CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201848Orig1s000

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document
HEPZATO KIT™ (melphalan) REMS

I. Administrative Information

Risk: severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events
Application Number: NDA 201848
Application Holder: Delcath Systems, Inc.
Initial REMS Approval: 08/2023

II. REMS Goal

The goal of the HEPZATO KIT REMS is to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

Objective: Minimize severe peri-procedural complications

III. REMS Requirements

Delcath Systems, Inc. must ensure that healthcare settings comply with the following requirements:

1. Healthcare settings that dispense HEPZATO KIT must:

To become certified to dispense	1. Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use. 2. Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications. 3. Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the REMS requirements on behalf of the healthcare setting. 4. Have the Authorized Representative review the product's Prescribing Information, Instructions for Use, Program Overview, and Didactic Modules. 5. Have the Authorized Representative enroll in the REMS by completing and submitting the Healthcare Setting Enrollment Form to the REMS. 6. Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT review the product's Prescribing Information and Instructions for Use. 7. Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT take the Program Overview, Didactic Modules, and Preceptorship training provided by Delcath Systems, Inc. 8. Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT

	successfully complete the Proctorship training provided by Delcath Systems, Inc., and successfully complete and submit the Criteria for Procedural Competency Checklist to the REMS. 9. Establish processes and procedures to ensure relevant new staff who will perform percutaneous hepatic perfusion procedures with HEPZATO KIT are trained.
Before administering	10. Obtain authorization to dispense each HEPZATO KIT by contacting the REMS to verify the percutaneous hepatic perfusion procedure team is qualified using the Procedure Team Qualification Status Form.
During and after administering, for at least 72 hours	11. Assess the patient for severe peri-procedural complications associated with HEPZATO KIT. Document and submit severe peri-procedural complications using the Severe Peri-Procedure-related Complications Adverse Events Documentation Form to the REMS.
To maintain certification to dispense, annually	12. Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use. 13. Have percutaneous hepatic perfusion procedure team members who have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter. 14. Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications. 15. If there is a change in Authorized Representative, have a new Authorized Representative enroll in the REMS by completing the Healthcare Setting Enrollment Form.
At all times	16. Maintain records of each percutaneous hepatic perfusion procedure team member's training. 17. Maintain records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation. 18. Maintain records that processes and procedures are in place and are being followed. 19. Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

Delcath Systems, Inc. must provide training to healthcare settings that dispense HEPZATO KIT.

The training includes the following educational materials: Program Overview, Didactic Modules. The training must be made available in hardcopy format and must be presented in-person or via live webcast.

The training also includes a Preceptorship (a live, in-person, observation experience) and a Proctorship (performing a live, in-person, percutaneous hepatic perfusion procedure with HEPZATO KIT observed and

evaluated by a Delcath Systems, Inc. representative) documented with a Criteria for Procedural Competency Checklist.

To support REMS operations, Delcath Systems, Inc. must:

1. Ensure the HEPZATO KIT is only distributed to certified healthcare settings.

2. Authorize dispensing for each procedure based on receipt of the Procedure Team Qualification Status Form to verify the percutaneous hepatic perfusion procedure team is qualified to perform procedures with HEPZATO KIT. The percutaneous hepatic perfusion procedure team is qualified if it includes healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use who have each successfully completed the training and performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.

   If the Procedure Team Qualification Status Form is not received and these criteria are not met, the healthcare setting is not authorized to dispense and administer HEPZATO KIT.

3. Establish and maintain a process to ensure that healthcare settings that want to become certified to dispense HEPZATO KIT and to maintain certification have a percutaneous hepatic perfusion procedure team with at least one healthcare provider with expertise in interventional radiology, anesthesiology, and perfusion, as described in the Instructions For Use.

4. Establish and maintain a REMS website, www.HEPZATOKITREMS.com. The REMS Website must include the option to complete all healthcare setting forms online and the option to print the Prescribing Information including Instructions For Use, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Website. The REMS website must not link back to the promotional product website(s).

5. Make the REMS website fully operational and all REMS materials available through the REMS Website or REMS Coordinating Center at the time HEPZATO KIT first becomes commercially available.

6. Establish and maintain a REMS Coordinating Center for the REMS participants 1-833-632-0457.

7. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS.

8. Ensure healthcare settings are able to enroll in the REMS via e-mail and online.

9. Ensure healthcare settings are able to obtain authorization to dispense and administer HEPZATO KIT by e-mail.

10. Notify healthcare settings within 7 calendar days after they become certified in the REMS.

11. Provide public access to a database of certified healthcare settings.

12. Report severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT as soon as possible to the FDA but no later than 15 calendar days from the initial receipt of the information by the applicant. This requirement does not affect the applicant's other reporting and follow-up requirements under applicable FDA regulations.

To ensure REMS participants' compliance with the REMS, Delcath Systems, Inc. must:

13. Verify annually that the certified healthcare setting has at least one qualified percutaneous hepatic perfusion procedure team(s) that includes at least one healthcare provider with expertise in

interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use and have performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter. If these qualifications are not met, the healthcare setting must have the healthcare provider(s) with the necessary expertise as described in the Instructions For Use complete the Didactic Modules and/or Proctorship training to re-certify.

14. Verify annually that the designated Authorized Representative's name and contact information correspond to those of the current designated Authorized Representative for the healthcare setting. If different, the healthcare setting must re-certify with a new Authorized Representative.

15. Establish and maintain a process to retrain percutaneous hepatic perfusion procedure team members who have not performed one procedure in the first six months following completion of the initial training, a second procedure in the next six months, and at least two procedures annually thereafter. The re-training must include the Didactic Modules. The Proctorship training must also be completed by a percutaneous hepatic perfusion procedure team member who has not performed a procedure with HEPZATO KIT within the preceding twelve months.

16. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: HEPZATO KIT distribution and dispensing; certification of healthcare settings, and audits of REMS participants. These records must be readily available for FDA inspections.

17. Establish and maintain a plan for addressing noncompliance with REMS requirements.

18. Monitor healthcare settings on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.

19. Audit annually: 1.) healthcare settings no later than 180 calendar days after the healthcare setting certification date and annually thereafter and 2.) the REMS Coordinating Center to ensure that all REMS processes and procedures are in place, functioning, and support the REMS requirements.

20. Take reasonable steps to improve operations of and compliance with the requirements in the HEPZATO KIT REMS based on monitoring and evaluation of the HEPZATO KIT REMS.

IV. REMS Assessment Timetable

Delcath Systems, Inc. must submit REMS Assessments at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (08/14/2023). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Delcath Systems, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the HEPZATO KIT REMS:

Enrollment Forms

Healthcare Setting:

1. Healthcare Setting Enrollment Form

Training and Educational Materials

Healthcare Setting:

2. Program Overview
3. Didactic Modules
4. Criteria for Procedural Competency Checklist

Patient Care Form

5. Severe Peri-Procedure-related Complications Adverse Events Documentation Form

Other Materials

6. Procedure Team Qualification Status Form
7. REMS Website

VI. Statutory Elements

This REMS is required under section 505-1 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1) and consists of the following elements:

1. Elements to Assure Safe Use:

- Health care settings that dispense HEPZATO KIT are specially certified under 505-1(f)(3)(B)
- HEPZATO KIT is dispensed to patients only in certain health care settings under 505-1(f)(3)(C)
- HEPZATO KIT is dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D)
- Each patient using HEPZATO KIT is subject to certain monitoring under 505-1(f)(3)(E)

2. Implementation System

3. Timetable for Submission of Assessments

Hepzato Kit
(HEPZATO for Injection / Hepatic Delivery System)

Healthcare Setting Enrollment Form

Phone: 1-833-632-0457
Email: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

Due to the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events, HEPZATO KIT is available only through a restricted program called the HEPZATO KIT REMS (Risk Evaluation and Mitigation Strategy). In order to dispense the HEPZATO KIT, healthcare settings must be certified in the HEPZATO KIT REMS.

Healthcare settings must designate an Authorized Representative to:

- Complete the certification process by completing the **Healthcare Setting Enrollment Form** on behalf of the healthcare setting.
- Oversee implementation and compliance with the HEPZATO KIT REMS requirements as outlined below.

Complete all required fields below and submit this enrollment form to the REMS Coordinating Center to via e-mail at coordinator@HEPZATOKITREMS.com or complete it online at www.HEPZATOKITREMS.com.

- Product orders cannot be placed until the healthcare setting certification is complete.
- Completion of this form does not guarantee your healthcare setting will be certified to dispense the HEPZATO KIT.
- The HEPZATO KIT REMS will provide confirmation of certification via e-mail after processing this form.

For additional information, or more copies of any of the HEPZATO KIT REMS materials, please visit the REMS Website at www.HEPZATOKITREMS.com or call the HEPZATO KIT REMS Coordinating Center at 1-833-632-0457.

HEALTHCARE SETTING INFORMATION (all fields are required)

☐ New Certification ☐ Change in Authorized Representative

Healthcare Setting Name:		
Address:		
City:	State:	ZIP Code:

AUTHORIZED REPRESENTATIVE RESPONSIBILITIES

On behalf of my healthcare setting, I am the Authorized Representative, designated by my healthcare setting, to carry out the certification process and oversee implementation and compliance with the HEPZATO KIT REMS on behalf of the healthcare setting.

To become certified to dispense, the healthcare setting must:

- Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.

As the Authorized Representative, I must:

- Review the product's Prescribing Information, Instructions for Use, **Program Overview**, and **Didactic Modules**.
- Enroll in the REMS by completing and submitting the **Healthcare Setting Enrollment Form** to the REMS.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT review the product's Prescribing Information and Instructions for Use.

REMS Use Only
Tracking Number:

Date:

- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT take the **Program Overview**, **Didactic Modules**, and Preceptorship training provided by Delcath Systems, Inc.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT successfully complete the Proctorship training and successfully complete and submit the **Criteria for Procedural Competency Checklist** to the REMS.
- Establish processes and procedures to ensure relevant new staff who will perform percutaneous hepatic perfusion procedures with HEPZATO KIT are trained.

Before administering, I and/or the healthcare setting staff must:

- Obtain authorization to dispense each HEPZATO KIT by contacting the REMS to verify the percutaneous hepatic perfusion procedure team is qualified using the **Procedure Team Qualification Status Form**.

During and after administering, for at least 72 hours, I and/or the healthcare setting staff must:

- Assess the patient for severe peri-procedural complications associated with HEPZATO KIT.
- Document and submit severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** to the REMS.

To maintain certification to dispense, annually, I must:

- Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use.
- Have percutaneous hepatic perfusion procedure team members who have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.
- If there is a change in Authorized Representative, have a new Authorized Representative enroll in the REMS by completing the **Healthcare Setting Enrollment Form**.

At all times, I must:

- Maintain records of each percutaneous hepatic perfusion procedure team member's training.
- Maintain records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation.
- Maintain records that processes and procedures are in place and are being followed.
- Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

By signing this form, I agree, on behalf of myself and my healthcare setting(s), to comply with all REMS Requirements.

AUTHORIZED REPRESENTATIVE INFORMATION (all fields are required)		
First Name:	Last Name:	
Credentials: ☐ MD ☐ DO ☐ RN ☐ PharmD/RPh ☐ NP/PA ☐ Other (please specify)		
Department:		
Phone:		E-mail:
Authorized Representative Signature:		**Date (MM/DD/YYYY):**

Authorized Representatives are encouraged to report any other serious adverse events to Delcath Systems, Inc. at 1-833-632-0458 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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REMS Use Only
Tracking Number:

Date:

HEPZATO KIT REMS Program

Phone: 1-833-632-0457
Email: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

What is the HEPZATO KIT REMS?

The HEPZATO KIT REMS (Risk Evaluation and Mitigation Strategy) is required by the US Food and Drug Administration (FDA) to ensure that the benefits of HEPZATO KIT outweigh the risks.

The goal of the HEPZATO KIT REMS is to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

Severe Peri-Procedural Complications

- Hemorrhage, hepatocellular injury, and thromboembolic events have been observed when HEPZATO has been administered via hepatic intra-arterial administration.
- Administration of HEPZATO requires general anesthesia and extracorporeal bypass of circulation which may cause life threatening or fatal adverse effects.
- Ensure the patient is euvolemic but do not overhydrate the patient.
- Monitor for these peri-procedural complications during the procedure and for at least 72 hours following the procedure.

What is the HEPZATO KIT?

HEPZATO KIT (HEPZATO for Injection/Hepatic Delivery System) is a closed circuit of catheters and filters utilized to deliver HEPZATO (melphalan) to the hepatic artery and to lower the concentration of the agent in the blood before it is returned to systemic circulation.

HEPZATO KIT (HEPZATO for Injection/Hepatic Delivery System) is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.

What are the HEPZATO KIT REMS requirements?

- Only certified healthcare settings can dispense HEPZATO KIT
- Certified healthcare settings must:
  - Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
  - Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.
  - Designate an Authorized Representative (AR) to carry out the certification process and oversee implementation and compliance with the REMS requirements on behalf of the healthcare setting.
- The percutaneous hepatic perfusion procedure team members must complete training to participate in procedures with HEPZATO KIT.
- During and after administering, for at least 72 hours, the healthcare setting must assess the patient for severe peri-procedural complications associated with HEPZATO KIT, document severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit to the REMS.

How does a healthcare setting become certified in the HEPZATO KIT REMS?

The healthcare setting must designate an AR to carry out the certification process and oversee implementation and compliance with the REMS requirements on behalf of the Healthcare Setting.

The AR must:

- Review the product's Prescribing Information, Instructions for Use, **Program Overview**, and **Didactic Modules.**
- Enroll in the REMS Program by completing and submitting the **Healthcare Setting Enrollment Form** to the REMS.
- Have the percutaneous hepatic perfusion team member that performs procedures with HEPZATO KIT review the product's Prescribing Information and Instructions for Use.
- Have the percutaneous hepatic perfusion team members that performs procedures with HEPZATO KIT review the **Program Overview**, **Didactic Modules**, and undergo the Preceptorship training provided by Delcath Systems, Inc.
- Have the percutaneous hepatic perfusion team members that performs procedures with HEPZATO KIT successfully complete the Proctorship training and complete and submit the **Criteria for Procedural Competency Checklist** to the REMS.
    - Delcath Systems, Inc. will coordinate with the AR to schedule the Preceptorship training and Proctorship training.
- Establish processes and procedures to ensure relevant staff who are new to the team and will perform percutaneous hepatic perfusion procedures with HEPZATO KIT are trained
    - Completed checklists should be maintained in training records at the healthcare setting.
- At all times:
    - Maintain records of each percutaneous hepatic perfusion procedure team member's training.
    - Maintain records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation.
    - Maintain records that processes and procedures are in place and are being followed.
    - Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

What does a healthcare setting need to do prior to administration of HEPZATO KIT?

Before administering, the authorized representative and/or healthcare setting staff must obtain authorization to dispense each HEPZATO KIT by contacting the REMS to verify the percutaneous hepatic perfusion procedure team is qualified using the **Procedure Team Qualification Status Form**

- The **Procedure Team Qualification Status Form** is used to document the dates each PHP team member completed their training and the dates of two prior procedures performed with HEPZATO KIT.
- The REMS will provide authorization for the healthcare setting to dispense HEPZATO KIT once the form is processed.
- If the **Procedure Team Qualification Status Form** is not received and these criteria are not met, the Healthcare Setting is not authorized to dispense HEPZATO KIT.

What does a healthcare setting need to do during and after administration of HEPZATO KIT?

During and after administering, for at least 72 hours, the healthcare setting must assess the patient for severe peri-procedural complications associated with HEPZATO KIT. If severe peri-procedural complications occur, the healthcare setting must document the adverse event using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit the form to the REMS**.**

All materials are available at www.HEPZATOKITREMS.com or by calling the REMS Coordinating Center at 1-833-632-0457.

Authorized Representatives can enroll online at www.HEPZATOKITREMS.com or by e-mail at coordinator@HEPZATOKITREMS.com.

Delcath

HEPZATO KIT contains HEPZATO (melphalan) for Injection/ Hepatic Delivery System (HDS)

Percutaneous Hepatic Perfusion Procedure

REMS Didactic Modules Training Program Modules 1 - 9

XXXXXXX.01
Effective Date: YYYY-MM-DD

Reference ID: 5226627

HEPZATO KIT REMS
Didactic Modules Training Overview

HEPZATO KIT Instructions For Use

Delcath Systems, Inc.’s detailed description of the clinical use of the HEPZATO KIT can be found in the Instructions For Use manual (IFU) and in the US Prescribing Information.

The IFU and US Prescribing Information should be thoroughly reviewed prior to training.

HEPZATO KIT REMS Didactic Modules Training Overview

- This Didactic training is intended to educate the Healthcare Setting staff on the Risk Evaluation and Mitigation Strategy (REMS) and the safe and effective use of HEPZATO (melphalan) and the HEPZATO KIT Hepatic Delivery System (HDS).
- HEPZATO KIT is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.
- HEPZATO KIT should only be utilized for percutaneous hepatic procedures (PHP) performed by qualified personnel trained in accordance with the IFU and the PI.

HEPZATO KIT REMS Didactic Modules Training Overview

- This training is comprised of nine didactic Modules
- Training requirements are established for each specialist role of the PHP Procedure team
- All PHP Procedure team members are required to complete the didactic module that provides an overview for their role in the procedure

Module #	Module	IR	Anesthesiology	Perfusionist
1	REMS Program Details and Requirements	Required	Required	Required
2	HEPZATO Overview	Required	Required	Required
3	Treatment Planning	Required	Required	Required
4	Perfusion Circuit	Optional	Required	Required
5	Drug Preparation & Injection	Optional	Optional	Required
6	Procedure Day	Required	Required	Required
7	Catheterization & Drug Infusion	Required	Optional	Required
8	Hemodynamics Management	Optional	Required	Optional
9	Post Procedure	Optional	Required	Optional

The Oncologist and other staff members may also complete Didactic Module training but are not required to complete this training.

HEPZATO KIT Clinical Treatment Team

HEPZATO KIT Clinical Treatment Team

PHP PROCEDURE TEAM (REQUIRES REMS TRAINING)

- **INTERVENTIONAL RADIOLOGIST (IR)**
  - IR or Surgical Oncologist must be the LEADER during the procedure and communication is paramount
- **ANESTHESIOLOGIST (AN)**
- **PERFUSIONIST (PF)**

OTHER HEPZATO KIT CLINICAL TREATMENT TEAM MEMBERS (DO NOT REQUIRE REMS TRAINING)

- **ONCOLOGIST** (Medical and/or Surgical; SO/MO)
  - Must commit to managing the patient before and after the procedure
  - May be involved during the procedure
- **PHARMACIST**
- **REGISTERED NURSE (RN)**
- **INTERVENTIONAL RADIOLOGY STAFF**
- **INTENSIVIST or CRITICAL CARE SPECIALIST**
  - Manages patient immediately post-procedure along with the SO/MO

Each health care professional must communicate and collaborate to ensure that each of the individual procedures are appropriately timed.

Module 1
Risk Evaluation and Mitigation Strategy (REMS) Program Details and Requirements

Delcath

Reference ID: 5226627

HEPZATO KIT REMS Didactic Modules Training

This educational didactic module contains information on serious adverse events associated with the use of HEPZATO KIT, including the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events. This is not a comprehensive list of adverse events associated with HEPZATO KIT. Please refer to the prescribing information for a comprehensive list of adverse events.

HEPZATO Indication

HEPZATO is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation.

What is a REMS?

- A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of HEPZATO KIT outweigh its risks.

- The goal of the HEPZATO KIT REMS is to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

HEPZATO KIT REMS Summary

- HEPZATO KIT is only available through the HEPZATO KIT REMS
- Healthcare settings that dispense HEPZATO KIT must be certified in the REMS
- PHP procedure team members that perform procedures with HEPZATO KIT must be trained

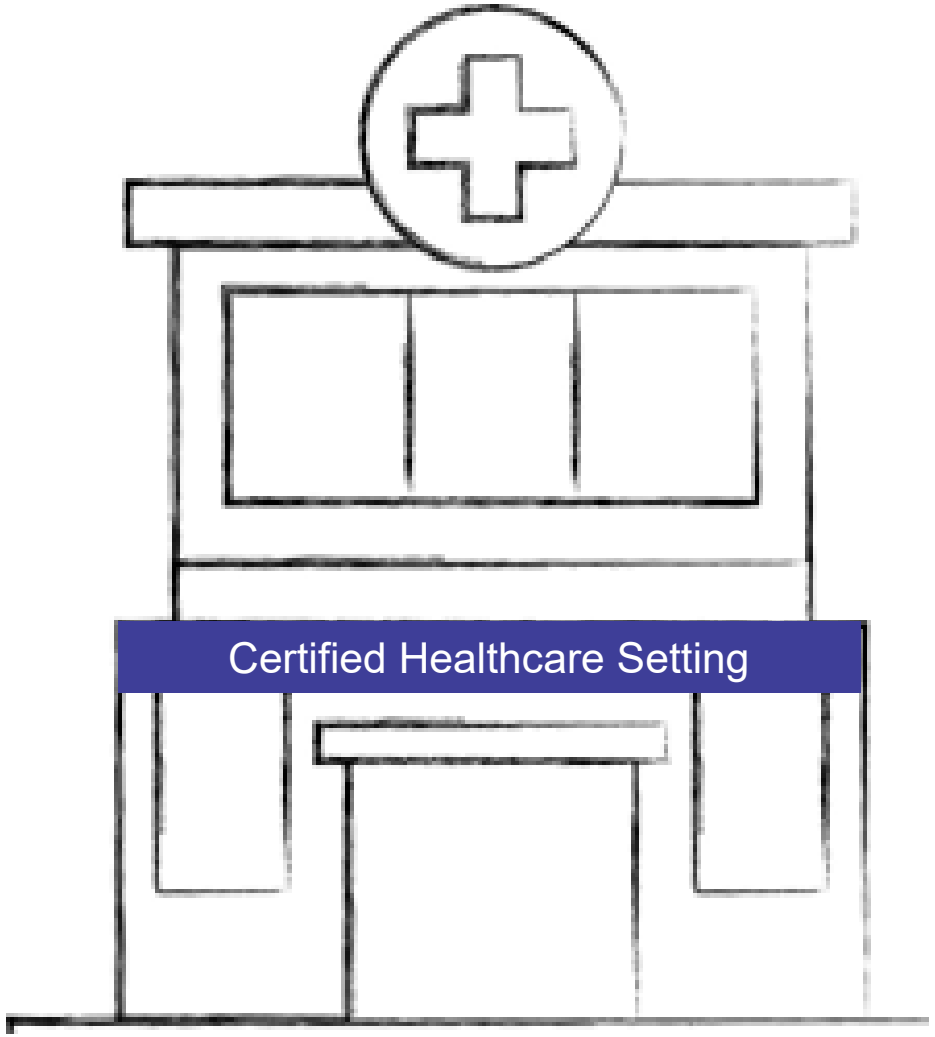
HEPZATO KIT Clinical Treatment Team

PHP Procedure Team

Interventional Radiologist

Anesthesiologist

Perfusionist



HEPZATO KIT Clinical Treatment Team - Others

Oncologist

Pharmacist

Chemotherapy HCP

Intensivist

Delcath

Percutaneous Hepatic Perfusion (PHP) Procedure Team

The percutaneous hepatic perfusion procedure team(s) must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion in accordance with the Instructions for Use.


Interventional Radiologist


Anesthesiologist


Perfusionist

Healthcare Setting Certification Requirements

As a condition of certification, the Healthcare Setting must:

- Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications

Authorized Representative Requirements

- The Healthcare Setting must designate an Authorized Representative (AR) to carry out the certification process and oversee implementation and compliance with the REMS requirements on behalf of the healthcare setting
- To become a certified, the Authorized Representative must:
  - Carry out the certification process and oversee implementation and compliance with the REMS requirements on behalf of the healthcare setting.
  - Review HEPZATO KIT REMS Prescribing Information, Instructions for Use, **Program Overview**, and this **Didactic Modules**
  - Enroll in the REMS Program by completing and submitting the **Healthcare Setting Enrollment Form** to the REMS
  - Establish processes and procedures to ensure new members of the PHP procedure team are trained and successfully complete the Proctorship training and complete and submit the **Criteria for Procedural Competency Checklist** to the REMS.

Who Can Be an Authorized Representative?

An Authorized Representative at the Healthcare Setting can be a:

- Physician
- Nurse
- Pharmacist
- Administrator
- Any responsible individual assigned by the Healthcare Setting

Percutaneous Hepatic Perfusion (PHP) Team Requirements

The PHP Procedural Team will be required to:

- Review the HEPZATO Prescribing Information and HEPZATO KIT Instructions for Use
- Review the **Program Overview**, this **Didactic Module** and undergo the Preceptorship Training provided by Delcath System, Inc.
- Successfully complete the Proctorship and **Criteria for Procedural Competency Checklist**

Before HEPZATO KIT Administration

Before administering HEPZATO KIT, the Healthcare Setting must:

- Obtain an authorization to dispense by contacting the REMS Coordinating Center to verify the PHP Procedure Team is qualified using the **Procedure Team Qualification Form**

During HEPZATO KIT Administration

During and for a minimum of 72 hours after the PHP procedure, the Healthcare Setting must:

- Assess the patient for severe peri-procedural complications associated with HEPZATO KIT.
- Document severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit to the REMS.
- Follow up may be virtual or via telephone in patients discharged prior to 72 hours

Maintain Healthcare Setting Certification

- To maintain the ability to dispense the HEPZATO KIT, a Healthcare Setting must:
  - Have a PHP procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion
  - Have PHP team members who have each performed one PHP procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter
  - Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications
  - Have a new Authorized Representative enroll in the REMS by completing the **Healthcare Setting Enrollment Form** and submitting it to the REMS

Healthcare Setting Responsibilities

- At all times, the Healthcare Setting must:
  - Maintain records of each PHP team members training
  - Maintain records of the PHP procedures performed with HEPZATO KIT and the associated PHP procedure team members' participation
  - Maintain records that indicate the processes and procedure are in place and being followed
  - Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all REMS specific processes and procedures are in place and being followed

HEPZATO KIT REMS Materials Summary

Program Overview	• Reviewed by the Authorized Representative and the PHP procedure team members • Educates on the key risks, management of the risks, and REMS requirements
Didactic Modules	• Reviewed by the Authorized Representative and the PHP procedure team members • Educates on the key risks, management of the risks, and REMS requirements
Healthcare Setting Enrollment Form	• Completed and submitted by a designated Authorized Representative • Agreement to comply with the REMS requirements
Criteria for Procedural Competency Checklist	• Completed by the PHP procedure team members as part of the Proctorship • Retained on-site as documentation of training and submitted to the REMS
Procedure Team Qualification Status Form	• Completed and submitted by the Authorized Representative and/or Healthcare Setting staff to obtain authorization to dispense each HEPZATO KIT to verify the PHP procedure team is qualified
Severe Peri-Procedure-Related Complications Adverse Events Documentation Form	• Completed and submitted by the Healthcare Setting to report any severe peri-procedural complications associated with HEPZATO KIT during and after administration for at least 72 hours
REMS Program Website	• Dedicated resource for REMS information

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HEPZATO KIT Procedural Overview

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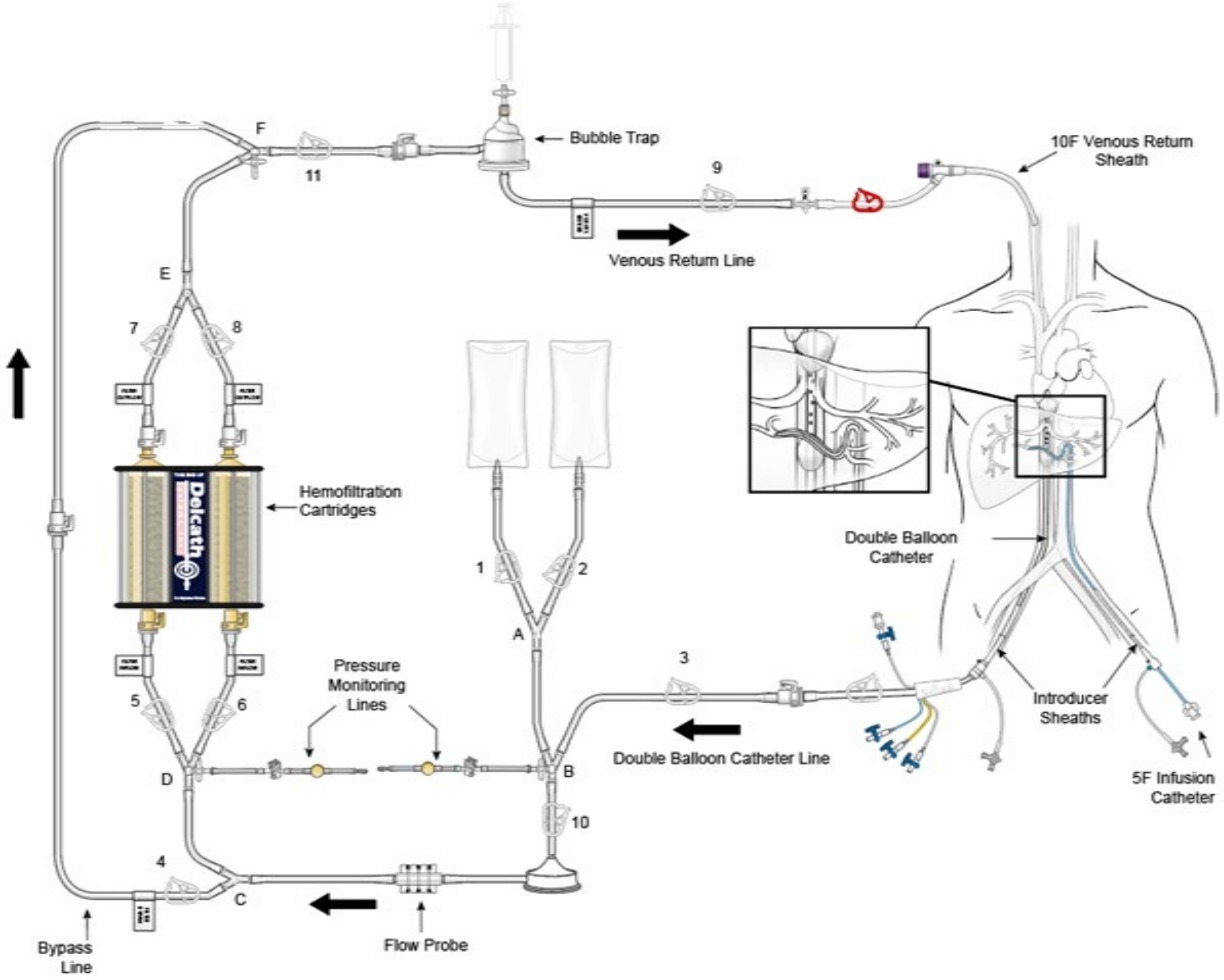
HEPZATO KIT

- HEPZATO KIT is a closed circuit of catheters and filters utilized to deliver a chemotherapeutic agent (melphalan) directly with simultaneous filtration of hepatic venous blood during drug infusion and washout, which results in loco-regional delivery of a relatively high melphalan dose but also reduced systemic exposure.
- There are risks including peri-procedural complications that may be severe and or life threatening
  - The prominent risks include hemorrhage, hepatocellular injury, and thromboembolic events



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Severe Peri-Procedural Complications

- **Hemorrhage, hepatocellular injury, and thromboembolic events have been observed when HEPZATO has been administered via hepatic intra-arterial administration.**
- Administration of HEPZATO requires general anesthesia and extracorporeal bypass of circulation which may cause life threatening or fatal adverse effects
- Ensure the patient is euvolemic but do not overhydrate the patient.
- Monitor for these peri-procedural complications during the procedure and for at least 72 hours following the procedure.

Contraindications

HEPZATO KIT is contraindicated in patients with:

- Active intracranial metastases or brain lesions with a propensity to bleed
- Liver failure, portal hypertension, or known varices at risk for bleeding
- Surgery or medical treatment of the liver in the previous 4 weeks
- Active cardiac conditions including, but not limited to, unstable coronary syndromes (unstable or severe angina or myocardial infarction), worsening or new-onset congestive heart failure, significant arrhythmias, or severe valvular disease
- History of allergies or known hypersensitivity to melphalan or a component or material utilized within the HEPZATO KIT including natural rubber latex, heparin, and severe hypersensitivity to iodinated contrast not controlled by antihistamines and steroids

Warnings and Precautions (1)

- Hemorrhage, hepatocellular injury, and thromboembolic events have been observed when melphalan has been administered via hepatic intra-arterial administration of HEPZATO. Administration of HEPZATO requires general anesthesia and extracorporeal bypass of circulation which may cause life threatening or fatal adverse effects. Ensure the patient is euvolemic but do not overhydrate the patient. Monitor for these peri-procedural complications during the procedure and for at least 72 hours following the procedure.
- To mitigate the risk of thromboembolic events, administer anticoagulation as described in the IFU during the procedure.

Warnings and Precautions (2)

- Due to the risk of bleeding, do not use in patients with uncorrectable coagulopathies and delay treatment with the HEPZATO KIT for at least 4 weeks after surgery or other medical procedure involving the liver. Platelets and clotting factors may be removed during the HEPZATO KIT procedure. Monitor platelets and coagulation parameters as described in the IFU. If life-threatening bleeding occurs during the procedure, reverse anticoagulation as described in the IFU and correct coagulopathy as appropriate. Discontinue anticoagulation with warfarin or other oral anticoagulants prior to the procedure until hemostasis has been restored after the procedure and no bleeding complications have been observed. Refer to the Prescribing Information of the anticoagulant agent for bridging recommendations for anti-coagulation prior to surgical procedures. Discontinue drugs affecting platelet function such as aspirin, non-steroidal anti-inflammatory drugs, or other anti-platelet drugs one week before the procedure.

Warnings and Precautions (3)

- Patients with abnormal hepatic vascular (especially arterial supply) or biliary (especially re-implantation of bile duct) anatomy or gastric acid hypersecretion syndromes may be at increased risk of peri-procedural complications or other severe adverse reactions. Screen patients for a history of prior surgeries involving the bile duct to assess whether the patient is an appropriate candidate for HEPZATO KIT and monitor patients for adverse reactions following HEPZATO KIT administration.
- Procedure-related reductions in blood pressure including severe hypotension can occur during the HEPZATO KIT procedure. Closely monitor blood pressure during the procedure. Patients may require fluid support and vasopressors. To reduce the risk of severe hypotension, temporarily discontinue ACE-inhibitors, calcium channel blockers, or alpha-1-adrenergic blockers for at least 5 half-lives prior to treatment with the HEPZATO KIT. If necessary, use other short-acting antihypertensive drugs to manage blood pressure during the peri-procedure period.

Warnings and Precautions (4)

- Hematologic adverse reactions, including thrombocytopenia, anemia, and neutropenia have been reported in patients treated with HEPZATO. The risk of hematologic adverse reactions may be increased in patients who have received prior chemotherapy, bone irradiation, or who have compromised bone marrow function.
- Monitor patients for severe infections, bleeding, and symptomatic anemia. Only administer HEPZATO in patients with platelets >100,000/microliter, hemoglobin ≥10.0 gm/dL and neutrophils >2,000/microliter. Administer transfusions or growth factors as appropriate

Warnings and Precautions (5)

- Hypersensitivity reactions, including anaphylaxis, have occurred in approximately 2% of patients who received an intravenous (IV) formulation of melphalan. These reactions with melphalan are characterized by urticaria, pruritus, edema, skin rashes, and in some patients, tachycardia, bronchospasm, dyspnea, and hypotension. Hypersensitivity can occur in patients with or without prior exposure to IV or oral melphalan.
- When a hypersensitivity reaction is observed, immediately terminate the hepatic arterial HEPZATO infusion and administer necessary supportive care.
- Patients with a history of allergic reactions to iodinated contrast may experience hypersensitivity reactions, including anaphylaxis, during treatment with the HEPZATO KIT. Premedicate patients with a history of allergic reaction to iodinated contrast prior to treatment with HEPZATO KIT. Do not administer HEPZATO KIT in patients with a history of severe allergic reactions or anaphylaxis to iodinated contrast.

Warnings and Precautions (6)

- Gastrointestinal adverse reactions including nausea and vomiting, abdominal pain, and diarrhea are common, and occurred in 84% of patients treated with HEPZATO in the FOCUS trial. Administer a proton-pump inhibitor the day prior to and the morning of the procedure. If anti-emetic treatment is required, pre-medicate with anti-emetic therapy in subsequent cycles.
- Melphalan has been shown to cause chromatid or chromosome damage in humans. Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with intravenous alkylating drugs including melphalan. Some patients also received other chemotherapeutic agents or radiation therapy. Precise quantification of the risk of acute leukemia, myeloproliferative syndrome, or carcinoma is not possible. Published reports of leukemia in patients who have received oral or IV melphalan (and other alkylating drugs) suggest that the risk of leukemogenesis increases with chronicity of treatment and with cumulative dose.

Warnings and Precautions (7)

- Based on animal studies and its mechanism of action, melphalan can cause fetal harm when administered to a pregnant woman. Melphalan is genotoxic, targets actively dividing cells, and was embryolethal and teratogenic in rats. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with HEPZATO and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with HEPZATO and for 3 months after the last dose.
- Melphalan-based chemotherapy regimens have been reported to cause suppression of ovarian function in premenopausal women, resulting in persistent amenorrhea in approximately 9% of patients. Reversible or irreversible testicular suppression has also been reported.

ADVERSE EVENTS AND COMPLICATIONS

In the multicenter, open label pivotal study, [FOCUS (NCT02678572)], serious adverse reactions occurred in 45% of patients who received HEPZATO. Serious adverse reactions occurring in ≥ 2% of patients were thrombocytopenia (10%), neutropenia (8%), febrile neutropenia (7%), platelet count decreased (6%), leukopenia (4.2%), cardiac arrest (3.2%), neutrophil count decreased (2.1%), hypoxia (2.1%), pleural effusion (2.1%), pulmonary edema (2.1%), and deep vein thrombosis (2.1%). Fatal adverse reactions occurred in 3 (3.2%) patients who were treated with HEPZATO; these included cardiac arrest, acute hepatic failure and bacterial peritonitis.

Adverse Event Reporting

- Reporting of serious adverse events after administration of HEPZATO KIT is vital for the continued monitoring of the risk/benefit balance of the use of HEPZATO KIT
- Healthcare providers must report severe peri-procedural complications including adverse events of hemorrhage, hepatocellular injury, and thromboembolic events using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** to Delcath Systems, Inc. via e-mail at coordinator@HEPZATOKITREMS.com
- Healthcare providers are encouraged to report other adverse reactions to Delcath at 1-833-632-0458 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

HEPZATO KIT REMS Information

For further information, please visit
www.HEPZATOKITREMS.com or call 1-833-632-0457

HEPZATO KIT™

Reference ID: 5226627

Module 2
HEPZATO KIT Overview

Delcath

Reference ID: 5226627

Module 2 Purpose and Objectives

The introductory module provides a general overview of HEPZATO KIT and PHP procedure including target patient population and indication, contraindications, general safety and precautions, and clinical efficacy/safety information. Training will prepare HCPs for individual education modules based on specialized role.

- Understand the mechanism of action of melphalan and the HDS and how these components work as a system.
- Understand melphalan clinical pharmacology, the pharmacokinetic profile, and how the system limits melphalan systemic exposure.
- Review target patient population and indications, contraindications, precautions, and special populations.
- Understand the safety and adverse events profile for HEPZATO KIT and methods to mitigate adverse events.

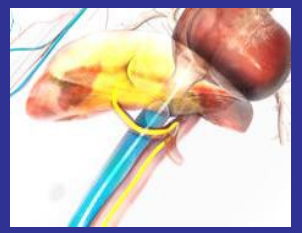
PHP Procedure with HEPZATO KIT

HEPZATO KIT is a drug/device combination product and is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver with no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amendable to resection or radiation.

The PHP Procedure with HEPZATO KIT is based on
3 principles

Isolation of the liver circulation through the occlusion of the inferior vena cava caudal and cranial of the hepatic veins.

Infusion of high dose melphalan directly into the liver to saturate hepatic parenchyma and residing cancer cells.



Filtration of the hepatic circulation to limit melphalan concentration before returning the blood to the systemic circulation thereby reducing melphalan systemic exposure.

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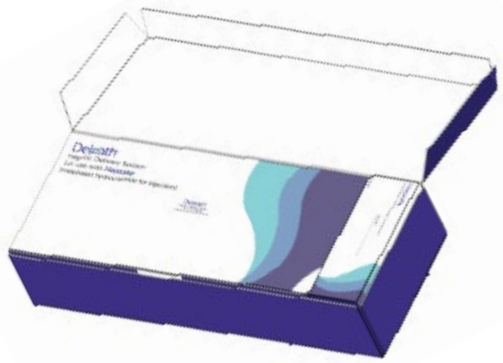
HEPZATO KIT System Components

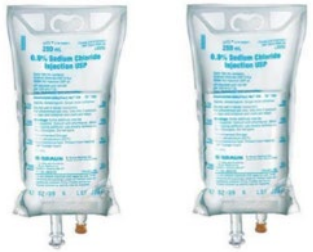
HEPZATO KIT consists of a closed circuit of catheters and drug specific filters utilized to deliver a chemotherapeutic agent (melphalan) to the hepatic artery and to lower the concentration of the agent in the blood before it is returned to systemic circulation.

HEPZATO KIT Shelf Box



(5x5) Melphalan Drug Pack

Secondary Diluent

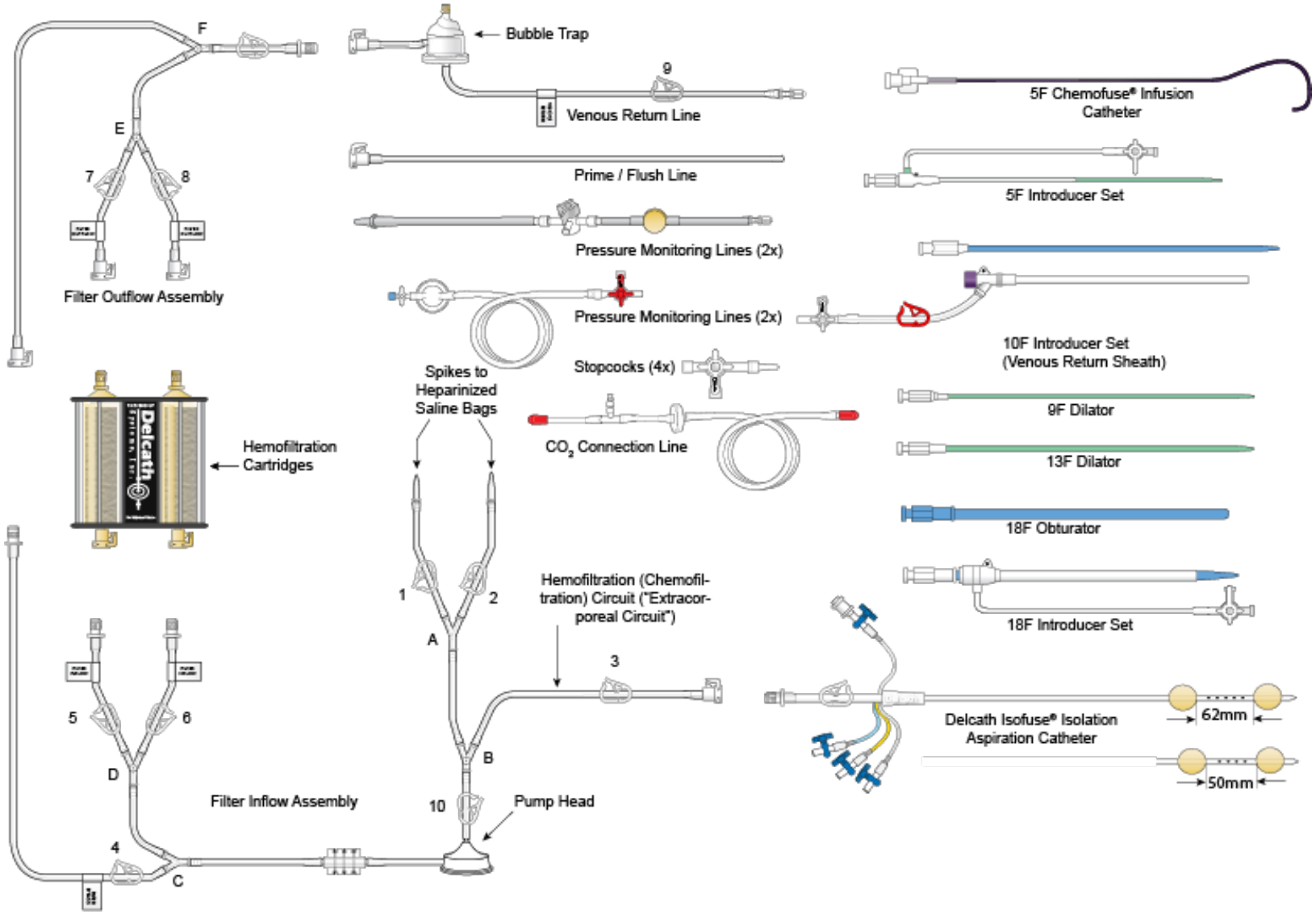


Drug KIT

HDS KIT

- **Double Balloon Catheter (DBC)**
- **Extracorporeal Circuit including Filter**
- **Sheaths and Obturators**
- **Multiple other smaller components**

Supplied Disposable Components



See IFU for full system description, including alphanumeric descriptions

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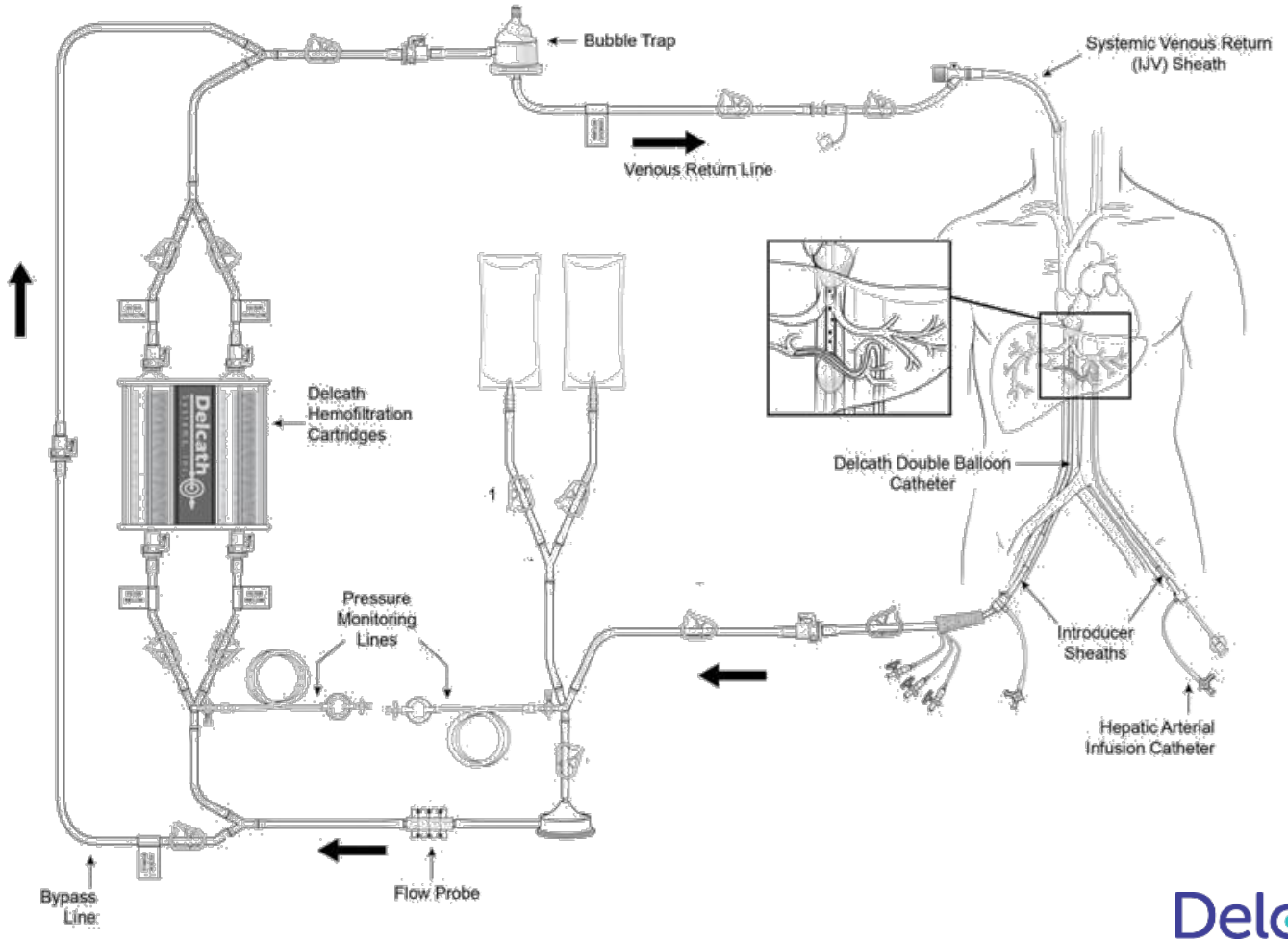
Assembled System

See IFU for full system description



Additional Items needed (not included)

- Bubble Trap holder
- Medtronic Bio-Console 560 Speed Controller System (“Pump”)
- Medtronic Bio-Probe TX50P (“Flow Transducer”)
- CO_2 Supply for Priming Dual Filter
- Drug Delivery Disposables:
  - One (1) Medrad 150mL Syringe (Polypropylene (PP)-Barrel & Polysioprene-Plunger) or equivalent
  - Two (2) Intravenous Administration Set with spike & drip chamber (Polyvinylchloride (PVC)-tubing, Acrylonitrile butadiene styrene (ABS) & Polyethylene (PE)-Drip Chamber & Polycarbonate (PC)-Luer) or equivalent
  - One (1) - 48” injector lines (PVC-Tubing & PC-Luer) or equivalent
  - Five (5) 3-way stopcocks (PC-body, High Density Polyethylene (HDPE) or Acetal-Handles) or equivalent
  - Three (3) 20 mL syringes (PP-Barrel & Polyisoprene-Plunger) or equivalent
- Microcatheters (Maximal Distal End OD = 2.8F) – for Selective Drug Infusion (at Interventional Radiologist discretion). Select one from Delcath qualified microcatheters listed below:
  - Merit Maestro (Merit Medical Systems, Inc., So. Jordan, UT, USA)
  - BSC Renegade Hi-Flo (Boston-Scientific Corp.; Natick, MA, USA)
  - Terumo Progreat (Terumo Medical Corp., Somerset, NJ, USA)

Healthcare Setting Requirements

The procedure must be performed in an appropriately equipped interventional radiology suite with fluoroscopy or an operating room designed and equipped similarly. Resuscitation personnel, equipment, and medication must be immediately available.

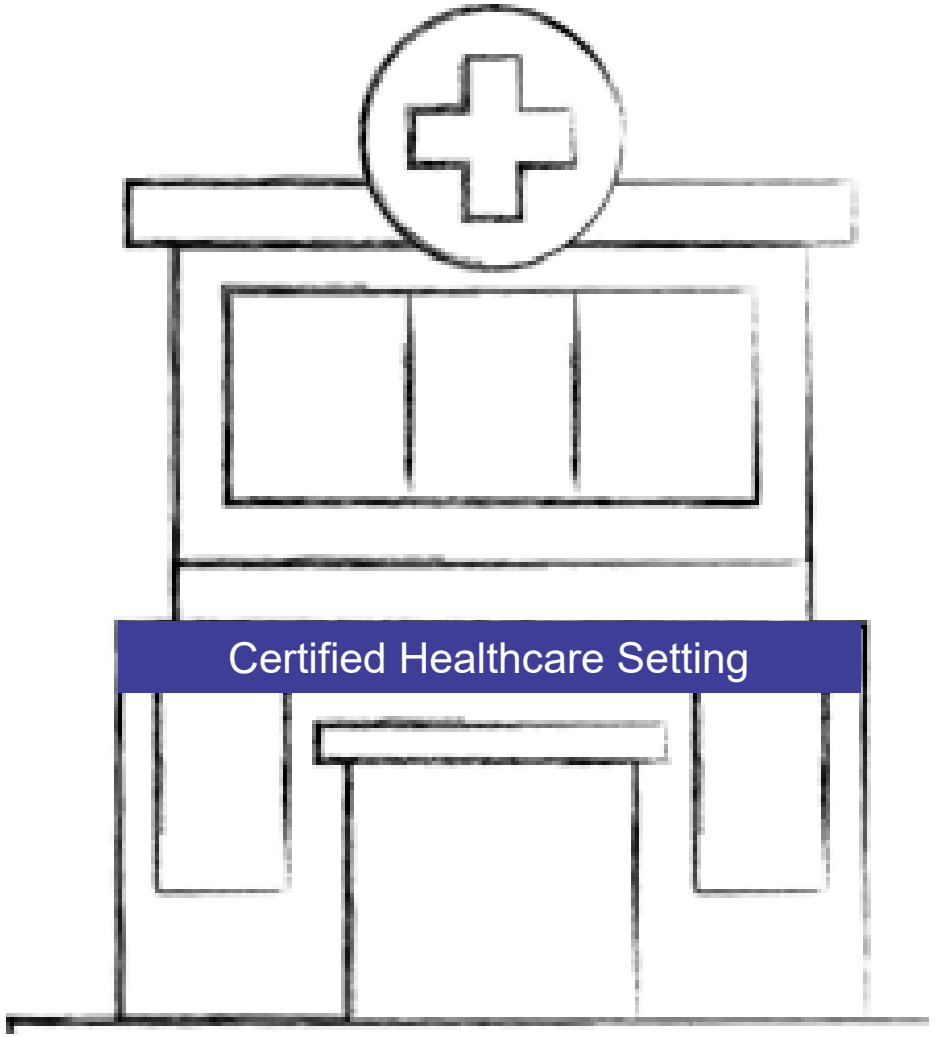
HEPZATO KIT Clinical Treatment Team

PHP Procedure Team Requires REMS Training

Interventional Radiologist

Anesthesiologist

Perfusionist



HEPZATO KIT Clinical Treatment Team – Others Do Not Require REMS Training

Oncologist

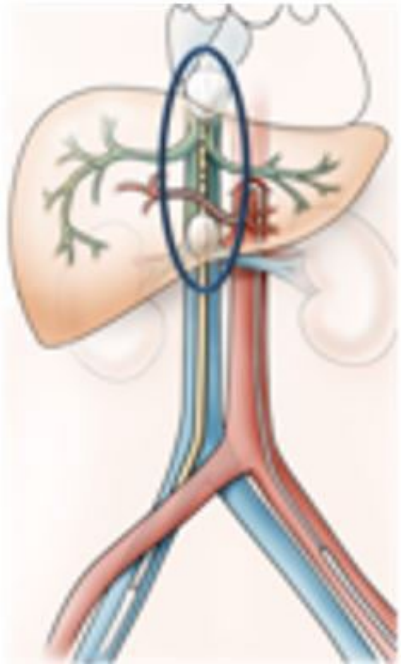
Pharmacist

Chemotherapy HCP

Intensivist

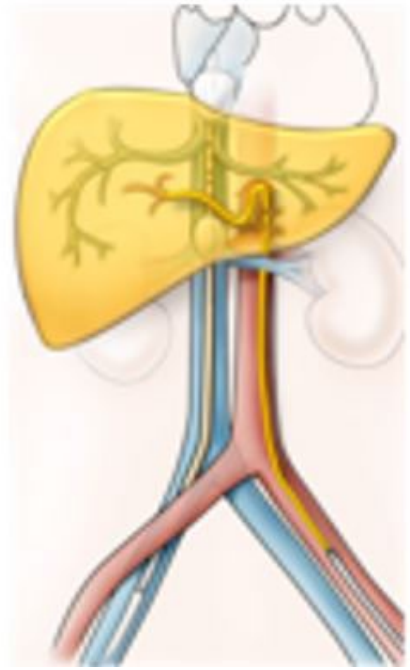
PHP Procedure with HEPZATO KIT

ISOLATION



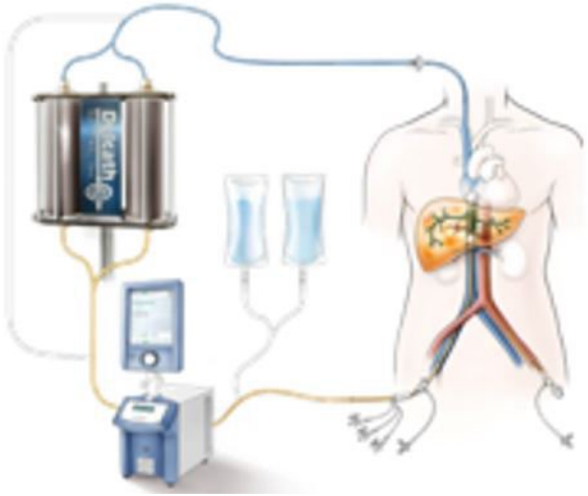
Isolates hepatic blood flow

SATURATION



A high dose of HEPZATO is delivered to the liver

FILTRATION

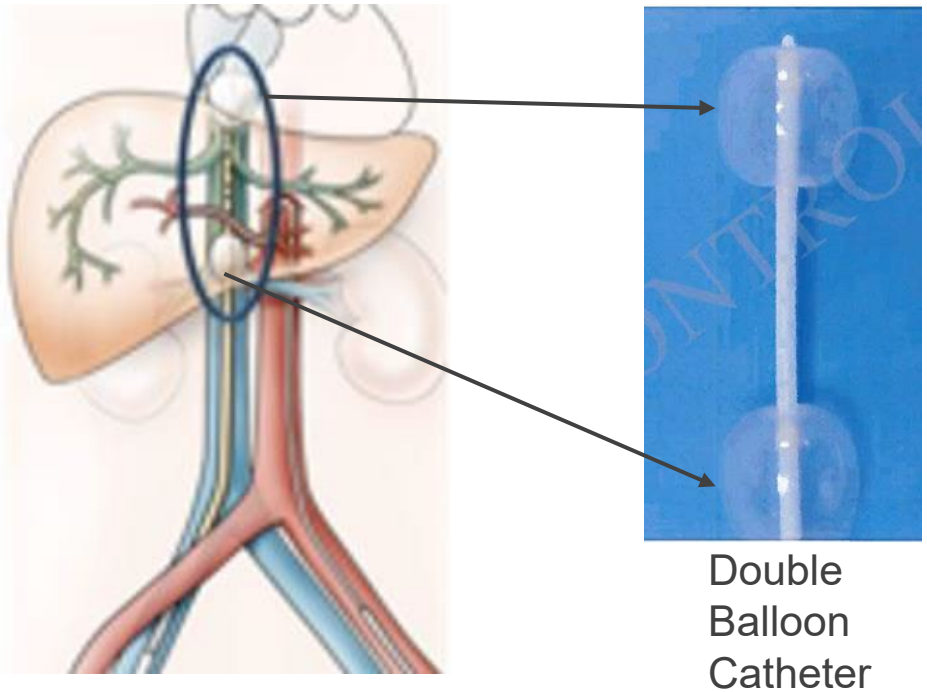


Venous blood from the liver is filtered to reduce melphalan concentration prior to returning the blood to systemic circulation

PHP Procedure with HEPZATO KIT

Isolation

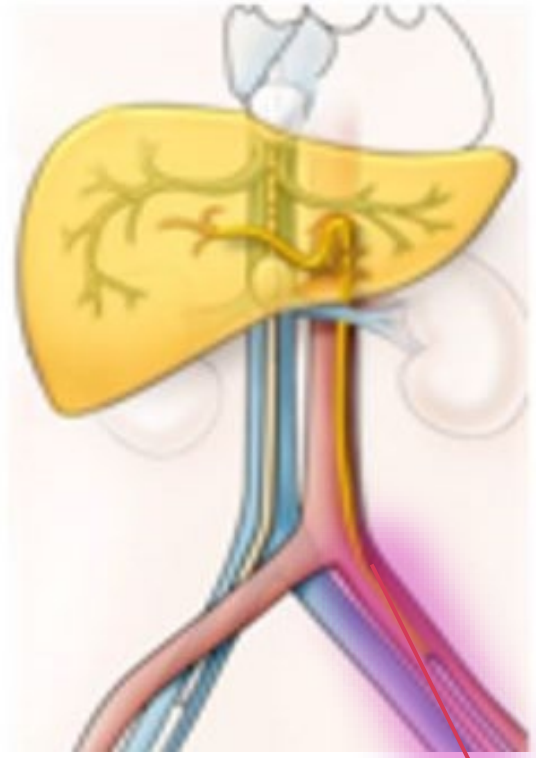
- The double balloon catheter allows for the isolation of the hepatic venous blood.
- Hepatic venous blood flow isolation allows melphalan to be concentrated within the liver.



Double Balloon Catheter

PHP Procedure with HEPZATO KIT

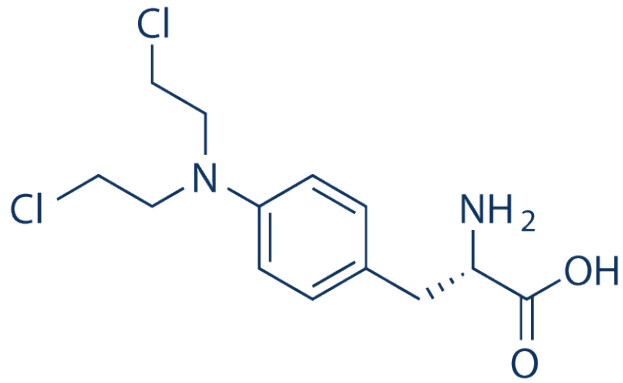
Saturation



- Saturation involves a high concentration of melphalan delivery to the liver through the hepatic artery.

HEPZATO (melphalan)

- It is used as a chemotherapy.
- It is also known as L-PAM pr L-phenylalanine.
- It is a bifunctional alkylating drug.

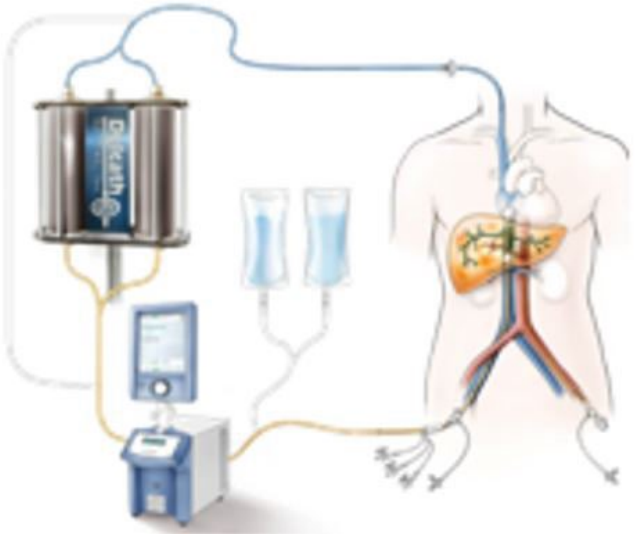


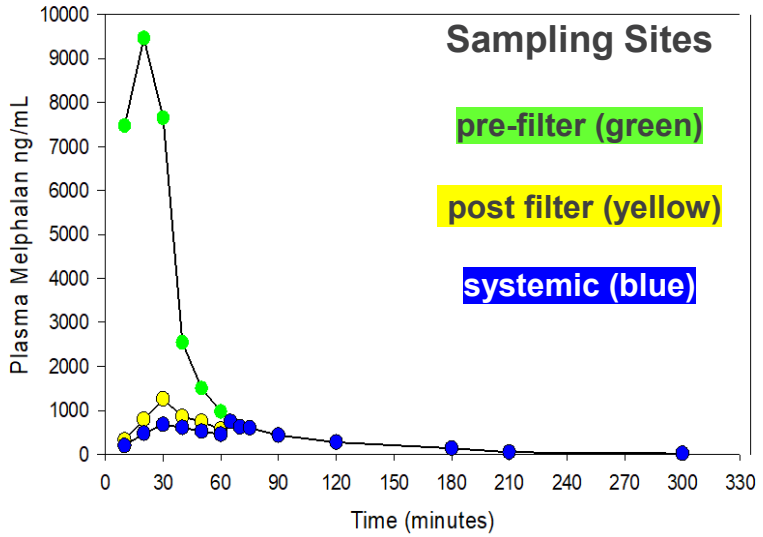
Vahrmeijer AL, van Dierendonck JH, Keizer HJ, Beijnen JH, Tollenaar RA, Pijl ME, et al. Increased local cytostatic drug exposure by isolated hepatic perfusion: a phase I clinical and pharmacologic evaluation of treatment with high dose melphalan in patients with colorectal cancer confined to the liver. Br JCancer. 2000;82(9):1539–46.

PHP Procedure with HEPZATO KIT

Filtration

- The extra corporeal bypass circuit reduces systemic melphalan exposure by ~90%.
- The majority of melphalan does not reach the systemic circulation due to the extracorporeal filtration procedure.





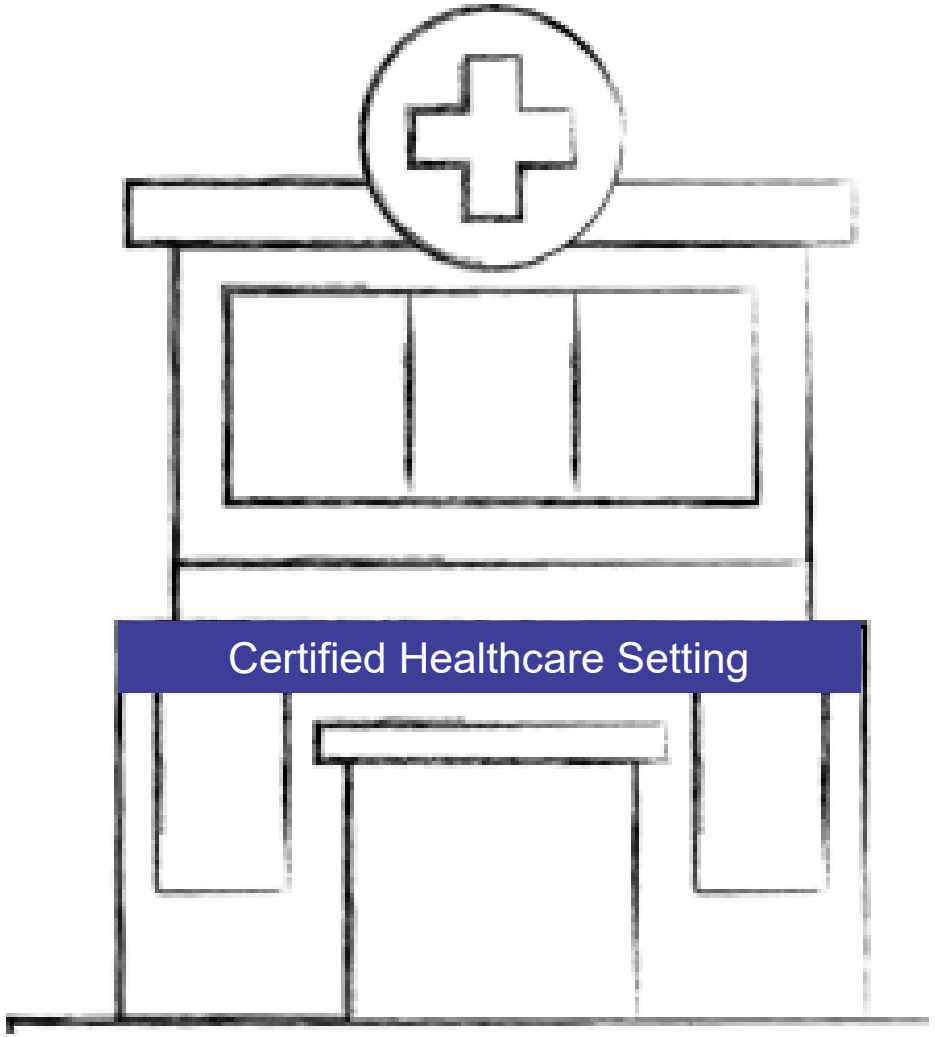
HEPZATO KIT Clinical Treatment Team

PHP Procedure Team Requires REMS Training

Interventional Radiologist

Anesthesiologist

Perfusionist



HEPZATO KIT Clinical Treatment Team – Others Do Not Require REMS Training

Oncologist

Pharmacist

Chemotherapy HCP

Intensivist

HEPZATO KIT Clinical Treatment Team

Oncologist (Medical Oncologist)

Experience
- Manage (metastatic) uveal melanoma patients
- Monitor and manage chemotherapy toxicities

Responsibilities
- Refer patient for PHP treatment
- Complete medical management of the patient pre- and post-operative care

Communicates
- Overall treatment plan and referrals

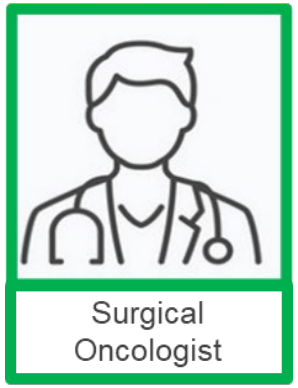
Coordinates with
- Interventional Radiologist, Surgical Oncologist, Anaesthesiologist, and other HCPs

HEPZATO KIT Clinical Treatment Team

Oncologist (Surgical Oncologist)

Experience
- Monitor and manage chemotherapy toxicities

Responsibilities
- May share leadership of procedure with the Interventional Radiologist
- Complete medical management of the patient pre- and post-operative care



Communicates
- HEPZATO use and risks
- HEPZATO KIT procedural risks

Coordinates with
- Medical Oncologist, Perfusionist, Surgical Oncologist, Anaesthesiologist, and other HCPs

HEPZATO KIT Clinical Treatment Team


Oncologist

Pre-Procedure	• Indications, contraindications, warnings and precautions • Clinical data summary: Efficacy and safety • Patient screening and eligibility • Pre procedure exam and prescribing pre procedure medications
Procedure	• Procedural related complications • HEPZATO dosing, preparation and delivery
Post-Procedure	• Mitigating and managing HEPZATO related adverse effects • Preparing patient for next treatment cycle

HEPZATO KIT PHP Procedure Team

Interventional Radiologist

Experience
- Advanced experience in vascular procedures and liver directed therapies

Responsibilities
- Leads the procedure
- Assess vascular anatomy
- Access vasculature using sheaths & catheters
- Inflate and deflate double balloons


Interventional Radiologist

Communicates
- Procedural directives
- Vascular anatomy and access
- Double balloon inflation

Coordinates with
- Perfusionist, Medical/Surgical Oncologist, Anaesthesiologist, and other HCPs

HEPZATO KIT PHP Procedure Team

Interventional Radiologist

Pre-Procedure	• Indications, contraindications, warnings and precautions • Clinical data summary: Efficacy and safety • Patient screening and eligibility • Identify HEPZATO infusion location based on disease burden and hepatic artery anatomy to ensure adequate drug infusion to the entire liver. • Pre procedure exam and prescribing pre procedure medications
Procedure	• HEPZATO KIT components and non-KIT required accessories • HEPZATO dosing, preparation and delivery • Vascular access sites and catheterization • Hepatic artery mapping and embolization when needed • Placing hepatic artery infusion catheter • Ordering and receiving HEPZATO

HEPZATO KIT PHP Procedure Team

Interventional Radiologist

Procedure (continued)	• Introducing and positioning the double balloon catheter (DBC). Technique for balloon expansion, catheter re-position, techniques for assessing and maintaining occlusion, troubleshooting, managing intra-procedural complications and catheter withdrawal. • Connecting extracorporeal circuit to patient • Expanding balloons • Administering HEPZATO • Monitoring for hepatic artery patency and/or spasm and methods to relieve spasm. • Procedural related complications
Post-Procedure	• Collapsing balloon, disconnecting from extracorporeal circuit and withdrawing catheters • Remove sheaths and close access sites • Monitor for bleeding

HEPZATO KIT PHP Procedure Team

Anesthesiologist

Experience
- Administration and monitoring of general anaesthesia
- Respiratory and cardiovascular surgical intervention and support

Responsibilities
- Management of sedation, analgesia, respiratory and blood pressure/ cardiovascular support
- Fluid administration and management
- Post procedure management


Anesthesiologist

Communicates
- Cardiac status – mean arterial pressure, blood pressure
- Vasopressor administration
- Respiratory status
- Post procedure protocol

Coordinates with
- Surgical Oncologist, Interventional Radiologist and Perfusionist, Intensivist

HEPZATO KIT PHP Procedure Team


Anesthesiologist

Pre-Procedure	• Patient assessment and eligibility for general anesthesia and mechanical ventilation • Patient screening for cardiac disease including coronary insufficiency, valvular heart disease and left ventricular systolic and diastolic dysfunction
Procedure	• Hemodynamic preparation and monitoring • Fluid preparation and management • Anticoagulation preparation and management • Vasopressor preparation and management • Preparing for Double Balloon Catheter balloon expansion in the IVC • Preparing for filters going “online” • Monitoring and managing extracorporeal filtration system

HEPZATO KIT PHP Procedure Team

Anesthesiologist

Post-Procedure	• Reverse coagulopathy • Monitor and manage hemodynamics • Maintain and support airway

HEPZATO KIT PHP Procedure Team

Perfusionist

Experience
- Extracorporeal circuit assembly and management

Responsibilities
- Verify KIT type based on IR order
- Checks for KIT expiration date
- Opens HEPZATO KIT
- Records KIT parts serial number before KIT set up
- Sets up HEPZATO KIT
- Establish, monitor, controls, and ends extracorporeal pump and veno-venous bypass circuit


Perfusionist

Communicates
- When the circuit is assembled
- When circuit lines are open and closed
- Activated clotting time
- Pump flow and pressures

Coordinates with
- Interventional Radiologist, Anaesthesiologist, (Surgical Oncologist), and procedural team

HEPZATO KIT PHP Procedure Team


Perfusionist

Pre-Procedure	• Warnings and precautions • HEPZATO KIT components and non-KIT required accessories
Procedure	• Setting up the extracorporeal circuit • Extracorporeal filtration circuit priming • Connecting extracorporeal circuit to patient • Monitoring anticoagulation status • Bringing extracorporeal circulation “online” • Managing and monitoring perfusion pump flow and pressures • Preparing for and bringing filters “online” • Monitoring and managing extracorporeal filtration system
Post-Procedure	• Preparing for and executing extracorporeal circuit shut down • Disconnecting patient from extracorporeal circulation • System breakdown and disposal

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HEPZATO KIT Clinical Treatment Team

Pharmacist

Experience
- Preparation of chemotherapeutic agents using national and local safety guidelines

Responsibilities
- Reconstitute HEPZATO
- Deliver reconstituted HEPZATO to procedural room

Communicates
- During HEPZATO delivery

Coordinates with
- Medical/Surgical Oncologist, Interventional Radiologist, Registered Nurse, Technicians

HEPZATO KIT Clinical Treatment Team

Pharmacist

Pre-Procedure	• Store 5x5 HEPZATO Drug Pack in the Pharmacy
Procedure	• Prepare HEPZATO according to HEPZATO KIT USPI • Coordinate timely delivery of HEPZATO to Interventional Radiology
Post-Procedure	• Discuss procedure for proper disposal of HEPZATO

HEPZATO KIT Clinical Treatment Team

Intensivist

Experience
- Manage critical care patients

Responsibilities
- Manages patient immediately post-procedure along with the SO/MO


Intensivist

Communicates
- With the medical or surgical oncologist and Interventional Radiologist

Coordinates with
- Anesthesiologist, Medical/Surgical Oncologist, Interventional Radiologist, Registered Nurse

HEPZATO KIT Clinical Treatment Team


Intensivist

Pre-Procedure	• Procedure induced physiological anomalies • Procedural related complications
Procedure	• Complications and adverse reactions
Post-Procedure	• Manage hematology and administration of blood products • Monitor hemodynamic status • Monitor for bleeding at access sites and retroperitoneal

Module 3
Treatment Planning

Reference ID: 5226627

Module 3 Purpose and Objectives

The introductory module provides a general overview of HEPZATO KIT and PHP procedure including target patient population and indication, contraindications, general safety and precautions, and clinical efficacy/safety information. Training will prepare HCPs for individual education modules based on specialized roles.

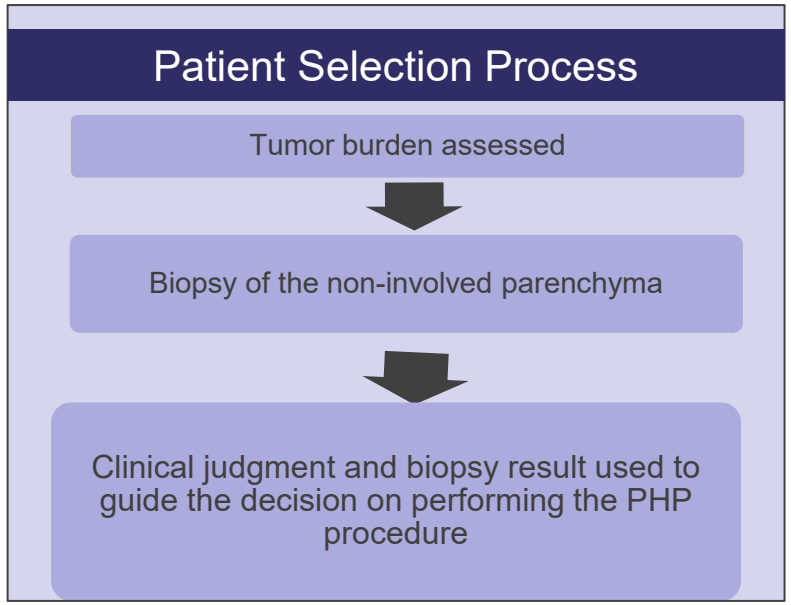
- Identify patients who would be suitable candidates for HEPZATO KIT therapy.
- Know process for preparing patients for HEPZATO KIT procedure.
- Understand importance of pre procedure imaging.
- Understand options for hepatic artery mapping.

Patient Selection – Characteristics

There are suitable characteristics that reduce procedural/device related risks.

Inclusion

- Patients should have less than 50% liver tumor burden.
- Liver disease must be measured by CT or MRI.
- There can be limited extrahepatic disease at baseline if the life-threatening component of progressive disease is in the liver.
- Patients should have an ECOG score of 0 to 1 at screening.
- Prior chemotherapy, radiotherapy, chemoembolization, or Immunoembolization is allowed with a washout period of 30 days.



HEPZATO KIT Preoperative Patient Assessment

After referral by the Medical Oncologist, a preoperative assessment of the patient is performed by the Anesthesiologist. A Cardiologist, and a Pulmonologist may be consulted for pre-operative clearance indicating adequate cardiac and pulmonary function, as per each institution's process or protocol.

A patient may not be eligible for HEPZATO KIT treatment if any of the following are present:

- Active coronary artery disease
- Severe angina
- Recent myocardial infarction
- Any congestive heart failure
- Significant ventricular arrhythmias
- Moderate to severe valvular disease
- Unable to withstand high dose vasopressor therapy
- Advanced COPD
- Unable to withstand mechanical ventilation

Treatment Planning and Preparation, Warnings & Precautions

Treatment Planning and Preparation

Treatment Planning

- No prior Liver medical treatments within 4 weeks
- Screen for prior surgeries that could affect liver vascular anatomy
- Patients should have < 50% tumor burden

Treatment Preparation

- Patients should discontinue chronic anti-coagulations therapies
- Patients must discontinue drugs treating hypertension
- Only manipulate intravascular catheters and fluoroscopic guidance
- Use caution to avoid air embolisms
- Contents are supplied sterile, inspect prior to use
- All components are single patient use only

Warnings and Precautions

- Peri-procedural complications (including hemorrhage, hepatocellular injury, and thromboembolic events)
- Myelosuppression
- Hypersensitivity Reactions
- GI Adverse Events (nausea, vomiting, abdominal pain, diarrhea)
- Carcinogenic/Mutagenic Effects
- Embryo-fetal toxicity
- Infertility

See Instructions For Use for detailed description of Warnings and Precautions

Delcath

PHP Procedure Team Communication & Patient Preparation

PHP Procedure Team Communication Tasks

- All HCPs should have an understanding and discussion on each expected task required before, during, and after the procedure
- The procedural team should have a pre-procedure discussion
- The procedural team should review the specific roles of each HCP throughout the procedure

Patient Preparation

The following exams, laboratory, or diagnostic tests should be performed to ensure patient fitness and eligibility such as:

- Fitness level
- Blood tests: full blood count, liver function test, thrombophilia screen, urea, electrolytes
- List of current medications and allergies
- EKG
- Likelihood of pregnancy status
- Likelihood of menstruation during PHP procedure window

Pre-Procedure Exams (1)

The preoperative angiograms should include and enable:

- Celiac and superior mesenteric artery injection
- Evaluate the portal vein for patency during celiac and superior mesenteric arteriography.
  - The presence of significant portal venous hypertension is a contraindication for Melphalan/HDS treatment.
- Completely examine the arterial supply to the liver and assess impact on chemotherapy infusion.
- Evaluation of portal venous supply, including splenic, superior mesenteric and portal veins – to determine patency and direction of flow
- Assessment for variant hepatic arterial and aberrant gastrointestinal (GI) branches – to prevent inadvertent infusion of GI or visceral branches

Pre-Procedure Exams (2)

The preoperative angiograms should include and enable:

- Assess liver blood supply and formulate a strategy for catheter placement to ensure adequate drug infusion to the entire liver. If the risk assessment is unfavorable or the anatomic variation is too complex to allow whole liver or sequential lobar catheterization for safe delivery of melphalan, the procedure must not be performed.
- Depending on vascular anatomy, a sequential lobar approach may be the best administration option which requires splitting the melphalan dose. This will require repositioning of the catheter during the procedure.
- A whole liver infusion (dosing) approach will likely require embolization of the gastroduodenal artery, but depends on its origin relative to the side branches of the distal proper hepatic artery. If the infusion catheter tip can be placed sufficiently distally to avoid retrograde reflux into the gastroduodenal artery, then the latter may not need to be embolized.
- Determination of optimal balloon spacing (50mm or 62mm)

Pre-Procedure Exams (3)

Embolization may be performed in order to avoid reflux or infusion into GI or Visceral arteries. Embolized areas may include the following vascular structures:

- Gastroduodenal artery (GDA)
- Left gastric artery (LGA), Right Gastric Artery (RGA)
- Hepatic variant anatomy (e.g., replaced hepatic artery)
- Aberrant or unusual anatomical variants

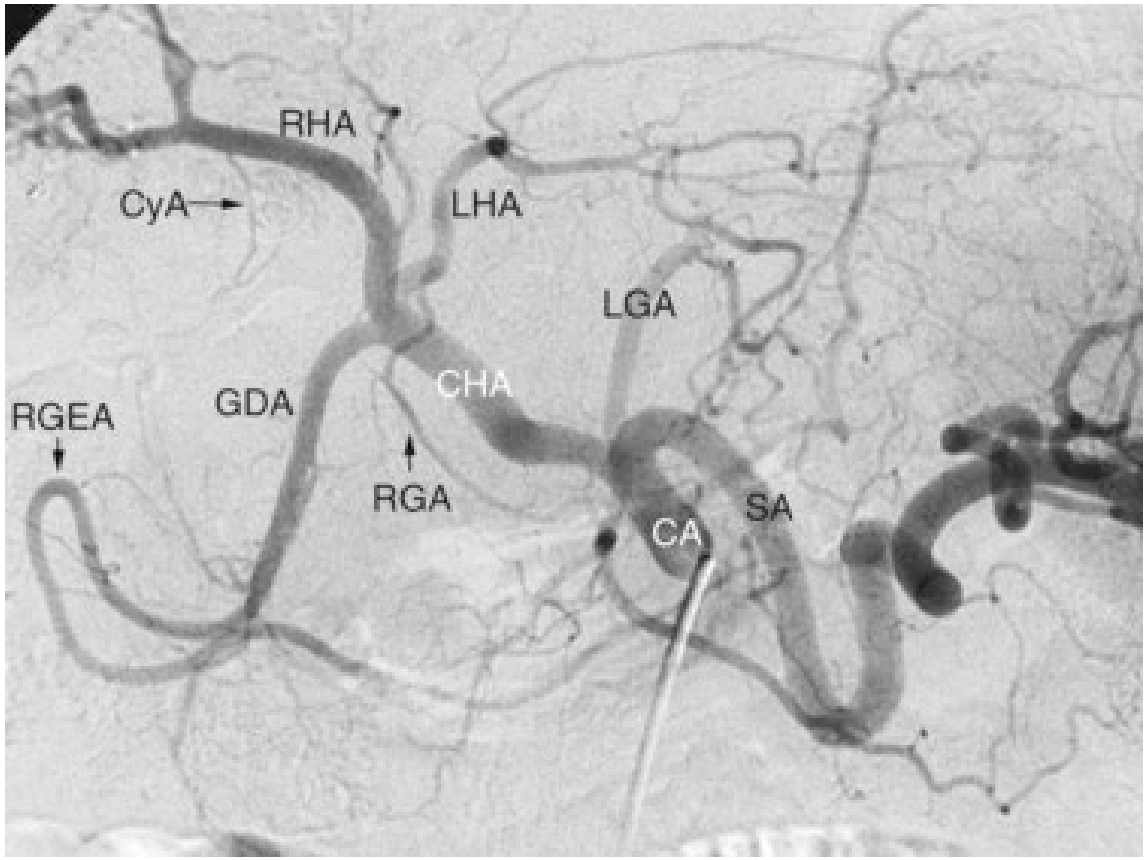
Pre-Operative Angiogram

Thorough search for any variant anatomy

Celiac and superior mesenteric artery mapping

Assessment of the hepatic arterial anatomy

Embolization of certain branches supplying the GI tract



Assess tumor blood supply and formulate a strategy for catheter placement

Select HEPZATO KIT, for balloon spacing, based on patient anatomy

HEPZATO dose planning including whole liver vs lobar delivery

Conventional celiac artery anatomy. CA, celiac axis; LGA, left gastric artery; SA, splenic artery; CHA, common hepatic artery; GDA, gastroduodenal artery; RGA, right gastric artery; RHA, right hepatic artery; LHA, left hepatic artery; CyA, cystic artery; RGEA, right gastroepiploic artery.

Treatment planning options can consist of dosing based on a sequential lobar or whole liver approach.

Delcath

Typical Schedule of Examinations Prior to PHP Procedure

3 Weeks Prior

- Baseline laboratory - medical history and physical examination
- Serum chemistries and electrolytes
- Complete blood count
- Baseline laboratory
- Concomitant disease
- Cardiac and pulmonary evaluation
- Liver function tests
- Prothrombin Time /Partial Thromboplastin Time
- Other medical tests as deemed necessary

2 Weeks Prior

- A baseline CT or MRI is acquired.
- This scan is needed to determine if there has been rapid advancement of the tumor from the time that the diagnostic scan was done.
- The extent of the disease is documented during this scan.
- Procedural risks are assessed including portal hypertension, liver cancer burden, cerebral bleeding risks and histories of surgical procedures.
- Hepatic Artery Mapping (has an optional time point)
- Pre-operative clearance

1 Week Prior

- Patient is screened for blood products.
- Blood Products (Type & Cross)
- Packed RBC, fresh frozen plasma, platelets, cryoprecipitate
- The preoperative hepatic artery mapping study may be performed.
- Pre-op medications prescribed
- Discontinuation of medications
- Hydration instructions
- Pre-op clearance

Procedure Preparation: Prior to Treatment (1)

- **Hydration**
  - May be started the night before the procedure or the day of the procedure
- **Allopurinol** (if tumor burden >25%)
  - As prophylaxis for electrolyte abnormalities, administer 300 mg/day orally 2–3 days before and 2-3 days following perfusion
- **Proton Pump Inhibitors**
  - To prevent gastritis which may occur as a result of regional melphalan absorption during the procedure, administer proton pump inhibitors
- **Anticoagulation**
  - The patient will be systemically anticoagulated with heparin during the procedure.
  - Administer heparin to the patient only AFTER placement of the 18F (femoral vein), 10F (jugular vein), and 5F (femoral artery) sheaths
  - The patient must be fully heparinized prior to the insertion of the Double Balloon Catheter into the inferior vena cava. Begin with an initial intravenous bolus of heparin at 300 units/kg, dose adjusted to achieve activated clotting time.
  - A minimum activated clotting time (ACT) of 400 seconds is necessary with a recommended ACT value > 450 seconds
  - Evaluate activated clotting time frequently (approximately every 5 minutes) until adequate anti-coagulation is established (ACT > 400 seconds)
  - DO NOT insert double balloon catheter into the patient Until ACT values are > 400 seconds.
  - Maintain activated clotting time at > 400 seconds throughout the procedure, assessing ACT values every 15 – 30 minutes depending on the patient's response and by administering intravenous heparin as needed.

Procedure Preparation: Prior to Treatment (2)

- **Anesthetic Management**
  - Treatment must be administered with patients being monitored and under general anesthesia. Emergency resuscitation equipment must be available during the procedure.

- **Blood Pressure Control**
  - Expect significant procedure related decrease of blood pressure when the balloons occlude blood return from the inferior vena cava (decreased cardiac inflow) and when the filters are brought into the extracorporeal bypass circuit. The reasons for filter-related hypotension are multifactorial, but hypersensitivity to non-physiological surfaces (inflammatory response), significant reduction in venous return and preload, and possible removal of catecholamines by the filters may play a role. To aid blood pressure maintenance for extracorporeal bypass, the following actions are recommended per institutional practice:
  - Pre-operative hydration and intra-procedural administration of colloids and crystalloids.
  - Vasopressor use in accordance with institutional practices to elevate mean arterial pressure to a target >65 mmHg
  - Blood pressure must be constantly monitored throughout the procedure and maintained at levels required for adequate perfusion of critical end-organs (i.e., >65 mmHg).

Pre-Procedure Infusion Plan

Coordination with the Pharmacy

- Prior to set up, provide pre-notification to the hospital pharmacy to be ready to prepare HEPZATO.
- An actual request for drug preparation and delivery should be timed so that the start of the infusion of HEPZATO is within thirty minutes of preparation.
- The filters should not be brought online until HEPZATO is in the procedure room. This minimizes filtration duration and associated complications.
- Drug administration should be completed within 60 minutes of the start of preparation.

Module 4
Perfusion Circuit

Delcath

Reference ID: 5226627

Module 4 Objectives

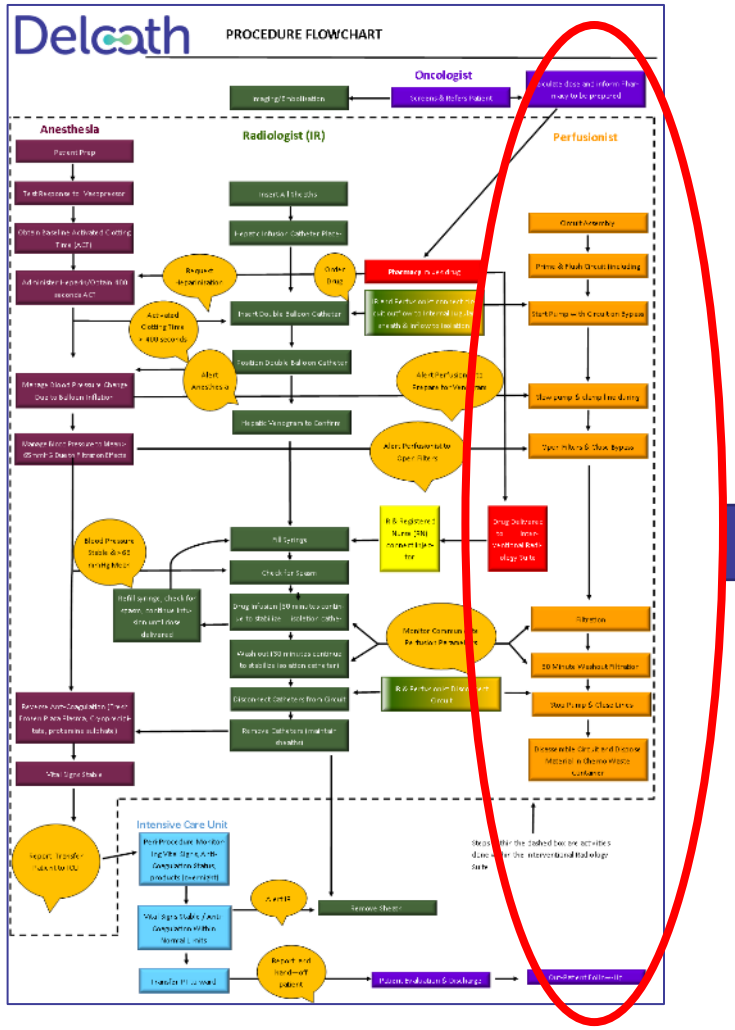

Perfusionist

Module 4 describes the responsibilities of the perfusionist in assembling the EFC and collaboration with the IR when connecting the patient to the extracorporeal circuit. HCPs will gain an understanding of the perfusion circuit components, setting up the system, managing the fluid path, connecting the system to the patient, bringing the filters online, troubleshooting flow related issues, and disconnecting the patient from the EFC.

- Understand and perform each step outlined in the IFU.
- Interpret extracorporeal pump flow metrics.
- Support proper anticoagulation in collaboration with the anesthetist.
- Identify EFC issues and know how to resolve these problems.
- **Communication** between the Perfusionist and the **other team members** is of **critical importance**.


Perfusionist

Perfusionist Procedural Tasks



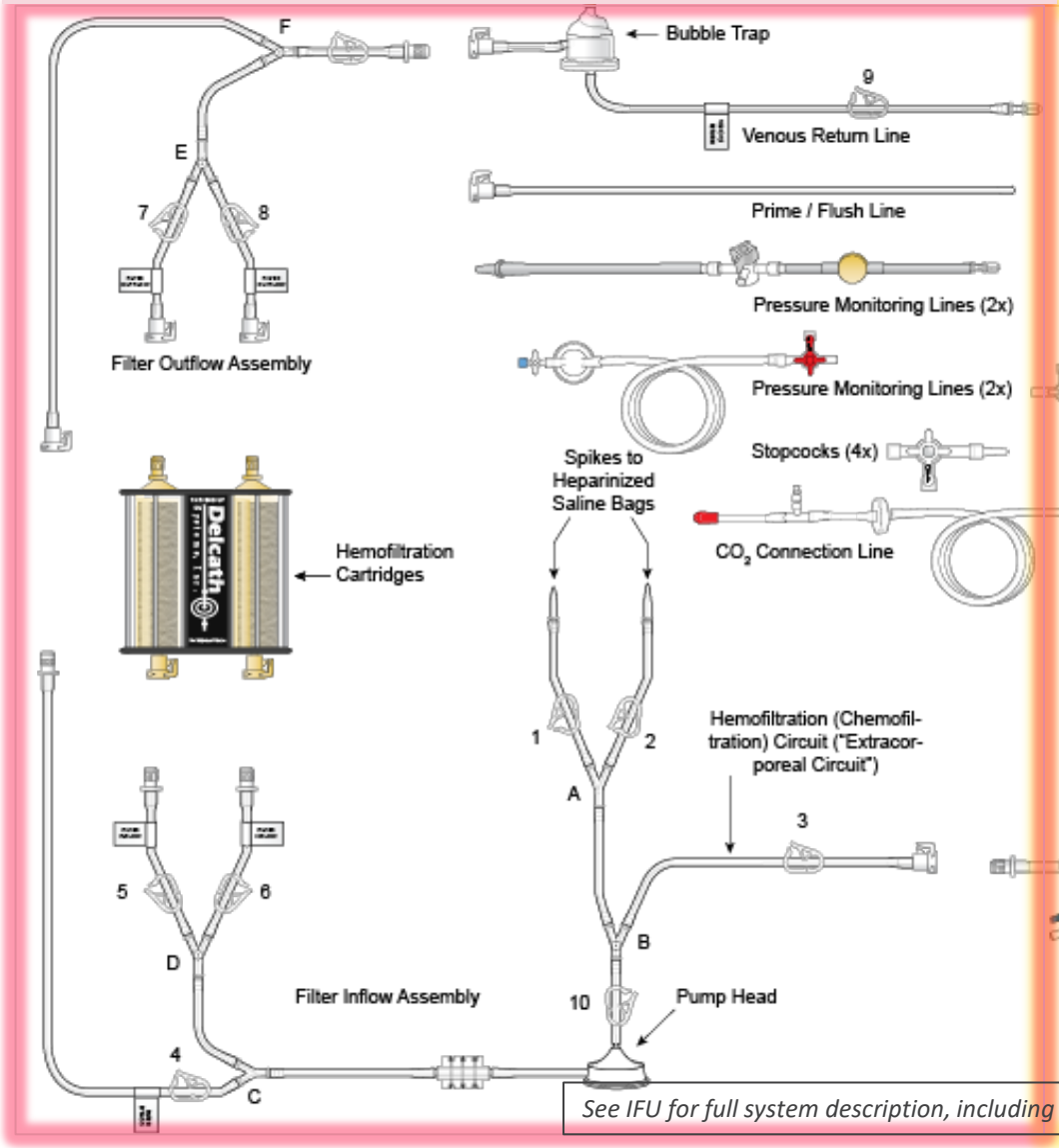
This module describes the steps the Perfusionist takes to during the procedure

- Circuit Assembly
- Prime & Flush Circuit (including Filter)
- Start Pump with Circuit on Bypass
- Slow pump & clamp line during venogram
- Open Filters & Close Bypass
- Filtration
- 30 Minute Washout Filtration
- Stop Pump & Close Lines
- Disassemble Circuit and Dispose Material in Chemo Waste Container

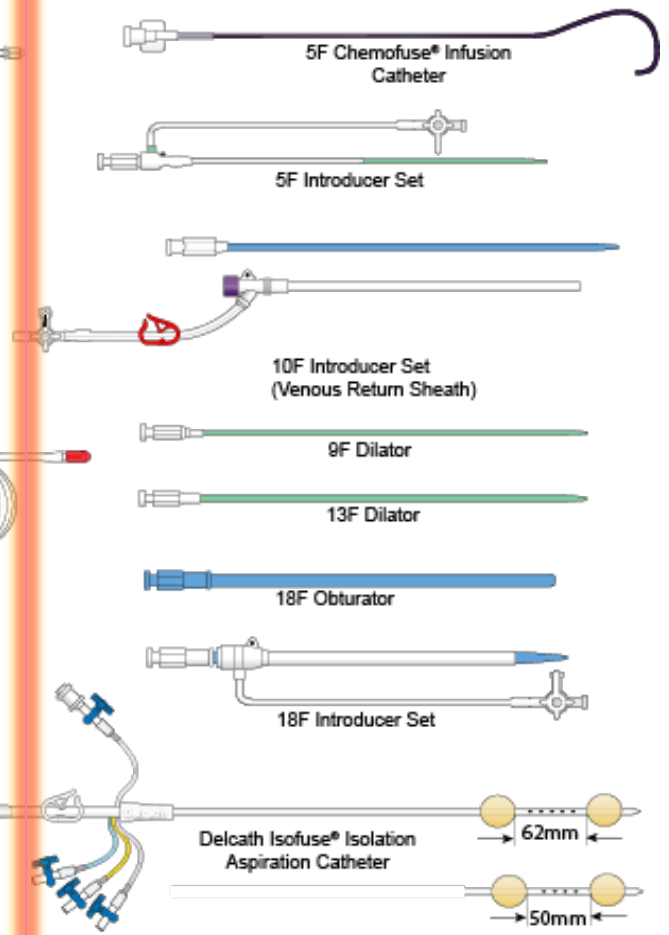
HEPZATO KIT Components

Perfusionist

Perfusionist



Interventional Radiologist



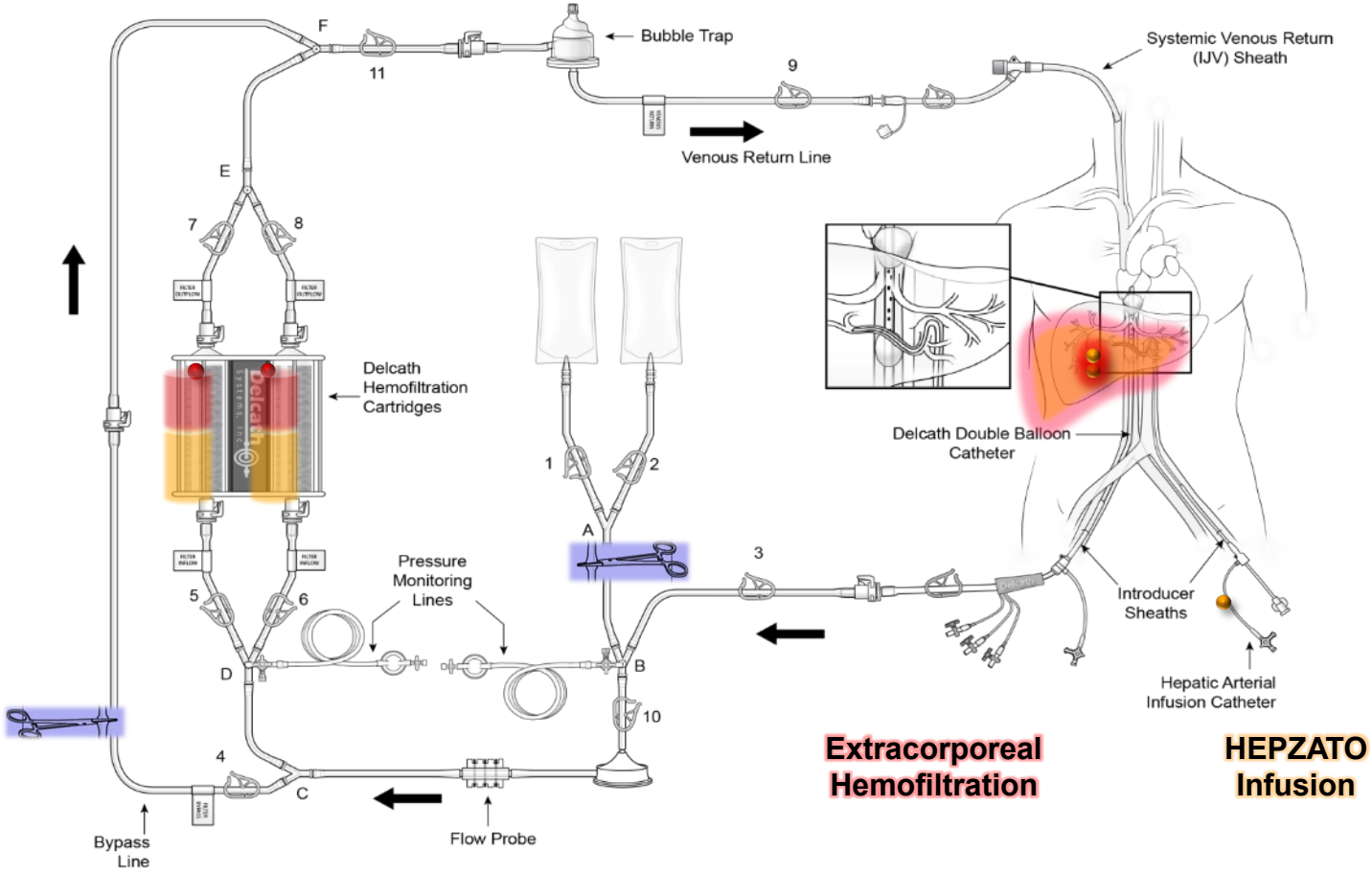
See IFU for full system description, including alphanumeric descriptions

Only components provided in the Hepatic Delivery System or specified by Delcath in the Instructions For Use are to be used to create the circuit.

HEPZATO KIT

Perfusionist

SYSTEM OVERVIEW



Note
• *Numbers 1-11 denote clamps used to control flow* • *Letters A-F denote "Y connectors*

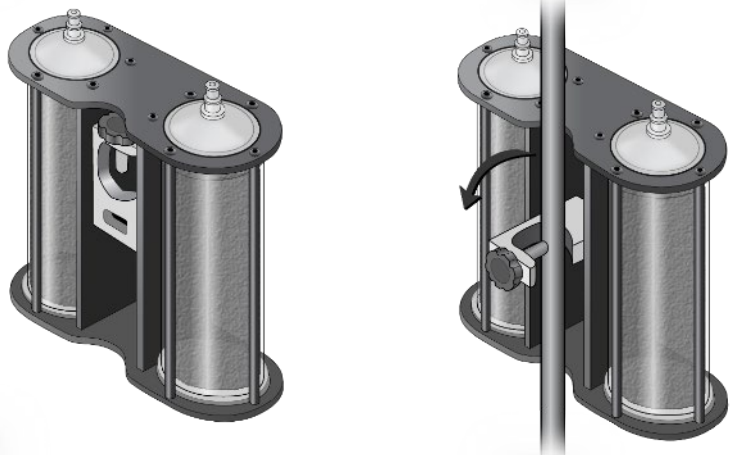
See IFU for full system description, including alphanumeric descriptions

1. Assemble the Extracorporeal Filtration Circuit

Perfusionist

Circuit Assembly

1. Prepare 9 liters of Heparinized Normal Saline
2. Remove Hemofiltration Dual Filter Cartridge from sterile pouch
3. Using guidance from the “THIS END UP” label on the faceplate, attach the filter to the intravenous pole using the built-in pole mount clamp.

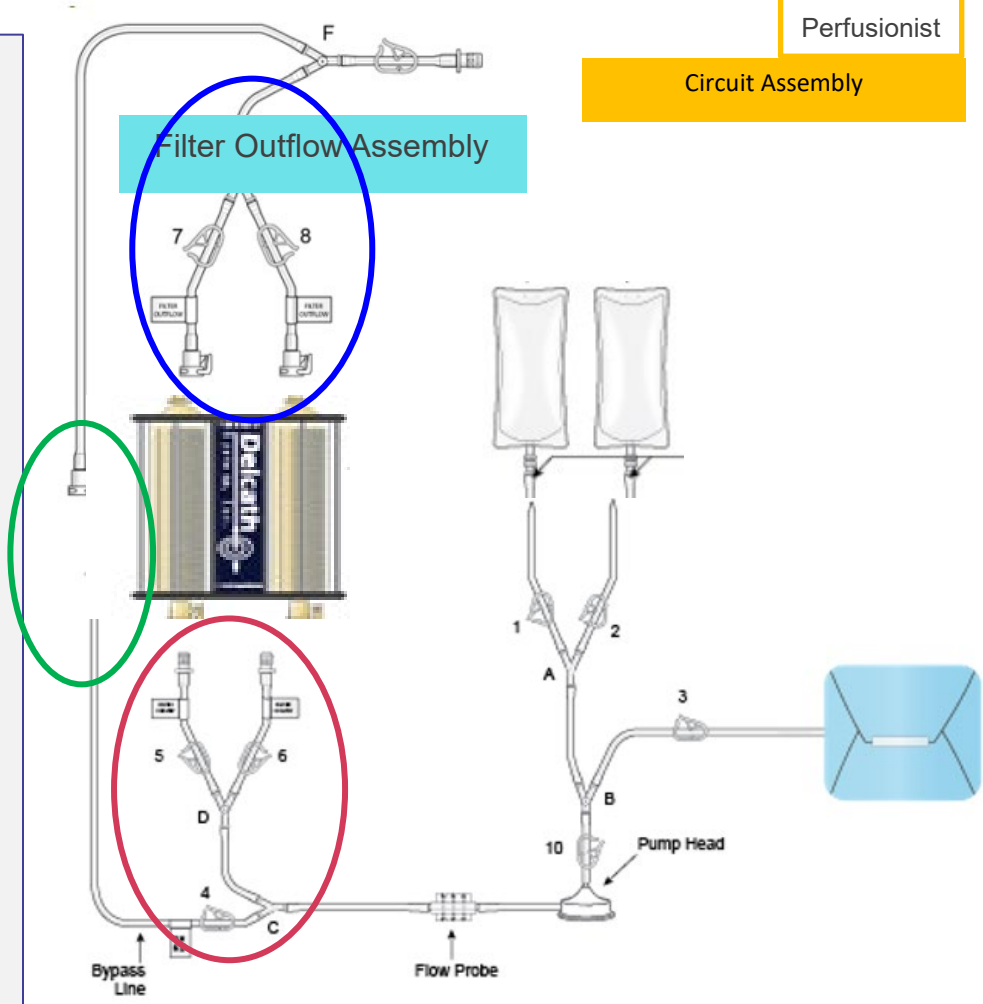


Extracorporeal Filter Circuit Setup – Filter & Circuit Assembly

Perfusionist

Circuit Assembly

1) Open the circuit tray and remove the components in the pouches. Set aside for later assembly.
2) Remove the "**Filter Inflow Assembly**" section from the circuit tray, place pump head on the pump drive motor, and insert flow probe into flow transducer.
3) Connect the Inflow lines (circled in red in the image to the right) to the cartridge inlet connectors located on the bottom of the dual filter.
4) To complete the assembly, push the quick connector couplings together, as shown (circled in red; male to female) until an audible "click" is heard to verify connection.
5) Remove the "**Filter Outflow Assembly**" section from its sterile pouch.
6) Connect the two outflow lines to the filter cartridge outlet connectors located on the top of the dual filter using the quick connector couplings (circled in blue; push and click).
7) Assemble the two ends of the **Bypass line** by pushing the quick connectors together (circled in green; push and click).



Extracorporeal Filter Circuit Setup – Prime Flush Line Assembly

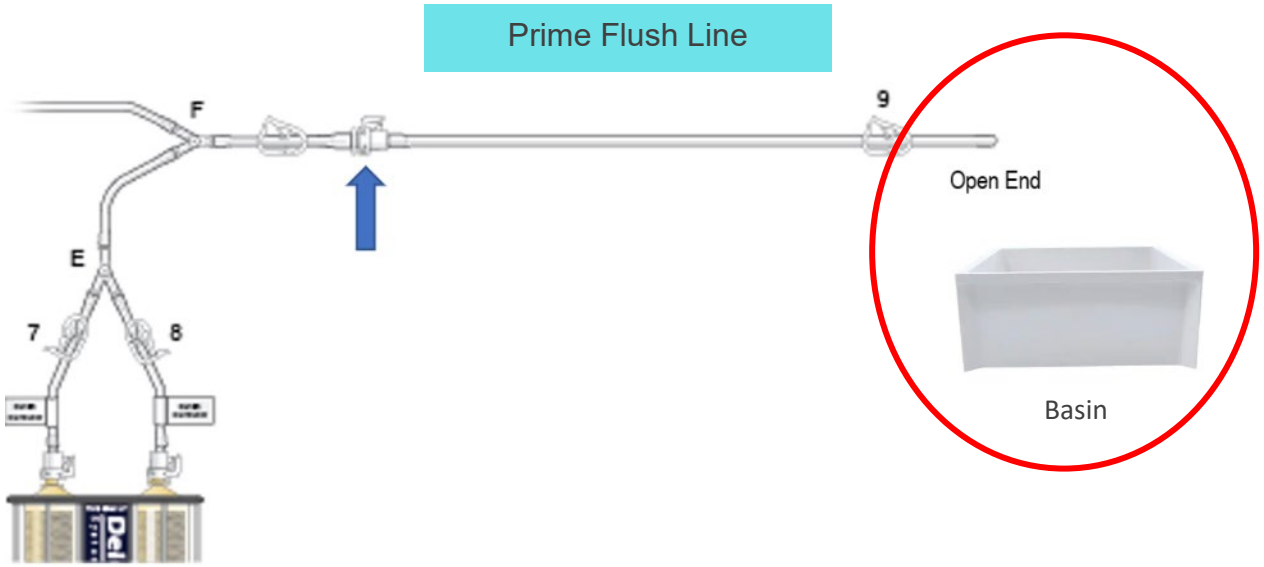
Perfusionist

Circuit Assembly

1) Remove the “Prime/Flush Line” from its sterile pouch.

2) Attach the prime/flush line to the filter outflow assembly using the quick connect coupling located distal to “Y”-connector at F (blue arrow).

3) Place the open end of the “Prime/Flush Line” into the basin for collecting the flushed effluent during filter hydration (circled in red).

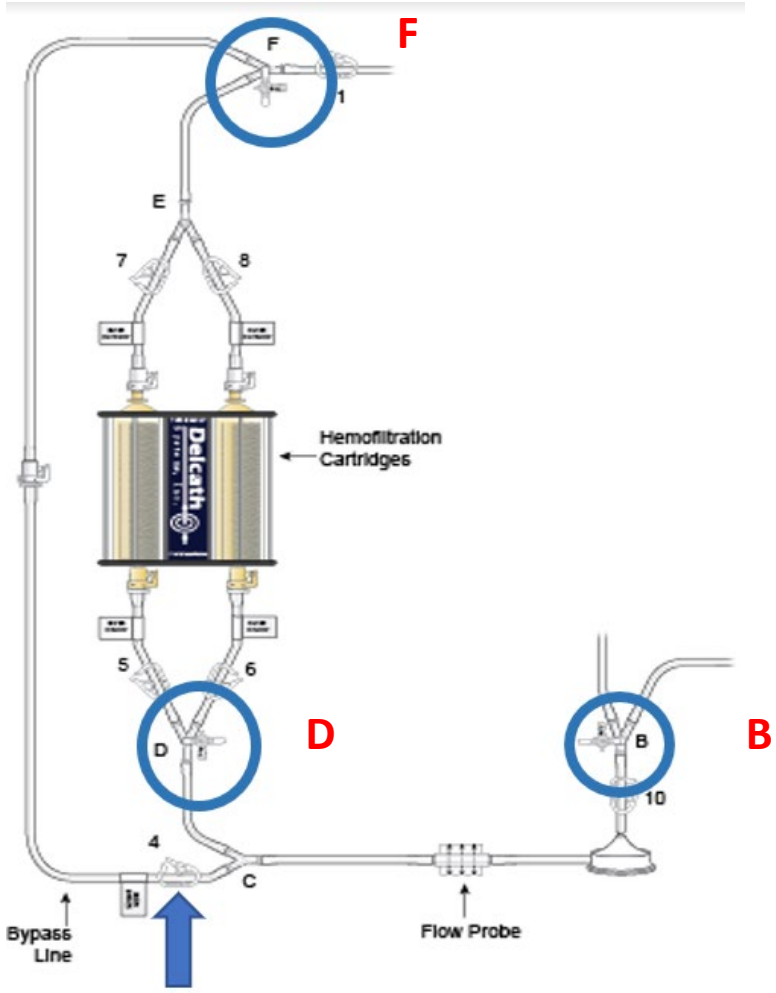


Extracorporeal Filter Circuit Setup – Stopcock Attachment Locations

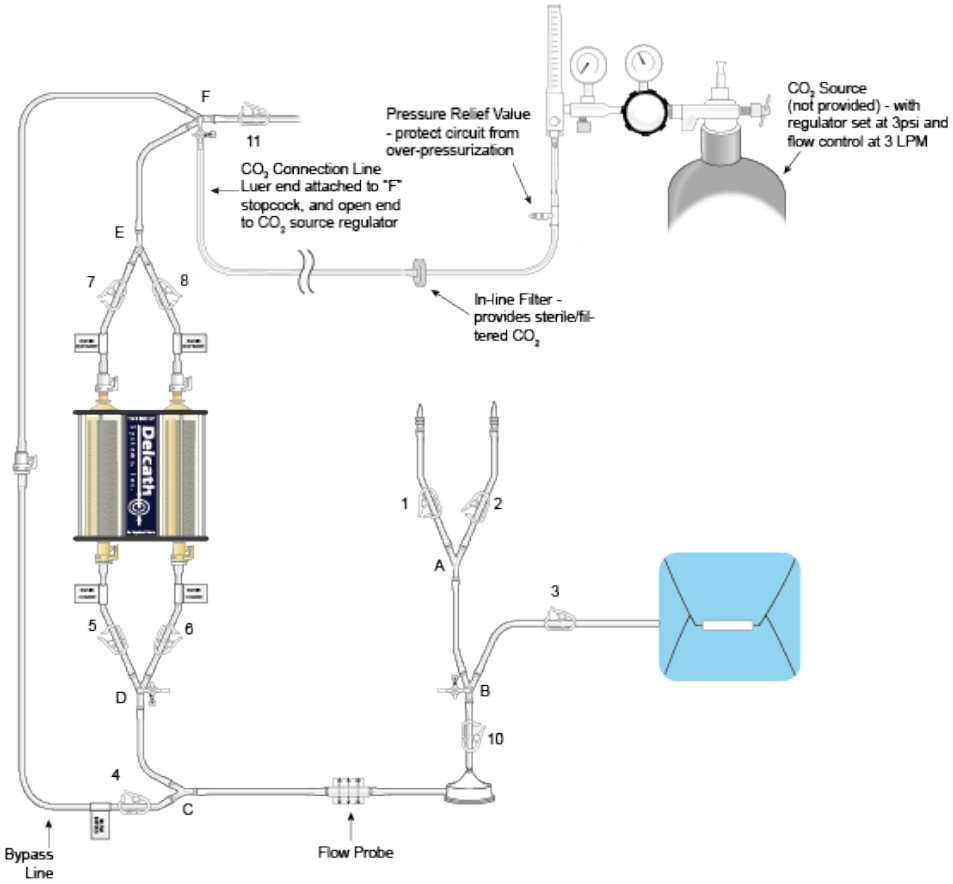
Perfusionist

Circuit Assembly

1) Attach the supplied stopcocks as identified by the blue circles to ports:
    1) “B” (pre-pump head pressure/suction)
    2) “D” (pre-filter pressure)
    3) “F” (outlet) Y-connector
2) Ensure all stopcocks are in the closed position (lever closed to the perfusion circuit).
3) Verify “Bypass Line” clamp 4 is open (Blue Arrow).



Extracorporeal Filter Circuit Setup – CO_2 Priming Connections



Circuit Assembly

Perfusionist

1) Close outlet clamp 11.

2) Attach the CO_2 connection line to the stopcock “F” and open the stopcock.

3) Connect the open end of the CO_2 connection line to the CO_2 source, and set the CO_2 source regulator to 3psi (approximately 3.0 liters per minute).

4) Start the CO_2 gas flow and allow the CO_2 to flow through the hemofiltration circuit.

5) Adjust CO_2 regulator to maintain 3psi (as necessary).

6) Verify CO_2 flow through the circuit.

7) Close bypass clamp (4) after approximately 1 minute to ensure flow through the hemofiltration cartridges.

8) Allow CO_2 to flow through the cartridges (after closing clamp 4) for at least 5 minutes.

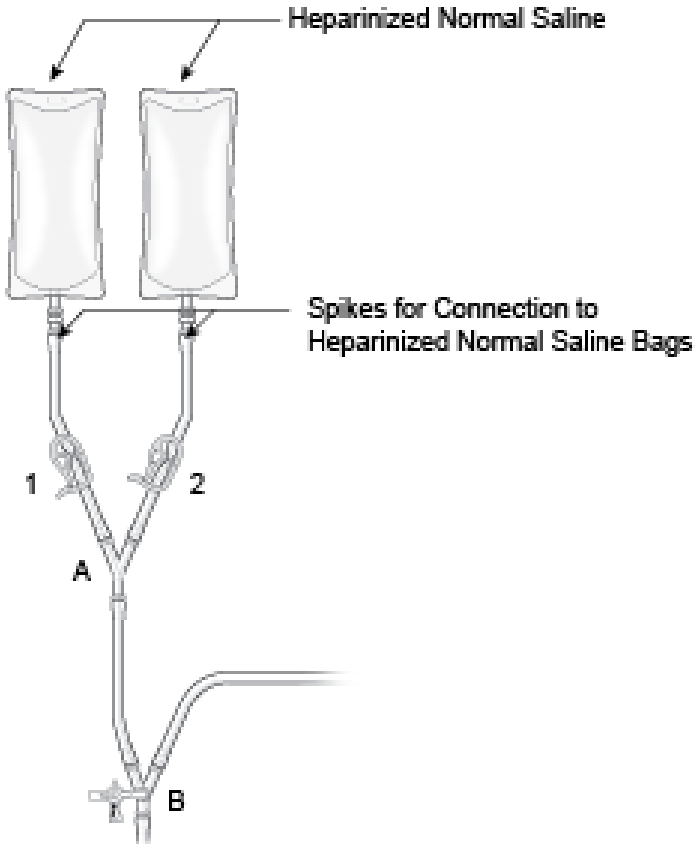
9) Leave saline clamps 1 and 2 closed. Close double balloon catheter line, clamp 3. Close filter inlet clamps 5 and 6. Then close filter outlet clamps (7, 8) to lock CO_2 within the circuit.

10) Stop the CO_2 flow and close the stopcock “F” and disconnect the CO_2 connection line and discard.

Extracorporeal Filter Circuit Setup – Heparinized Saline Bags Connections

Perfusionist

Circuit Assembly



1) Hang two bags of the heparinized sterile normal saline and connect to circuit by using the spikes to allow for gravity priming of circuit components.

IMPORTANT: Use strict aseptic technique while spiking the heparinized normal saline bags.

Ensure there are two (2) liters of normal saline available for later use

Extracorporeal Filter Circuit Setup – Prime Double Balloon Catheter Line

Perfusionist

Circuit Assembly

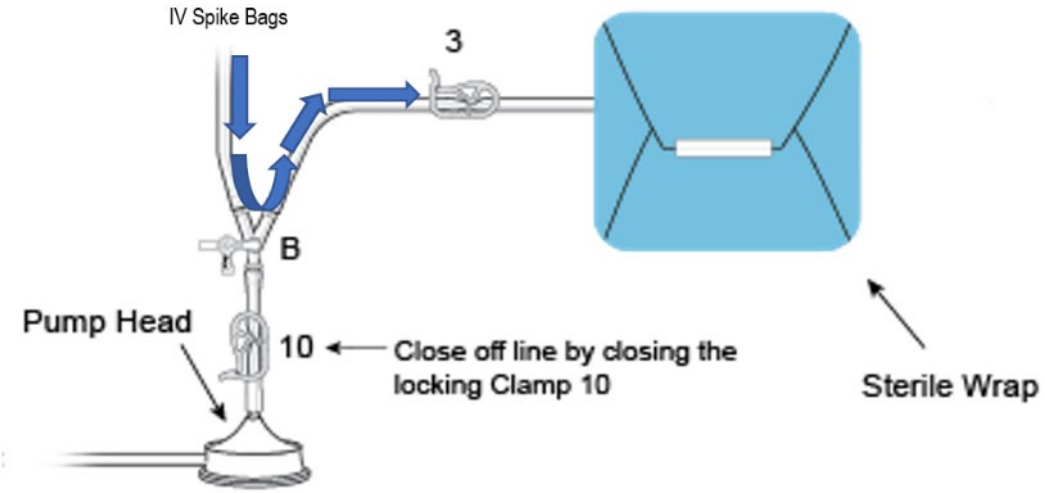
1) Close pre-pump clamp 10.

2) Confirm that stopcock “B” is in the closed position (the lever is pointed toward the circuit tubing to the right).

3) Open double balloon catheter line clamp 3.

4) Open saline line (clamp 1 or 2), to allow heparinized normal saline to prime line only up to clamp 3, blue arrows demonstrating flow direction. **Do not allow excess heparinized normal saline to fill sterile wrap.**

5) Close clamp 3.



Extracorporeal Filter Circuit Setup – Prime Bypass Line

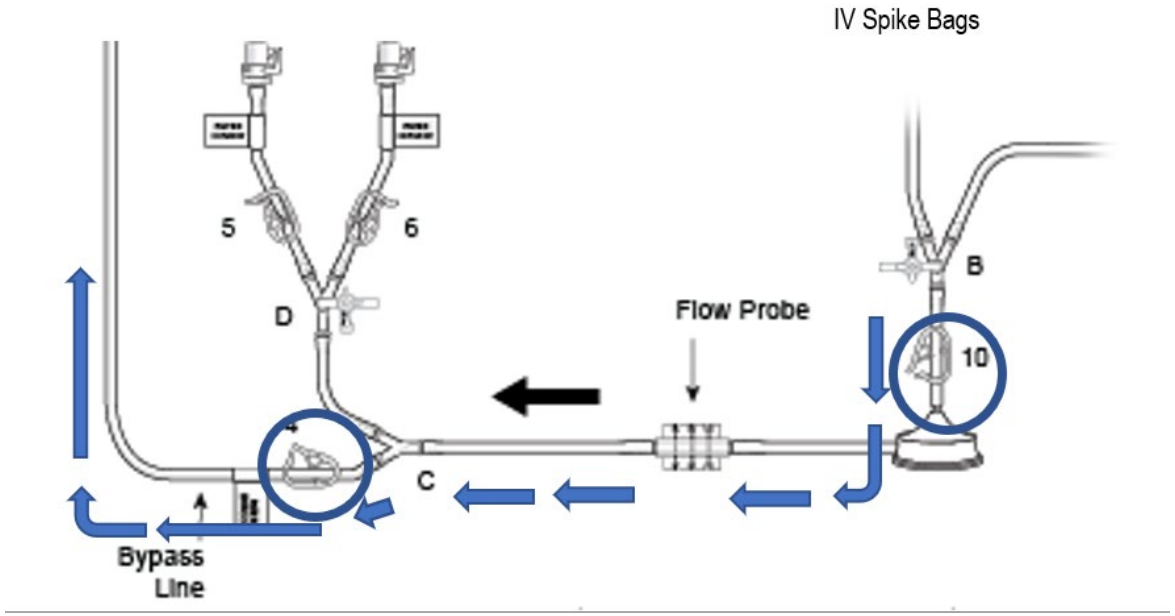
Perfusionist

Circuit Assembly

1) Inspect that stopcock “D” is in the closed position (the lever is pointed toward the circuit tubing to the left).

2) Prime the pump head and bypass lines by opening clamps 10 and 4.

3) Close clamp 4.

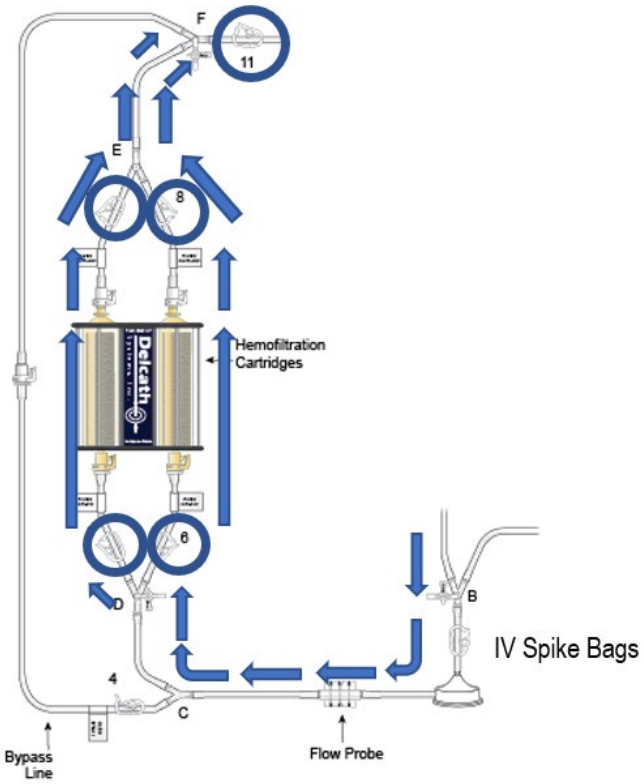


Extracorporeal Filter Circuit Setup – Prime Filter Cartridges

Perfusionist

Circuit Assembly

1) Inspect that stopcock “F” is in the closed position (the lever is pointed upward).
2) Open filter inlet clamps (5, 6).
3) Open filter outlet clamps (7, 8).
4) Open circuit outlet clamp (11).
5) Adjust the flow of heparinized normal saline into the filter to a suggested starting rate of 0.1 liters per minute (increasing slowly up to 0.5 liters per minute when the filters are completely filled). Note: Hemostats (forceps) are required to adjust flow rate if using gravity.
6) Note that filter cartridges will have a mottled appearance indicating the presence of gas bubbles.
7) Allow heparinized normal saline to flow through the filters and out the “Prime/Flush Line” for approximately 6-10 minutes or until the filter appears gas free (solid black).
8) Once all gas appears to have been displaced, gently roll the cartridges between palm of hands to encourage trapped gas bubbles to rise. **CAUTION: Do not use excessive force when rolling the plastic housing.**
9) Inspect the entire cartridge for trapped gas by turning the cartridge within housing to visualize the entire filter. If there are gas bubbles gently roll the cartridges to free the trapped gas.
10) When Filter Cartridges are gas free, flush with an additional six (6) liters of heparinized normal saline (3 L/cartridge).
11) Close filter clamps 5, 6, 7, 8 and outlet clamp 11.



Extracorporeal Filter Circuit Setup – Prime Venous Return Line and Bubble Trap (1)

Perfusionist

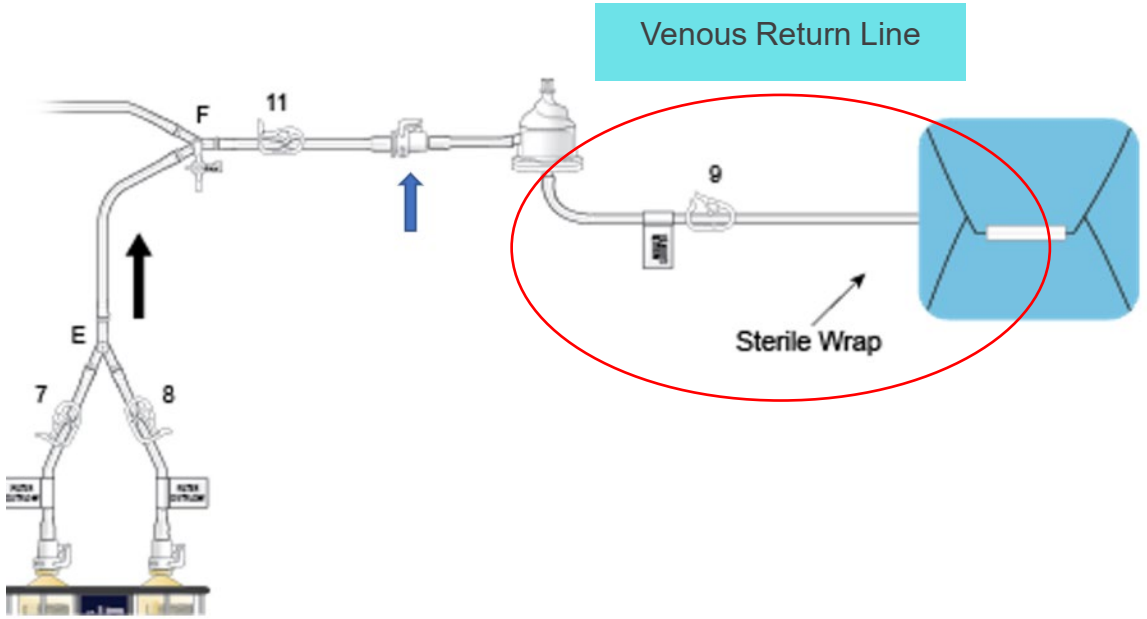
Circuit Assembly

1) Disconnect and dispose of the “Prime/Flush Line”, by pressing in the latch located on the female quick connect coupling and pulling it apart.

2) Open the Venous Return sterile pouch and remove the venous return line and built-in bubble trap.

3) Attach the female to the male quick connector (push and click) located (blue arrow) by outlet clamp (11).

4) Position the bubble trap in the bubble trap holder higher than filter cartridges.



Extracorporeal Filter Circuit Setup – Prime Venous Return Line and Bubble Trap (2)

Perfusionist

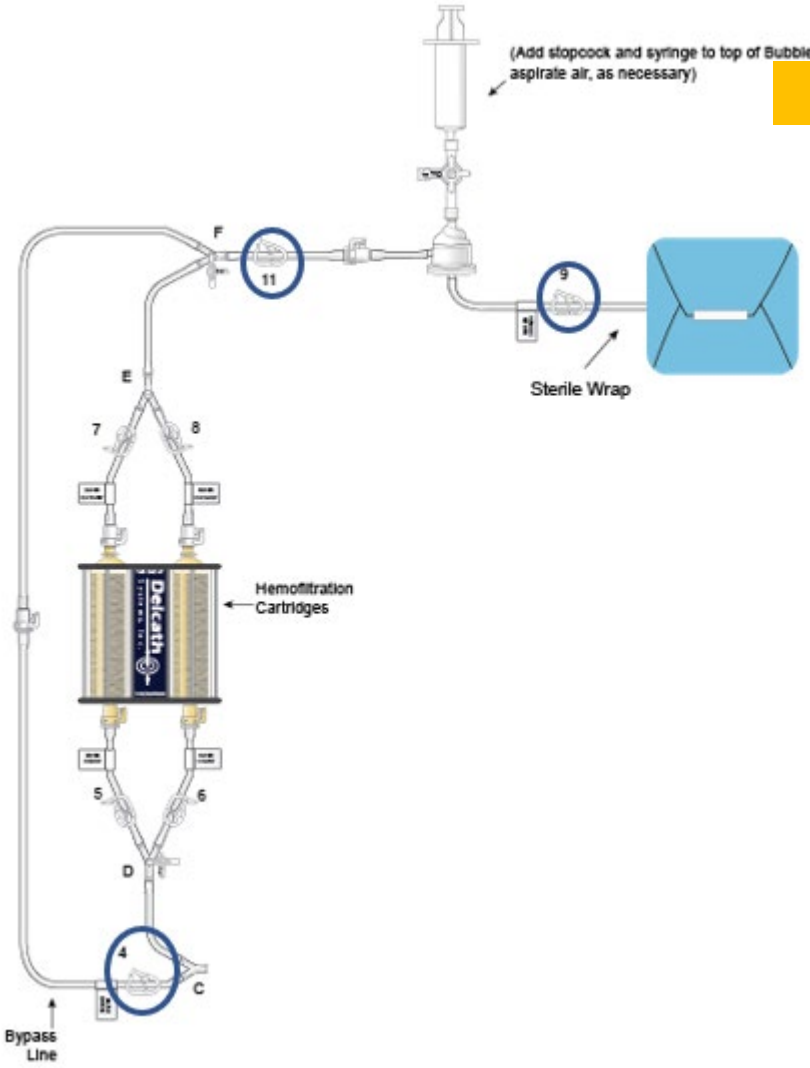
Circuit Assembly

1) Attach stopcock to bubble trap and use syringe to aspirate air, as necessary.

2) Prime venous return line and bubble trap by opening clamps 4, 11 and 9

3) Prime up to clamp 9. Do not allow saline to enter blue sterile pack.

4) Close clamp 9 once venous return line and bubble trap are primed up to clamp 9.



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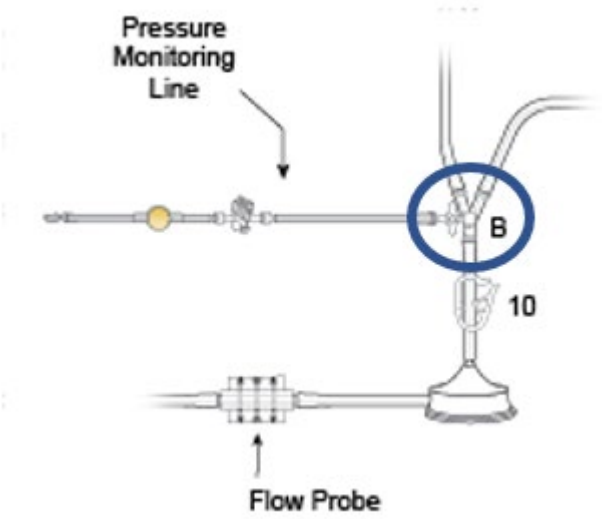
Extracorporeal Filter Circuit Setup – Pre-Pump Pressure Line Attachment & Priming (1)

Perfusionist

Circuit Assembly

1) Attach pre-pump (to measure negative pressure – pump suction) pressure monitoring line to stopcock “B” and prime.



Extracorporeal Filter Circuit Setup – Pre-Pump Pressure Line Attachment & Priming (2)

Perfusionist

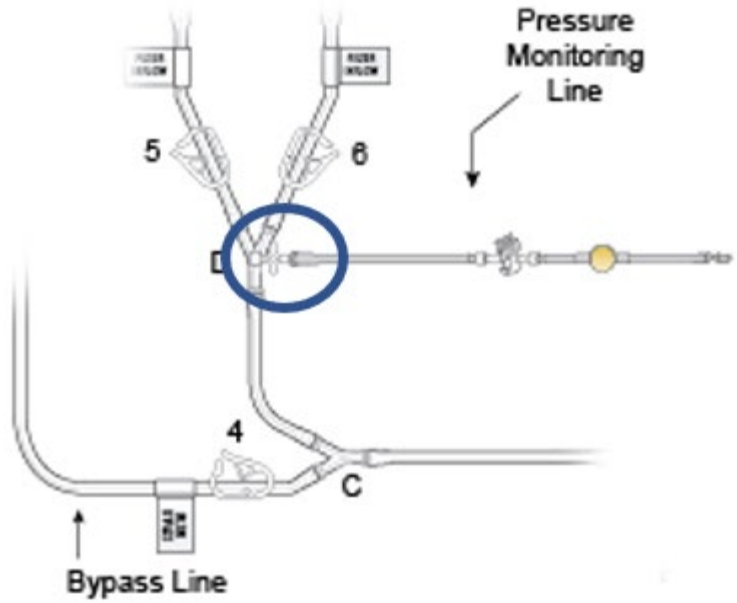
Circuit Assembly

1) Attach pre-filter (to measure positive pressure – pre-filter) pressure monitoring line to stopcock “D” and prime.

2) Attach the pressure monitoring lines to the P1 and P2 ports on the rear of the Medtronic Bio-Console 560 Speed Controller System.

3) Zero the pressure transducers (refer to Medtronic Bio-Console 560 System Manual for details).

4) Coiled pressure monitoring lines are included for use with DLP Pressure Display Boxes, as necessary.



Extracorporeal Filter Circuit Setup – Pressure Test Circuits

Perfusionist

Circuit Assembly

1) Pressure test circuit by slowly ramping up the pump head speed (RPM) until a pressure reading of 300 mmHg is achieved on the pressure transducer attached to the line on Y-connector “D” (pre-filter).

2) Visually inspect all connections and cartridges to ensure no leaks are present.

3) Turn off pump and close cartridge inlet (5, 6) and outlet (7, 8) clamps. Ensure bypass line clamp (4) is open.

4) Ensure there are two liters of normal saline available for later use.

5) Warning: Ensure that all air is purged from the system prior to use in order to avoid an air embolism.

ECF System is now primed, hydrated, de-bubbled, and ready for use

Perfusionist Procedural Awareness - Pump Flow Rate

The flow rate of the pump should be maintained between 0.4 – 0.8 L/min

Pre pump pressure (suction side) should not be more negative than −250 mmHg, as lower pressures indicate possible catheter collapse or kink.

Pre-cartridge pressures (pre-filter) should not exceed 200 mmHg, as higher pressures indicate increasing filter resistance potentially due to thrombus or a kinked return line. Check filters to assure free flow and return line for kinks.

Procedural Team Awareness - Before Veno-Venous Bypass

Prior to opening the veno-venous bypass circuit:

1) HEPZATO should be fully reconstituted and prepared for injection.

2) The activated clotting time should be > 400 seconds.

3) Vasopressor agents should be prepared and ready for injection.

Procedural Team Awareness - Veno-Venous Bypass

Perfusionist

Circuit Assembly

Pump Speed	Starting the Medtronic pump at a low speed to allow blood flow from the double balloon catheter into perfusion circuit.
Extracorporeal Filtration Circuit Clamps	It is important to open all of the clamps EXCEPT for the filter inlet and outlet clamps, which are clamps 5-8. During veno-venous bypass, blood will bypass the filters and be returned to the internal jugular vein.
Blood pressure	Blood pressure should be carefully monitored, and the mean arterial pressure should be above 65 mmHg.

HCP Communications *Before* Bringing Filter Cartridges Online

Interventional Radiologist

Interventional Radiologist Communicates:

- The hepatic veins are fully isolated
- When to start and stop the pump

Slow pump & clamp line during venogram

Open Filters & Close Bypass

Filtration

Anesthesiologist

Anesthesiologist Communicates:

MAP is > 65 mmHg

Bringing Hemofiltration Cartridges Online

Open Filters and Close Bypass

Perfusionist

Leaving the bypass line open, open clamps on the left cartridge (5 and 7) and allow blood to displace the heparinized normal saline into the patient.

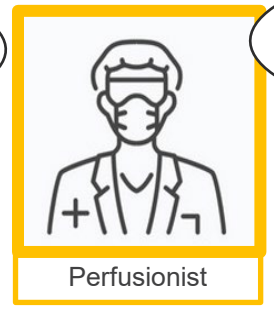
After the heparinized normal saline is in the left cartridge and its lines is fully replaced with blood, wait approximately 30 seconds and open clamps on the right cartridge (clamps 6 and 8), while keeping the bypass line open.

Once the heparinized normal saline in the right cartridge and its lines is fully replaced with blood, wait approximately 30 seconds and then close the bypass line by securely closing clamp 4.

Add a reusable tube clamp as a redundant bypass closure mechanism high on the bypass line in clear view of the team.

Anesthesiologist

Anesthesiologist Communicates:
- ✓ Blood Pressure is…
- ✓ MAP is controlled



Perfusionist

Perfusionist Communicates:
- ✓ Filter 1 is open
- ✓ Filter 2 is open
- ✓ Bypass line is closed ?

Hemofiltration Cartridges Method

Start Pump with Circuit on Bypass

Slow pump & clamp line during venogram

Perfusionist

Filters brought online sequentially to limit large blood pressure reduction

Left cartridge is opened and charged first

Blood pressure is checked before proceeding

Right cartridge is then opened and charged

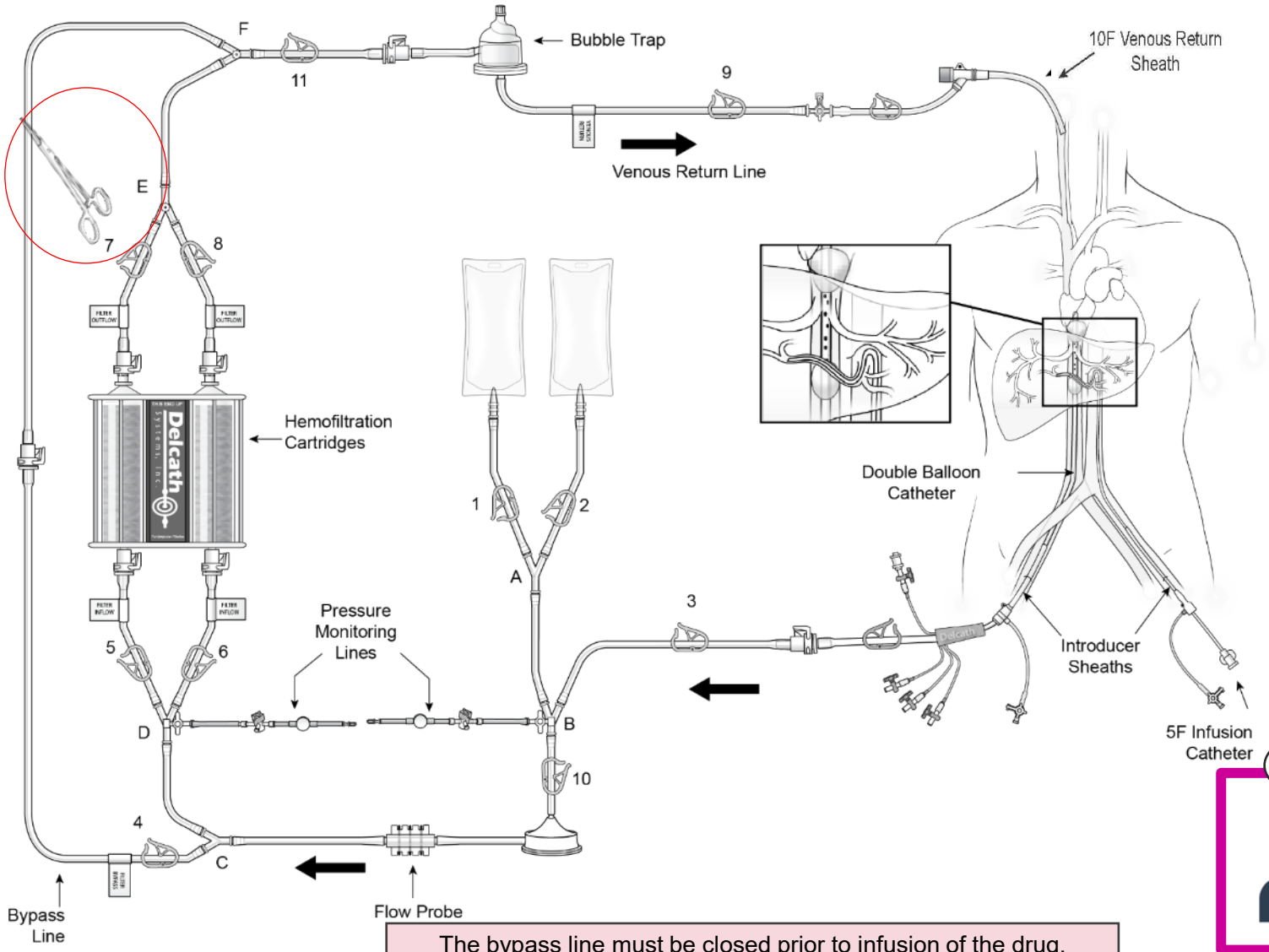
Complete Filtration Established

Delcath

Complete Hemofiltration

The tube clamp can be used to close the bypass line, at the area close to the upper Y connector and in easy view of the procedural team.

This will ensure that every HCP can see that the bypass line is closed during filtration.



The bypass line must be closed prior to infusion of the drug.

Perfusionist

Open Filters & Close Bypass

Filtration

Anesthesiologist

Anesthesiologist Communicates:
Blood Pressure is…

Delcath

PHP Procedure Monitored Events & PHP Team Member Roles

- Monitor Bubble-trap for entrapped air
- Check for leaks from any part of the circuit
- Monitor blood flow rate

Perfusionist

- Maintain DBC position
- Spasm check
- Check for DBC leaks
- Positioning infusion catheter

Interventional Radiologist

- Monitor systolic, diastolic, and mean arterial blood pressure
- Monitor heart rate and vital signs
- Correct as needed

Anesthesiologist

Establishing Hemofiltration

Perfusionist

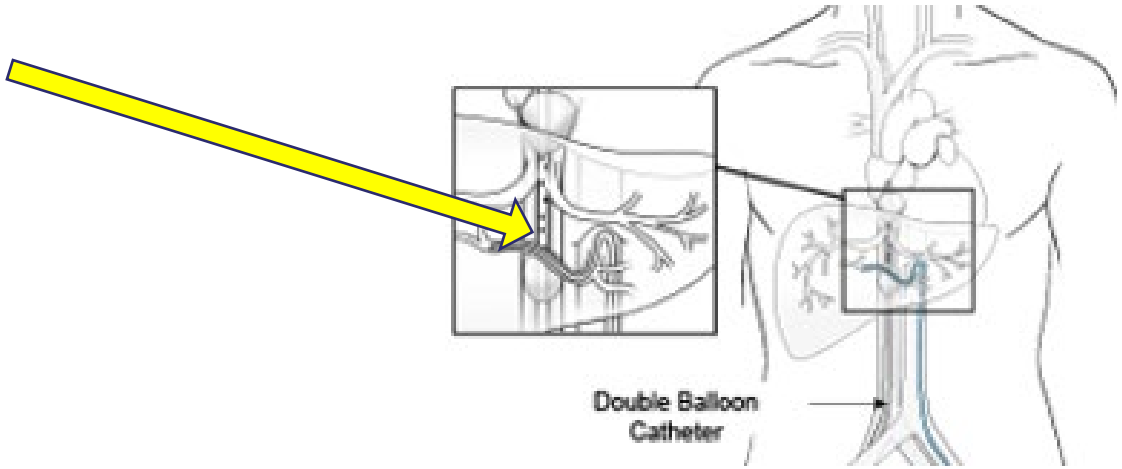
Filtration

Blood Flow During Hemofiltration

Venous blood is aspirated from the central lumen through the fenestrations in the Isofuse Catheter

This blood flows through the Isofuse Catheter to the pump through the Bypass Line

Blood is returned to the patient through the venous return sheath



Procedure - Drug Infusion

Filtration

30 Minute Washout Filtration

Hemofiltration is maintained for

First 30 minutes:
Drug infusion phase

Last 30 minutes:
Washout period

- Helps to maintain hemofiltration
- Monitors blood flow rate
- Monitors Pump Pressures
- Checks for circuit leaks
- Records ACT

Post Procedure - Blood Return

Perfusionist

30 Minute Washout Filtration

To return blood to the patient the Interventional Radiologist instructs the Perfusionist to open clamps for saline flush and this pushes the blood through filter and back into patient's internal jugular vein.

The effectiveness of the return of blood to a patient is dependent on the central venous pressure and the amount of fluid given.

Ending Extracorporeal Circulation

Perfusionist

Disassemble Circuit and Dispose Material in Chemo Waste Container

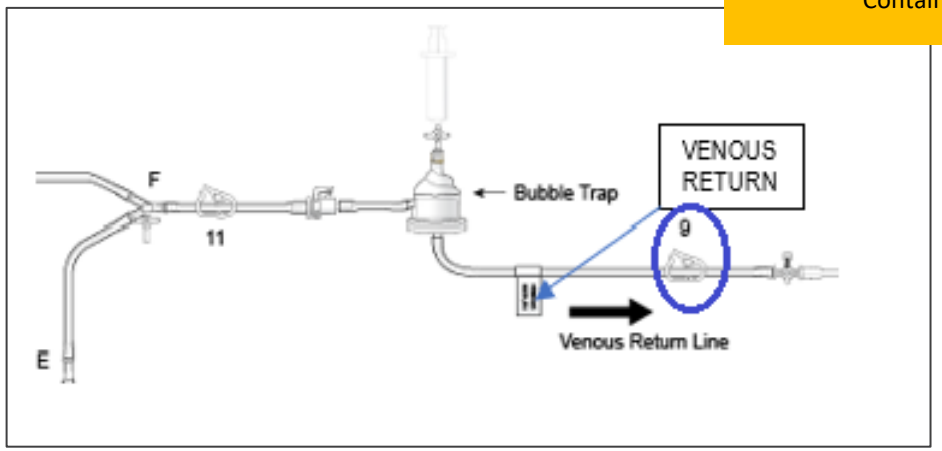
At the end of the 30-minute wash-out period:

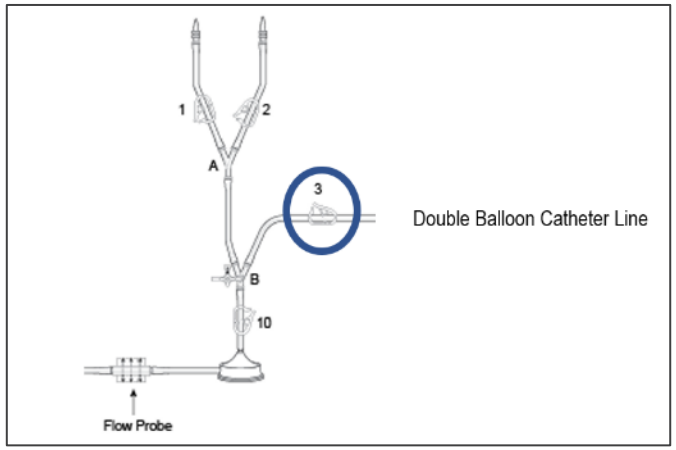
1) IR fully collapses the caudal balloon.

2) IR fully collapses the cephalad balloon.

3) Perfusionist discontinues filtration by:

- Reducing the pump RPM to 1000
- Closing clamps 3 and 9
- Stopping flow by turning off the pump.





Delcath

PHP Procedure Team End of Procedure Roles

Perfusionist

Disassemble Circuit and Dispose Material in Chemo Waste Container

- Stops all ECF flow
- Opens bypass line
- Assists with blood return
- Appropriately disposes all components

Perfusionist

- Collapses DBC
- Disconnects DBC
- Disconnects internal jugular introducer from the ECF

Interventional Radiologist

- Vasopressor weaned/discontinued
- Normalizes coagulation
- Post procedural medications

Anesthesiologist

Module 5
Drug Preparation and Injection

Deloath

Reference ID: 5226627

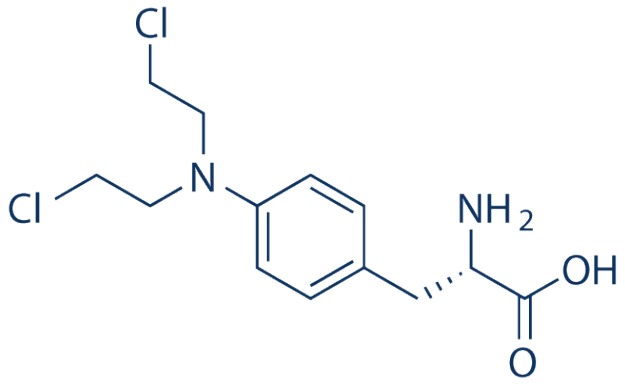
Module 5 Objectives

Module 5 describes the responsibilities of the pharmacists and interventional radiology nurse/technician who are responsible for the drug preparation and delivery system preparation, respectively.

- Understand how to reconstitute, store and transport HEPZATO.
- Coordinate timing of the prepared HEPZATO so delivery occurs as soon as possible to limit melphalan degradation and procedure time for the patient.

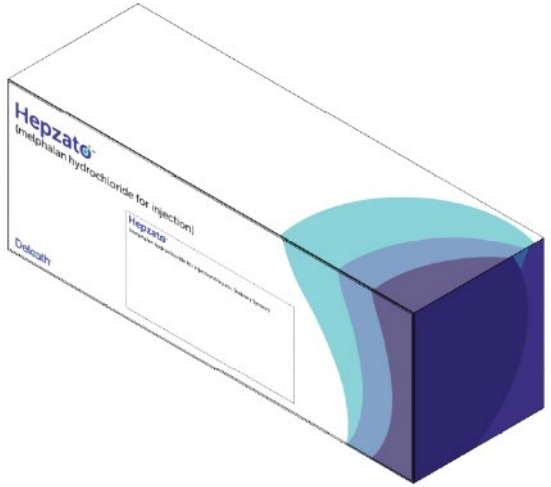
HEPZATO (melphalan) Injection

- It is used as a chemotherapy.
- It is also known as L-PAM pr L-phenylalanine.
- It is a bifunctional alkylating drug.

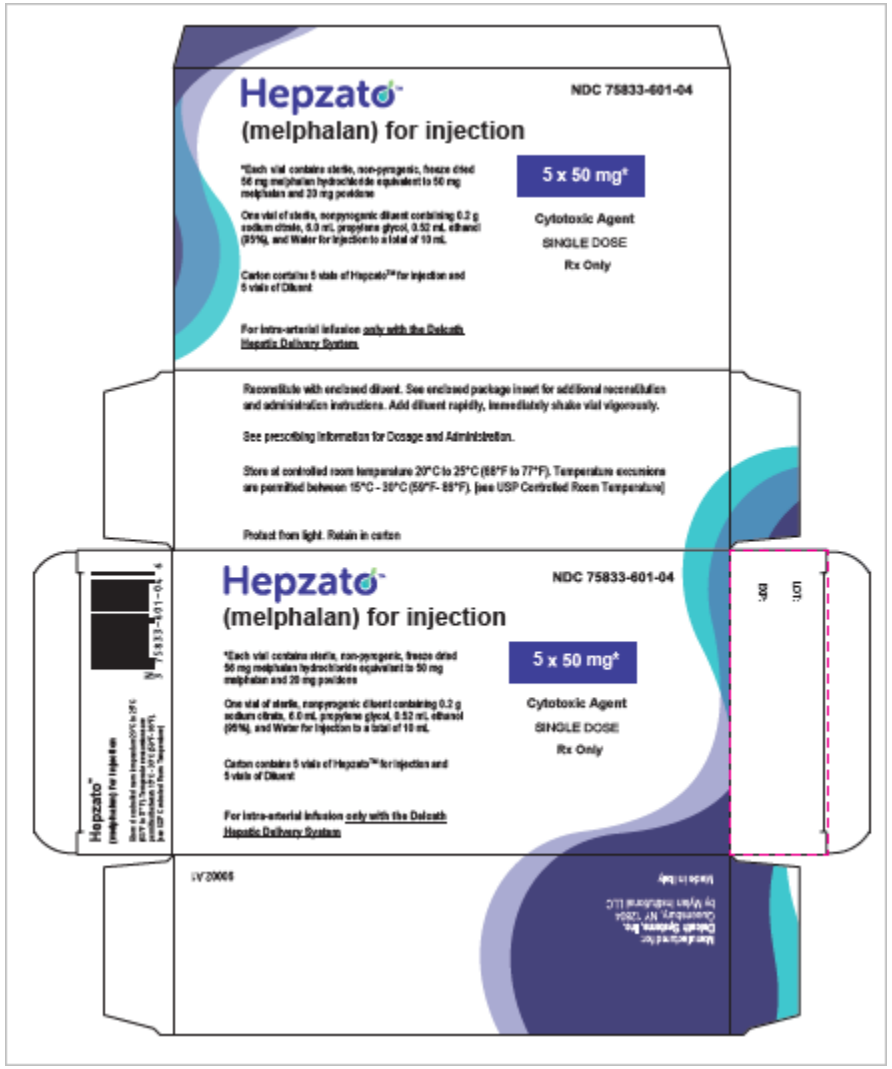


Vahrmeijer AL, van Dierendonck JH, Keizer HJ, Beijnen JH, Tollenaar RA, Pijl ME, et al. Increased local cytostatic drug exposure by isolated hepatic perfusion: a phase I clinical and pharmacologic evaluation of treatment with high dose melphalan in patients with colorectal cancer confined to the liver. Br JCancer. 2000;82(9):1539–46.

HEPZATO (melphalan) for Injection



- Wear gloves in preparation and handling.
- If skin or mucosa contact is made, immediately wash with soap and water.
- Follow institutional guidelines and protocols.



Each vial of HEPZATO for injection contains melphalan equivalent to 50 mg melphalan and 20 mg povidone

0.9% Sodium Chloride Injection is used as the approved secondary diluent

Calculation of Ideal Body Weight for HEPZATO Dosing

	Height	Ideal Body Weight
Men	≥ 152 cm	52 kg + (0.75 kg/cm of height greater than 152 cm)
	< 152 cm	52 kg – (0.75 kg/cm of height less than 152 cm)
Women	≥ 152 cm	49 kg + (0.67 kg/cm of height greater than 152 cm)
	< 152 cm	49 kg – (0.67 kg/cm of height less than 152 cm)

The HEPZATO dose may be calculated 1 to 2 days before the treatment by the Medical Oncologist.

Total HEPZATO dose = Calculated Ideal Body Weight x 3mg

NOTE: Total dose not to exceed 220mg.

HEPZATO Preparation

Pharmacist

Prepared by Pharmacy per physician's prescription

Reconstitute each HEPZATO vial with 10 mL of supplied diluent

Doses up to 110 mg

dilute reconstituted HEPZATO in 250 mL 0.9% sodium chloride injection

Doses between 111 mg – 220 mg

dilute reconstituted HEPZATO in 500 mL 0.9% sodium chloride injection

The 250 mL and 500 mL solutions will require multiple injection cycles

HEPZATO Preparation

Pharmacist

Chemotherapy HCP

Visual inspection for particulates in HEPZATO solution

If particulates are observed
DO NOT USE

HEPZATO Infusion Process

Chemotherapy HCP

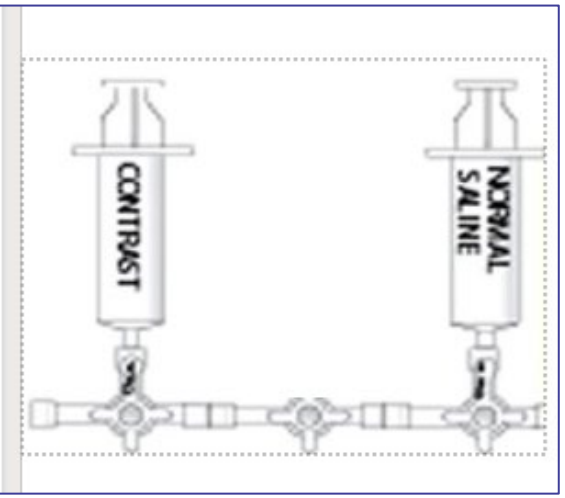
HEPZATO solution syringe refills

Interventional Radiologist

Checks for:

- ✓ Hepatic artery spasms
- ✓ Balloon position confirmation
- ✓ Balloon expansion against vena cava walls

HEPZATO Administration Injection Line Setup – Syringes



Undiluted iodinated contrast agent is attached to the injection line, and it is used for checking hepatic artery spasm via CT.

Nitroglycerin should be kept in the procedural room, and it must be administered intra-arterially to alleviate spasms.

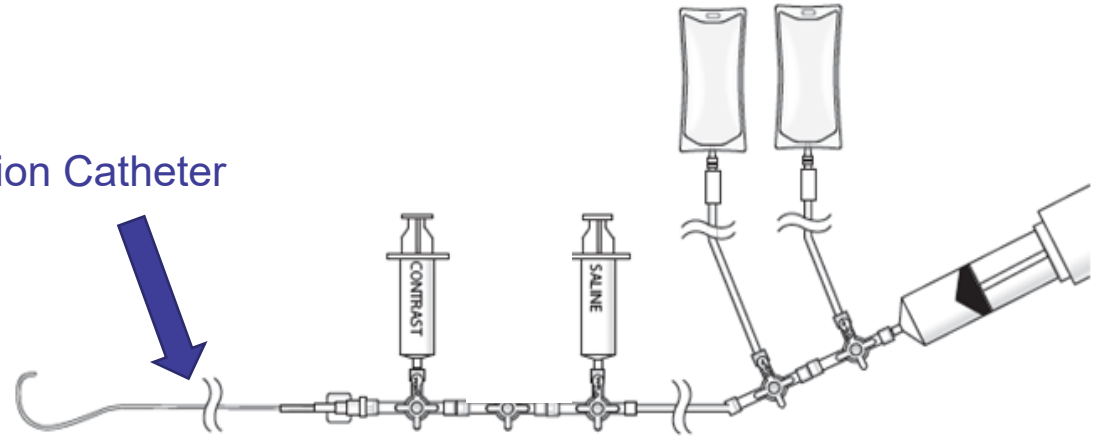
Normal saline is attached to the injection line, and it is drawn into the saline syringe for priming and flushing the hepatic arterial infusion line during the procedure.

Syringe	Volume and Concentration to Prepare in Syringe
Contrast	20 mL of undiluted iodinated contrast agent
IANTG	5 mL of diluted nitroglycerin 100 mcg/mL solution
Saline	20 mL of 0.9% Sodium Chloride injection

HEPZATO Administration Injection Line Setup – Catheter Connection

Note: this connection is done after drug arrives in the room.

Connect the Infusion Catheter



Items needed but not included in HDS
(1) Medrad 150 mL syringe
(2) Intravenous Administration Sets
(3) 48” Injector Lines
(5) 3-way stopcocks
(3) 20 mL syringes

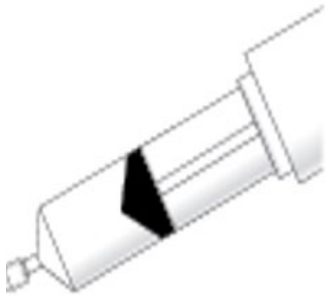
- Connect the Infusion Catheter (5F catheter or a microcatheter coaxially introduced through the 5F catheter).
- Maintain catheter patency by hospital catheter infusion protocols (e.g., infuse heparinized saline: the concentration of heparin should be 1000 units per 500 mL of normal saline).

HEPZATO Administration – Arterial Catheter

- HEPZATO is administered by infusion via a 5F arterial catheter or a Delcath-qualified microcatheter.
- It is introduced coaxially through the 5F catheter into the proper hepatic artery.
- At the discretion of the Interventional Radiologist, a microcatheter may be used when selective tip placement is preferred for the drug infusion.
- Delcath has qualified three different microcatheters for use with the HEPZATO KIT.

See IFU and USPI for complete HEPZATO information

Drug Injector System Setup



150 mL syringe installed into the drug injector

Injector flow rate set to 25 mL/minute OR 0.4 mL/second

Injection volume entered

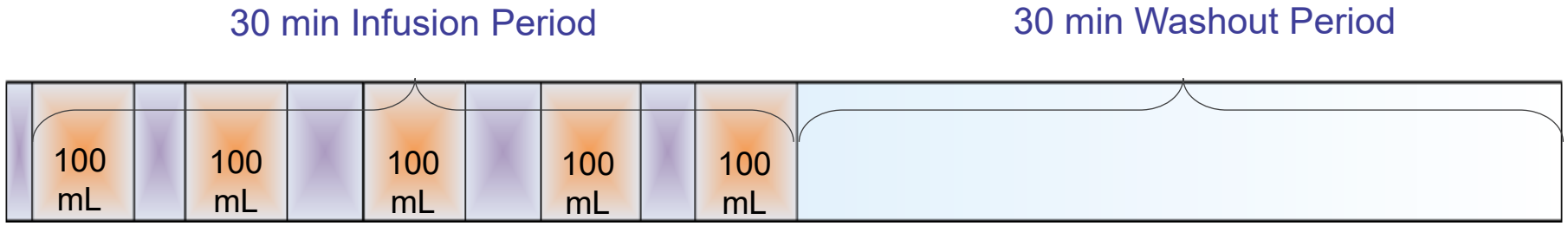
100 mL per injection

Requires multiple injection cycles

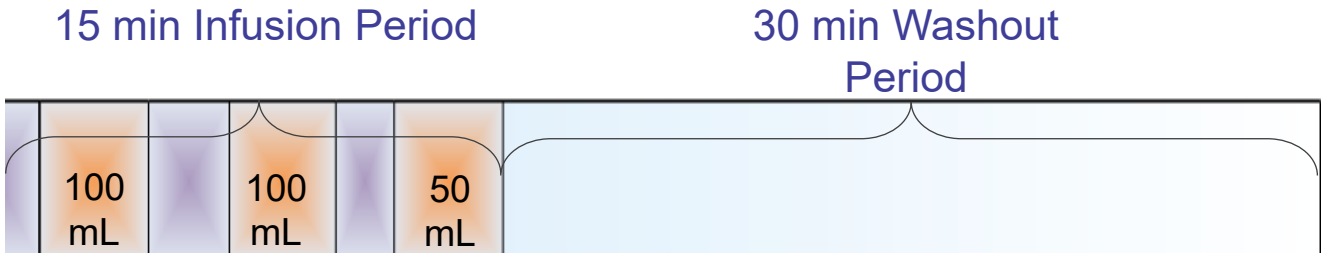
HEPZATO infusion must be completely administered within 30 minutes

HEPZATO Drug Injector & Infusion Timing

500 mL Total Infusion (25 mL/min)



250 mL Total Infusion (25 mL/min)



Reference ID: 5226627

HEPZATO Delivery Parameters & Precautions

Delivery Parameters

- Total volume of **500 mL** – 5 infusions of 100 mL at 25mL/min
- Total volume of **250 mL** – 2 infusions of 100 mL + infusion of 50 mL at 25 mL/min

Delivery Precautions

- Immediately stop the procedure if leakage is detected outside of the isolated region and cannot be corrected.
- Once the infusion of HEPZATO has started, Do NOT deflate balloons unless administration of drug has been stopped and a full washout cycle (30 minutes) has been completed.

Module 6
Procedure/Treatment Day

Reference ID: 5226627

Module 6 Objectives

Module 6 describes PHP Procedure Team responsibilities on the day of the procedure. This includes patient preparation and procedural methodology. The content is specific for the IR, anesthesiologist, and perfusionist.

- Describe required pre procedure imaging, laboratory testing, and medications.
- Understand team coordination and intraprocedural communications.
- Know procedure day medication, supplies and blood product needs.

Typical Schedule of Examinations Prior to PHP Procedure

3 Weeks Prior

- Baseline laboratory - medical history and physical examination
- Serum chemistries and electrolytes
- Complete blood count
- Baseline laboratory
- Concomitant disease
- Cardiac and pulmonary evaluation
- Liver function tests
- Prothrombin Time /Partial Thromboplastin Time
- Other medical tests as deemed necessary

2 Weeks Prior

- A baseline CT or MRI is acquired.
- This scan is needed to determine if there has been rapid advancement of the tumor from the time that the diagnostic scan was done.
- The extent of the disease is documented during this scan.
- Procedural risks are assessed including portal hypertension, liver cancer burden, cerebral bleeding risks and histories of surgical procedures.
- Hepatic Artery Mapping (has an optional time point)
- Pre-operative clearance

1 Week Prior

- Patient is screened for blood products.
- Blood Products (Type & Cross)
- Packed RBC, fresh frozen plasma, platelets, cryoprecipitate
- The preoperative hepatic artery mapping study may be performed.
- Pre-op medications prescribed
- Discontinuation of medications
- Hydration instructions
- Pre-op clearance

Delcath

HEPZATO KIT Pre-Operative Activities

Ensure timely scheduling of preoperative activities

Imaging studies

Procedural room reservation

Laboratory testing

Hospital bed reservation

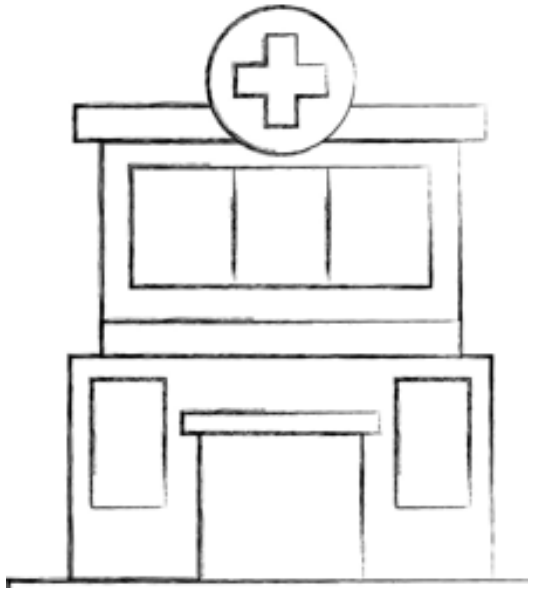
Medication requirements including new prescriptions

Appointments with:
- Medical Oncologists
- Interventional Radiologist
- Anesthesiologist

HEPZATO KIT Treatment Day Guidance

All medications and supportive measures must be determined and administered in accordance with:

Institutional policies, guidelines, procedures



Delcath's Hepatic Delivery System Instructions For Use (IFU)

HEPZATO prescribing information

Delcath

Treatment Day Verifications

The Perfusionist verifies the following:

1) The expiration date, reference number, and lot number of the KIT.

2) The contents of the HEPZATO KIT.

3) Sets up the extracorporeal filtration circuit.

4) A full tank of CO_2 is in the procedural room.

5) The ACT machine is in the procedural room.

Perfusionist

Treatment Day Verifications

The Interventional Radiologist verifies the following:

1) The correct HEPZATO KIT (balloon spacing 50mm or 62mm) is in the procedure room.
2) The time that HEPZATO will be delivered by the pharmacy.
3) Any recent patient lab results which are pertinent to the procedure.
4) The treatment start time.
5) That all the medical materials needed for the procedure are in the operating room.
6) That all PHP Procedure team members are in attendance.

Interventional Radiologist

Treatment Day Verifications

The Anesthesiologist verifies the following:

1) The anesthesia medications are in the procedural room.

2) The vasopressor pump or line is set up.

3) There is patient access for delivery of medications.


Anesthesiologist

Treatment Day Verifications

The Chemotherapy HCP verifies the following:

1) The drug injector is in the room.

2) The drug injector is set up.

3) The components that are not included in the HEPZATO KIT are available and organized on the Interventional Radiology suite's tables.

Patient Treatment Day Preparation

The patient is:

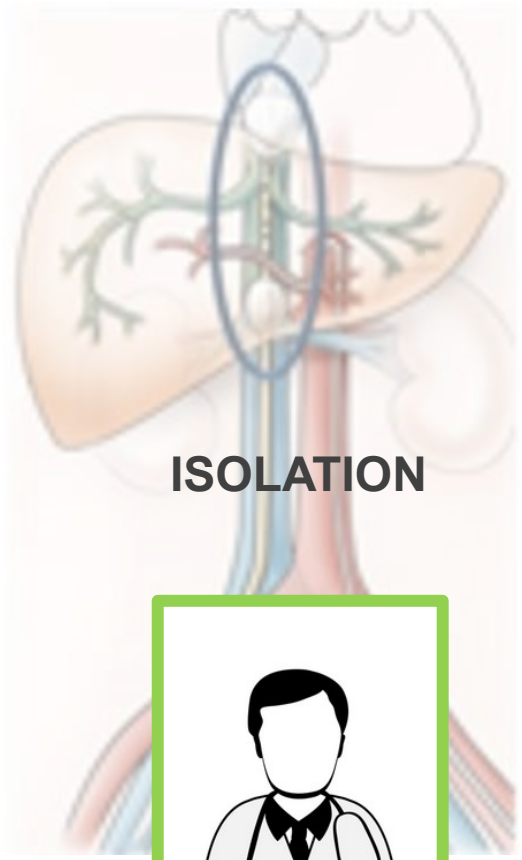
- Provided with details on forbidden medications
  (oral anti-coagulants, ACE inhibitors, calcium channel blockers, alpha-1- adrenergic blockers, thrombin inhibitors, aspirin, NSAIDs)
- Provided with details about medications that will be administered during the procedure
- Administered pre-procedure medications

Hydration

- The patient must be properly hydrated before the procedure.
- Dehydration increases the risk of unstable blood pressure and difficulty maintaining mean arterial pressures above 65 mmHg.
- Instructions are given to drink plenty of clear liquids prior to bed the night before the procedure.
- Hydration is initiated at admittance to the hospital on the day of the procedure.

Excessive hydration pre-procedure or intra-procedure can increase post procedure complications.
In some cases, excessive hydration may prolong mechanical ventilation due to head and neck edema.

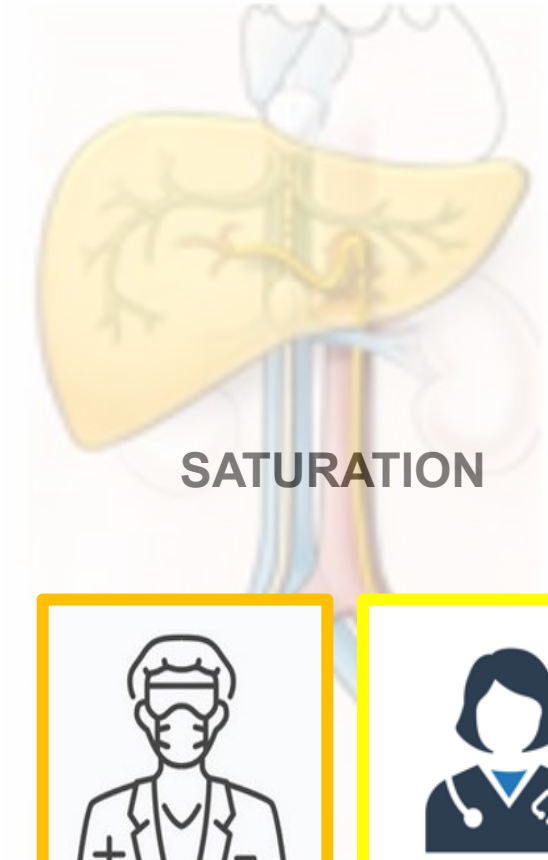
PHP Procedure Team Roles and Responsibilities



ISOLATION

Interventional Radiologist

Catheterization Placements

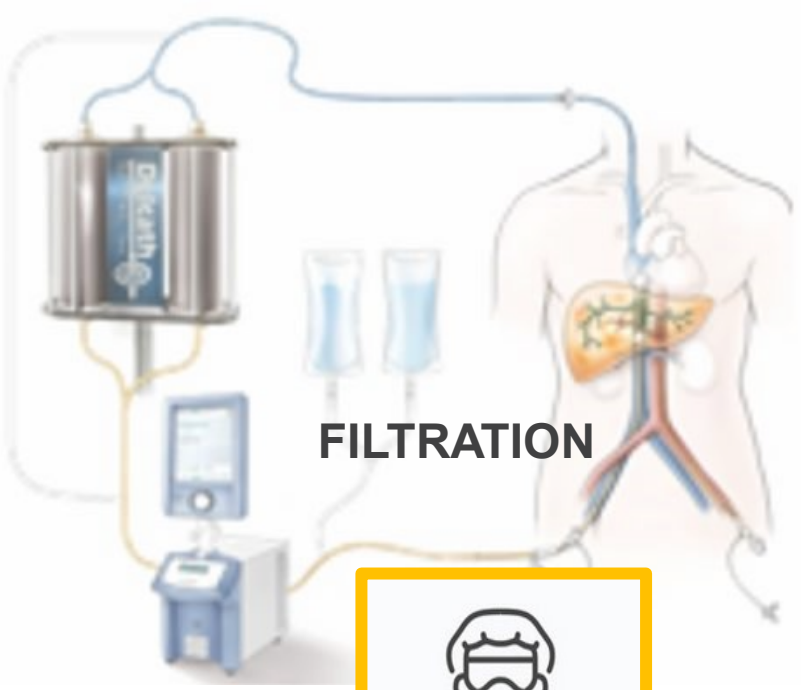


SATURATION

Perfusionist

Chemotherapy HCP

Drug Infusion Administration



FILTRATION

Perfusionist

Extracorporeal Circuit Filtration Management

Delcath

Medications That are Administered During the Procedure

All medications and supportive measures must be determined and administered in accordance with each institution's policies, guidelines, procedures.

Hydration
necessary to compensate for procedural blood displacement

Heparin Anticoagulation
Maintain activated clotting time at > 400 seconds throughout the procedure

Anesthetic Management
Procedure is conducted under general anesthesia

Blood Pressure Control
Significant procedure-related blood pressure decrease expected
Maintain systemic blood pressure at >65 mmHg

Medications That Should Be Withheld

ACE inhibitors
Calcium channel blockers
Alpha 1 adrenergic blockers

Increase vasopressor resistance

Coumadin
Thrombin Inhibitors
Aspirin
NSAIDs

Increase procedural bleeding risks

Medications Delivered During the Procedure

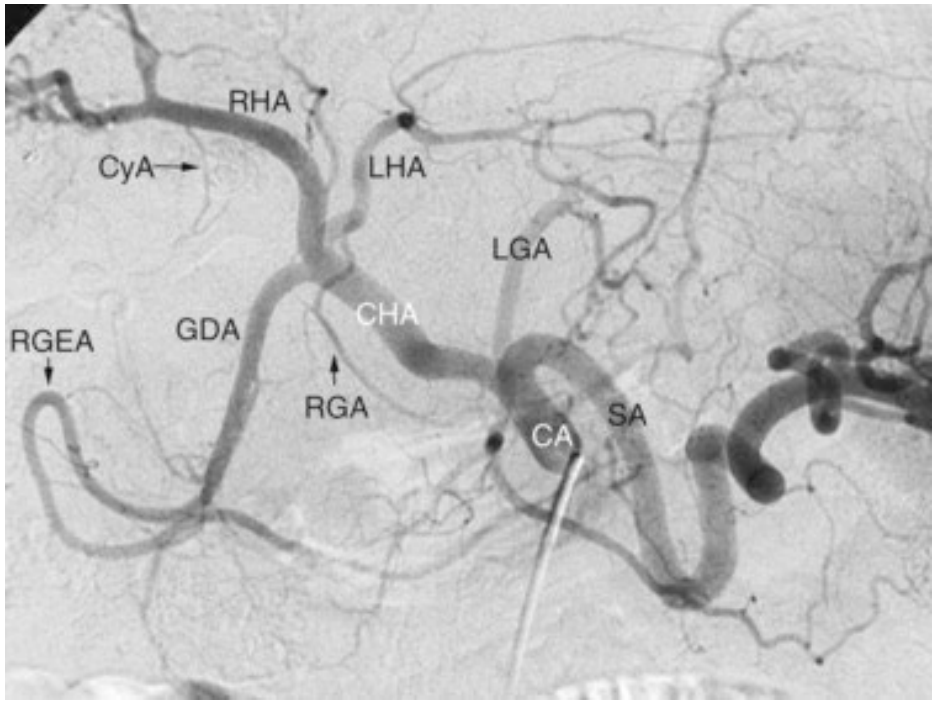
Heparin
Maintain anticoagulation

Norepinephrine, Epinephrine
For blood pressure management

Beta Blockers
Heart rate management
dependent on heart rate

Treatment Day Angiogram

Hepatic Artery Angiogram and Mapping



Conventional celiac artery anatomy. CA, celiac axis; LGA, left gastric artery; SA, splenic artery; CHA, common hepatic artery; GDA, gastroduodenal artery; RGA, right gastric artery; RHA, right hepatic artery; LHA, left hepatic artery; CyA, cystic artery; RGEA, right gastroepiploic artery.

The arterial supply to the liver must be completely examined the day of the procedure if not previously done one week prior.

Determinations

- Possible impact of chemo infusion
- Embolization needs

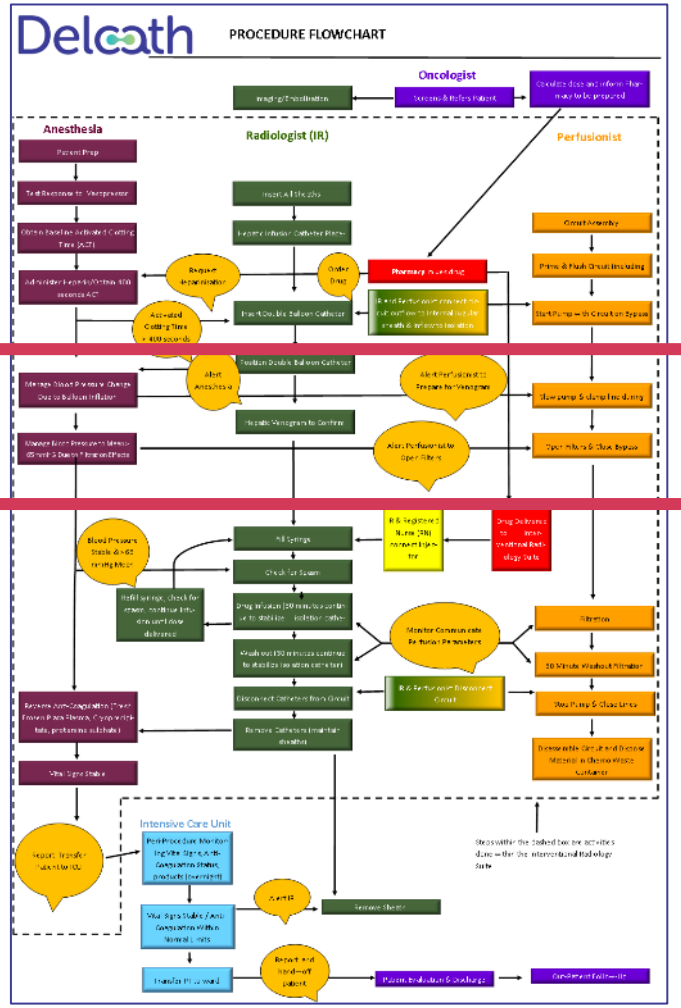
PHP Procedure Team Tasks and Key Communications

- Each PHP Procedure Team member has separate workstreams during the procedure
- There are critical points during the procedure where key information between the 3 PHP Procedure Team members needs to be shared
- Natural pause points in the procedure, where all 3 PHP Procedure Team members must be aligned
  - the moment before Double Balloon Catheter (DBC) is expanded
  - when extracorporeal filtration begins
  - before drug delivery begins

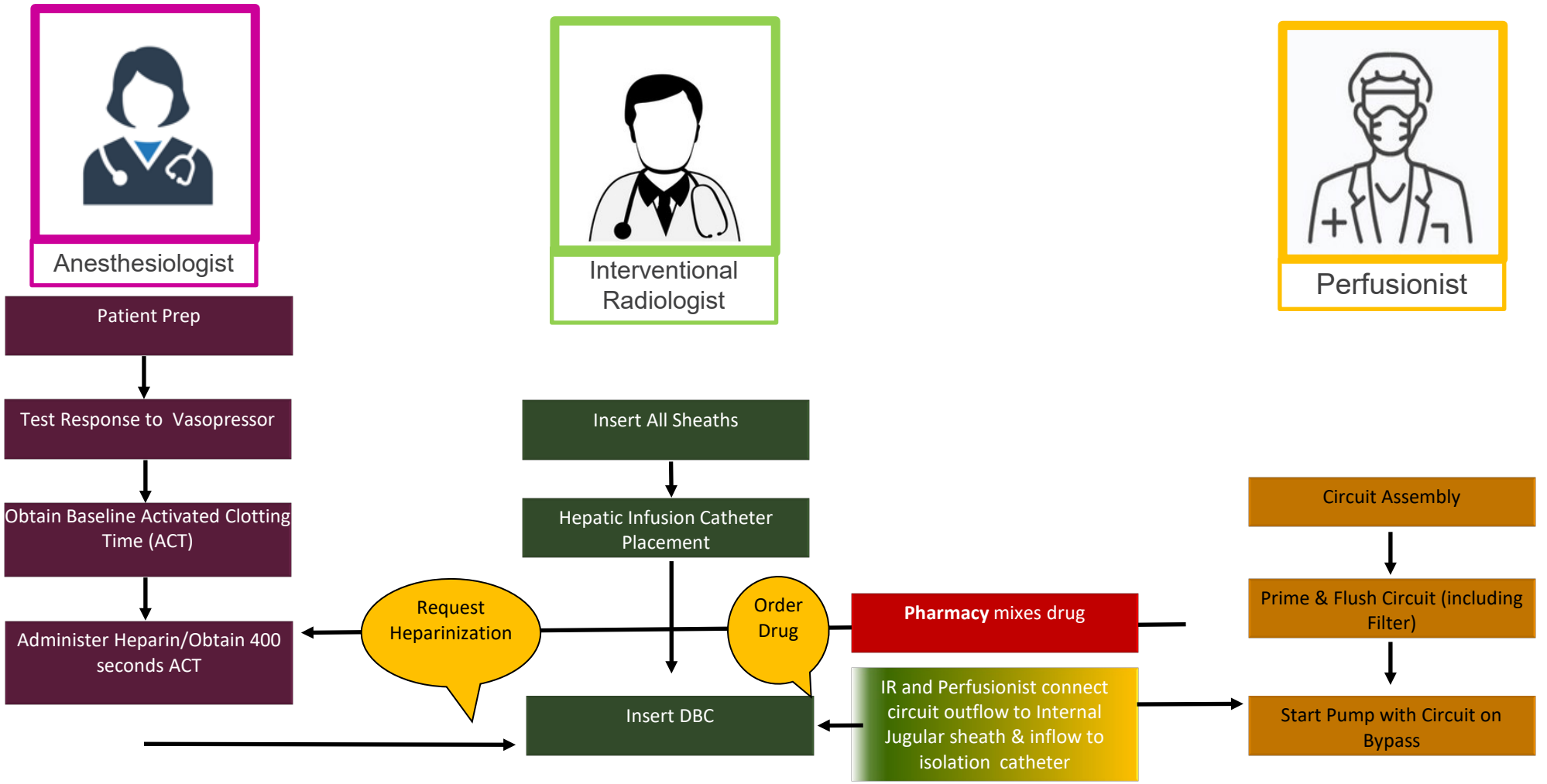
Pre-Filtration

Inflate DBC,
Begin Filtration

Deliver HEPZATO



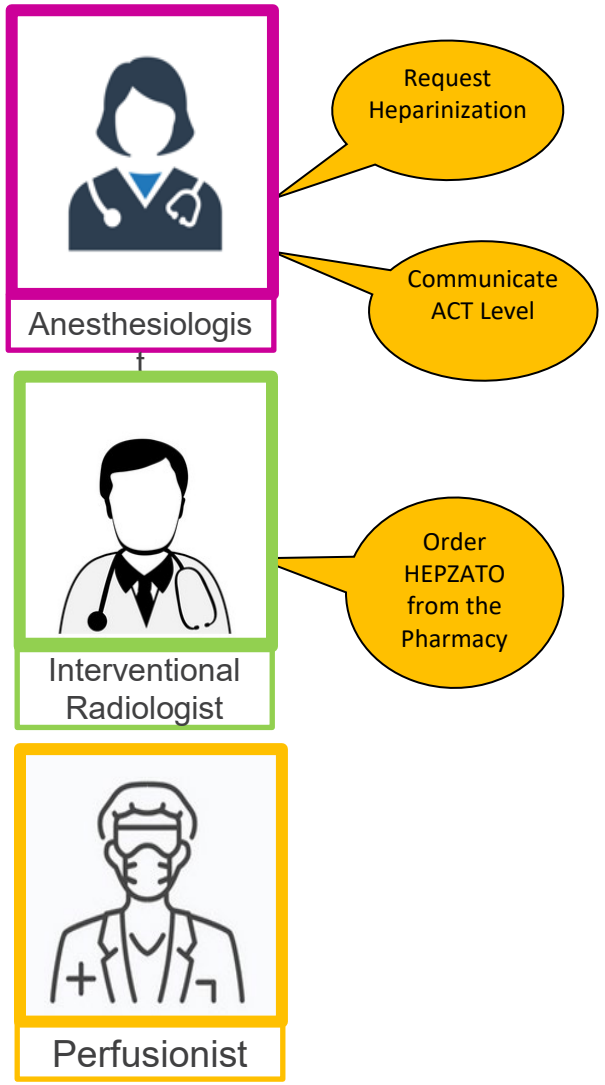
Prepare to Expand Double Balloon Catheter (DBC) and Bring the Filters “on-line”



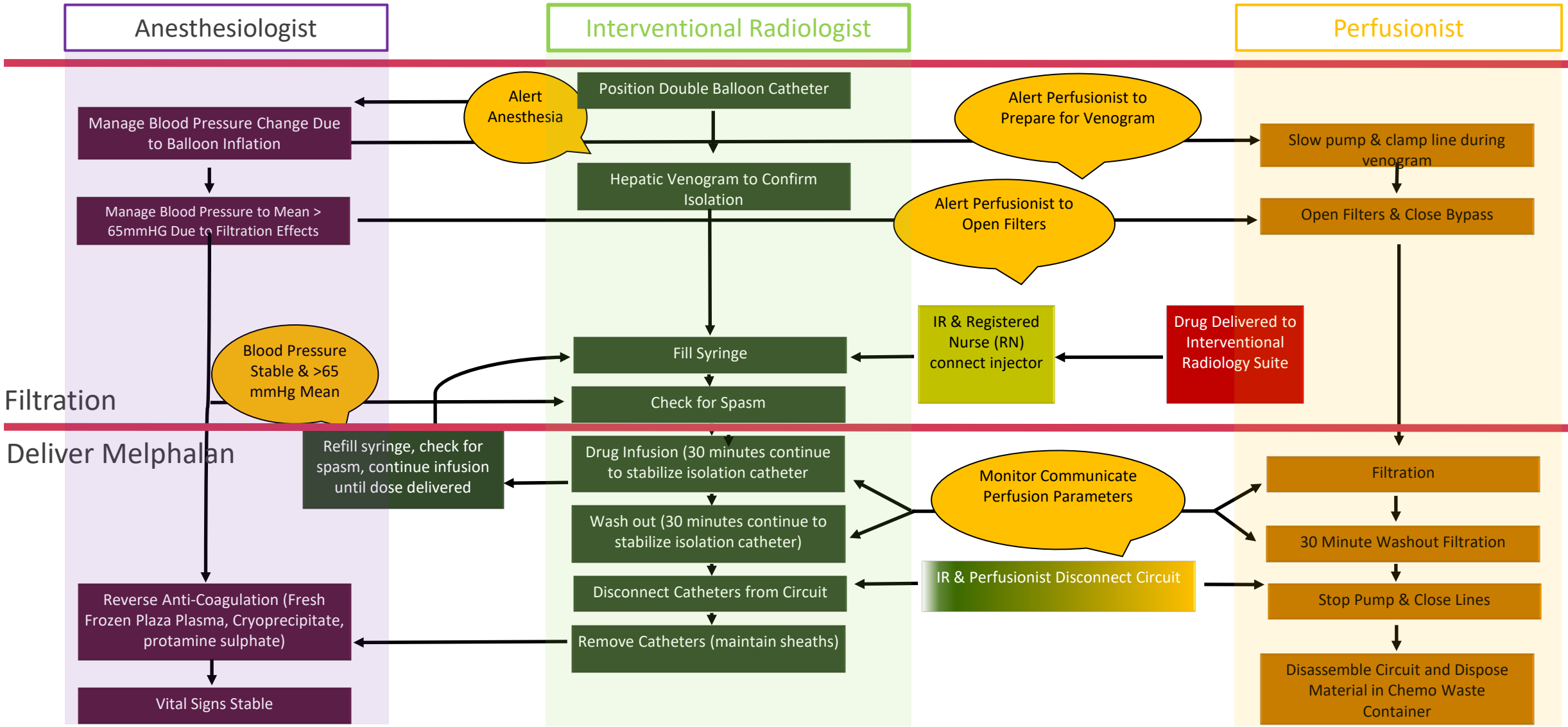
PHP Procedure Team tasks prior to Double Balloon Catheter (DBC) inflation and bringing filters on-line

Just prior to bringing the filter “on-line” the 3 PHP Procedure Team members should:

- Anesthesia
  - Complete patient preparation
  - Test response to vasopressors
  - Administer heparin
  - Obtain a minimum 400 ACT
  - Communicate the ACT to the IR
- Interventional Radiology
  - Insert all sheaths and catheters including:
  - Place Hepatic Infusion Catheter
  - Place Double Balloon Catheter (without inflating balloons)
  - Order HEPZATO from the Pharmacy
- Perfusion
  - Complete circuit assembly
  - Prime and flush circuits (including filters)

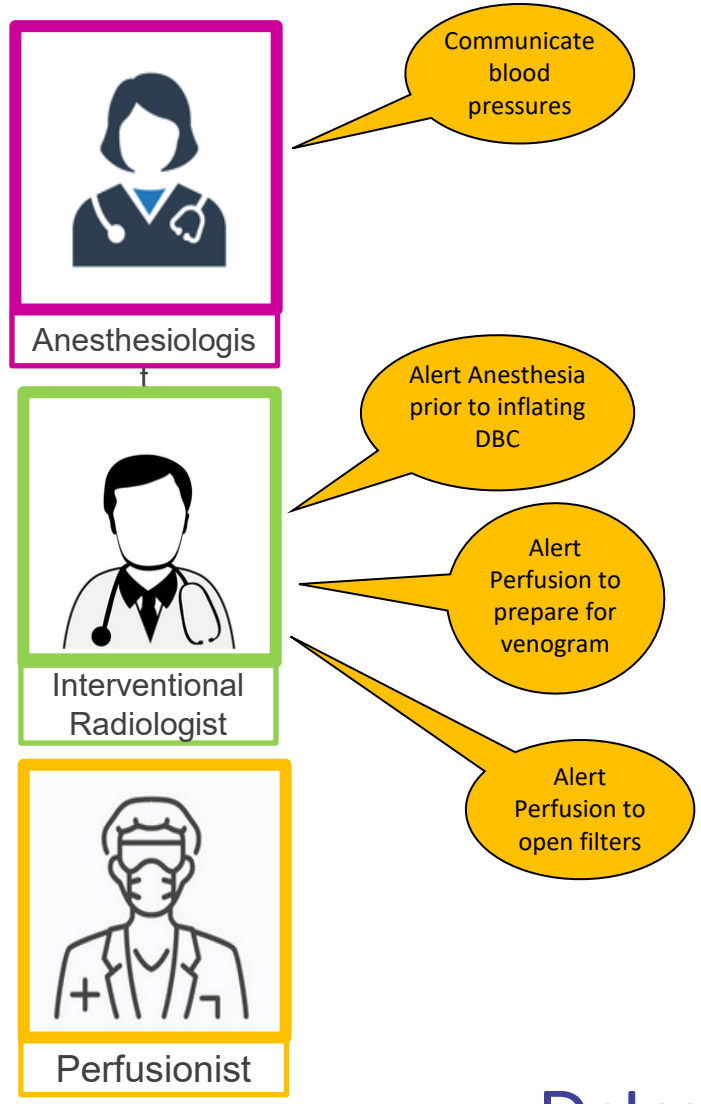


Inflate Double Balloon Catheter (DBC), Bring Filters On-Line, and Deliver HEPZATO



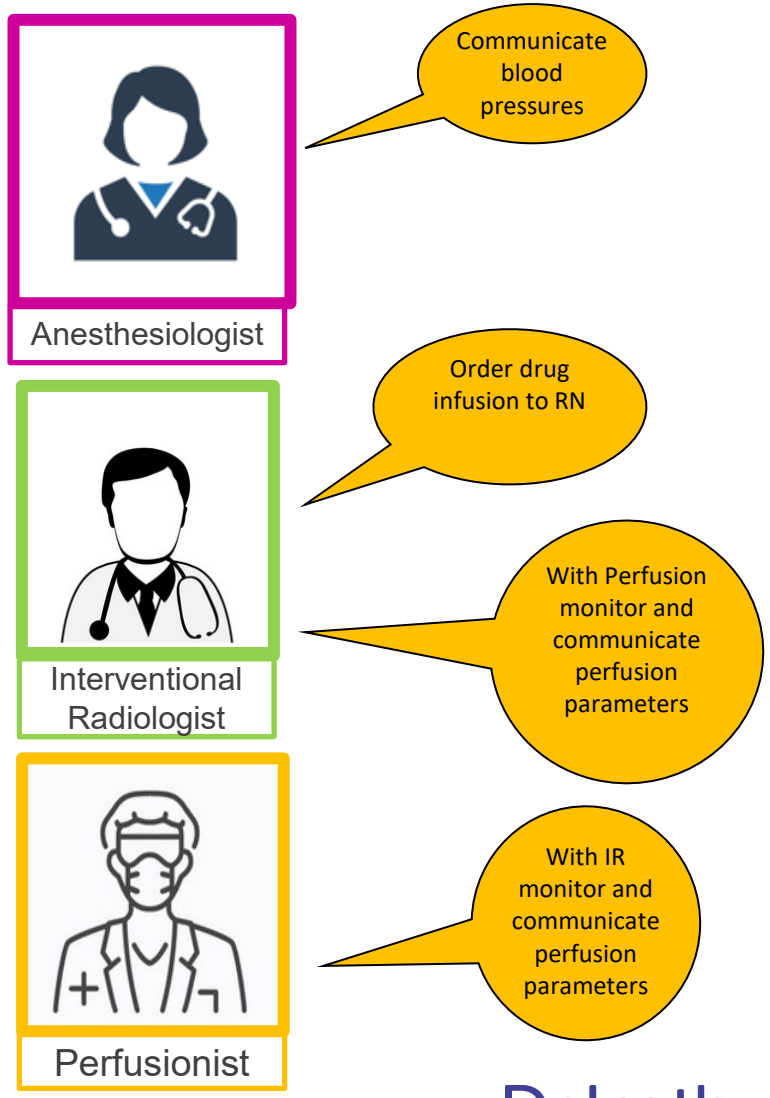
Bringing Filters on-line, Filtration, prior to HEPZATO Delivery

- Anesthesia
  - Manage blood pressure changes
    - Double Balloon Catheter (DBC) inflation
    - Brining filters on-line
  - Maintain blood pressure mean > 65 mmHg
- Interventional Radiology
  - Position DBC
  - Inflate DBC
  - Conduct a hepatic venogram to confirm isolation
  - Fill intra-arterial nitroglycerin Syringe
  - Check for vascular spams
- Perfusion
  - Start pump
  - Bring the filters on-line one at a time (according to IFU instructions)



HEPZATO Delivery, Washout and End of PHP Procedure

- Anesthesia
  - Manage blood pressure changes during filtration/ HEPZATO delivery
  - Maintain blood pressure > 65 mmHg
  - Reverse anti-coagulation
- Interventional Radiology
  - HEPZATO infusion (30 minutes)
  - Wash out (30 minutes)
  - Disconnect catheters from circuit
  - Remove catheters and disconnect circuit
- Perfusion
  - Monitor filtration parameters
  - 30 minutes melphalan filtration
  - 30 minutes washout filtration
  - Stop pump and close lines
  - Disassemble circuit and dispose into chemo waste container



Delcath

Perfusionist Procedural Awareness - Pump Flow Rate

The flow rate of the pump should be maintained between 0.4 – 0.8 L/min

Pre pump pressure (suction side) should not be more negative than −250 mmHg, as lower pressures indicate possible catheter collapse or kink.

Pre-cartridge pressures (pre-filter) should not exceed 200 mmHg, as higher pressures indicate increasing filter resistance potentially due to thrombus or a kinked return line. Check filters to assure free flow and return line for kinks.

IR Procedural Flow - Hepatic Artery Spasm

Once the blood pressure is stabilized the IR **injects contrast agent** to check for hepatic artery spasm.

If spasm is observed :

Possible Cause	→	vasopressor therapy & low mean arterial pressure
Effect	→	reflux of melphalan into proximal non-embolized gastrointestinal branches or incomplete delivery of melphalan
During procedure	→	perform Angiography every 5 minutes
Spasm Relief	→	100 mcg/injection of intra-arterial nitroglycerin in hepatic artery

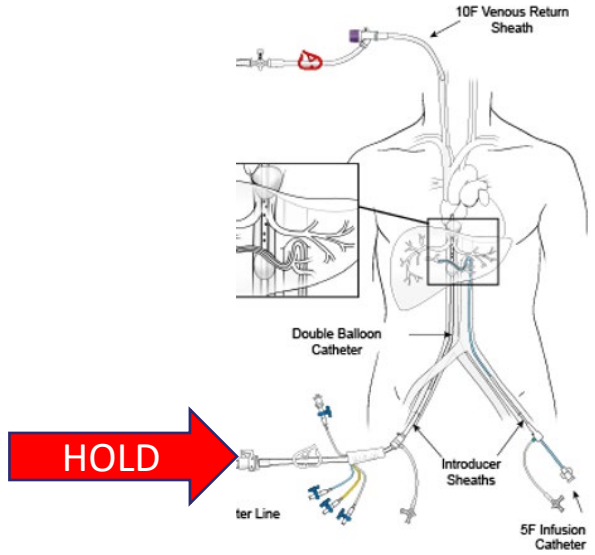
If there is a persistent intractable spasm, the procedure should be stopped.

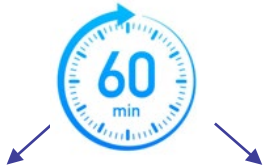
IR Procedural Flow – Infusion, Filtration & Double Balloon Catheter (DBC) Management

Once the IR approves the start of HEPZATO infusion, a 100 mL bolus is administered at 25 mL/second flow rate using drug injector (estimated 4 min infusion time).

The IR maintains a gentle hold of the DBC position during the entire infusion period.

HEPZATO is refilled into the drug injector and the IR performs a spasm check.





First 30 minutes: HEPZATO Infusion	Last 30 minutes: Washout Period

The DBC position checked fluoroscopically every 4 to 5 minutes during drug administration and filtration to ensure continued hepatic venous isolation

Post PHP Procedure - Blood Return

To return blood to the patient the Interventional Radiologists instructs the Perfusionist to open clamps for saline flush and this pushes the blood through the filter and back into the patient's internal jugular vein.

The effectiveness of the return of blood to the patient is dependent on the central venous pressure and the amount of fluid given.

End of PHP Procedure: Roles and Responsibilities

Perfusionist

- Stops all Extracorporeal Filtration Circuit (EFC) flow
- Opens bypass line
- Assists with blood return
- Appropriately disposes all components

Interventional Radiologist

- Collapses Double Balloon Catheter (DBC)
- Disconnects DBC
- Disconnects internal jugular introducer from the EFC

Anesthesiologist

- Vasopressor weaned/discontinued
- Normalizes coagulation
- Administers post procedural medications

Module 7
Catheterization, Isolation & Saturation

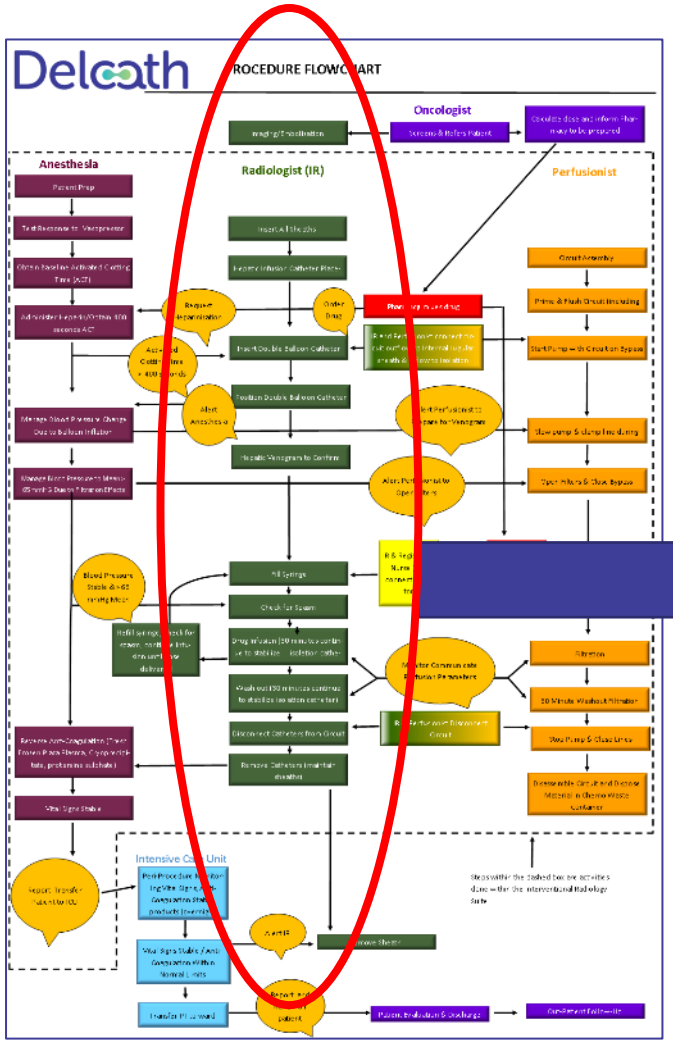
Delcath

Module 7 Objectives

Module 7 describes the responsibilities of the Interventional Radiologist (IR) on the day of the procedure. This includes catheterization, hepatic isolation, and contrast administration during drug infusion.

- Properly insert and place introducers and catheters.
- Understand procedural techniques that affect filter efficacy and systemic melphalan exposure.
- Confirm hepatic artery anatomy, determining whole liver vs lobar infusion approach and optimal hepatic artery catheter location.
- Assess appropriate Double Balloon Catheter (DBC) position and stabilization.
- Understand process to administer HEPZATO and how to split HEPZATO dose for sequential lobar approach.

Interventional Radiologist Procedural Tasks



This module describes the steps the Interventional Radiologist takes during the procedure.

- Imaging/Embolization
- Insert All Sheaths
- Insert Double Balloon Catheter
- Hepatic Infusion Catheter Placement
- Position Double Balloon Catheter
- Hepatic Venogram to Confirm Isolation
- Fill Syringe
- Check for Spasm
- Drug Infusion (30 minutes continue to stabilize isolation catheter)
- Wash out (30 minutes continue to stabilize isolation catheter)
- Disconnect Catheters from Circuit
- Remove Catheters (maintain sheaths)

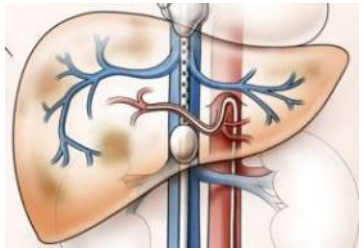
Interventional Radiologist

Delcath

Interventional Radiologist Responsibilities

The Interventional Radiologist is the lead physician during the PHP Procedure with HEPZATO KIT and has the following responsibilities:

- Arterial Mapping
- Introducer Placement
- Catheter Positioning
  - The liver blood supply needs to be assessed in order to formulate a strategy for catheter placement.
  - This helps to ensure adequate drug infusion to the entire liver.
  - Dependent on vascular anatomy, this may require repositioning of the catheter during the procedure
- Spasm Management
- Contrast administration during drug infusion



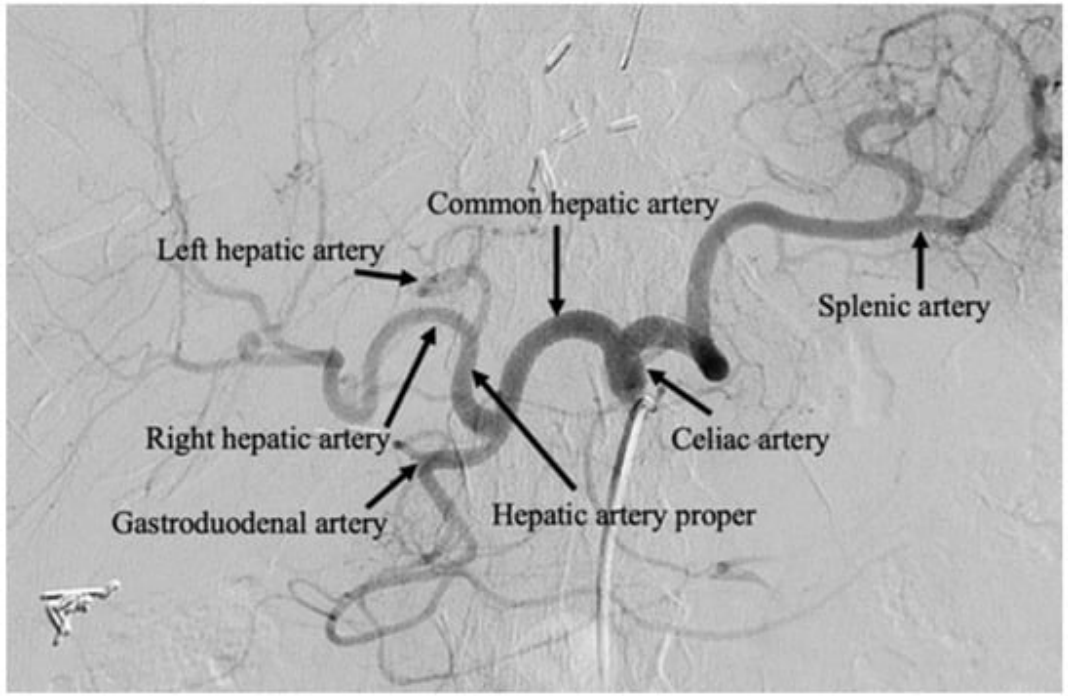
PHP Procedure Eligibility Evaluation


Interventional Radiologist

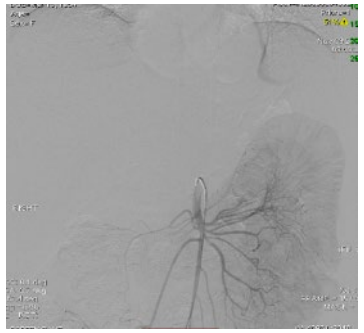
In order to determine eligibility for each patient, the IR evaluates the following:

- Prior surgeries that could potentially affect normal hepatic biliary and vascular anatomy
- Reimplanted anatomy; such as the common bile duct which can increase risk of biliary tree infection

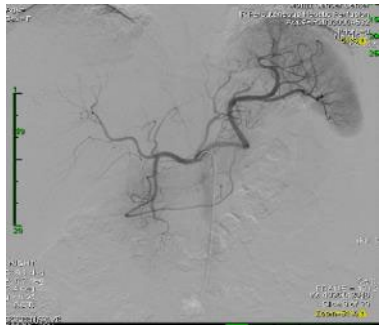
The arterial anatomy is assessed during the mapping process and can consist of a superior mesenteric artery angiogram and a celiac angiogram



Superior Mesenteric Artery Angiogram



Celiac Angiogram



Angiographic evaluation decreases the risk of infusion failure and reflux of melphalan

IR Procedural Awareness

Interventional Radiologist

Before the PHP procedure the IR should confirm the following :

- KIT Type Decision (balloon spacing 50mm or 62mm)
- Confirm KIT is in the IR Suite
- HEPZATO ordered from the pharmacy
- The patient's most recent lab results
- The treatment start time
- The PHP Procedure team is present

During the PHP procedure the IR must:

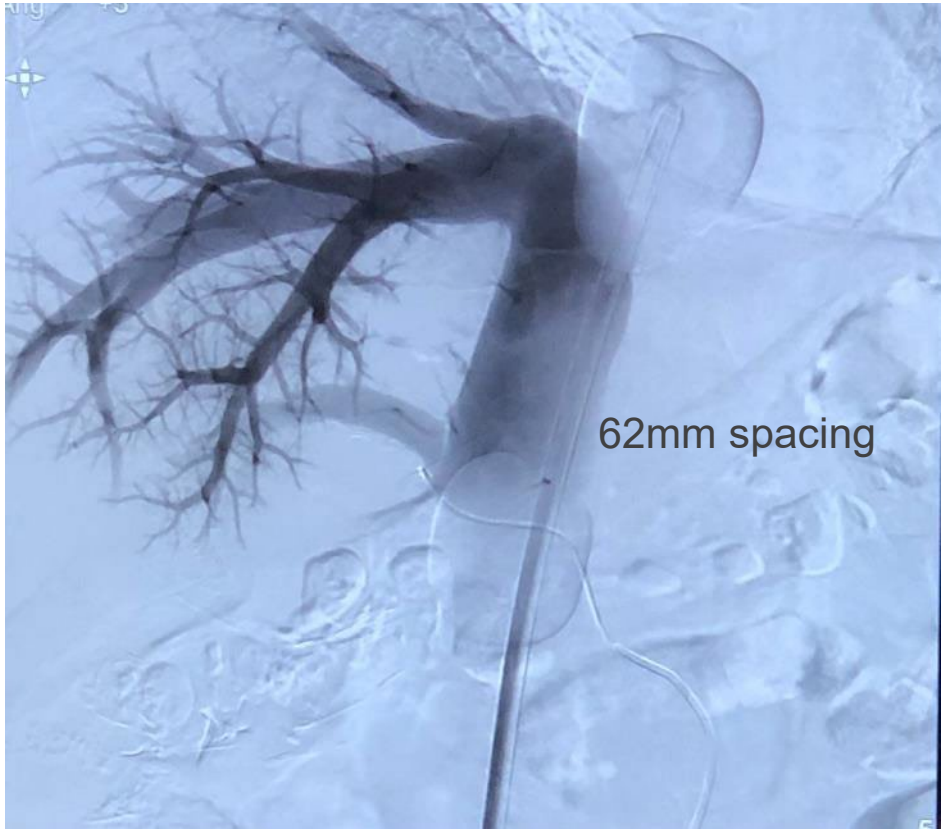
- Lead a PHP Procedure team brief
- Ensure that the Anesthesia team is prepared, and that required medications are at hand
- Confirm that hemofiltration circuit is set up by the Perfusionist
- Confirm HEPZATO arrival time

Selection of Balloon Spacing

The HEPZATO KIT comes available with two different lengths of balloon spacing: 50mm and 62mm:

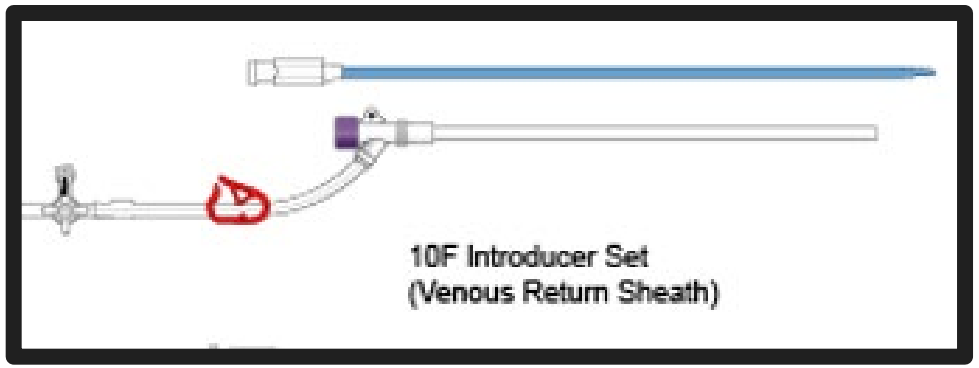
Variables that affect the choice of balloon spacing length:

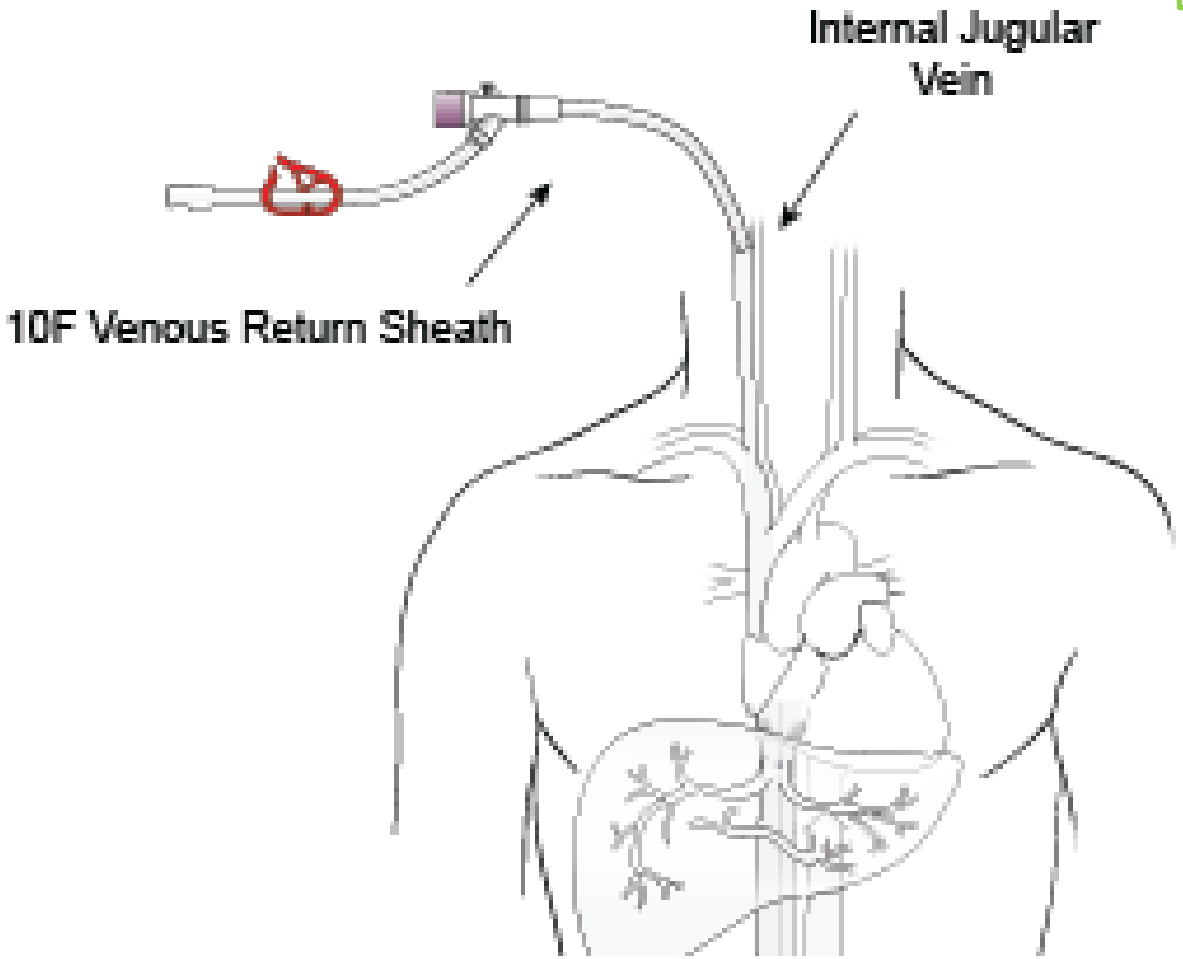
- Variation in the length of the retro-hepatic segment of the inferior vena cava
- Relative positions of hepatic and renal veins



Important: IR needs to decide which KIT (50mm or 62mm spacing) will be used for the PHP procedure **before** the actual PHP procedure

IR Procedural Flow - Insert 10F Introducer Set

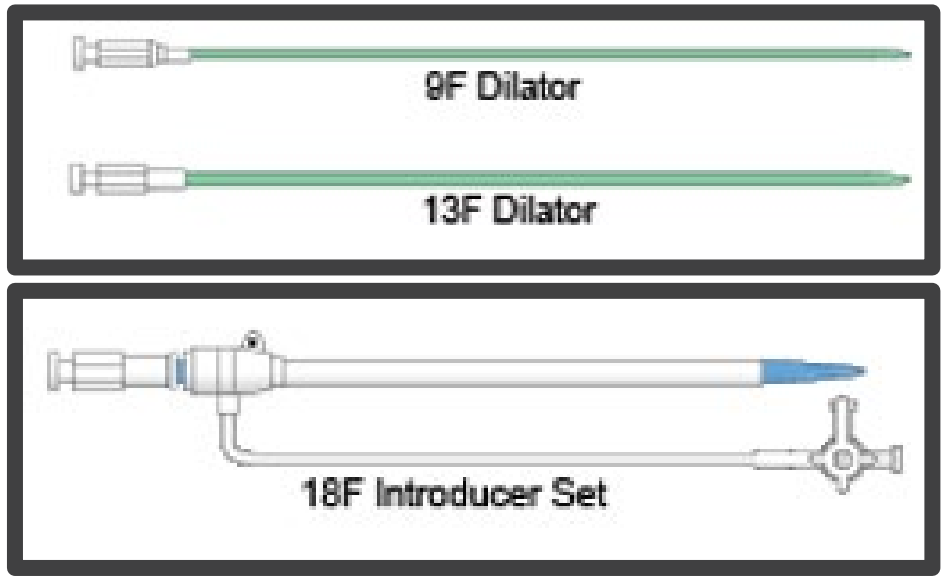


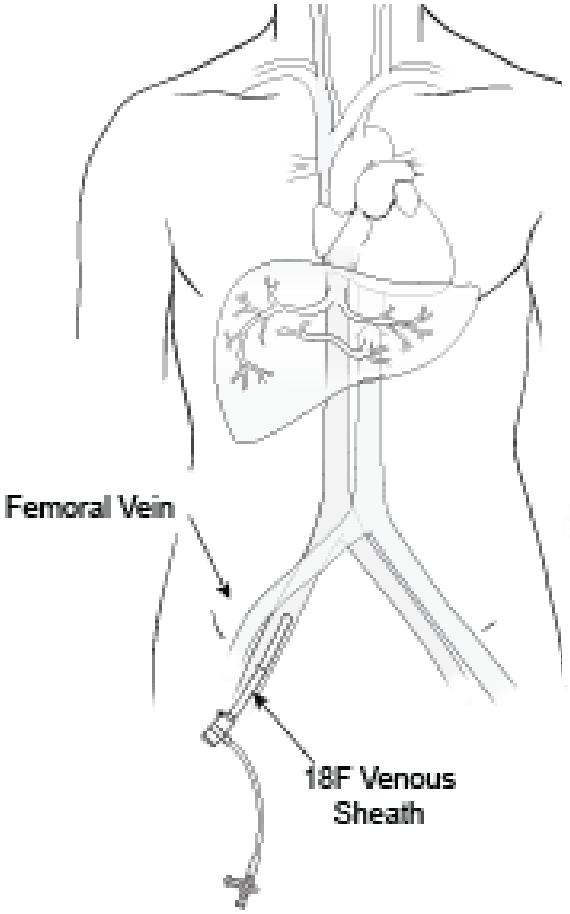


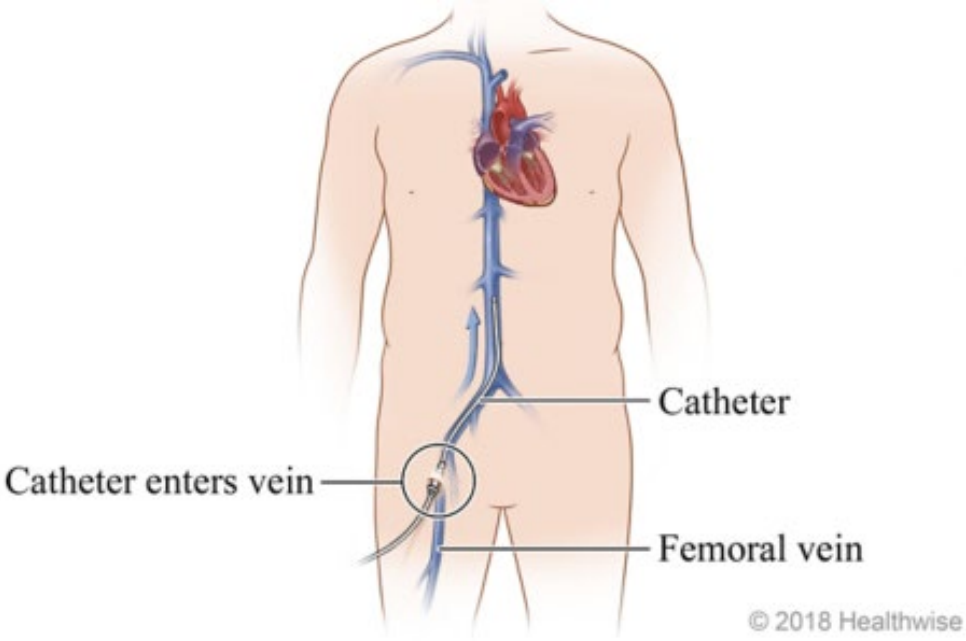
- Flush sheath with sterile heparinized saline
- Insert venous return sheath into internal jugular vein

Interventional Radiologist

IR Procedural Flow - Insert 18F Venous Sheath





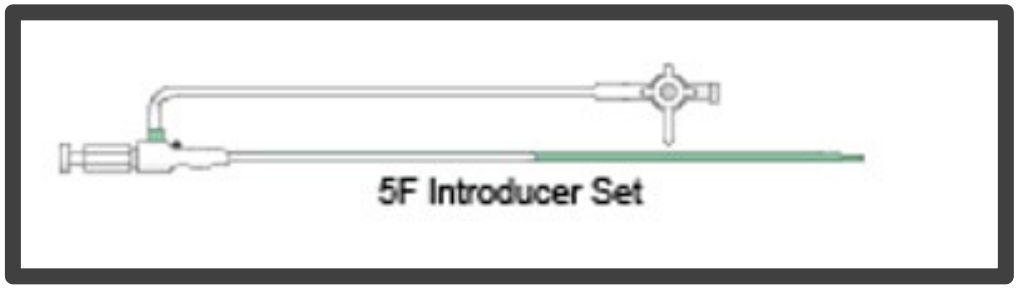


- Perform serial dilation with dilators
- Insert 18F femoral sheath

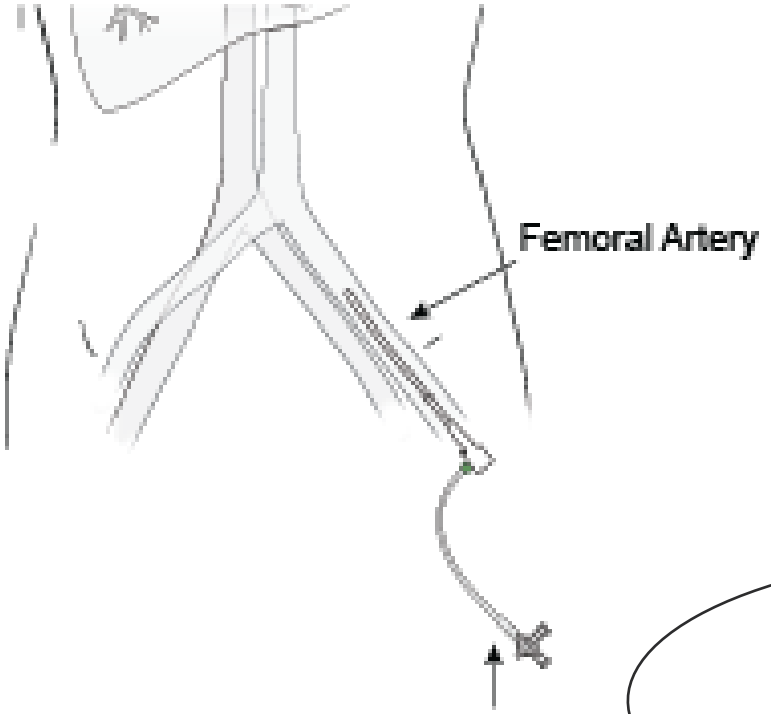
Femoral vein access

Interventional Radiologist

IR Procedural Flow - Insert 5F Introducer Set



- Flush 5F sheath
- Place 5F sheath into the femoral artery



Interventional Radiologist

IR: Can heparin be administered?

Interventional Radiologist

IR Procedural Flow - Hepatic Vascular Mapping

Map Hepatic Artery Anatomy

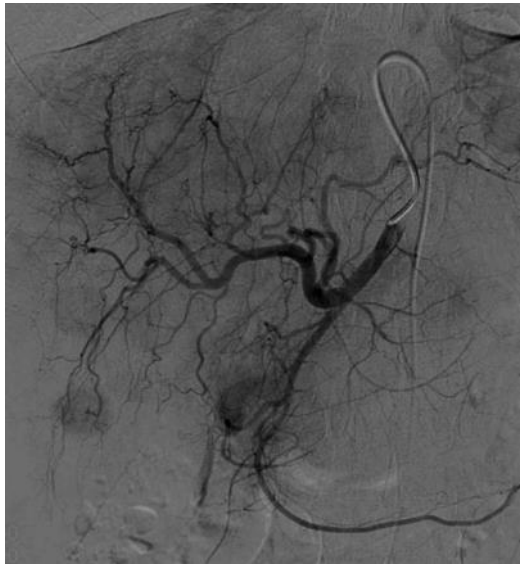
↓

Embolize As Needed

The Interventional Radiologist needs to create an infusion plan based on hepatic artery mapping.

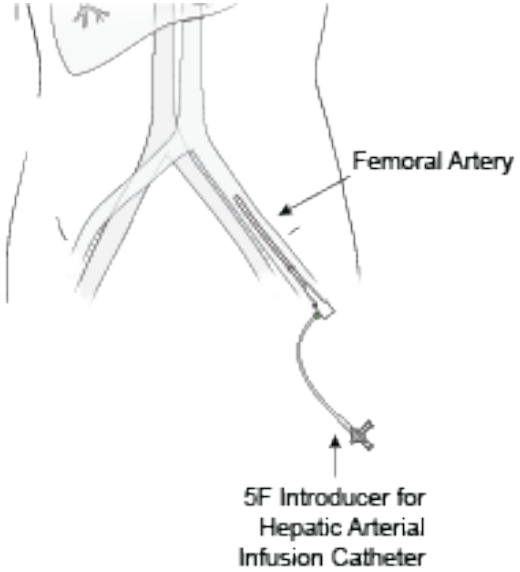
The infusion plan ensures that all hepatic arteries are adequately perfused.

A selective infusion strategy may be used when the catheter is positioned distal to non-hepatic arterial branches.



IR Procedural Flow - Insert Hepatic Artery Infusion Catheter

Place Hepatic Artery Catheter



- The 5F infusion catheter is introduced through the 5F introducer sheath into the femoral artery.
- The infusion catheter and microcatheter is placed in the desired position for HEPZATO infusion.

IR Procedural Flow - Catheter Location


Interventional Radiologist

Based on evaluation of hepatic artery, two different infusion strategies can be utilized: lobar infusion or whole liver infusion.

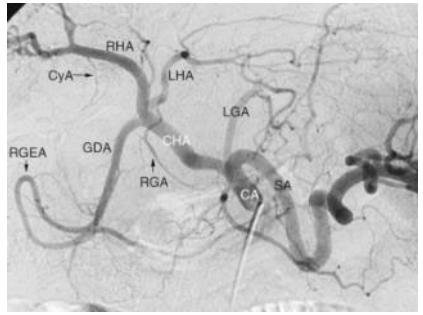
If performing a lobar infusion approach:

- The catheter is positioned to isolate a lobe
- The treatment is administered sequentially
- It requires HEPZATO dose splitting
- Dosing to each lobe is based on relative liver volume and is traditionally a 60% (right lobe) to 40% (left lobe) split.
- The catheter must be repositioned during HEPZATO infusion
- It is suggested to begin with the most difficult catheterization point in order to minimize catheter repositioning time

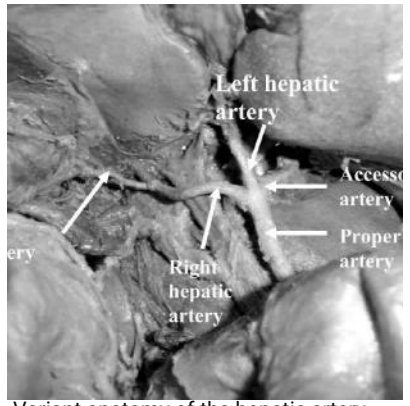
If performing a whole liver infusion approach:

Performing a whole liver infusion approach is dependent on arterial blood flow
Whole liver infusion may require minimal embolization.

Distal catheter placement to non-hepatic arterial branches can reduce requirements for embolization. adequate catheter positioning minimizes risk of infusion failure and reflux.



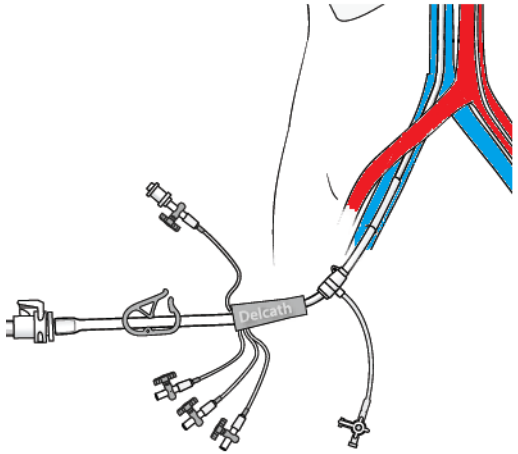
Embolotherapeutic Strategies for Hepatocellular Carcinoma: 2020 Update, Kishore et al, Cancers

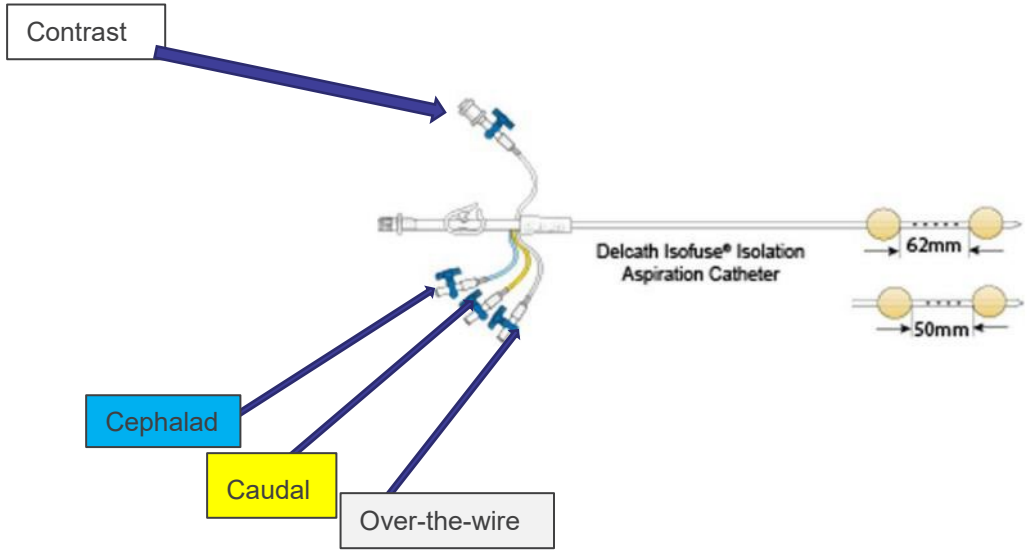


Variant anatomy of the hepatic artery in adult Kenyans, European Journal of Anatomy, 2007, Kitungu et al.

Delcath

IR Procedural Flow - Insert Double Balloon Catheter (DBC)





In preparation of the placement of the DBC:

- HEPZATO should be in the room
- The ACT must be above 400 seconds

Placement of the DBC :

- The DBC catheter should be flushed with heparinized saline via the contrast port and over-the-wire port and central lumen via the extracorporeal system.
- The DBC catheter is inserted through 18F sheath.

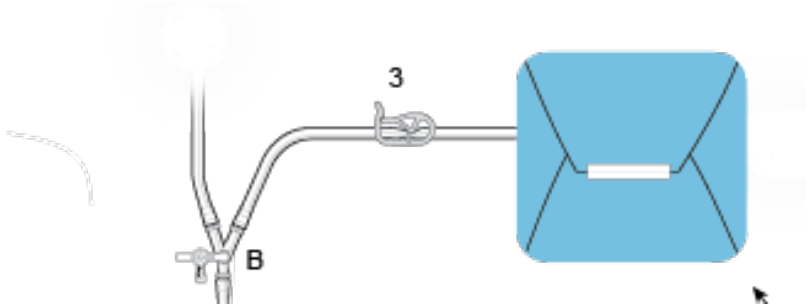
Interventional Radiologist

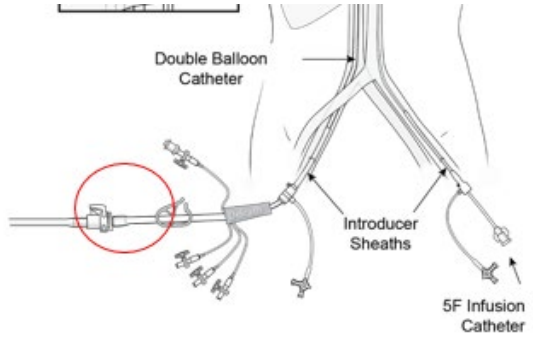
IR Procedural Flow - Catheter & Hemofiltration Connection

To connect the double balloon catheter to the circuit:

The sterile wrap needs to be removed from the hemofiltration circuit DBC line.

A wet connection can be made from the hemofiltration DBC line to the DBC catheter by opening saline clamps 1 and 2 and clamp 3.

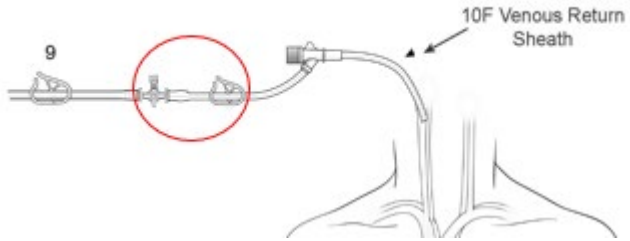




To connect the venous return line to the circuit:

The sterile wrap is removed from the hemofiltration venous return line.

The hemofiltration circuit is connected to the venous return line to the stopcock of the 10F venous return sheath in the jugular vein.



IR Procedural Flow - Establishing Hemofiltration & Isolation

Start ECF Bypass Circuit

When HEPZATO has been delivered to the procedural room and the connection of the hemofiltration circuit to catheters has been made, the perfusionist turns on the pump and then bypass can be started.

Bypass:

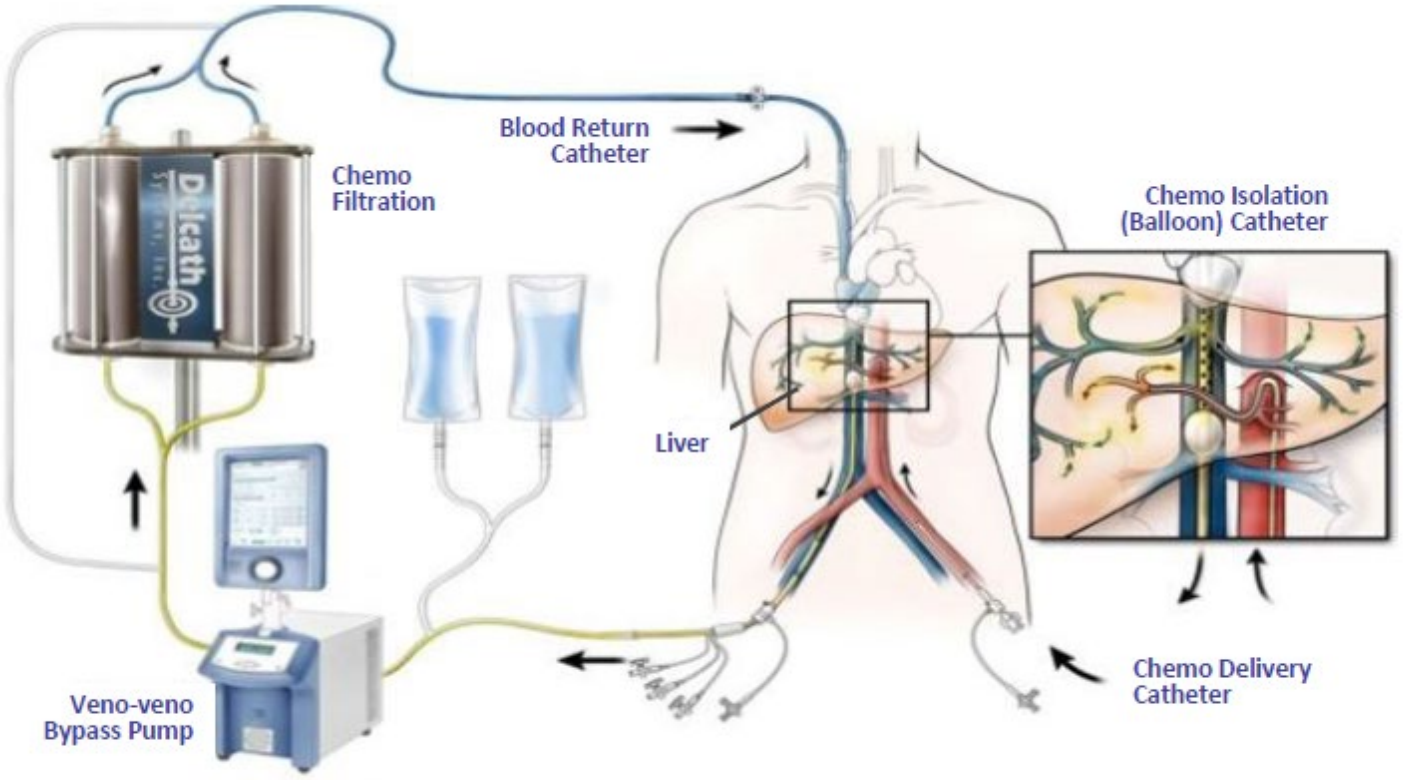
Venous blood aspirated from central lumen

Blood flows through fenestrations in DBC

Blood flows through the pump

Blood flows through the bypass line

Blood returns to the patient through the venous return sheath



During Hemofiltration and Isolation, the Perfusionist continuously monitors the pump pressures

Vasopressor Administration

- Prior to occlusion of vena cava and inflation of balloons a vasopressor response test is performed by the Anesthesiologist.

- Initial occlusion of the inferior vena cava leads to a significant decrease of systemic blood pressure. It is of critical importance to maintain the blood pressure above 65 mmHg.

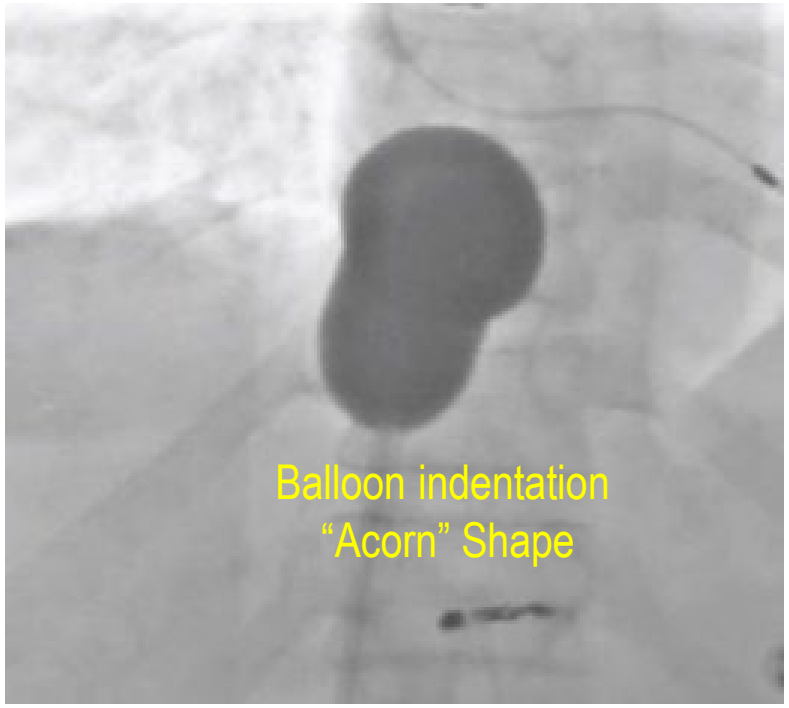
- If response to vasopressors is adequate, the double balloon catheter may be inflated.

Reference ID: 5226627

IR Procedural Flow - Balloon Expansion

Interventional Radiologist

The balloon is expanded until the lateral edges become effaced with the inferior vena cava wall.



The cephalad balloon must occlude inferior vena cava just *above* the *highest* hepatic vein

The caudal balloon must occlude inferior vena cava just *below* the *lowest* hepatic vein

Never move or reposition the DBC when the balloons are fully expanded.

DO NOT collapse balloons unless HEPZATO administration has been stopped or after completion of infusion, including a 30-minute washout cycle.

The Perfusionist must carefully monitor the circuit flow rate during balloon inflation.

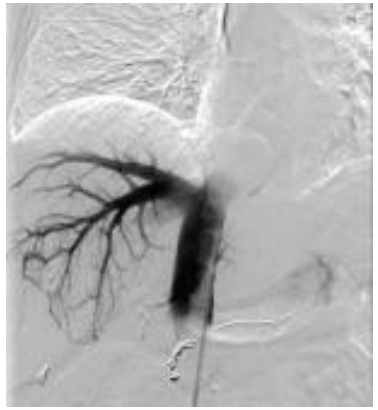
Delcath

IR Procedural Flow - Hepatic Venous Isolation Confirmation & Leak Assessment

Iodinated contrast medium is injected through the contrast port to assess isolation of the segment.

To check for balloon leaks:

1. The Perfusionist stops the pump.
2. The IR checks for leaks by injected contrast agent through the DBC
3. If no leak is seen, the Perfusionist starts the pump again.

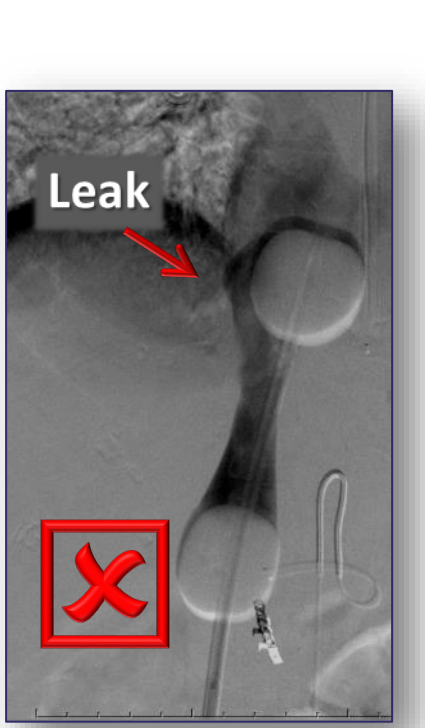


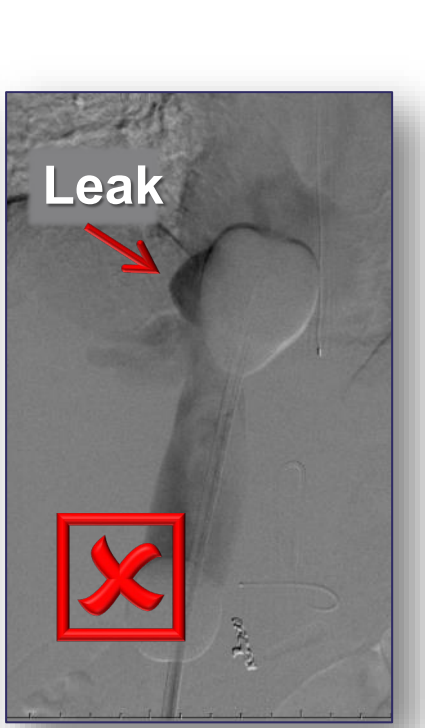
Hemofiltration Circuit Flow is re-established by:

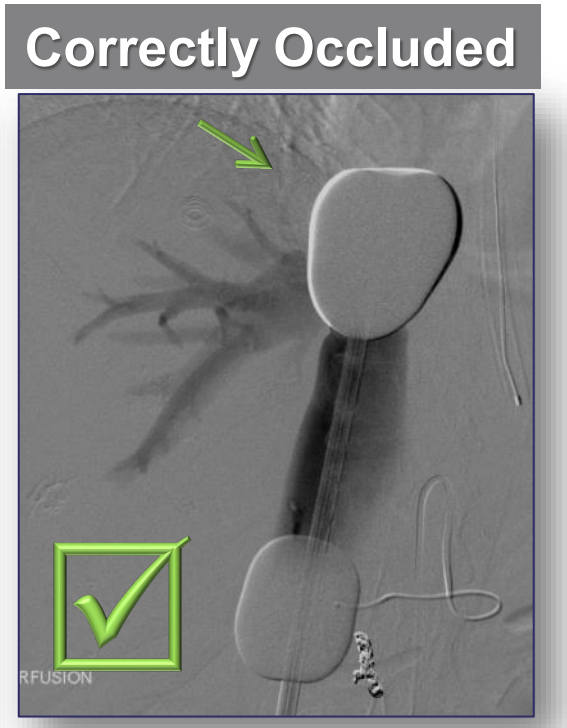
1. Restarting the centrifugal pump
2. Increasing pump speed to approximately 2200 RPMs or the previously established flow rate

If the **DBC** is not in the proper position, collapse both balloons (caudal balloon first) and then reposition the catheter, while maintaining flow in the hemofiltration circuit

IR Procedural Flow - Balloon Occlusion







Balloon Inflation Volumes		
Balloon	**Cephalad**	**Caudal**
Maximum Volume	**38 mL**	**38 mL**

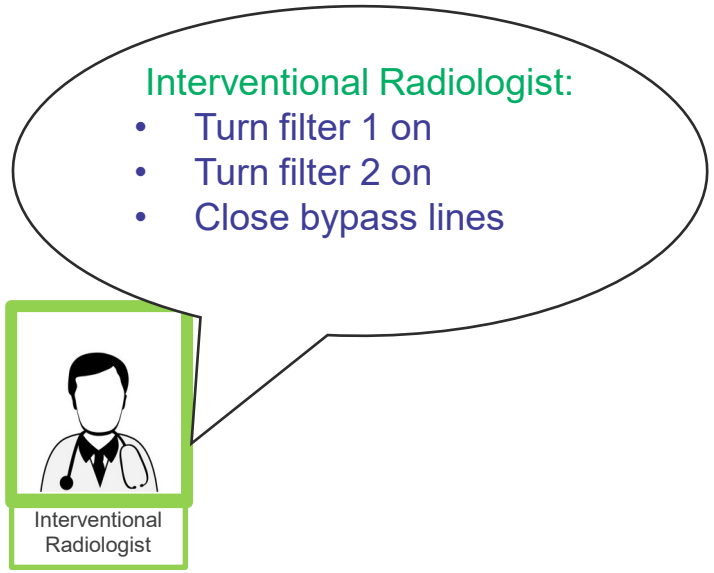
- Under fluoroscopy, the balloons are partially inflated with approximately 15-25 mL of dilute contrast media.
- Inflation of the balloons may give it a rounded appearance.

The balloons must not be over inflated. Overinflation could cause the balloons to burst and result in life-threatening injury.

Opening Filters & Blood Pressure Management

The process for turning on the filters:

- The flow is checked by the IR.
- The IR instructs the Perfusionist to turn the filters on; usually one filter at a time.
- The bypass line is kept open as each filter is opened.
- After both filters are filled with blood, the bypass line is closed after 3 minutes of flow.
- The blood pressure is monitored for 2 to 5 minutes.



IR Procedural Flow - Hepatic Artery Spasm

Once the blood pressure is stabilized the IR **injects contrast agent** to check for hepatic artery spasm.

If spasm is observed:

Possible Cause	→	vasopressor therapy & low mean arterial pressure
Effect	→	reflux of melphalan into proximal non-embolized gastrointestinal branches or incomplete delivery of HEPZATO
During procedure	→	perform Angiography every 5 minutes
Spasm Relief	→	100 mcg/injection of intra-arterial nitroglycerin in hepatic artery

If there is a persistent intractable spasm, the procedure should be stopped.

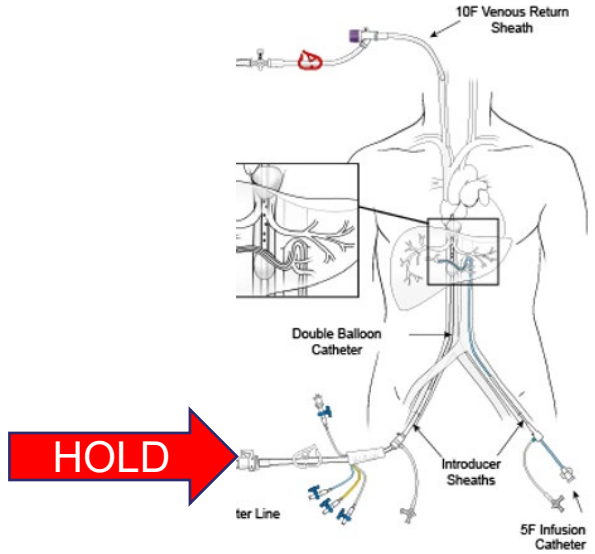
IR Procedural Flow – Infusion, Filtration & Double Balloon Catheter (DBC) Management

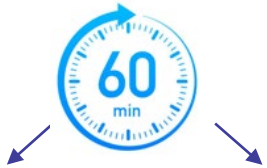

Interventional Radiologist

Once the IR approves the start of HEPZATO infusion a 100 mL bolus is administered at 25 mL/second flow rate using drug injector. (estimated 4 min infusion time).

The IR maintains a gentle hold of the DBC position during the entire infusion period.

HEPZATO is refilled into the drug injector and the IR performs a spasm check.





First 30 minutes:
HEPZATO Infusion

Last 30 minutes:
Washout Period

The DBC position checked fluoroscopically every 4 to 5 minutes during drug administration and filtration to ensure continued hepatic venous isolation

Delcath

IR Procedural Flow – Procedure End

- The IR may return blood to the patient at the end of the washout period. Blood return may be dependent on central venous pressure and the amount of fluid given.
- To return blood to the patient the IR instructs the Perfusionist to open clamps for saline flush and this flush pushes the blood through the filter and back into patient's internal jugular vein.
- At the end of blood return the Perfusionist properly disposes all the hemofiltration lines, pump, and the filters.
- The Anesthesia team starts post procedural medications.

Anesthesiologist

Module 8
Anesthesia, Anticoagulation and Hemodynamic Management

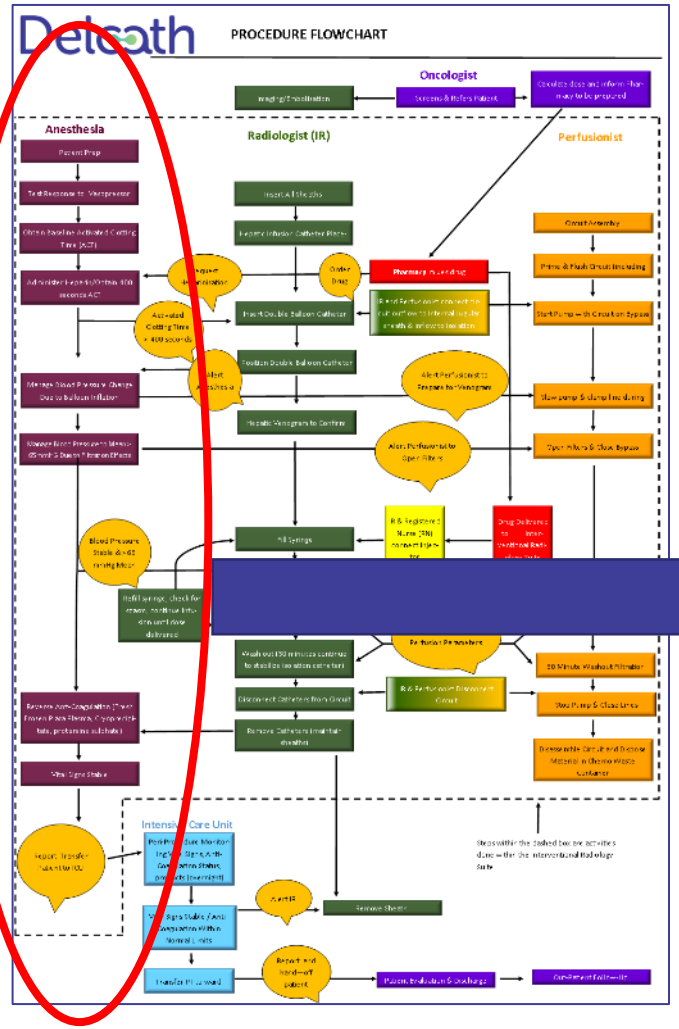
Reference ID: 5226627

Module 8 Objectives

Module 8 describes the responsibilities of the anesthesiologist/anesthetist on the day of the procedure. This includes medically clearing the patient for the PHP Procedure with HEPZATO KIT, managing preoperative medications, managing anesthesia, blood oxygenation, acid/base balance, core body temperature, hydration, anticoagulation, and blood pressure. Patient to be assessed for adequate cardiopulmonary function.

- Managing preoperative medications.
- Managing hydration optimizing blood pressure and EFC flow rate.
- Managing anticoagulation.
- Managing blood pressure.

Anesthesiologist Procedural Tasks



This module describes the steps that the Anesthesiologist takes during the procedure.

Anesthesiologist

- Patient Prep
- Test Response to Vasopressor
- Obtain Baseline Activated Clotting Time (ACT)
- Administer Heparin/Obtain 400 seconds ACT
- Manage Blood Pressure Change Due to Balloon Inflation
- Manage Blood Pressure to Mean > 65mmHG Due to Filtration Effects
- Reverse Anti-Coagulation (Fresh Frozen Plaza Plasma, Cryoprecipitate, protamine sulphate)
- Vital Signs Stable

Delcath

HEPZATO KIT Preoperative Patient Assessment

After referral by the Medical Oncologist, a preoperative assessment of the patient is performed by the Anesthesiologist, the Cardiologist, and the Pulmonologist.
Each HCP must adjudicate pre-operative clearance indicating adequate cardiac and pulmonary function.

A patient may not be eligible for HEPZATO KIT treatment if any of the following are present:

- Active coronary artery disease
- Severe angina
- Recent myocardial infarction
- Any congestive heart failure
- Significant ventricular arrhythmias
- Moderate to severe valvular disease
- Unable to withstand high dose vasopressor therapy
- Advanced COPD
- Unable to withstand mechanical ventilation

Procedure – Anesthesia Team

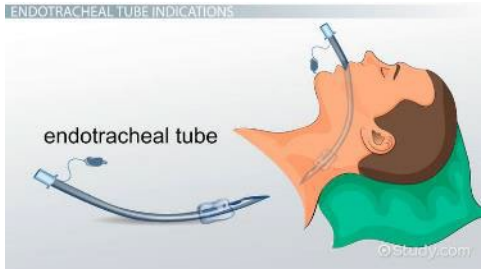
Anesthesiologist

Anesthesia Induction

- A bair hugger can be used to keep the patient warm.
- The Anesthesiology team may use an endotracheal tube or a laryngeal mask to induce anesthesia.

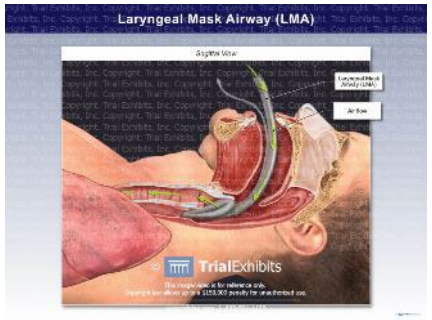
Bair Hugger

Endotracheal tube



or

Laryngeal mask



Procedure – Anesthesia Team

- To optimize the fluid balance, boluses of fluids such as saline and crystalloids are administered via the central venous catheter during anesthesia induction and line insertion.
- The variation of the pump flow informs of fluid responsiveness.
- Vasopressors such as norepinephrine and epinephrine are administered to manage drops in blood pressure.

Anticoagulation

Baseline activated clotting time (ACT) acquired

Heparin is administered

A minimum ACT of 400 seconds is achieved

- Anesthesiology administers vasopressors
- Anesthesiology checks vital signs

- IR confirms vitals with Anesthesia
- IR prepares for catheter placement

Interventional Radiologist: What is the ACT?

Anesthesiologist: Vasopressors have been administered

Delcath

PHP Procedure – Anesthesiologist Role


Anesthesiologist

OR


Perfusionist

- The Anesthesiologist or the Perfusionist obtains the baseline ACT

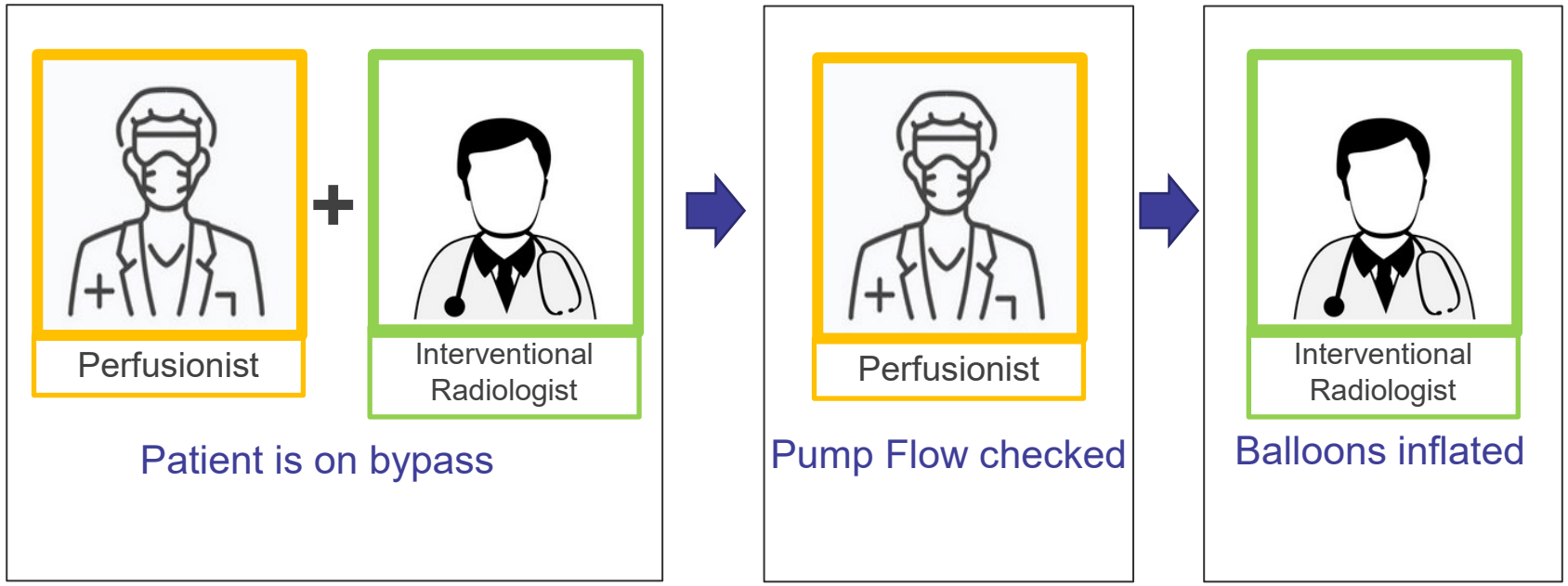

Anesthesiologist


Interventional Radiologist

- The Anesthesiologist administers Heparin
- The Anesthesiologist administers vasopressors to maintain blood pressure *before* DBC placement by the IR

Anticoagulation is required to assure free extracorporeal flow and filtration

PHP Procedure – Anesthesia Responsibilities



The Anesthesiologist:

- Monitors the blood pressure
- Administers vasopressors
- Stabilizes the mean arterial pressure

PHP Procedure – Anesthesia Responsibilities

Filters brought online

Anesthesiologist stabilizes the MAP

Extracorporeal circulation filtration stopped

Anesthesiologist discontinues vasopressors

PHP Procedure – Post Procedure

The Anesthesiologist

- Discontinues heparin
- Weans off vasopressors
- Administers fluids
- Extubates the patient
- Initiates recovery
- Removes endotracheal tube or laryngeal mask
- Removes arterial catheter and closure device
- May leave femoral venous sheath and jugular sheath in position

Optional

- Give fresh frozen plasma (FFP) and thrombocytes

Anesthesiologist

Module 9
Post-Procedure Management and Discharge

Delcath

Reference ID: 5226627

Module 9 Objectives

Module 9 describes the responsibilities of the intensivist to recover the patient after the procedure. This includes reversing anticoagulation, removing intravascular introducers (sheaths), normalizing hematologic abnormalities (e.g., anemia and thrombocytopenia), and normalizing procedural abnormalities (e.g., metabolic acidosis and hypothermia).

- Mechanisms reversing anticoagulation and safe removal of vascular sheaths.
- Correcting hematologic abnormalities.
- Correcting metabolic acidosis and hypothermia

NOTE: Patients should be assessed for severe peri-procedural complications associated with HEPZATO KIT for at least 72 hours after the procedure.

Severe peri-procedural complications should be documented and submitted to the REMS using the Severe Peri-Procedure-related Complications Adverse Events Documentation Form.

Follow up may occur virtually or via telephone for patients discharged prior to 72 hours.

Post Procedural Recommendations

Prior to discharge after the PHP Procedure with HEPZATO it is recommended that the following procedure-related events are corrected:

- Clotting
- Liver function
- Anemia
- Platelet abnormalities
- Neutrophil counts

Corrections of post-procedure events should follow institutional guidelines and clinical judgment.

End of Procedure - Anticoagulation Interventions & Hematologic Abnormalities

To reverse anticoagulation and attend to procedural induced coagulopathies

- Protamine is titrated to normalize the Activated Clotting Time (ACT).
- Clotting factors may be replenished by administration of cryoprecipitate and/or Fresh Frozen Plasma.

To correct hematologic abnormalities

- Platelets should be replaced according to institutional guidelines.
- Ensure that the platelet count is greater than 50,000/mm^3 and patient coagulation status is normalized before safely removing sheaths.
- Blood product replacement should be considered if patient has significant blood loss. It is suggested to follow institutional guidelines for administration of packed red blood cells, follow anemia hospital protocols, and transfuse accordingly.

Patient Discharge & Follow Up

Discharge

- Prior to discharge, physiologic abnormalities should be reviewed and reversed.

Medical Oncologist responsibilities

- Follow up with the patient after hospital discharge.
- Clear the patient for subsequent treatment.
- Evaluate need for dose adjustment or treatment discontinuation.
- Administer prophylactic treatment to manage hematologic toxicities.
- Monitor patient on an outpatient basis after hospital discharge for HEPZATO related toxicities

Hepzato™ Kit
(HEPZATO for Injection / Hepatic Delivery System)

Criteria for Procedural Competency Checklist

Phone: 1-833-632-0457
E-mail: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

HEPZATO KIT is only available through the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

Percutaneous Hepatic Perfusion Procedural Team members that perform procedures with HEPZATO KIT must review the product's Prescribing Information, Instructions for Use, **Program Overview**, **Didactic Modules**, undergo the Preceptorship training, and must also successfully complete the Proctorship training provided by Delcath Systems, Inc.

To document completion of training requirements, complete and submit this form online at www.HEPZATOKITREMS.com or email to coordinator@HEPZATOKITREMS.com.

☐ New Form ☐ Updated Form Date Submitted to REMS: _____

Authorized Representative (all fields are required)	
First Name:	Last Name:
E-mail:	Phone:

Healthcare Setting Information (all fields are required)		
Healthcare Setting Name:		
Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:

Specialist Role: (all fields are required)	
Specialist Role: ☐ Interventional Radiology ☐ Anesthesiology ☐ Perfusion	
First Name:	Last Name:
National Provider Identifier (NPI) #:	
Healthcare Setting Name:	
Credentials: ☐ MD ☐ DO ☐ Other, please specify. _____	
Title:	

REMS Use Only
Tracking Number:

Date:

Criteria for Procedural Competency Checklist

Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:
E-mail:	Phone:	
Date Prescribing Information, Instructions for Use, **Program Overview**, and **Didactic Modules** Reviewed:	Date:	Trainer Name:
Date of Preceptorship Training Provided by Delcath:	Date:	Trainer Name:
Date of Proctorship Training Provided by Delcath:	Date:	Trainer Name:

REMS Use Only
Tracking Number:

Date:

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Severe Peri-Procedure-Related Complications Adverse Events Documentation Form

Phone: 1-833-632-0457
Email: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

HEPZATO KIT is only available through the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risk of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

During and for at least 72 hours after administering HEPZATO KIT, patients must be assessed for severe peri-procedural complications following the percutaneous hepatic perfusion (PHP) procedure. Follow up may occur virtually or via telephone for patients discharged prior to 72 hours.

Severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events must be reported by completing and submitting this form to the REMS Coordinating Center via e-mail at coordinator@HEPZATOKITREMS.com or online at www.HEPZATOKITREMS.com.

Any severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events that may be identified within 72 hours of administration of HEPZATO KIT, are required to be reported within 24 hours of awareness to Delcath Systems, Inc. at 1-833-632-0457 or www.Delcath.com or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Reporter Information (all fields are required)

First Name:	Last Name:
E-mail:	Phone:
Credentials: ☐ MD ☐ DO ☐ RN ☐ PharmD/RPh ☐ NP/PA ☐ Other (please specify)	
Title:	

Healthcare Setting Information (all fields are required)

Healthcare Setting Name:	REMS ID:	
Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:

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(HEPZATO for Injection / Hepatic Delivery System)

Severe Peri-Procedure-Related Complications Adverse Events Documentation Form

Serious Adverse Event Reporting

Complete the below to report severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events.

Date of the PHP Procedure: _____ **MM/DD/YYYY**					
Date of Onset of the Serious Adverse Event: _____ **MM/DD/YYYY**					
Patient Initials: ____	**Date of Birth:** _____ **MM/DD/YYYY**		**Gender: □ Male □ Female □ Other □ Prefer not to answer**		
	If Yes, Seriousness Criteria for Each Event				
Event	**Death**	**Hospitalization**	**Life-Threatening**	**Important Medical Event**	**The PHP procedure was aborted due to this event**
Hemorrhage □Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
Hepatocellular injury □Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
Thromboembolic events □Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
Other Severe Peri-procedural Complications	**Death**	**Hospitalization**	**Life-Threatening**	**Important Medical Event**	**The PHP procedure was aborted due to this event**
	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No
	□Yes □No	□Yes □No	□Yes □No	□Yes □No	□Yes □No

Please provide any additional Details of Event(s), including any signs and symptoms of hemorrhage, any liver enzyme elevations (ALT/AST) above 3x ULN or any signs of symptoms of liver injury, any signs and symptoms of thromboembolic event, or other serious adverse events attributable to the procedure. Include details, rationale, and root cause related to the percutaneous hepatic perfusion procedure that further describe the adverse event. If PHP procedure was aborted, describe the reasons in detail.

_____

_____

_____

_____

_____

_____

_____

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Severe Peri-Procedure-Related Complications Adverse Events Documentation Form

By signing this form, you consent to having the percutaneous hepatic perfusion procedure team contacted for further information regarding this report of a serious adverse event. Pertinent laboratory results will be requested.

REPORTER INFORMATION (All fields are required)	
First Name:	Last Name:
Phone:	E-mail:
Reporter Signature:	**Date (MM/DD/YYYY):**

Definitions of seriousness criteria:

- Fatal - Report adverse events that occurred during or shortly after the procedure and that you suspect resulted in or lead to death (i.e., the AE causes or leads to death).
- Life-threatening – Report adverse events that in your opinion put the patient at substantial risk of dying, or use or continued use of product might have resulted in the death of the patient. This does not include any AE that, had it occurred in a more serious form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization. Report if admission to the hospital or prolongation of hospitalization was a result of an adverse event that occurred during of shortly after the procedure. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- Adverse Event which results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- Adverse Event which results in congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Any other significant Medical Events that in the treating physician's judgment may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above.

Note: The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to the NCI CTCAE criteria).
The event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness must be independently assessed for each AE.

Hepzato™ Kit
(HEPZATO for Injection / Hepatic Delivery System)

Procedure Team Qualification Status Form

Phone: 1-833-632-0457
E-mail: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

HEPZATO KIT is only available through the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS) to mitigate the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events.

Healthcare settings that dispense HEPZATO KIT must be certified and percutaneous hepatic perfusion (PHP) procedure team members who perform PHP procedures with HEPZATO KIT must be qualified by meeting the following requirements:

- Having a PHP procedure team with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions For Use
- Reviewing the Prescribing Information, Instructions for Use, **Program Overview**, **Didactic Modules**, and completing of the Preceptorship training and Proctorship training provided by Delcath Systems, Inc.
- Performing one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter

The above qualifications must be confirmed to obtain authorization prior to dispensing <u>each</u> HEPZATO KIT for administration by completing and submitting this form to the REMS Coordinating Center via e-mail at HEPZATOKIT@REMS.com or online at www.HEPZATOKIT.com.

Authorized Representative (all fields are required)	
First Name:	Last Name:
E-mail:	Phone:
Department:	

Healthcare Setting Information (all fields are required)		
Healthcare Setting Name:		
Address Line 1:		
Address Line 2:		
City:	State:	ZIP Code:

Anticipated Percutaneous Hepatic Perfusion Procedure Date
Anticipated Procedure Date:

Hepzato™ Kit
(HEPZATO for Injection / Hepatic Delivery System)

Procedure Team Qualification Status Form

Phone: 1-833-632-0457
E-mail: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

Specialist Role: Interventional Radiology (All fields are required)		
First Name:	Last Name:	
National Provider Identifier (NPI) #:		
Healthcare Setting Name:		
Date Prescribing Information including Instructions for Use, **REMS Program Overview**, and **Didactic Modules** Reviewed:	Date:	Trainer Name:
Date of Preceptorship Training Provided by Delcath:	Date:	Trainer Name:
Date of Proctorship Training Provided by Delcath:	Date:	Trainer Name:
Dates of Two (2) Prior Procedures Performed with HEPZATO KIT:		

Specialist Role: Anesthesiology (All fields are required)		
First Name:	Last Name:	
National Provider Identifier (NPI) #:		
Healthcare Setting Name:		
Date Prescribing Information including Instructions for Use, **REMS Program Overview**, and **Didactic Modules** Reviewed:	Date:	Trainer Name:
Date of Preceptorship Training Provided by Delcath:	Date:	Trainer Name:
Date of Proctorship Training Provided by Delcath:	Date:	Trainer Name:
Dates of Two (2) Prior Procedures Performed with HEPZATO KIT:		

Specialist Role: Perfusion (All fields are required)		
First Name:	Last Name:	
National Provider Identifier (NPI) #:		
Healthcare Setting Name:		
Date Prescribing Information including Instructions for Use, **REMS Program Overview**, and **Didactic Modules** Reviewed:	Date:	Trainer Name:
Date of Preceptorship Training Provided by Delcath:	Date:	Trainer Name:
Date of Proctorship Training Provided by Delcath:	Date:	Trainer Name:
Dates of Two (2) Prior Procedures Performed with HEPZATO KIT:		

HEPZATO KIT™ Risk Evaluation and Mitigation Strategy (REMS)

What is the HEPZATO KIT REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA).

The FDA has determined that a REMS is necessary to ensure that the benefits of HEPZATO KIT outweigh the risks of severe peri-procedural complications including hemorrhage, hepatocellular injury, and thromboembolic events associated with HEPZATO KIT.

Healthcare Settings

Healthcare Settings must be certified in the HEPZATO KIT REMS in order to dispense HEPZATO KIT.

Healthcare Setting Certification

Indication

HEPZATO is indicated as a liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissue or lungs that is amenable to resection or radiation.

Certify in the HEPZATO KIT REMS

Healthcare Setting Certification

Resources for Healthcare Professionals

- Healthcare Setting Enrollment Form
- Program Overview
- Didactic Modules
- Criteria for Procedural Competency Checklist
- Severe Peri-Procedure-related Complications Adverse Events Documentation Form
- Procedure Team Qualification Status Form

Download All Resources

Reporting Adverse Events

Reporting of suspected adverse events after administration of HEPZATO KIT therapy is vital for the continued monitoring of the risk/benefit balance of therapy.

To report serious adverse events* including hemorrhage, hepatocellular injury, and thromboembolic events using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** to Delcath Systems, Inc. via e-mail at coordinator@HEPZATOKITREMS.com

To report any other serious adverse events* to Delcath at 1-833-632-0458 or to or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

*Serious adverse events are defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Have Questions?

Contact the HEPZATO KIT REMS by calling 1-833-632-0457

Healthcare Settings

HEPZATO KIT REMS Requirements

Healthcare Settings must be certified in the HEPZATO KIT REMS to be able to dispense HEPZATO KIT.

As a condition of certification, Healthcare Settings, must:

- Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications
- All percutaneous hepatic perfusion procedure team members must be trained to participate in procedures with HEPZATO KIT.

How does my Healthcare Setting become certified in the HEPZATO KIT REMS?

1. **Step 1:** Designate an Authorized Representative to complete the certification process and oversee implementation and compliance with the HEPZATO KIT REMS on behalf of the Healthcare Setting

2. **Step 2:** Have the Authorized Representative review the following materials:
   - Product's Prescribing Information including Instructions for Use,
   - **Program Overview,** *and*
   - **Didactic Modules**

3. **Step 3:** Have the Authorized Representative complete the *Healthcare Setting Enrollment Form* and submit it to the REMS Program
   - Online
   - By e-mail

4. **Step 4:** The Authorized Representative must ensure oversight and compliance with the HEPZATO KIT REMS by:
   - Ensuring that the percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
   - Ensuring that the HCPs in the PHP procedure team have completed the required training. If a new HCP is going to be added to the PHP procedure team, ensuring that they undergo the training requirements in the REMS training program.
   - Ensuring that the percutaneous hepatic perfusion procedure team members have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.
   - Ensuring that there is an on-site interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.
   - Maintaining records of each percutaneous hepatic perfusion procedure team member's training.
   - Maintaining records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation.
   - Maintaining records that processes and procedures are in place and are being followed.
   - Complying with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

   If the Hospital designates a new Authorized Representative, the new Authorized Representative must review the **REMS Training Program** and complete a new **Healthcare Setting Enrollment Form**.

How does my Healthcare Setting maintain certification in the HEPZATO KIT REMS, annually?

1. **Step 1:** Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.

2. **Step 2:** Ensure that the HCPs in the procedural team have completed the required training. If a new HCP is going to be added to the procedural team, ensure that they undergo the training requirements in the REMS training program.

3. **Step 3:** Have percutaneous hepatic perfusion procedure team members who have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.

4. **Step 4:** Have an on-site interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.

5. **Step 5:** If there is a change in Authorized Representative, have a new Authorized Representative enroll in the REMS Program by completing the **Healthcare Setting Enrollment Form**.

What are the REMS requirements for dispensing HEPZATO KIT?

1. **Step 1:** Before administering, obtain an authorization to dispense a HEPZATO KIT for each procedure by completing the **Procedure Team Qualification Status Form** and submitting it to the HEPZATO KIT REMS Coordinating Center.

2. **Step 2:** Upon receipt of the **Procedure Team Qualification Status Form**, by the REMS Coordinating Center, verification of the healthcare setting's certification will occur. Once verified, the REMS Coordinating Center will provide authorization to dispense to the Authorized Representative via e-mail.

3. **Step 3:** Assess the patient for severe peri-procedural complications associated with HEPZATO KIT during and after the procedure for at least 72 hours. Document severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit to the REMS Coordinating Center.

For more information on HEPZATO KIT REMS requirements contact the REMS Coordinating Center at 1-833-632-0457.

HEPZATO Kit Healthcare Setting Enrollment Form

Phone: 1-833-632-0457
Email: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

HEPZATO KIT is only available through the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS).

In order to dispense the HEPZATO KIT, Healthcare Settings must be certified in the HEPZATO KIT REMS and obtain authorization to dispense.

Healthcare Settings must designate an Authorized Representative to:

- Complete the certification process by completing the **Healthcare Setting Enrollment Form** on behalf of the Healthcare Setting.
- Oversee implementation and compliance with the HEPZATO KIT REMS requirements as outlined below.

Complete all fields below and select "Submit" button.

- Product orders cannot be placed until the Healthcare Setting certification is complete.
- Completion of this form does not guarantee your Healthcare Setting to be certified to dispense the HEPZATO KIT.
- The HEPZATO KIT REMS will provide confirmation of certification via e-mail after processing this form.

HEALTHCARE SETTING INFORMATION

○ New Certification ○ Change in Authorized Representative

Healthcare Setting Name *

Address *

City * | State * | ZIP Code *

PA

AUTHORIZED REPRESENTATIVE RESPONSIBILITIES

On behalf of my Healthcare Setting, I am the Authorized Representative, designated by my Healthcare Setting, to carry out the certification process and oversee implementation and compliance with the HEPZATO KIT REMS on behalf of the Healthcare Setting.

To become certified to dispense, the Healthcare Setting must:

- Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.

As the Authorized Representative, I must:

- Review the product's Prescribing Information, Instructions for Use, Program Overview, and **Didactic Modules**
- Enroll in the REMS by completing and submitting the Healthcare Setting Enrollment Form to the REMS.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT review the product's Prescribing Information and Instructions for Use.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT take the **Program Overview**, **Didactic Modules**, and Preceptorship training provided by Delcath Systems, Inc.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT successfully complete the Proctorship and successfully complete and submit the **Criteria for Procedural Competency Checklist** to the REMS.
- Establish processes and procedures to ensure new members of the PHP procedure team are trained.

Before administering, I and/or the Healthcare Setting staff must:

- Obtain authorization to dispense each HEPZATO KIT by contacting the REMS Coordinating Center to verify the percutaneous hepatic perfusion procedure team is qualified using the **Procedure Team Qualification Status Form**.

During and after administering, for at least 72 hours, Healthcare Setting staff must:

- Assess the patient for severe peri-procedural complications associated with HEPZATO KIT.
- Document severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit to the REMS.

To maintain certification to dispense, annually, I must:

- Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
- Have percutaneous hepatic perfusion procedure team members have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.
- If there is a change in Authorized Representative, have a new Authorized Representative enroll in the REMS Program by completing the **Healthcare Setting Enrollment Form**.

At all times, I must:

- Maintain records of each percutaneous hepatic perfusion procedure team member's training.
- Maintain records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation.
- Maintain records that processes and procedures are in place and are being followed.
- Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

By signing this form, I agree, on behalf of myself and my Healthcare Setting(s), to comply with all REMS Requirements.

AUTHORIZED REPRESENTATIVE INFORMATION

First Name * | Last Name *

Credentials

○ MD ○ DO ○ RN ○ PharmD/RPh ○ NP/PA ○ Other (please specify)

Phone * | E-mail *

Authorized Representative Signature (sign in box below)

Healthcare providers are encouraged to report other adverse reactions to Delcath at 1-833-632-0458 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Cancel | Submit

HEPZATO Kit Healthcare Setting Enrollment Form

Phone: 1-833-632-0457
Email: coordinator@HEPZATOKITREMS.com
Web: www.HEPZATOKITREMS.com

INSTRUCTIONS

HEPZATO KIT is only available through the HEPZATO KIT Risk Evaluation and Mitigation Strategy (REMS).

In order to dispense the HEPZATO KIT, Healthcare Settings must be certified in the HEPZATO KIT REMS and obtain authorization to dispense.

Healthcare Settings must designate an Authorized Representative to:

- Complete the certification process by completing the **Healthcare Setting Enrollment Form** on behalf of the Healthcare Setting.
- Oversee implementation and compliance with the HEPZATO KIT REMS requirements as outlined below.

Complete all fields below and select "Submit" button.

- Product orders cannot be placed until the Healthcare Setting certification is complete.
- Completion of this form does not guarantee your Healthcare Setting to be certified to dispense the HEPZATO KIT.
- The HEPZATO KIT REMS will provide confirmation of certification via e-mail after processing this form.

HEALTHCARE SETTING INFORMATION

○ New Certification ○ Change in Authorized Representative

Healthcare Setting Name *

Address *

City * | State * | ZIP Code *

PA

AUTHORIZED REPRESENTATIVE RESPONSIBILITIES

On behalf of my Healthcare Setting, I am the Authorized Representative, designated by my Healthcare Setting, to carry out the certification process and oversee implementation and compliance with the HEPZATO KIT REMS on behalf of the Healthcare Setting.

To become certified to dispense, the Healthcare Setting must:

- Have percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.

As the Authorized Representative, I must:

- Review the product's Prescribing Information, Instructions for Use, Program Overview, and **Didactic Modules**
- Enroll in the REMS by completing and submitting the Healthcare Setting Enrollment Form to the REMS.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT review the product's Prescribing Information and Instructions for Use.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT take the **Program Overview**, **Didactic Modules**, and Preceptorship training provided by Delcath Systems, Inc.
- Have the percutaneous hepatic perfusion procedure team members that perform procedures with HEPZATO KIT successfully complete the Proctorship and successfully complete and submit the **Criteria for Procedural Competency Checklist** to the REMS.
- Establish processes and procedures to ensure new members of the PHP procedure team are trained.

Before administering, I and/or the Healthcare Setting staff must:

- Obtain authorization to dispense each HEPZATO KIT by contacting the REMS Coordinating Center to verify the percutaneous hepatic perfusion procedure team is qualified using the **Procedure Team Qualification Status Form**.

During and after administering, for at least 72 hours, Healthcare Setting staff must:

- Assess the patient for severe peri-procedural complications associated with HEPZATO KIT.
- Document severe peri-procedural complications using the **Severe Peri-Procedure-related Complications Adverse Events Documentation Form** and submit to the REMS.

To maintain certification to dispense, annually, I must:

- Have a percutaneous hepatic perfusion procedure team(s) that must include healthcare providers with expertise in interventional radiology, anesthesiology, and perfusion as described in the Instructions for Use.
- Have percutaneous hepatic perfusion procedure team members have each performed one procedure in the first six months following completion of training, a second procedure in the next six months, and at least two procedures annually thereafter.
- Have the following on-site: interventional radiology suite or operating room with fluoroscopy and with resuscitation personnel, equipment, and medications.
- If there is a change in Authorized Representative, have a new Authorized Representative enroll in the REMS Program by completing the **Healthcare Setting Enrollment Form**.

At all times, I must:

- Maintain records of each percutaneous hepatic perfusion procedure team member's training.
- Maintain records of the percutaneous hepatic perfusion procedures performed with HEPZATO KIT and the associated percutaneous hepatic perfusion procedure team members' participation.
- Maintain records that processes and procedures are in place and are being followed.
- Comply with audits carried out by Delcath Systems, Inc., or a third party acting on behalf of Delcath Systems, Inc., to ensure that all training, processes, and procedures are in place and are being followed.

By signing this form, I agree, on behalf of myself and my Healthcare Setting(s), to comply with all REMS Requirements.

AUTHORIZED REPRESENTATIVE INFORMATION

First Name * | Last Name *

Credentials

○ MD ○ DO ○ RN ○ PharmD/RPh ○ NP/PA ○ Other (please specify)

Phone * | E-mail *

Authorized Representative Signature (sign in box below)

Healthcare providers are encouraged to report other adverse reactions to Delcath at 1-833-632-0458 or to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Cancel | Submit

HEPZATO KIT Healthcare Setting EnrollmentForm

HEPZATO **KIT** REMS Healthcare Setting Enrollment Form successfully submitted.

The HEPZATO KIT REMS will provide confirmation of certification via e-mail after processing this form.

HEPZATO KIT Healthcare Setting EnrollmentForm

HEPZATO **KIT** REMS Healthcare Setting Enrollment Form successfully submitted.

The HEPZATO KIT REMS will provide confirmation of certification via e-mail after processing this form.

HEPZATO KIT™
(melphalan) for Injection/
Hepatic Delivery System (HDS)

Healthcare Setting Locator

Find a certified Healthcare Setting.

*Zip Code

*Search Radius

Within 25 miles

Search >

HEPZATO KIT™
(melphalan) for Injection/
Hepatic Delivery System (HDS)

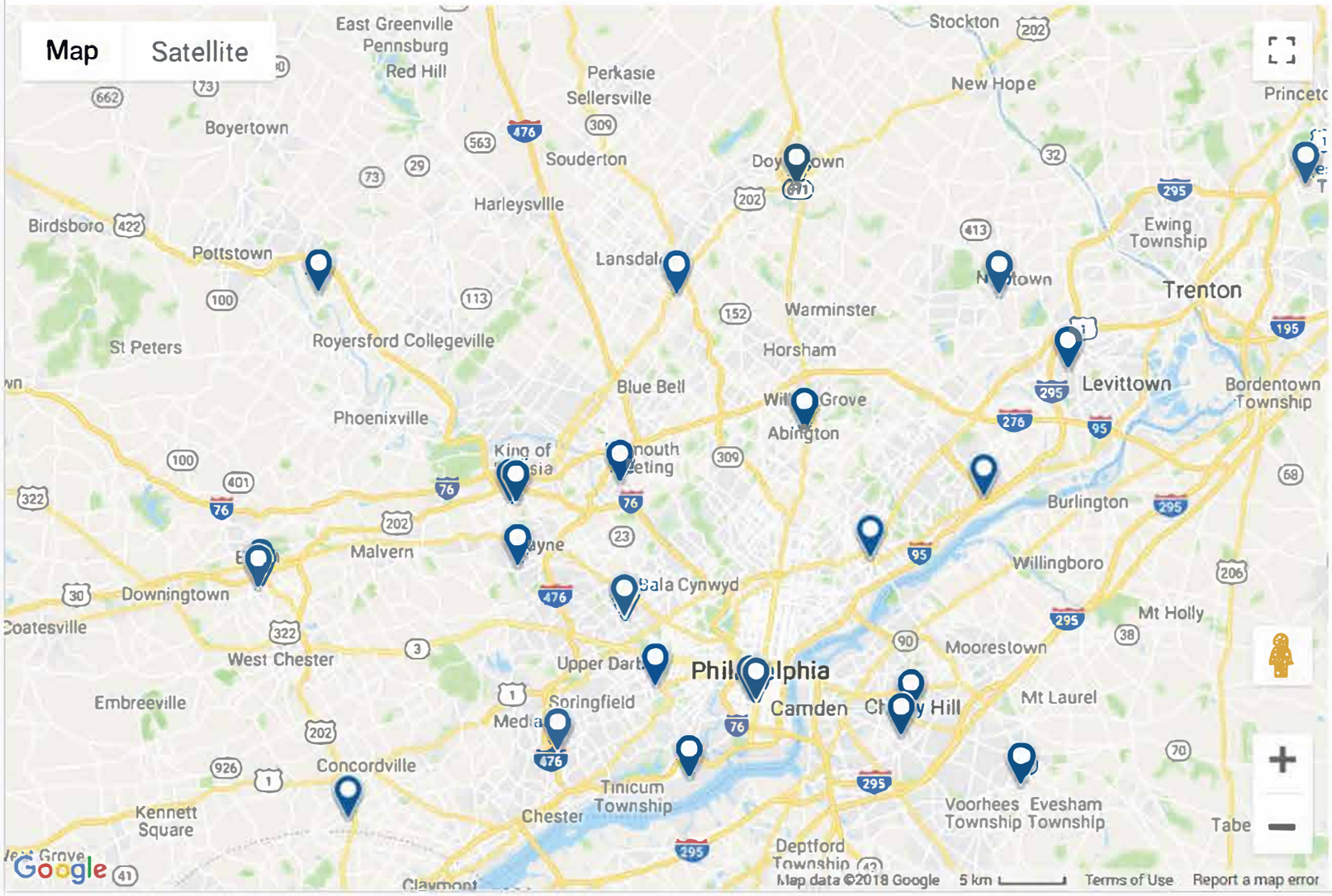
Healthcare Setting Locator

Find a certified prescriber near you.

*Zip Code
12345

*Search Radius
Within 25 miles

Search ›



HCS NAME 75.1 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
DIRECTIONS

HCS NAME 75.6 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
DIRECTIONS

HCS NAME 75.6 miles
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Blue Bell, PA 19422
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Blue Bell, PA 19422
555 555-1212
DIRECTIONS

HCS NAME 76.2 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
DIRECTIONS

HCS NAME 76.6 miles
100 Main St
Blue Bell, PA 19422
555 555-1212
DIRECTIONS

HCS NAME 77.1 miles

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARC R THEORET
08/14/2023 07:57:40 PM