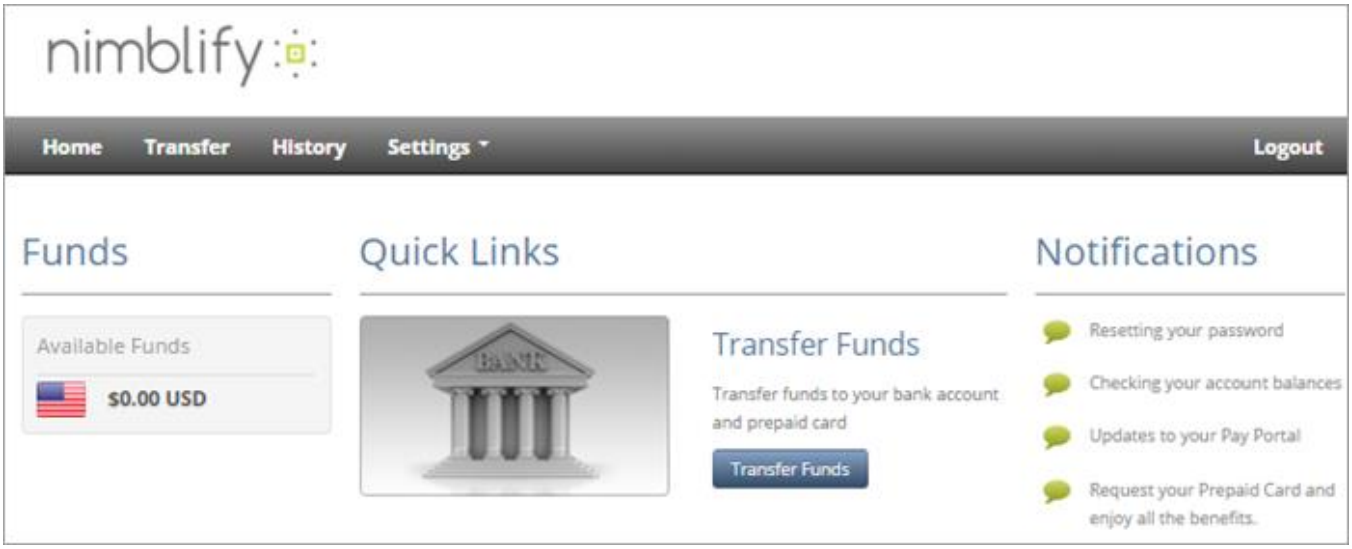
You decide how to access the funds in your account. You can choose direct deposit into a bank account or a paper check by mail. You also decide whether you want to receive payments automatically or keep money in the Nimblify account until you request it.

Activate your account

1. Check your email for a message with the subject: "Welcome *your name* to Nimblify".
2. Click the link in the email.
3. Follow the instructions that appear. **NOTE**: for Account Type, choose Individual.
4. After you activate your account, you will see the Nimblify Home page.

Can't find the e-mail?
Check your junk mail folder.

Still can't find it?
Go to https://nimblify.paylution.com , click Resend Activation E-mail, and enter your e-mail address.

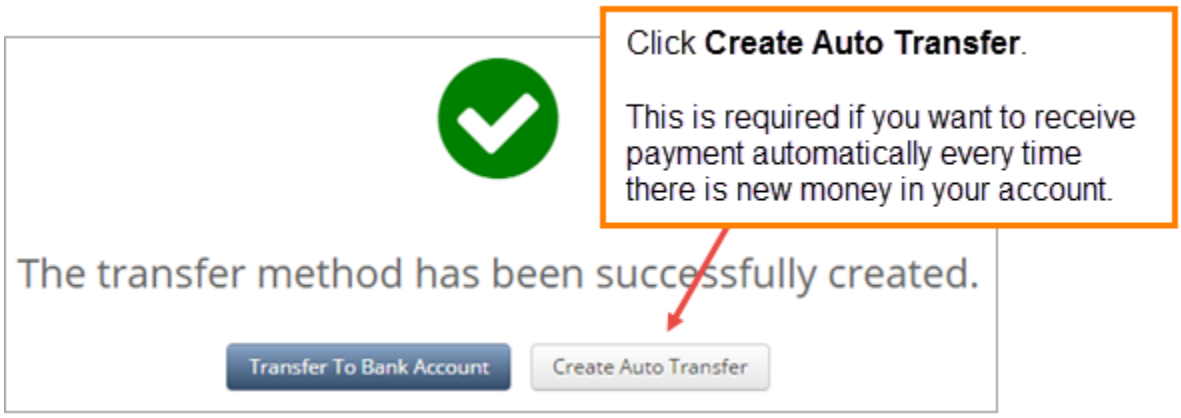


Set up bank account or choose paper check

1. From the Home page, click **Transfer Funds**.
2. The Transfer Center will open. Click **+ New Transfer Method**.
3. Choose a payment method:

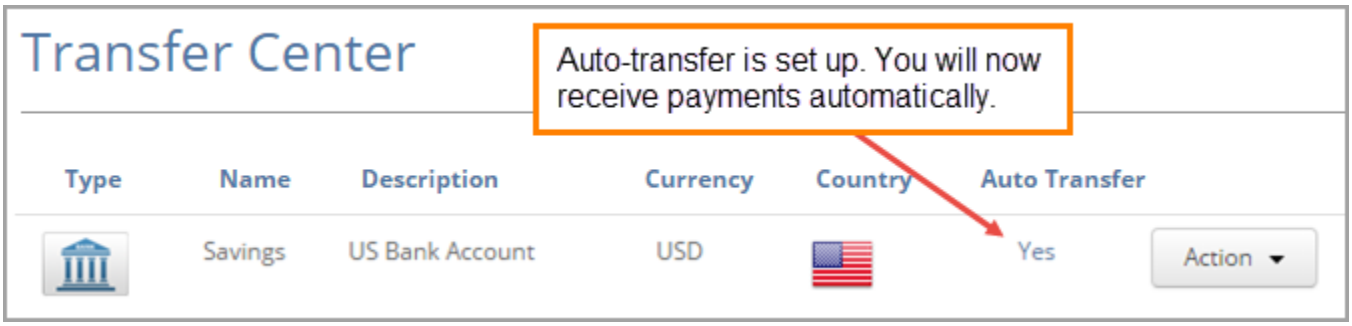
Bank Account	Paper Check
• Click **Continue**. • Enter your bank information and click **Continue**. • Confirm the information.	• Click **Continue**. • For Remember As, create a name such as "Check". • Click **Confirm**.

4. When your payment information is saved, you will see a green circle with a checkmark.
5. There's one more step before your payment is fully set up. Click **Create Auto Transfer**.



6. You will be asked "Automatically transfer all of my account balances to the following account?" Click **Confirm**.

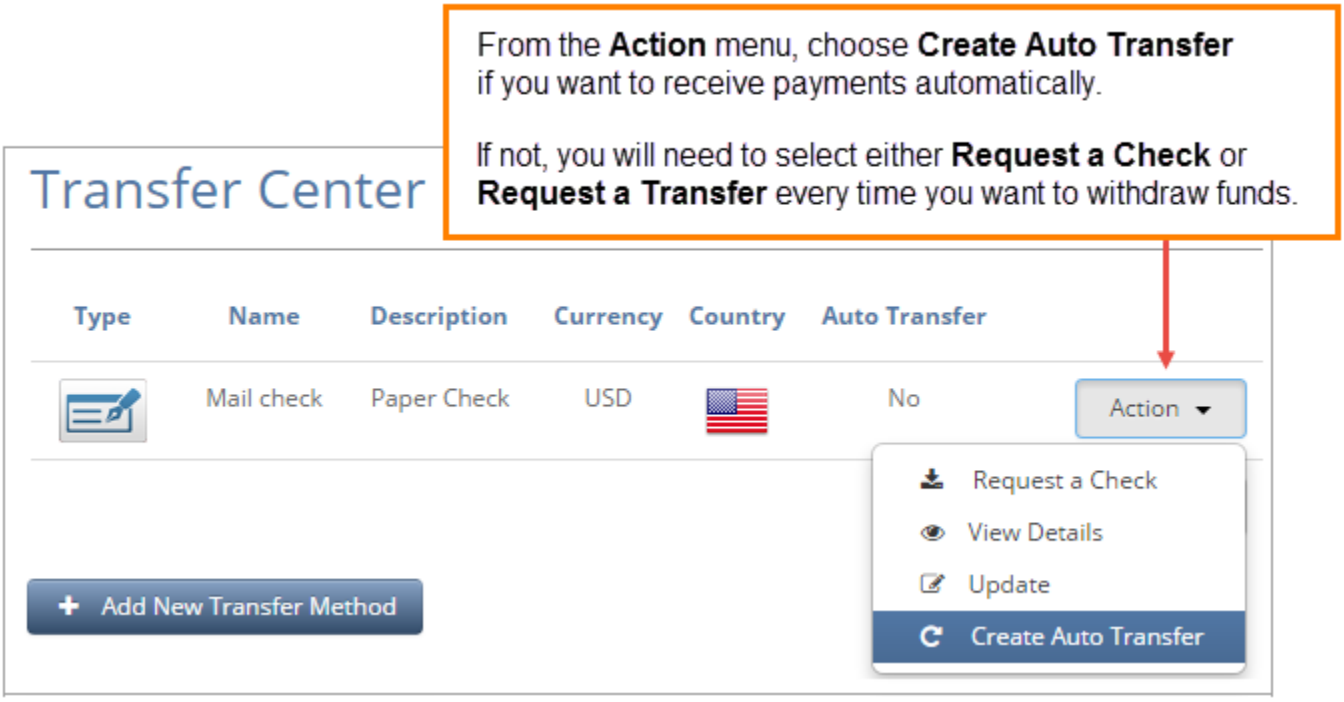
You are done when the payment method listed in the Transfer Center with Auto Transfer set to **Yes.**



Troubleshooting

Didn't receive your check or bank deposit?

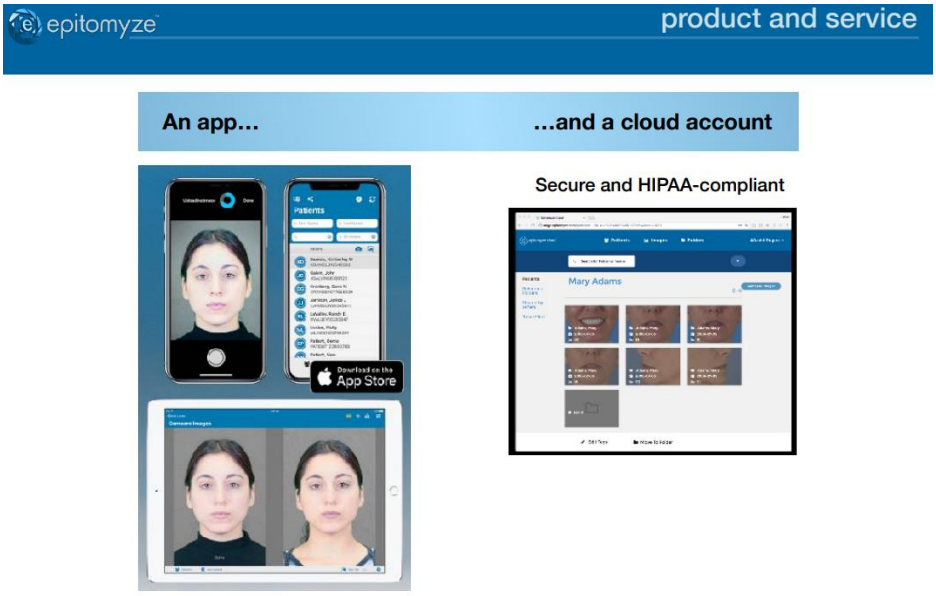
1. From the Home page, click **Transfer Funds**.
2. The **Transfer Center** will open. Make sure that:
   - Your payment method is listed
   - **Auto Transfer** is set to **Yes**

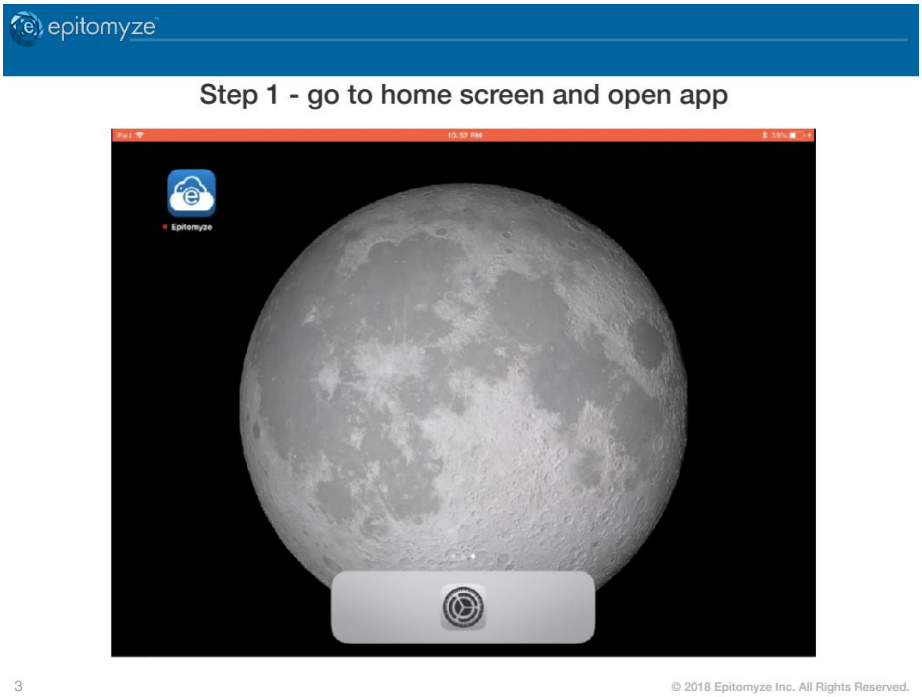


Still have questions?

Call **1-855-316-5166**, or click the **Contact Us** link at the bottom right of the Nimblify home page to send an e*mail.*

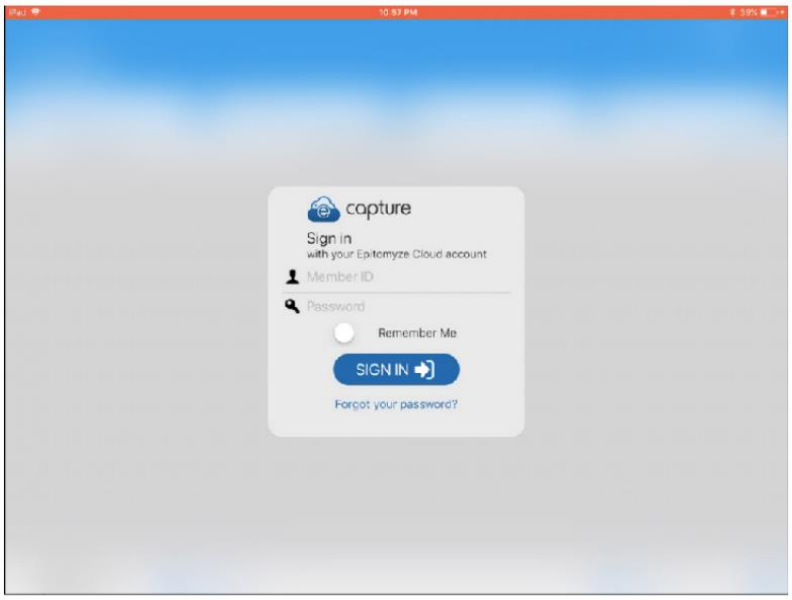
Epitomyze™ imaging software





epitomyze

Step 2 - log in



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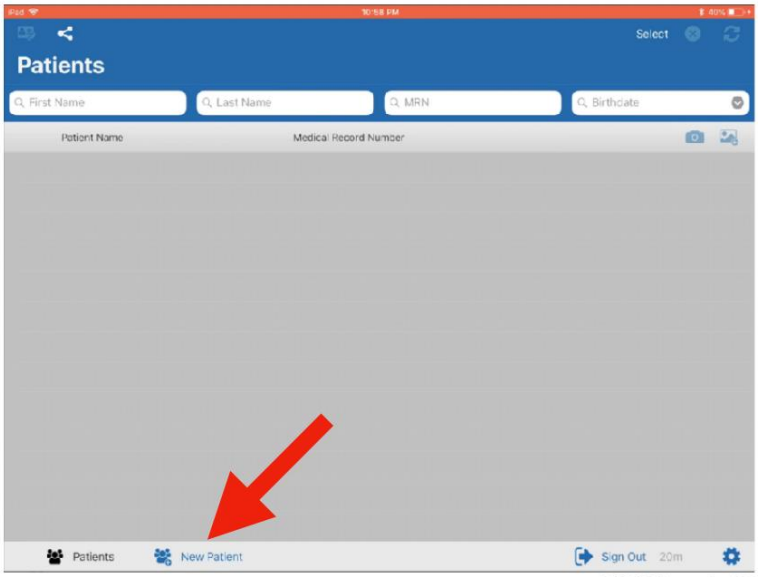
Step 3 - create new patient



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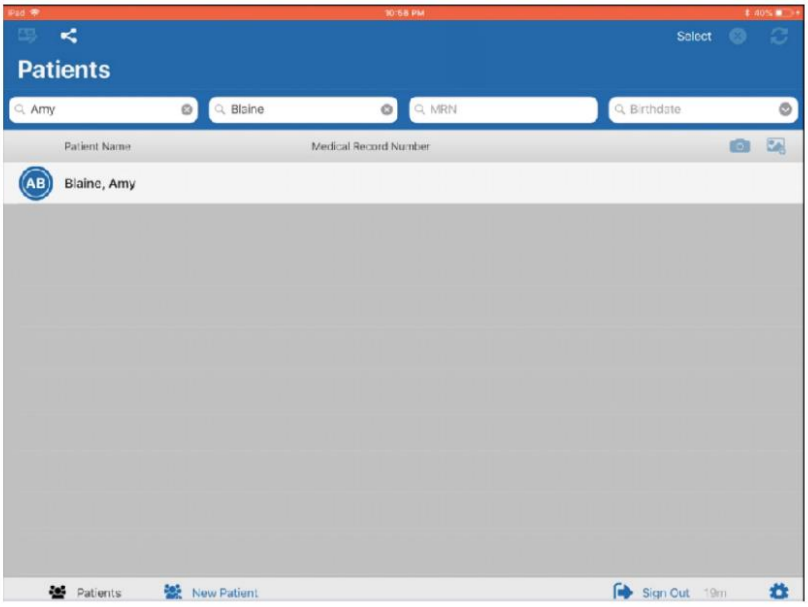
Step 4 - select patient



6

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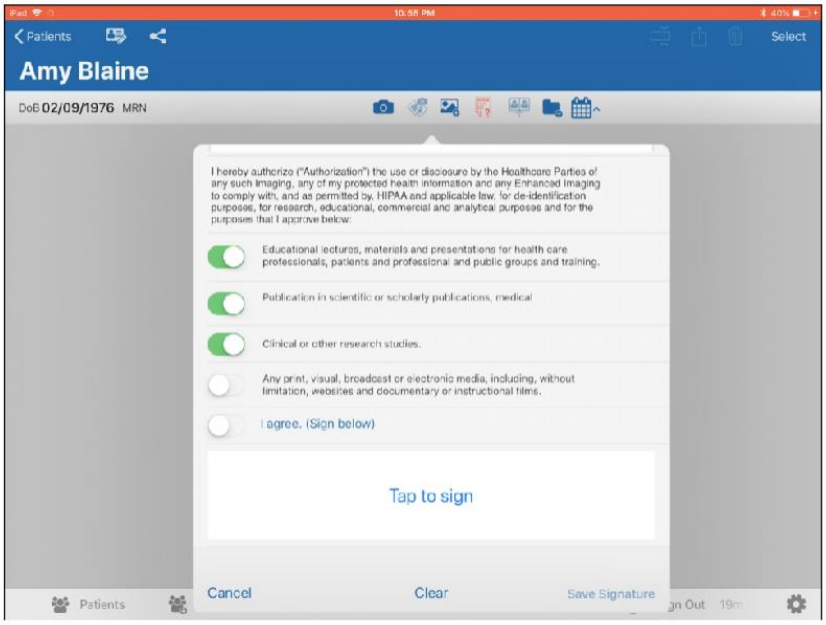
Step 5 - have patient sign photo consent



7

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Step 6 - take photo(s) or video(s) , click done when finished

8

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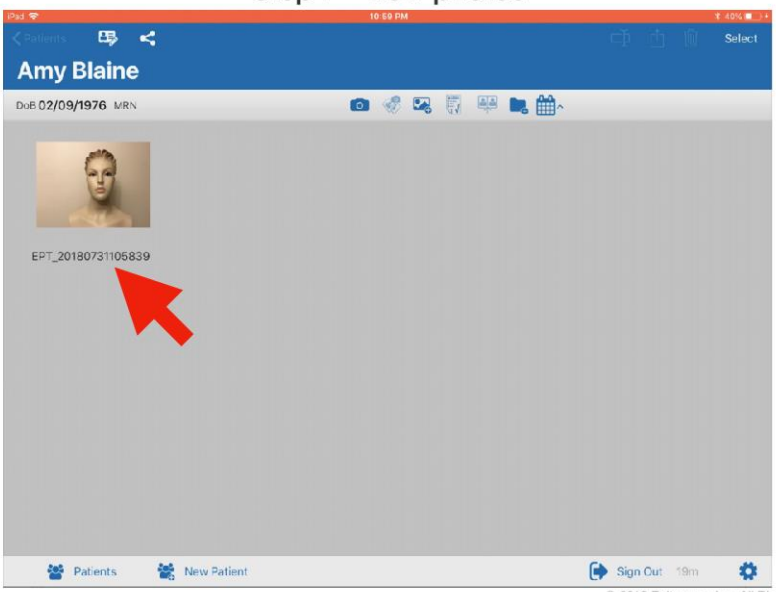
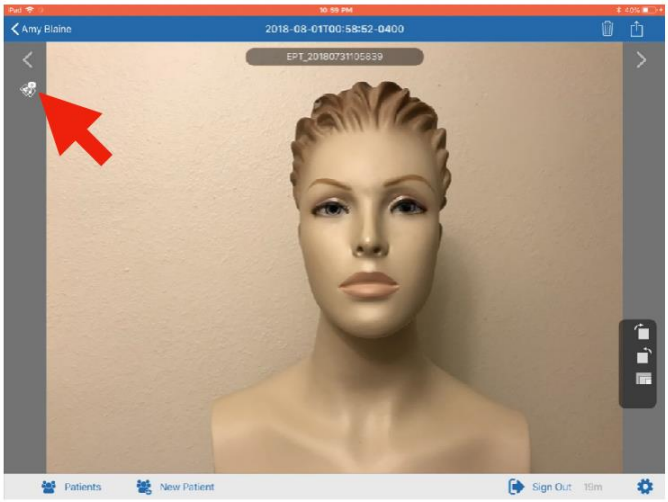
Step 7 - view photos



9

epitomyze intro

Step 9 - if desired, select live image overlay tool to reproduce angle and orientation of photo



11


epitomyze
intro
Step 10 - use slider to adjust transparency of overlay and capture photo, click done when finished
Done
12
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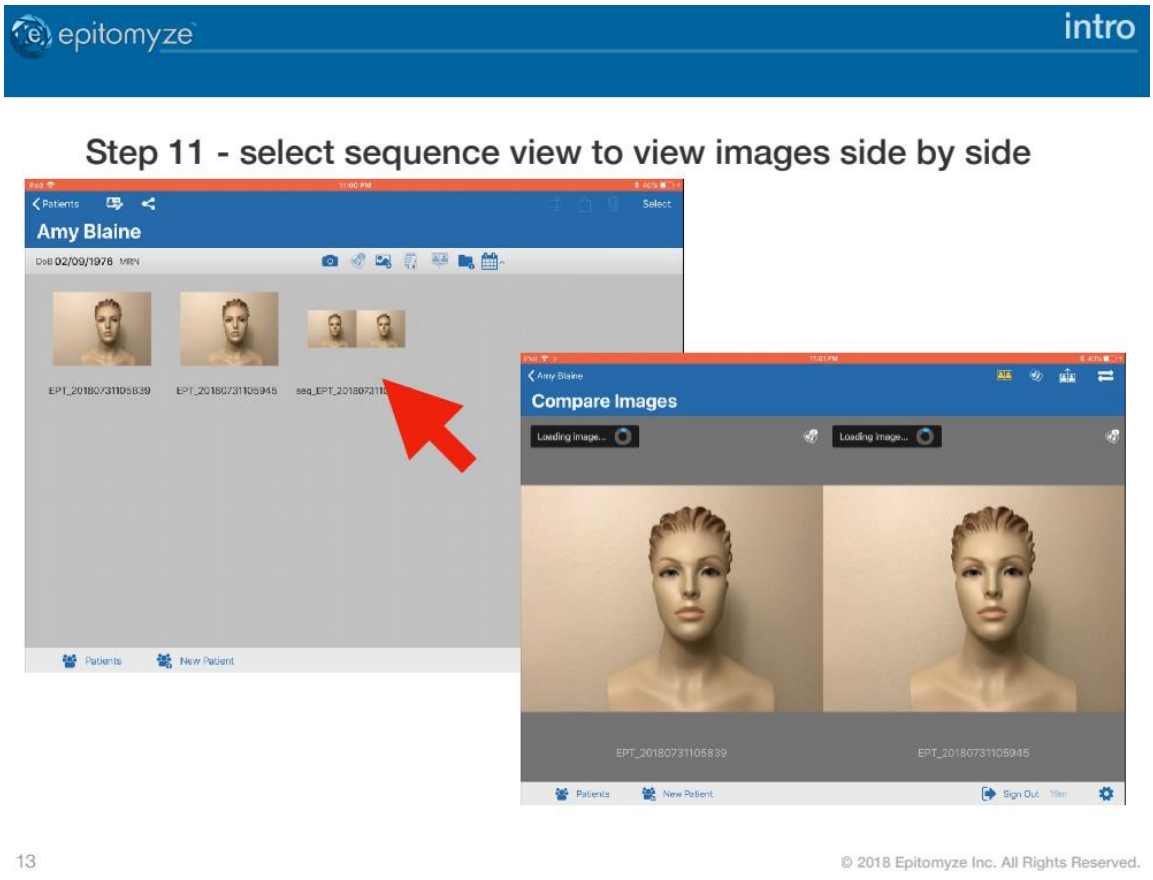

Video link for more detailed instruction (the video is long but most of what you should need is in the first 10 minutes): https://www.youtube.com/watch?v=_aCsUEeVnX0