# Document Coversheet

Study Title: Feasibility Pilot of Hepatic Arterial Infusion Chemotherapy in a Rural Catchment Area, Using the Codman Vascular Catheter With the Synchromed II Pump, for Patients With Unresectable Colorectal Cancer Liver Metastases or Unresectable Intrahepatic Cholangiocarcinoma

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| Institution/Site: | University of Kentucky |
| Document (Approval/Update) Date: | 12/19/22 Protocol |
| NCT Number: | NCT04276090 |
| IRB Number | 55664 |
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Cavnar – clinicaltrials.gov record NCT04276090 - Feasibility Pilot of Hepatic Arterial Infusion Chemotherapy in a Rural Catchment Area, Using the Codman Vascular Catheter With the Synchromed II Pump, for Patients With Unresectable Colorectal Cancer Liver Metastases or Unresectable Intrahepatic Cholangiocarcinoma

**Statistical Analysis Plan**

A sample of 34 patients provides an exact, two-sided 90% confidence interval with a width equal to 0.25 when the success rate of completion is assumed to be 80%. The lower and upper limits of the 90% confidence interval for successful completion rate are 0.65 and 0.90, respectively.

For the primary objective defined as safety based on successful completion rate, the proportion will be calculated along with exact 90% binomial confidence interval.

For secondary endpoints, feasibility including percent pump loss attributable to missed pump fills, therapy completion at 3 and 6 months will be summarized descriptively using proportions and exact binomial confidence intervals. The mSIPAT will be completed during screening by the treating investigators; the mSIPAT yields a rating for each potentially eligible patient regarding candidacy status for pump implantation. As described in Section 12.2, mSIPAT scores will be associated with factors indicating treatment adherence (e.g., number of missed clinic visits during the study) using two sample t-tests or Spearman correlation coefficients. Other psychosocial, lifestyle factors, mSIPAT will be summarized and correlated using correlation coefficients while changes over time will be assessed using paired t-tests or longitudinal mixed models. Association of these endpoints with successful completion rate, feasibility, clinical response will be assessed using linear models.

All patients who received HAI intervention will be included in the safety analysis of this study. Adverse event (AE) data and corresponding toxicity grades during each cycle of treatment will be summarized. Treatment-related toxicity will be monitored by usual clinical grading and laboratory parameters such serum alkaline phosphatase, bilirubin. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal (from study treatment) and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal (from study treatment). Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5). Other safety assessments such as rate of 30-day catheter malfunction, requirement for additional postop intervention will also be summarized as proportions and 90% exact binomial confidence intervals.

Overall Response Rate based on RECIST will also be summarized with confidence intervals.

Pharmacokinetic model will be performed to estimate PK parameters (AUC, half-life, clearance) using descriptive statistics of each of these measures for all patients.

# MCC-19-GI-109-PMC: Amendment 4, version date 19DEC2022

This Amendment 4 pvd 19DEC2022 submission comprises revisions to the current approved protocol (Amendment 3, protocol version date 12APR2021).

| Protocol Development History – Original Version to Current Version, w/ major Summary of Changes noted | |
|---|---|
| Original Protocol, 11/11/2019 | GI CCART approval, 11/11/2019. |
| | FRC submission, 11/11/19 |
| | IRB submission, 11/11/19 |
| 11/18/2019 | FRC review. Resolution: Approved, with minor changes. FRC granted request for deferment of edits to be incorporated into the anticipated revision per PRMC review. |
| 11/22/2019 | PRMC Initial Full Review of the original protocol.<br>Resolution: Conditional Approval with administrative edits requested. |
| 11/27/2019 | Protocol revised to incorporate edits from both FRC and PRMC. |
| Revision, V1 12/2/2019 | PRMC administrative review of the revised protocol (i.e., edits requested by PRMC on 11/22/2019). Resolution: PRMC full approval. |
| 12/18/2019 | IRB review.<br>Resolution: new version formatting, response to IRB required changes |
| Revision, V2 1/2/2020 | Protocol was revised and resubmitted to PRMC and IRB, incorporating edits from PRMC and IRB. |
| 1/9/2020 | PRMC approved Revision V2 protocol. |
| 1/10/2020 | Initial coverage analysis received from UKHC Central Research Support Office. |
| 1/15/2020 | FDA IDE granted, active. |
| 2/4/2020 | IRB approved Revision V2. |
| Revision, V3 3/5/2020 | Protocol revised to incorporate minor edits revealed in initial mock-up of study forms build and coverage analysis. |
| 4/28/2020 | Open to Accrual |
| 1st Amendment 6/3/2020 | Protocol revised to incorporate minor edits in order to align with clinic/OR workflow after the initial three patients were enrolled on-study. |
| 2nd Amendment 2/18/2021 | Protocol revised to clarify that patients with preexisting gastric bypass or biliary stents are eligible (3.1.12 and Section 6.3) under certain considerations. |
| 3rd Amendment 4/12/2021 | Protocol revised to clarify holds/dose modifications (in 6.5, 7.2, 7.4), to clarify expedited reporting exclusions (i.e., attributions in 10.7) and clarify that EGFR inhibitors are allowed. |
| **5/17/2022** | PI Closed the study to accrual as FDA approved Intera Pump for HAI; study will remain under Active IRB application until planned follow-up of enrolled patients is completed, and study data is finalized, cleaned and locked (i.e., after results are published). |
| **4th Amendment 12/19/2022** | Protocol was updated to note closure of study accrual prior to meeting accrual goal, stemming from FDA approval of the Intera 3000 Pump. |

**MCC Protocol #: MCC-19-GI-109-PMC**

**ClinicalTrials.gov Identifier:** NCT04276090

**TITLE:** Phase I Safety and Feasibility pilot of hepatic arterial infusion (HAI) chemotherapy in a rural catchment area, using the Codman tapered vascular catheter with the Synchromed II pump, for patients with unresectable colorectal cancer liver metastases (CLM) or unresectable intrahepatic cholangiocarcinoma (IHC)

**Short Title:** HAI as liver-directed therapy for mCRC and IHC



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|---|---|---|
| Principal Investigator: | Michael Cavnar, MD | Surgical Oncology, UK College of Medicine |
| Co-PI: | Reema Patel, MD | Medical Oncology, College of Medicine |
| Co-Investigators: | Joseph Kim, MD | Surgical Oncology, College of Medicine |
| | Jill Kolesar, PharmD | Director, Precision Medicine Center, Markey Cancer Center; Professor, College of Pharmacy |
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| | Jeri Reynolds, RN | Responsible Research Nurse<br>Research Nurse Manager, Precision Medicine Center |
| Statistician and MCC Shared Resource Facilities: | Heidi L. Weiss, PhD | Professor and Director, Biostatistics and Bioinformatics Shared Resource Facility<br>Associate Director of Shared Resource Facilities, Markey Cancer Center |
| | Elisha Comer | Biospecimen Procurement & Translational Pathology |
| IITs Office | Leigh Anne Faul, PhD | Director, Investigator-Initiated Trials Office |
| Data Management | Jennifer Land | Senior Clinical Data Manager |



**Funding Source:** American Cancer Society Internal Research Grant (PI, Cavnar)

**Commercially Available Devices:**
Codman 3000 Series Constant-Flow Implantable Infusion Pump - Tapered Catheter (IP-37957) (FDA indication)
Medtronic Model 8637 Synchromed II programmable implantable infusion pump (former FDA indication, now off-label use)

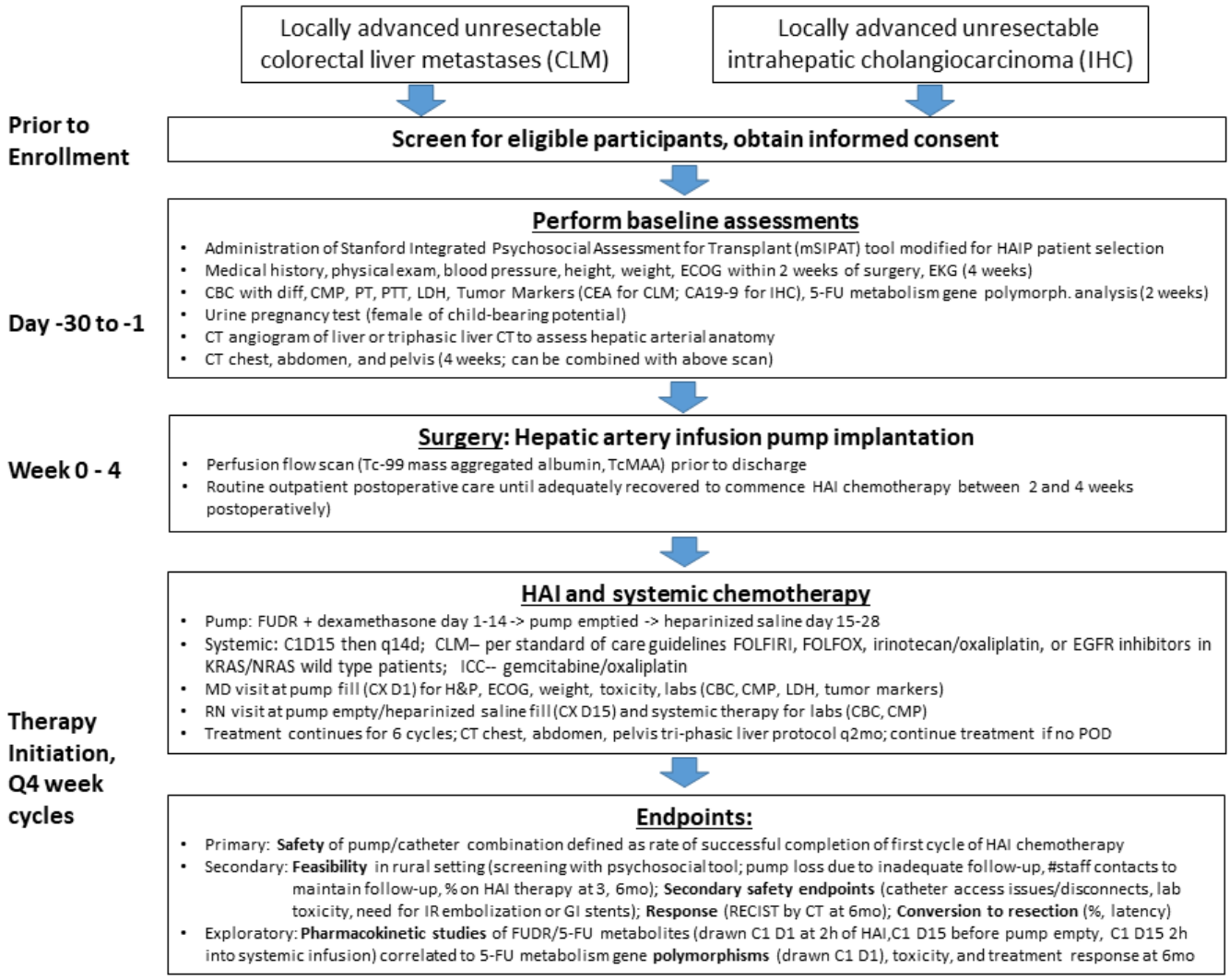
**Commercially Available Agents:** FUDR via HAI, coupled with systemic chemotherapy per standard of care

**IDE Sponsor-Investigator:** Michael Cavnar, MD

**IDE Status:** Active, FDA IDE #: G190313, approved on 1/15/2020

**Protocol Type / Version # / Version Date:** Amendment #3 / 12.April.2021
Amendment #4 / 19. December. 2022

**SCHEMA**




Note to Schema:

Per current SOC guidelines, patients with CLM may be administered EGFR inhibitors targeting driver mutations concurrent with systemic chemotherapy (e.g., KRAS/NRAS wildtype, etc.).

## Protocol Summary

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| **Study Description:** | Due to discontinuation of the Codman C3000 pump, an alternate device is necessary to continue serving patients in need of hepatic arterial infusion chemotherapy. This study aims to test the safety of hepatic artery infusion pump placement, a standard surgical procedure, and intraarterial chemotherapy initiation with the standard medication floxuridine (FUDR), using the Medtronic Synchromed II pump combined with the Codman arterial catheter in patients with unresectable colorectal liver metastases and unresectable intrahepatic cholangiocarcinoma. We hypothesize that complication and pump loss rates will be low and similar to previously published rates for the Codman system. |
| **Objectives:** | Primary Objective: In patients with unresectable colorectal liver metastases or unresectable intrahepatic cholangiocarcinoma, determine the safety of hepatic artery infusion pump placement, a standard surgical procedure, and intraarterial chemotherapy initiation with the standard medication (FUDR), using the Medtronic Synchromed II pump combined with the Codman vascular catheter and standard of care systemic chemotherapy |
| | Secondary Objectives:<br>1. Assess the feasibility of a hepatic artery infusion pump (HAIP) program in a predominantly rural patient catchment area<br>2. Measure overall response rate to standard hepatic artery infusion chemotherapy (FUDR) combined with standard systemic chemotherapy (tailored to primary disease) and percent conversion to resectability.<br>Exploratory objectives:<br>Develop a population model for the pharmacokinetics of FUDR in patients undergoing HAI combined with 5-fluorouracil (5-FU)-based systemic chemotherapy |
| **Primary Endpoint:** | Safety of pump/catheter combination, defined as successful administration of one full cycle of HAI chemotherapy |
| **Secondary Endpoints:** | 1. Additional safety endpoints will be assessed:<br>a. 30-day postoperative serious adverse events related to pump implantation<br>b. 30-day catheter malfunction leading to inability to use (e.g., catheter disconnects, inability to successfully access pump)<br>c. requirement for additional postoperative interventions, e.g., interventional radiology stents or embolization in order to achieve primary function of the pump<br>d. treatment-related toxicity will be monitored by usual clinical grading and laboratory parameters such serum alkaline phosphatase, bilirubin<br>2. Feasibility will be assessed by:<br>a. Percent of patients screened that are declined due to high risk of failure. Screening to assess suitability for HAI pump placement is augmented by the SIPAT, Stanford Integrated Psychosocial Assessment for Transplant, a psychosocial assessment tool designed to assess the suitability for organ transplant modified to assess risk of pump loss.<br>b. Percent pump loss due to inability to attend follow-up appointments for pump fills<br>a. Number of missed appointments requiring re-schedule<br>b. Number of interventions (phone calls) to assure follow-up and prevent pump loss<br>c. Percent of patients who remain on HAI therapy at 3 and 6 months<br>These feasibility endpoints *will be correlated with distance of residence from the Markey Cancer Center in Lexington, KY.*<br>3. Overall response rate, measured by RECIST v1.1 criteria using CT at 6 months.<br>4. Percent downstaged to resectable status and latency to resection |

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| **Exploratory Endpoints:** | We will build a population model for the pharmacokinetics of systemic 5-FU combined with HAI FUDR:<br>a. In order to assess the relative contribution of HAI and systemic therapy:<br>i. Plasma levels of FUDR, an active metabolite of 5-FU, will be measured at 2h of Cycle 1 Day 1, and at the end of HAI treatment Cycle 1 (Day 15; prior to administration of systemic chemotherapy).<br>ii. Plasma levels of FUDR will be measured immediately after a systemic bolus of 5FU or 2 hours after starting a systemic continuous infusion of 5-FU<br>b. Levels will be correlated to gene polymorphisms in 5-FU drug metabolism genes (dihydropyrimidine dehydrogenase (DYPD), thymidylate synthetase (TYMS), and glutathione S-transferase (GSTP1))<br>c. Levels and polymorphisms will be correlated to treatment response by RECIST, and toxicity |
| **Study Population:** | 2 subgroups of patients:<br>1) Unresectable liver metastases from colorectal cancer<br>2) Unresectable liver-confined intrahepatic cholangiocarcinoma<br>*Sample size *:* Up to 34 patients total (30 evaluable), from the two disease subgroups<br>* accrual was closed prior to meeting N of 34 due to approval of another HAI pump. Study accrued 21 patients prior to closure.<br>*Age:* adults, defined as 18 yrs or older<br>*Health Status*: adequate fitness to undergo major abdominal surgery<br>*Gender*: inclusive<br>*Race/Ethnicity*: inclusive<br>*Geographic Location*: no exclusions based on geography |
| **Study Site** | Single site: Markey Cancer Center of the University of Kentucky – Chandler Hospital and Precision Medicine Clinic |
| **Phase** | Phase 1 - safety and feasibility |
| **Description of the Study Intervention** | The Medtronic pump is attached to a Codman vascular catheter and implanted using routine surgical techniques for HAI. After recovery from surgery and confirmation of pump function by nuclear perfusion flow study, patients will undergo HAI with FUDR 0.12 mg/kg/day with dexamethasone 1 mg/day for two weeks alternating with heparinized saline for two weeks. This will be paired with disease-appropriate systemic therapy at standard doses as per SOC guidelines administered in 2-week cycles (FOLFOX, FOLFIRI, irinotecan/oxaliplatin, and/or EGFR inhibitors for patients with appropriate driver mutations for colorectal cancer, and gemcitabine/oxaliplatin or gemcitabine alone for intrahepatic cholangiocarcinoma) |
| **Study Duration:** | 3 years |
| **Participant Duration:** | 7 months unless downstaged to resectable disease, in which case patient will be followed on-study for an additional 6 months. |

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# 1. OBJECTIVES

## 1.1 Primary Objective

Assess the safety of this Hepatic Artery Infusion (HAI) pump/catheter combination in delivery of HAI therapy, concurrent with standard of care systemic chemotherapy in the population.

Safety is operationally defined as successful completion of one full cycle of HAI. Early failures in the HAIP implementation process will be assessed, including:

- Complications from surgical implantation (i.e., pump failure due to surgical complication)
- Dysfunction of the HAI pump/catheter combination
  - catheter disconnection
  - inability to access pump
- Thrombosis
- Inappropriate perfusion
  - inadequate liver perfusion
  - extrahepatic perfusion not correctable by interventional radiology procedures
- Initial toxicity of HAI + systemic chemotherapy that prohibits additional HAI therapy

## 1.2 Secondary Objectives

1.2.1 Feasibility of an HAIP program in a predominantly rural patient catchment area. Feasibility as defined by:

1.2.1.1 Percent pump loss attributable to missed pump fills

- Number of missed appointments requiring re-schedule
- Inability to attend appointments for pump fills, assess reasons/barriers transportation, etc.)
- Number of interventions (phone calls) to assure follow-up and prevent pump loss

1.2.1.2 Therapy completion at 3- and 6-months (Percent of patients who remain on HAI therapy at 3-, 6-months)

1.2.1.3 Distance in miles from the institution

Pump loss and therapy completion will be correlated to the distance of the patient's residence from the cancer center in Lexington, KY.

1.2.2 Measure Overall Response Rate to standard hepatic artery infusion chemotherapy (FUDR) combined with standard systemic chemotherapy (tailored to primary disease), and conversion to resection at 6-months measured via RECIST v1.1

## 1.3 Exploratory Objectives

Pharmacokinetics profiles will be conducted in order to accomplish the following objectives:

- Evaluate plasma concentrations of FUDR after hepatic arterial administration.
- Estimate the relative contribution of intravenous administration of 5-FU and hepatic artery administration of FUDR on plasma FUDR concentrations.
- Develop a population pharmacokinetic model for 5-FU, FUDR and 5-fluorodeoxyuridine monophosphase (FdUMP)

# 2. BACKGROUND

## 2.1 Liver Metastases from Colon Cancer and Cholangiocarcinoma

In the United States, it is estimated that 145,600 people will be diagnosed with colorectal cancer and that 51,020 people will die from this disease in 2019[9]. Venous drainage from the colon and rectum allow cancer cells to travel to the liver via the portal vein. This anatomical fact explains why the liver is the most frequent and often the only site of metastatic disease from colorectal cancer. Synchronous or metachronous hepatic metastases will afflict approximately 20% of all patients with colorectal cancer [10], and approximately 50% of colorectal cancer deaths are due to liver metastases [11]. In highly selected patients with resectable hepatic metastases, 5-year overall survival (OS) ranges from 20% to 35%, suggesting that if liver metastases can be effectively controlled, a long-term survival benefit may result [12]. However, systemic chemotherapy without surgical resection (i.e., in unresectable disease) is generally non-curative and requires continuous therapy. This treatment approach alone rarely yields long-term survivors, with a median survival of roughly 20 months with modern chemotherapy [12], with cumulative toxicity building during therapy. In this setting, hepatic artery infusion (HAI) chemotherapy offers an adjunctive therapy to systemic chemotherapy +/- surgical resection. In patients with unresectable disease limited to the liver, HAI is delivered with the intention of prolonging survival, and in some patients, converting the disease to resectable status. This strategy has also been applied to unresectable intrahepatic cholangiocarcinoma (IHC), as discussed below.

## 2.2 Hepatic Arterial Infusion chemotherapy: rationale and pharmacology

The hepatic artery is the main supply of nutrients for liver metastases (>3mm in diameter), while the portal vein maintains and supplies the normal liver parenchyma [13, 14]. This anatomical difference together with pharmacologic factors provide the rationale for liver-directed HAI. The liver metabolizes certain drugs during the first pass through the hepatic arterial circulation, which results in high local concentrations of the infused drug with minimal systemic toxicity. Drugs with high total body clearance and a short plasma half-life are the most suitable for hepatic arterial infusion. These facilitate the delivery of high concentrations of chemotherapy directly to liver metastases while minimizing toxicity to the remaining liver and body. **FUDR**, the active metabolite of fluorouracil (5-FU), is one such optimal agent for administration via HAI. Up to 99% of FUDR is extracted by the liver during first pass which results in a hepatic/systemic ratio of 100-400, compared to a hepatic extraction rate of 19-55% for 5-FU resulting in a hepatic/systemic ratio around 10[15, 16]. Dosing of HAI therapy currently is based on studies mostly from the 1970s and 1980s. Modern pharmacokinetic studies have not been performed, particularly in the setting of combined systemic chemotherapy. Since the time of these initial studies, understanding of 5-FU metabolism has increased substantially. It is now known that single nucleotide polymorphisms (SNP) of the dihydropyrimidine dehydrogenase gene (DPYD) are associated with widely different levels of toxicity [17]. It is unknown whether these SNPs or polymorphisms in other genes in this metabolic pathway are associated with response rates or toxicity in the setting of HAI combined with systemic chemotherapy.

## 2.3 **Unresectable Colorectal Liver Metastases (CLM)**

### 2.3.1 Systemic Chemotherapy for unresectable CLM

For patients with unresectable colorectal cancer with metastases confined to the liver, regional treatment of metastatic disease has been a topic of considerable interest given the underwhelming response rates to systemic chemotherapy alone[10]. Modern combination chemotherapy for unresectable CLM rarely results in 5-year survival and is associated with a median survival of roughly 20 months [12]. Likewise, irinotecan alone, irinotecan/cetuximab, and oxaliplatin/5-fluorouracil (5-FU)/leucovorin (LV) will produce responses ranging from 9% to 22% in patients whose tumors have progressed on first-line chemotherapy. However, the median survival time for these patients after second-line therapy is 12 months or less [18, 19]. Local ablative therapies including microwave and radiofrequency ablation have been shown to effectively control small metastatic deposits in the liver but based on current technological limitations it is difficult to treat patients with lesions greater than 3 cm or who have more than 3 or 4 metastatic deposits in the liver.

### 2.3.2 Regional (HAI) Therapy for Unresectable CLM

Among patients with metastatic colorectal cancer, many patients have liver-only disease at the time of progression on first-line therapy, prioritizing the rationale for regional chemotherapy. Many regional chemotherapeutic interventions have been attempted over the last several decades to control hepatic disease. Of the available liver-directed regional therapy options, the hepatic artery infusion pump (HAIP) has been utilized primarily at Memorial Sloan Kettering Cancer Center, and has robust toxicity and efficacy data obtained through several prospective trials [20-24]. In a Cancer and Leukemia Group B trial (CALGB 9481) comparing HAI FUDR/LV/Dexamethasone (Dex) with systemic 5FU/LV, the response rate (48% vs 25%, respectively) and median survival time (24 vs 20 months; p=0.0013) were higher in the HAI group. Although time to hepatic progression was better in the HAI arm compared with the systemic arm (9.8 vs 7.3 months; p=0.034), the time to extrahepatic progression was better in the systemic arm (7.7 vs 14.8 months; p=0.029) [24]. Data from this trial led to several conclusions. First, FUDR delivery via HAI is more effective in controlling hepatic disease than systemic 5-FU alone. Second, patients with metastatic colorectal cancer, even those with ostensibly liver-confined disease, have micro-metastases in multiple organs. Finally, an optimal approach to patients with liver -dominant metastatic colorectal cancer is liver control with FUDR delivered via HAI in combination with systemic chemotherapy to control extrahepatic disease. Fortunately, systemic toxicity from HAI FUDR is extremely rare, allowing full doses of systemic chemotherapy to be administered concurrently. Indeed, combining HAI with systemic chemotherapy results in improved efficacy relative to either approach alone, as discussed below.

In a phase I study of 36 patients with liver-only metastases to examine toxicity of combination HAI with modern systemic agents, the response rate was high compared with other second-line therapies [22]. The partial response rates were 90% and 87% with the HAI plus oxaliplatin/irinotecan and HAI plus oxaliplatin/5-FU/LV combinations, respectively. More than 50% of patients showed a greater than 75% reduction in their tumor, and seven patients were able to undergo liver resection, two of whom had complete pathologic response. Combination therapy with HAI FUDR and dexamethasone plus systemic oxaliplatin/irinotecan or oxaliplatin/5-FU/LV was safe and well tolerated. Importantly, the combination of HAI and systemic oxaliplatin did not impact the dose of oxaliplatin or irinotecan that could be administered nor the dose schedule. A separate phase 1 study evaluated HAI floxuridine and dexamethasone plus systemic chemotherapy with oxaliplatin/irinotecan in 49 patients with unresectable liver metastases (53% previously

treated with chemotherapy) [23]. Ninety-two percent of the 49 patients responded, with complete or partial response in 8% and 84%, respectively, and 23 (47%) were able to undergo complete resection. This is remarkable, as these patients had extensive disease -- 73% had > five liver lesions, 98% had bilobar disease, and 86% had ≥ six segments involved. For chemotherapy-naïve and previously treated patients, the median survival from the start of HAI therapy was 50.8 and 35 months, respectively, while these groups may be expected to have only a 20 month and 12-month median OS with modern chemotherapy [12, 18, 19]. Interestingly, variables reflecting extensive anatomic disease, such as number of lesions or number of vessels involved, were not significantly associated with the probability of resection.

A prospective phase II trial evaluated the rate of conversion to resection in 49 patients with unresectable CLM who received HAI and systemic chemotherapy [3]. The trial was powered to detect an increase in conversion to resection from 15% to 30%, which represents approximately a doubling of the conversion rate reported from systemic chemotherapy trials. Combination HAI and systemic therapy resulted in very high response rates in both previously treated (72%) and chemotherapy-naïve patients (82%). The primary endpoint of the study (conversion to resection) was achieved, with 47% of patients undergoing complete resection. Among the whole cohort, overall survival was 38 months, and 1- and 3-year survival rates were 92% and 55%, respectively. These results are encouraging, especially considering the high rate of previously treated patients, the large bulk of disease, and the oncologic adverse features that most patients exhibited. Overall, numerous randomized studies have shown marked efficacy of HAIP in the setting of unresectable CLM **(Table 1)**. Thus, patients with CLM who have not responded to conventional first-line chemotherapy may benefit from regional chemotherapy if the disease remains largely confined to the liver and this site of disease will be survival-limiting.

**Table 1:** Randomized clinical trials documenting the response rate of HAIP FUDR in CLM

| *Trial Reference* | *Publication Year* | *# of Patients* | *Response Rates* |
|---|---|---|---|
| Chang et al. | 1987 | 32 | 62% |
| Kemeny et al. | 1987 | 48 | 53% |
| Hohn et al. | 1989 | 75 | 42% |
| Martin et al. | 1990 | 39 | 48% |
| Wagman et al. | 1990 | 100 | 55% |
| Rougier | 1992 | 81 | 41% |
| Lorenz & Muller | 2000 | 53 | 43% |
| Kemeny | 2006 | 68 | 47% |

As mentioned above, regional therapy for liver metastases can be undertaken with modalities other than the HAIP. Today, the most common alternative modality, as endorsed by the National Comprehensive Cancer Network (NCCN), is radioembolization (Y90). Although this is an interventional radiology procedure and can be ordered by any treating physician, the procedures are invasive and may be associated with significant complications [25]. From the available literature, **Table 2** summarizes history data regarding efficacy and complications of both HAIP and radioembolization for chemo-refractory metastatic colorectal cancer. Although these two modalities have not been compared head-to-head in a randomized trial, retrospective comparison favors HAIP for efficacy in terms of conversion to resection, and toxicity.

| **Table 2:** Comparisons of Efficacy and Complications in HAIP vs Radioembolization | | |
|---|---|---|
| | **HAIP** [3, 26, 27] | **Radioembolization** [25, 27-29] |
| Required Procedures | 1 | 2 |
| **COMPLICATIONS** | | |
| Pump Infection | 2.5% | 0% |
| Thrombosis | 6% | 1% |
| Radiation Gastritis/Ulcer | 0% | 5-10% |
| Biliary Injury Requiring Stents | 5% | 5-8% |
| Hepatic Insufficiency/Failure | <1% | 4% |
| Radiation Pneumonitis | 0% | 20% |
| Diarrhea | 20% | 37% |
| **EFFICACY** | | |
| Partial Response Rate | 76% | 10% |
| Conversion to Resection | 47% | <1% |

### **2.3.3** Adjuvant therapy following liver resection using HAI

Although this study aims to investigate unresectable disease, significant data are available from study of HAI in the adjuvant setting after complete resection of CLM and is worth mentioning as background. The recurrence rate following liver resection for colorectal cancer metastases is on the order of 60-70%. The liver represents the only site of recurrence in two thirds of these relapses [30]. Thus, adjuvant liver-directed therapy to reduce the risk of liver recurrence and improve survival is a very reasonable therapeutic approach. Four randomized trials have compared adjuvant hepatic arterial chemotherapy (HAI) therapy after resection of colorectal cancer liver metastases with adjuvant systemic therapy or a control arm. Of these four studies, three showed a significantly longer hepatic disease-free survival (DFS) as well as OS [31-35].

A report from MSKCC (Memorial Sloan Kettering Cancer Center) compared the long-term survival of 287 patients with resected colorectal liver metastases that received adjuvant HAI and systemic therapy on four consecutive adjuvant protocols from 1991 to 2009. The patients were divided into two groups, based on whether they received therapy before or after 2003, thus reflecting changes in the systemic chemotherapy used in the management of colorectal cancer. The difference in the 3-year and 5-year overall survival between the two patient groups (after 2003 or before 2003) was 92% and 73% versus 78% and 56% ($p<0.01$) respectively, demonstrating the excellent survival obtained with resection, HAI and modern chemotherapy [36]. Another more recent publication from MSKCC looked at 2,368 consecutive patients who underwent liver resection of colorectal metastases. 785 had HAI and 1583 did not, and these patients were compared using propensity score matching. The HAI group of patients had significantly higher disease burden but had a longer median survival of 67 months versus 44 months for those treated with adjuvant systemic chemotherapy alone ($p<0.01$)[37]. Interestingly, this effect was most marked in patients with low clinical risk scores. We aim to establish the safety of HAI using the Medtronic pump combined with the Codman vascular catheter in unresectable CLM and IHC, however, further study beyond that will include using the pump for adjuvant therapy.

## 2.4 Intrahepatic Cholangiocarcinoma (IHC)

### 2.4.1 Incidence and Prevalence of IHC

Primary IHC is the second most common primary hepatic malignancy. Using Surveillance, Epidemiology, and End Results (SEER) data, it was found that from 1973 to 2012 the annual incidence of IHC increased from 0.44 to 1.18 per 100,000, representing a 2.3% annual increase, with the trend increasing to 4.4% per year in the last decade [38]. This increase may be partly due to more accurate diagnosis, with an evolving definition of IHC in the literature, and less "cancer of unknown primary" during the later time period. Most IHC are unresectable at presentation, with about half of patients being stage IV, a group with a 5 year survival rate of 2%. Resection remains the modality associated with the best outcome, with 5 year survival of 30-40% after resection in highly selected patients [39]. However, patients with localized unresectable IHC have a median survival of less than 12 months.

### 2.4.2 Systemic Therapy for IHC

Multiple systemic regimens have been evaluated and shown to have limited efficacy. The Advanced Biliary Cancer [ABC] trial comparing systemic gemcitabine and cisplatin versus gemcitabine alone in advanced biliary tract cancer produced a median PFS of 8 and 5 months ($p<0.001$), respectively, with an OS difference of 3.6 months (11.7 versus 8.1 months, respectively, $p=0.001$)[40]. Objective response rate was poor, with only 26% having partial/complete response with gemcitabine/cisplatin compared to only 16% with gemcitabine alone [40]. The combination of gemcitabine/oxaliplatin (GEMOX) as first-line therapy offers similarly poor results. Among patients with locally advanced or metastatic biliary tract cancer, the objective response rate of GEMOX was 20.5% (9/44, non-gallbladder cancers), with a median PFS of 3.8 months and OS of 11.0 months [46]. Since resection is associated with better outcomes, there is substantial interest in downsizing unresectable tumors that are confined to the liver to resectability status.

### 2.4.3 Regional (HAI) Monotherapy for IHC

Given the limited efficacy of systemic therapy in IHC, regional therapy has been attempted to obtain greater response leading to potential curative resection. Recently, a phase II study was conducted at MSKCC evaluating the efficacy of HAI FUDR (without systemic component) in patients with primary liver cancer [4]. This study included 34 patients: 26 with IHC and 8 with hepatocellular carcinoma (HCC). The response rate was 47% and the median time to progression (TTP) was 7.4 months (CI 5.30-9.28), hepatic TTP of 10.1 months (CI 7.14-12.86) and overall survival of 29.5 months (CI 21.28-32.70). Patients with IHC appeared to derive greater benefit, with a partial response rate of 54% (compared to 25% for HCC), although the number of HCC patients was much lower. The therapy was well-tolerated, with only one Grade 2 elevation in AST. The response rate and TTP observed in this study were higher than those reported for any systemic chemotherapeutic regimen (ABC trial partial/complete response was 26% for gemcitabine/cisplatin [40]), suggesting an important role for regional chemotherapeutic strategies in the treatment of unresectable IHC. Thus, since most initial treatment failures in IHC occurred in the liver, improving drug delivery to the liver appeared to be a means of enhancing the results of regional therapy [4].

### 2.4.4 Regional (HAI) Therapy in Combination with Systemic Chemotherapy

Building on these initial results, a second study was initiated and completed at MSKCC, evaluating the efficacy of HAI FUDR combined with systemic bevacizumab in patients with liver-only IHC or HCC disease. The rationale for this study was that bevacizumab would normalize the tumor vasculature and improve FUDR delivery, however, the trial was halted early due to increased biliary toxicity with the addition of bevacizumab. Twenty-two patients were enrolled, 18 with IHC and 4 with HCC. The overall response rate was less than the first study at 32%, and the median TTP was 8.8 months [41]. Subsequently, retrospective analysis of 525 IHC patients evaluated at MSKCC from 2000-2012 revealed unresectable disease (locally advanced or metastatic) in 236, of whom 104 with disease confined to the liver underwent treatment with HAI and systemic therapy (usually gemcitabine/cisplatin; n=78 or 75%) or systemic therapy alone (n=26, 25%) [5]. The response rate trended towards higher with combined therapy (59% vs 39%, p=0.11). OS was longer in the combined group (30.8 vs 18.4 months, p<0.001), a difference that was maintained in patients with node-positive disease. Eight patients with initially unresectable tumors responded enough to undergo complete resection, with a median OS of 37 months (range, 10-92 months) [5]. A recent trial evaluated the combination of hepatic arterial infusion of floxuridine and systemic administration of gemcitabine and oxaliplatin among patients with unresectable intrahepatic cholangiocarcinoma. The overall response rate was 58% (22/38) and disease control of primary tumor at 6-months was 84% (32/38). Four patients were able to undergo resection and 1 patient had complete response, with a median PFS of 11.8 months and median OS of 25.0 months (range, 0-56.5 months) [47].Collectively, findings from these trials provide substantial rationale for HAI in unresectable IHC patients, although further study is necessary.

## 2.5 Toxicity and Complications from Regional (HAI) Therapy

### 2.5.1 Side Effects from FUDR

Toxicity from HAI FUDR therapy includes biliary toxicity, gastric ulceration, and diarrhea. Close monitoring of liver function and routine use of proton pump inhibition is imperative. If diarrhea is pronounced, shunting to the bowel of HAI infused therapy should be considered. Biliary toxicity is of particular importance, due to the fact that the hepatic artery supplies blood to the bile ducts almost exclusively. Fortunately, concomitant administration of HAI dexamethasone with FUDR mostly abrogates this toxicity. An early randomized study of HAI therapy with FUDR with or without dexamethasone in patients with CLM showed a reduction in hyperbilirubinemia from 30% to 9%, and was associated with higher response rates [42]. As a result, standard HAI includes FUDR and dexamethasone.

Biliary toxicity during HAI therapy may manifest clinically as elevations of aspartate transaminase (AST), alkaline phosphatase, and bilirubin. In the setting of jaundice, obstruction due to a biliary stricture (malignant or post-surgical) must be ruled out prior to concluding that liver dysfunction is due to HAI therapy. An endoscopic retrograde cholangiopancreatogram (ERCP) may demonstrate biliary sclerosis secondary to HAI therapy which, if focal, may be alleviated with a biliary stent. Elevations in liver function without associated stricture are typically successful managed with dose reductions and holding therapy while administering HAI dexamethasone.
With appropriate expertise, the HAIP can be placed with minimal risk to the patients.

2.5.2 Side Effects from Implantation of Hepatic Artery Infusion Pump and Catheter

**Table 3** summarizes the perioperative complications observed in 544 patients treated consecutively at MSKCC.

| **Table 3:** Perioperative complications observed in 544 consecutive patients undergoing HAIP [26] | | |
|---|---|---|
| **Type of Complication** | **Percentage of Patients** | **Percent Salvaged** |
| Pump Malfunction | 1% | 100% |
| Pump Pocket | | |
| Infection | 0.7% | 50% |
| Hematoma | 0.2% | 100% |
| Migration | 0.2% | 100% |
| Arterial | | |
| Hemorrhage | 0.2% | 100% |
| Thrombosis | 2.3% | 31% |
| Extra-hepatic Perfusion | 1.6% | 100% |
| Incomplete Perfusion | 1.6% | 75% |

## 2.6 Discontinuation of Production of the Codman HAI Pump

The manufacturer of the C3000 Codman Pump, the main device used for HAI, terminated production of the pump in April 2018. The design of the pump contains many unique components, and several suppliers of those components have ceased operations, thus limiting the availability of critical parts that enable the pump to be manufactured to the approved specifications. Thus, alternate means of employing HAI need to be devised in order to continue to offer this therapy. The Medtronic Pump combined with a Codman vascular catheter (still being manufactured) have previously been successfully used off label at MSKCC. If safety is demonstrated in a larger population, this would provide an option for appropriate patients to receive HAI.

## 2.7 Preliminary Data Using Alternative Pump and Catheter Configurations

Since discontinuation of production of the Codman C3000 pump in 2018, there are no devices on the market with FDA-approved indication for HAI to serve as an alternative. Historically, Medtronic developed a pump with an FDA indication for HAI, however, since the Codman pump was the only pump with substantial market share, Medtronic never sought indication for the newer generation pump, Synchromed II, now widely used for pain indications. Over 8,000 Synchromed II pumps have been implanted for a variety of diseases, with safety data maintained in a registry (personal communication, Medtronic). At 75-months, the Synchromed II pump demonstrates a 97.2% device reliability. Given its previous generation model having successfully been used for HAI and the extensive safety data, this pump is deemed an adequate substitute.

After the Codman pumps stopped being manufactured in April of 2018, a group of surgeons and medical oncologists at MSKCC discussed using Medtronic pumps in an off-label capacity as a replacement for the Codman pumps based on these previous experiences. Since May 30, 2018, approximately 50 Medtronic Synchromed II pumps spliced to Codman vascular catheters have been implanted for both CLM and IHC, without substantial complications or toxicity outside of

what would be expected from routine experience (personal communication, Nancy Kemeny, MD). In particular, there have been no instances of pump disconnection or failure due to splicing the two systems together. Currently, MSKCC has a safety trial of this device combination underway, and several other institutions are following suit in order to continue to offer HAI to patients.

## 2.8 Rationale for the Study and Selected Endpoints & Hypotheses

With no devices currently available and FDA approved for HAI therapy, the surgical oncology community stands to lose a powerful tool to address regional disease in patients with colorectal liver metastases and lose an evolving promising treatment for unresectable IHC.
By combining two devices (the Medtronic Synchromed II pump and the Codman vascular catheter) each individually with a long safety record, and with existing preliminary safety data out of MSKCC for this combination, we believe this trial moves the field towards having a viable replacement device to continue HAI. Additionally, there is substantial momentum within the surgical oncology community to develop large scale national trials of HAI – establishing a program at the University of Kentucky poises our program to be a leader in this process. In order to do this, we must establish the feasibility of an HAIP program in a mostly rural catchment area.

## 2.9 Rationale for Primary Objective

*2.9.1 Safety of this HAI pump/catheter combination in delivery of HAI concurrent with standard of care systemic chemotherapy*

Due to discontinuation of the Codman C3000 pump, an alternate device is necessary to continue serving patients in need of hepatic arterial infusion chemotherapy. In patients with unresectable colorectal liver metastases or unresectable non-metastatic intrahepatic cholangiocarcinoma, we aim to determine **the safety** of hepatic artery infusion pump placement, a standard surgical procedure, and intraarterial chemotherapy initiation with the standard medication (FUDR), using the Medtronic Synchromed II pump connected to the Codman vascular catheter, combined with standard of care systemic therapy. Our primary endpoint (**successful completion of one full cycle of HAI**) is a conglomerate safety measure designed to assess early failure anywhere in the process of implementing HAI – this includes complications from surgical implantation, pump/catheter combination dysfunction, and initial toxicity of HAI/systemic chemotherapy that would be prohibitive of further HAI therapy. This endpoint will capture early pump failures due to technical (surgical) complications, as well as early functional issues related to catheter disconnection, inability to access, thrombosis, and inappropriate perfusion (extrahepatic perfusion not correctable by interventional radiology procedures or inadequate liver perfusion for treatment). If we are able to show a high rate of successful implementation of HAI in our MCC program, this combined safety data from other programs using this combination on trial (MSKCC, NCI), and off label (Duke, Penn, Northwestern, others) will build momentum toward making this device combination the new standard of care of HAI in the United States. Likewise, we believe this will set the stage for further multi-institutional randomized trials of HAI combined with modern systemic chemotherapy.

## 2.10 Rationale for Secondary Endpoints:

*2.10.1 Feasibility of a HAIP program in predominantly rural patient catchment area:*

Widespread dissemination of HAI therapy approach is limited by the pump's design, specifically the pump fails if it is allowed to run out of fluid. With a fluid reservoir of 20mL and a flow rate of 1 mL per day, pump fill appointments are scheduled every 2 weeks. If the pump runs out, the catheter typically thromboses and is unsalvageable. HAI pumps typically are left implanted in patients for several years, sometimes indefinitely if maintenance treatment is ongoing for unresectable disease.

Although HAI itself has been used safely and effectively for decades, this treatment option is available at only a few large, urban medical centers, with MSKCC being the dominant site. Patients who undergo HAI treatment must be willing to commit to trips to Lexington for the lifetime of the pump (or a medical center capable of filling the pump, which currently comprises only a select few centers in the country). At MSKCC, pumps are usually not removed for several years if the patient remains without evidence of disease (in patients receiving adjuvant therapy after complete resection), and in patients receiving definitive therapy for unresectable CLM or IHC, the pump is typically left indefinitely unless systemic progression occurs rendering it useless, in which case it is removed (outpatient surgery). Thus, the **commitment to undergo HAIP placement and HAI is substantial.**

Markey Cancer Center and University of Kentucky serve central and eastern Kentucky, which includes Appalachia. Appalachia has the highest rates of cancer in the nation (prevalence, incidence and mortality), driven by rampant poverty that limits or negates access to cancer screening and treatment. Patients presenting to the MSKCC HAIP program differ greatly from the patients of Kentucky, with affluence, reliable transportation and private insurance. MSKCC patients have ample resources and motivation required to make trips every two weeks back/forth to New York, or are able to receive ongoing HAI treatment and management at a more local medical center (after pump placement at MSKCC). In contrast, the patient catchment at the University of Kentucky includes residents of the entire state, and portions of Ohio, West Virginia, and Tennessee. The socioeconomic status of these patients varies greatly. While some of our patients (typically from Lexington or the surrounding area) are affluent and have private insurance, a large proportion of our patients live >100 miles from Lexington, are of lower socioeconomic status, and lack private insurance. Nevertheless, based on our anecdotal experience, there are highly motivated patients from both groups who would be candidates for HAI therapy, as described above. To the best of our knowledge, the feasibility of an HAIP program in a largely rural catchment area has never been studied in a clinical trial. Selection of patients appropriate for this treatment will be enhanced by consideration of the practical requirements of HAI, e.g., transportation and resources to complete required biweekly clinic visits. We will adapt and use the validated *Stanford Integrated Transplant Assessment Tool (*SIPAT, a standardized psychosocial questionnaire that evaluates patient suitability for organ transplant) modified for HAI pump therapy (modifications noted in Appendix B). We will be able to show that HAI is feasible in this setting by selecting only the patients who are most appropriate [1]). In a prospective study, high SIPAT score predicted higher numbers of organ transplant rejection episodes, hospitalizations, infection, and social support system failures [2]. We believe that this tool, modified to assess suitability for HAIP, will improve patient selection to help avoid pump loss. Using this tool, we anticipate a very low loss of pump due to inability to attend requisite follow-up. Simultaneously, we will also monitor how work-intensive it is to assure these patients keep follow-up appointments (e.g., number of patient contacts/phone calls initiated/received outside scheduled clinic visits).

*2.10.2 Overall Response Rate to HAI FUDR concurrent with standard chemotherapy and conversion to resection at 6-months post-treatment.*

Based on a prospective phase II trial of HAI in unresectable CLM we anticipate approximately 70% overall response by RECIST criteria in previously treated CLM, and approximately 80% in chemotherapy-naïve [3]. 47% of these patients eventually underwent resection after downstaging of their tumors with HAI therapy. In patients with unresectable IHC, based on the phase II study of HAI in IHC, we anticipate an approximately 50% overall response rate [4] and based on retrospective data, approximately 10% downstaging to resectability [5].

## 2.11 **Rationale for Exploratory Objectives (Correlatives):**

*2.11.1 Develop pharmacokinetics profiles to examine plasma concentrations of FUDR associated with IV chemotherapy versus HAI administration.*

FUDR, the active metabolite of 5-FU, is commonly used to treat hepatic metastases via HAI. To our knowledge, plasma concentrations of FUDR administered via HAI have never been reported. Gene polymorphisms in dihydropyrimidine dehydrogenase (DYPD), thymidylate synthetase (TYMS), and glutathione S-transferase (GSTP1) [6], as well as select patient-level factors (age, sex, weight, body surface area) can influence both response and adverse effects to 5-FU [7], however, their influence on FUDR via HAI is unknown. This study, which combines systemic intravenous administration of 5-FU and HAI of FUDR, provides a unique opportunity to understand the distribution and metabolism of 5-FU and FUDR as predictors of therapeutic response and adverse effects (toxicities). Specifically, 5-FU, FUDR and FdUMP plasma concentrations will be evaluated in with a validated LC/MSMS assay as previously described [8]. Data will be analyzed by a nonlinear mixed-effects modeling approach using the NONMEM system (Version VI, NONMEM Project Group, UCSF/Globomax and PDx-Pop Version 3.1). Xpose4 and S-PLUS (Insightful Corp, Seattle, Washington) are used for goodness-of-fit assessment and model evaluation. Both intrahepatic and plasma administration will be simultaneously analyzed in the single model. In addition, polymorphisms in DYPD, TYMS and GSTP1 will be evaluated for association with adverse effects (toxicity) and clinical outcome (treatment response, conversion to resection).

## 2.12 Hypotheses of the Study:

We hypothesize that the combination of the Codman catheter with the Synchromed II will be safe and patients on our trial will show similar data regarding safety as published in the literature from other trials using Codman pump+catheter, as well as emerging preliminary data for the current device combination from MSKCC. We hypothesize after application of the proposed screening tools we will demonstrate feasibility of an HAIP program in our mostly rural catchment area. Pharmacokinetic studies of 5-FU metabolism and HAI have not been performed in the era of combined systemic therapy with HAI. Our study aims to provide modern pharmacokinetic data and study the relationship between polymorphisms in 5-FU gene metabolism, toxicity, and response to HAI FUDR combined with systemic chemotherapy.

### 2.13 Early study closure due to FDA approval of the Intera 3000 pump

When the Codman 3000 pump went off the market, a group of investors--some of them former HAIP patients from MSKCC--formed a company called Intera Oncology, with the goal of returning the pump to the market. This company acquired the rights to the Codman 3000 from J&J, and initiated a new manufacturing chain to produce the same device. The newly produced pump was then dubbed the Intera 3000 pump, which received FDA approval in June 2021. The premise of the MCC-19-GI-109-PMC study was to test the off-label device combination of the Medtronic Synchromed II pump with the Codman catheter, however, now an FDA-approved alternative pump existed. We queried the Medtronic representatives to determine whether there were any plans to obtain approval for study device combination, and there were no such plans. Thus, given the lack of equipoise to continue testing the off-label combination in the setting of a newly approved device, we made the decision to close the study to further accrual, with completion of the 21 enrolled subjects as previously planned.

## 3. PATIENT SELECTION

### 3.1 Inclusion Criteria

3.1.1 Patients ≥ 18 years of age

3.1.2 Histologically confirmed **unresectable* colorectal adenocarcinoma metastatic to the liver** with no definitive clinical or radiographic evidence of extrahepatic disease.
Clinical or radiographic evidence of metastatic disease to peri-hepatic lymph nodes will be allowed, provided it is amenable to resection. Up to 5 lung metastases are allowable, provided they are stable (or responding) in number and size for a minimum of 2-months of systemic chemotherapy and are amenable to SBRT.

**(OR)**

Histologically confirmed **unresectable* intrahepatic cholangiocarcinoma**, with presence of less than 70% liver involvement.
Clinical or radiographic evidence of metastatic disease to peri-hepatic lymph nodes will be allowed, provided it is amenable to resection and there is no distant metastatic disease.

**The definition of resection is complex and consensus about resectability is typically made by a multi-disciplinary tumor board comprising hepatobiliary surgeons and radiology. Generally, a minimum of two contiguous liver segments are required in the future liver remnant, although substantially more liver volume may be required in the setting of pre-existing liver disease or extensive preoperative chemotherapy-related hepatocellular injury.*

3.1.3 ECOG Performance Status of 0 - 1 (**APPENDIX A**)

*3.1.4* Lab Values ≤ 14 days prior to study enrollment:
- absolute neutrophil count ≥1,500/mcL
- Total Bilirubin ≤ 1.5 mg/dL
- AST/ALT < 5 x institutional upper limit of normal (ULN)
- Platelets ≥ 100,000/mcL
- Creatinine < 1.5 mg/dL
- HGB ≥ 9 g/dL
- INR ≤ 1.5

3.1.5 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.6 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.7 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load

3.1.8 Prior chemotherapy is acceptable if last dose given ≥ 3 weeks prior to study enrollment.

3.1.9 Any investigational agent is acceptable if last dose administered ≥ 3 months before study enrollment.

3.1.10 Received a positive candidacy rating for HAIP chemotherapy as assessed by treating investigators via the modified Stanford Integrated Psychosocial Assessment for Transplant (mSIPAT; **APPENDIX B**).
Ratings indicating positive candidacy for HAIP Chemotherapy are as follows:
Patients with mSIPAT rating of "Excellent Candidate" are eligible
Patients with mSIPAT rating of "Good Candidate" are eligible

3.1.11 Eligibility status of patients rated "Minimally Acceptable Candidate for HAIP Chemotherapy" on the mSIPAT will be at the discretion of the treating investigators. Treating investigator confirmed eligibility of any patient who received a rating of "Minimally Acceptable Candidate" on the mSIPAT.

3.1.12 Patients with AXIOS™ stents (or similar) used to connect the small intestine to the gastric remnant after a prior gastric bypass for access for ERCP/stent in the setting of biliary obstruction are eligible at the discretion of the investigator. Considerations regarding eligibility comprise removal of the stent prior to HAIP implantation, or the placement of the HAIP catheter at least 5cm away from the AXIOS stent.

## 3.2 Exclusion Criteria

3.2.1 Presence of distant non-liver metastatic disease confirmed by radiographic evaluation. Clinical or radiographic evidence of metastatic disease to regional peri-hepatic lymph nodes will be allowed, provided it is amenable to resection.
For the colorectal carcinoma only: Up to 5 lung metastases are allowable, provided they are stable (or responding) in number and size for a minimum of 2-months of systemic chemotherapy and are amenable to SBRT.

3.2.2 Prior radiation to the liver, including external beam, SBRT, Y90. Prior radiation therapy to the pelvis is acceptable.

3.2.3 Active infection, hepatic encephalopathy

3.2.4 Clinical evidence of portal hypertension (ascites, gastroesophageal varices or portal vein thrombosis) are exclusions. Note that surgically-related ascites does not exclude the patient.

3.2.5 Female patients who are pregnant or lactating – or planning to become pregnant within 6 months after the end of the treatment (female patients of child-bearing potential must have negative pregnancy test prior to surgery)

3.2.6 If in the opinion of the treating investigator a patient has any serious medical problems which may preclude receiving this type of treatment

3.2.7 Patients with history or known presence of primary CNS tumors, seizures not well-controlled with standard medical therapy; Patients with a history of stroke within 3 months or with substantial residual deficit, based on investigator discretion

3.2.8 Serious or non-healing active wound, ulcer, or bone fracture

3.2.9 Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the HAIP chemotherapy (i.e., investigational regimen)

3.2.10 Rating of "Poor/High Risk Candidate" on the modified Stanford Integrated Psychosocial Assessment of Transplant (mSIPAT**; APPENDIX B**) as assessed by treating investigator

3.2.11 Patients with psychiatric illness or social situations that would limit compliance with study requirements. Examples include: active substance abuse, active severe ETOH abuse, etc.

3.2.12 Inability to reliably commit to traveling to Lexington, KY every 2 weeks for duration of the study treatment (6 months). Patient must have readily identifiable, reliable primary and back-up modes of transportation regardless of weather.

### 3.3 Inclusion of Women, Minorities and Children

There is no exclusion of patients based on sex, ethnicity or race. For these reasons, the study results are expected to be generalizable to the Medicare beneficiary population.

# 4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES

## 4.1 Protocol Review and Monitoring Committee and Institutional Review Board

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee (PRMC). Additionally, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, and UK IRB.

## 4.2 Investigator and Research Associate Registration with MCC

All investigators must be qualified by education, training and experience to assume responsibility for the proper conduct of human subject research. Investigators are responsible for being able to provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation and training per institutional, state and federal guidelines. All investigators conducting MCC trials will register with the MCC Clinical Research Office and complete all requisite training and registrations per MCC SOPs.

### 4.2.1 Delegation of Tasks Log (DTL)

All MCC studies require a Delegation Task Log which is maintained by the MCC Regulatory Unit of the Clinical Research Office.

The DTL for this study has training requirements as follows:
In order to be added to the DTL for a given study, each staff member must have appropriate training to conduct assigned duties including but not limited to protocol-specific training. The DTL log will identify the protocol version on which each staff member was trained when being added to a study.

The Principal Investigator and Co-Investigator are responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Principal Investigator, Co-Investigator and statistician have access to the study data at all times through OnCore. All decisions regarding dose modifications of HAI require consultation with the Principal Investigator.

## 4.3 Screening Guidelines

4.3.1 Overview

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be recruited from medical and surgical oncology clinics at the University of Kentucky Markey Cancer Center, with oversight by the Principal Investigator. The consenting professional will explain in detail the study to the patient and will review the informed consent with the patient (Section 4.4). Broadly, patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. A copy of the signed informed consent form is provided to the patient. Upon obtaining consent, study staff will register potentially eligible patients in the OnCore database. During the screening and enrollment process, registering individuals (study staff and PI) will be required to complete a protocol-specific Eligibility Checklist for each patient. The PI or treating physician signing the Eligibility Checklist is confirming whether or not the patient is eligible to enroll in the trial. Upon confirmation of eligibility, the patient will be enrolled into the study as participant (i.e., on-study date is entered in OnCore).

4.3.2 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject’s legally appointed

representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.3.3 Screening and Enrollment Guidelines

During screening for eligibility, the PI will complete the mSIPAT (modified Stanford Integrated Psychosocial Assessment for Transplant [1]- see **Appendix** B.1 for original and **Appendix B.2**, for the modified version). This screening questionnaire, completed by the primary investigator in consultation with the treatment team, yields a score of candidacy for pump implantation and HAI chemotherapy**.**

- mSIPAT Score corresponding to "Excellent Candidate" and "Good Candidate" will be considered optimal to proceed with baseline assessments for enrollment to the trial.
- mSIPAT Score corresponding to "Minimally Acceptable Candidate" will require review of risk factors and remediation plan until acceptable to the primary investigator.
- mSIPAT Scores corresponding to "Poor Candidate" and/or "High Risk Candidate" will be declined for trial participation.

Additional pre-treatment evaluation includes the following:

- Medical history, Physical Exam, Blood Pressure, Height / Weight: within 2 weeks prior to pump implantation surgery
- EKG: within 4 weeks prior to surgery
- Port-A-Cath placement: any time prior to surgery
- Imaging to determine arterial anatomy of the liver and suitability for HAI: CT Angiogram of the liver, or triphasic liver CT can be done up to 6 months prior to surgery to meet this requirement, provided no surgical interventions on the liver have taken place in the interim.
- Imaging to determine extent of disease and liver involvement: Contrast-enhanced CT scan of chest, abdomen, pelvis, must be done within 4 weeks prior to surgery. [If a CT C/A/P was done with a triphasic liver protocol or angiogram protocol, this will suffice as well for this requirement as long as the time (within 4 weeks) is appropriate. Please note that while CT is the preferred imaging modality, MRI may be necessary in certain situations. MRI is allowable on study, although the pump must be interrogated after MRI (since the motor is design to stall in the MRI magnet to avoid inadvertent bolus).
- Urine pregnancy test (female of child-bearing potential): prior to surgery
- ECOG performance status: within 2 weeks prior to surgery
- CBC with diff/platelets and CMP (albumin, BUN, creatinine, alk phos, AST, ALT, bilirubin): within 2 weeks prior to treatment start
- CEA (if CLM) or CA19-9 (if IHC); within 2 weeks prior to treatment start
- LDH: within 2 weeks prior to treatment start and every 2 weeks during treatment, as clinically indicated to assess liver dysfunction
- Viral serologies (hepatitis and HIV): these will be checked as clinically indicated among patients with known or suspected HIV/HBV/HCV to assess current viral load

### 4.4 Eligibility Confirmation and Enrollment

The following information should be reviewed by the Clinical Research Nurse (CRN) / Clinical Research Associate (CRA) with the study physician per MCC SOPs to confirm eligibility:

- Copy of required laboratory tests
- Pathology reports
- Physician dictations
- Imaging reports
- Signed patient consent form
- HIPAA authorization form
- Referring physician records as available
- Other required screening procedures when applicable
- Eligibility Checklist

Once eligibility is confirmed, the CRN/CRA will complete subject enrollment to the study in the OnCore database. To complete the enrollment process, the CRN/CRA will complete the OnCore on-study form, which comprises the following:

- Assignment of a patient study number
- diagnosis
- date of diagnosis
- histology
- entry of the On-Study date

### 4.5 Perfusion flow scan (TcMAA):

Perfusion flow scan is to be done after pump implantation surgery, before the patient is discharged from the hospital. Radiotracer is injected through the infusion port of the pump to assure the liver is evenly perfused and there is no extrahepatic perfusion. Extrahepatic perfusion must be addressed (usually by interventional radiology) prior to treatment.

### 4.6 General Guidelines

Issues that would cause delays in initiation of treatment (surgery or HAI or systemic chemotherapy administration) should be discussed with the Principal Investigator.

## 5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

| **Specimen Collection and Handling** | | |
|---|---|---|
| Research labs for correlative studies | • Blood specimens for analysis of FUDR plasma concentrations<br>• Blood specimens for gene polymorphisms using the PAXgene DNA extraction kit | Research labs are drawn by phlebotomists in clinic and sent to institutional central lab for processing and analysis |

### 5.1.1 Pharmacokinetics

We will build a population model for the pharmacokinetics of 5-FU, FUDR and FdUMP during systemic 5-FU combined with HAI FUDR:

In order to assess the relative contribution of HAI and systemic therapy:

- For HAI treatment: Plasma levels of FUDR, the active metabolite of 5-FU, will be measured at 2h after starting an infusion of HAI (Cycle 1 Day 1) and at the end of HAI treatment in Cycle 1 (specifically, Cycle 1 Day 15, prior to administration of systemic chemotherapy). At each timepoint collect 10mL whole blood into EDTA tube.
- Systemic chemotherapy: Plasma levels of FUDR will be measured immediately after a systemic bolus of 5FU or 2 hours after starting a systemic continuous infusion of 5-FU on Cycle 1 Day 15. At each timepoint collect 10mL whole blood into EDTA tube.

### 5.1.2 FUDR Levels and Gene Polymorphisms

5-FU, FUDR and FdUMP plasma concentrations will be evaluated in with a validated LC-/MS/MS assay as previously described [8]. Data will be analyzed by a nonlinear mixed-effects modeling approach using the NONMEM system (Version VI, NONMEM Project Group, UCSF/Globomax and PDx-Pop Version 3.1). Xpose4 and S-PLUS (Insightful Corp, Seattle, Washington) are used for goodness-of-fit assessment and model evaluation. Both intrahepatic and plasma administration will be simultaneously analyzed in the single model. In addition, polymorphisms in DYPD, TYMS and GSTP1 will be evaluated for association with adverse effects (toxicity) and clinical outcome (treatment response, conversion to resection).

- For polymorphism testing, collect one 8.5mL PAXgene DNA tube prior to initiation of HAI (FUDR administration) on Cycle 1 Day 1.

5.1.3 Summary Table for Specimen Collection

| Time Point | Specimen | Send Specimens To: |
|---|---|---|
| **Day 1 of Cycle 1: 5-Flouracil plasma concentrations and PBMCs for RNA** | | |
| | • 8.5mL blood in PAXGene DNA tube | BPTP |
| | • 10mL whole blood in EDTA | BPTP |
| **Day 15 of Cycle 1: 2 draws for 5-Flouracil plasma concentrations** | | |
| | • 10mL whole blood in EDTA at pump emptying (prior to initiation of systemic chemotherapy) | BPTP |
| | • 10mL whole blood in EDTA after initiation of the systemic chemotherapy administration (either immediately after a bolus infusion **or** 2 hours after starting a continuous infusion) | BPTP |

## 6. TREATMENT PLAN

### 6.1 Overview of Study Design / Intervention

A total of 34 patients will be enrolled for definitive treatment of unresectable CLM or unresectable non-metastatic intrahepatic cholangiocarcinoma. Patients will undergo surgical placement of the Medtronic pump connected to the Codman catheter. HAI FUDR will be given with disease-tailored systemic chemotherapy. The initial primary safety endpoint will be successful administration of one full cycle of HAI (C1D1 – 14). Additional safety, feasibility, and response data will be recorded and reported. We estimate an accrual rate of 1 patient a month.

| **Unresectable metastatic Colon Cancer** | | | | |
|---|---|---|---|---|
| | **Cycle 1** | | **Cycles 2-6** | |
| | HAI Mono Only | Systemic Only | Combo FUDR + Chemo | Systemic Only |
| HAI Pump[1] | FUDR + Dexamethasone<br>*(14-day infusion, D1-14)* | N/A<br>*(pump is emptied & refilled with Heparin+Saline)[2]*<br>*(14-day infusion, D15-28)* | FUDR, Dexamethasone, Heparin & Saline<br>(14-day infusion, D1-14) | N/A<br>*(pump is emptied, and refilled with Heparin+Saline)[2]*<br>*(14-day infusion, D15-28)* |
| SOC Systemic Chemo [3] | N/A | FOLFOX, FOLFIRI or Irinotecan/ Oxaliplatin<br>Given on Day 15, Per SOC | FOLFOX, FOLFIRI or Irinotecan/ Oxaliplatin<br>Given on Day 1, Per SOC | FOLFOX, FOLFIRI or Irinotecan/ Oxaliplatin<br>Given on Day 15, Per SOC |
| SOC targeting driver mutations (e.g., KRAS/ NRAS Wildtype, etc.) | N/A | FDA-approved agents (e.g., Panitumumab for EGFR)<br>Given per SOC | FDA-approved agents (e.g., Panitumumab for EGFR)<br>Given per SOC | FDA-approved agents (e.g., Panitumumab for EGFR)<br>Given per SOC |

1: The following HAI FUDR dosing will be used:
HAI FUDR [ (0.12 mg/kg/day) x wt (kg) x (20mL or 40mL depending on pump reservoir size implanted) X 0.9) ] / pump flow rate (1mL/day)
Dexamethasone [1 mg/day * (20mL or 40mL depending on pump reservoir size implanted)] / pump flow rate (1mL/day)

2: Patients who are allergic to heparin will receive Fondaparinux and saline in the pump instead.

3: Dosing of systemic therapy will be according to established routine practice guidelines. Thus, :
Patients with colon cancer will receive systemic chemotherapy that will consist of either FOLFIRI, FOLFOX, or Irinotecan/oxaliplatin at the discretion of the oncologist. Per current SOC guidelines, EGFR inhibitors targeting driver mutations (e.g., KRAS/NRAS wildtype) will be administered as appropriate.
- FOLFOX comprises FOLinic Acid (Leucovorin Calcium), Fluorouracil (5-FU) and OXaliplatin.
- FOLFIRI comprises FOLinic Acid (leucovorin calcium), Fluorouracil (5-FU), and Irinotecan.

| **Unresectable, non-metastatic Intra-hepatic Cholangiocarcinoma (IHC)** | | | | |
|---|---|---|---|---|
| | **Cycle 1** | | **Cycles 2-6** | |
| | HAI Mono Only | Systemic Only | Combo FUDR + Chemo | Systemic Only |
| HAI Pump[1] | FUDR + Dexamethasone<br><br>*(14-day infusion, D1-14)* | N/A<br><br>*(pump is emptied & refilled with Heparin+Saline)* [2] *(14-day infusion, D15-28)* | FUDR, Dexamethasone, Heparin & Saline<br><br>(14-day infusion, D1-14) | N/A<br><br>*(pump is emptied & refilled with Heparin+Saline)* [2]<br><br>*(14-day infusion, D15-28)* |
| SOC Systemic Chemo [3] | N/A | Gemcitabine or Gemcitabine/ Oxaliplatin, Per SOC<br><br>Given on Day 15, Per SOC | Gemcitabine or Gemcitabine/ Oxaliplatin<br><br>Given on Day 1, Per SOC | Gemcitabine or Gemcitabine/ Oxaliplatin<br><br>Given on Day 15, Per SOC |

1: The following HAI FUDR dosing will be used:
HAI FUDR [ (0.12 mg/kg/day) x wt (kg) x (20mL or 40mL depending on pump reservoir size implanted) X 0.9) ] / pump flow rate (1mL/day)
Dexamethasone [1 mg/day * (20mL or 40mL depending on pump reservoir size implanted)] / pump flow rate (1mL/day)

2: Patients who are allergic to heparin will receive Fondaparinux and saline in the pump instead.

3: Dosing of systemic therapy will be according to established routine practice guidelines. Thus, :
Patients with cholangiocarcinoma will receive Gemcitabine/Oxaliplatin or Gemcitabine alone at the discretion of the oncologist.

### 6.2 Implantation of Synchromed II infusion pump and Codman vascular catheter

All patients will undergo surgery to have the Medtronic Synchromed II pump and Codman vascular catheter placed before HAI therapy can begin. This procedure is a standard surgical procedure which involves an exploratory laparotomy, isolation of the gastroduodenal artery, and placement of the vascular catheter at the junction of the hepatic artery and gastroduodenal artery. During the procedure, the Medtronic pump is connected to the Medtronic connector as seen in **Figure 1**. The Medtronic connector will be cut **(Figure 2)** before the metal phalange at the end of the connector so the Codman catheter can then be connected to the cut end of the Medtronic connector **(Figure 3, 4)**. Silk ties will be used on both ends of the catheter to ensure the fit to the connection is secure.

**Figure 1:**

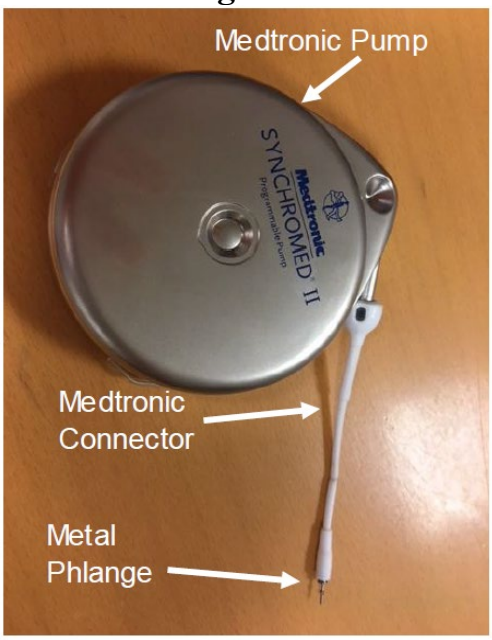



**Figure 2**:


**Figure 3:**

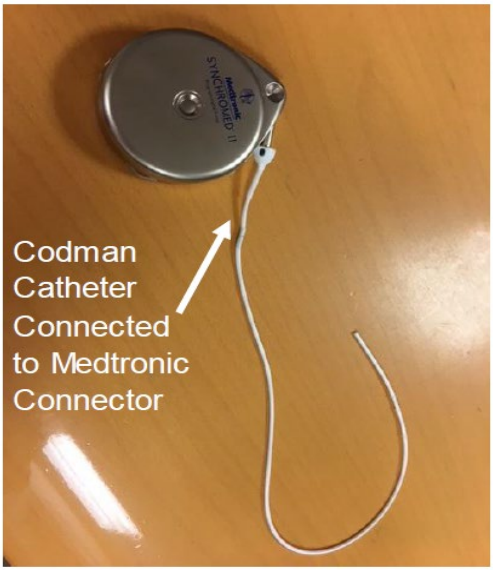
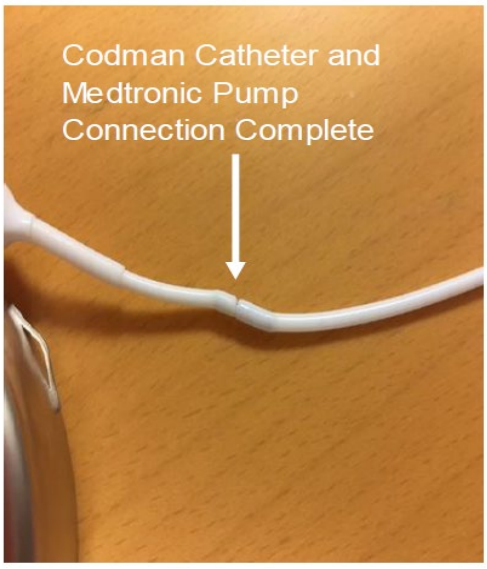



**Figure 4:**




Previously, the Codman pump only had one reservoir size available (20mL). In contrast, Medtronic Synchromed II pump offers two reservoir sizes, 20mL and 40mL. These models have identical pump mechanisms, and differ only in reservoir size, with no known differences in safety (personal communication, Medtronic). Patient preference and body habitus will be taken into account in deciding which reservoir to use, and the final decision will be at surgeon discretion.

Chemotherapy with HAI FUDR/dexamethasone will commence no sooner than 14 days after surgery, and only after a nuclear perfusion study (TcMAA) demonstrates appropriate hepatic perfusion and no extrahepatic perfusion. Any extrahepatic perfusion must be addressed prior to

commencement of chemotherapy; usually, this requires interventional radiology embolization of small side branches of the hepatic or gastroduodenal arteries.

On Day 1 of each Cycle, all patients will receive HAI FUDR [(0.12 mg/kg/day) x wt (kg) x (20mL or 40mL depending on which reservoir is implanted) X 0.9)/ pump flow rate (1ml/day)] and dexamethasone ([1 mg/day *20 or *40] / pump flow rate) on Day 1 of each cycle (1 Cycle = 28 days).

**Unresectable colorectal liver metastases**

- Patients will receive either FOLFIRI, FOLFOX, or Irinotecan/oxaliplatin (regimen determined at oncologist discretion; standard dosages) which will begin after the first cycle of HAI chemotherapy is completed (Day 15 of cycle 1) and then every Cycle Day 1 and Day 15. In addition, EGFR inhibitors may be administered for study patients with driver mutations (e.g., KRAS/NRAS wildtype) as appropriate per current SOC guidelines.
- CT C/A/P triphasic liver protocol every 2 months. A window of +/-14 days for scans is allowed in order to accommodate patient schedules.
- Treatment will continue for 6 months in the absence of toxicity or patient withdrawal. If the patient is responding at the completion of the study protocol, the patient will be assessed by a multidisciplinary tumor board for suitability for liver resection (if adequate downsizing has occurred) or continued HAI/systemic therapy off trial.
- If a patient becomes resectable at the 2- or 4-month imaging endpoint, they will not be resected unless they refuse further pump chemo or have a toxicity which prevents further pump chemo.

**Unresectable intrahepatic cholangiocarcinoma**

- Patients will receive Gemcitabine and Oxaliplatin or Gemcitabine alone (regimen determined at oncologist discretion; standard dosages) after the first cycle of HAI chemotherapy is completed (Day 15 of cycle 1) and then every Cycle Day 1 and Day 15.
- CT C/A/P every 2 months during treatment. A window of +/-14 days for scans is allowed in order to accommodate patient schedules.
- Treatment will continue for 6 months in the absence of toxicity or patient withdrawal. If the patient is responding at the completion of the study protocol, the patient will be assessed by a multidisciplinary tumor board for suitability for liver resection (if adequate downsizing has occurred) or continued HAI/systemic therapy.
- If a patient becomes resectable at the 2- or 4-month imaging endpoint, they will not be resected unless they refuse further pump chemo or have a toxicity which prevents further pump chemo.

### 6.3 Surgical Treatment Plan

Prior to the patient going into the Operating Room (OR) for surgery, the patient‘s surgeon will communicate with the OR staff to assure the appropriate materials (pump and catheter) are available for the selected date. The surgery to implant the Medtronic pump will be done at

University of Kentucky Albert B. Chandler Hospital, and is a same day admission. The surgery will be performed with the standard technique as has been employed at MSKCC and other

institutions for decades. Patients will undergo general anesthesia. The pump implantation is an open procedure. Pump implantation can be done at the same time as a colon resection for the primary tumor (for CLM). In addition, minor liver resection/ablation may be combined with pump placement as long as it is not done with the intent to entirely clear the liver of disease, rather, it is intended to clear the future liver remnant (i.e., minor resection/ablation of several left liver metastases with plans for possible future right hepatectomy and left liver as future liver remnant).

If extrahepatic metastatic disease (i.e., peritoneal carcinomatosis) is found in the operating room, the pump will not be implanted. The Medtronic pump will be sutured to the anterior abdominal fascia. The Codman catheter is inserted into the gastroduodenal artery. The Codman catheter will be cut at an appropriate length determined by the surgeon judging from the location of the pump in the abdominal wall (a right-sided pump has a shorter distance to the gastroduodenal artery compared to a left-sided pump). The Medtronic catheter will be fed onto one side of the metal Codman catheter connector. Next, the Codman catheter will be fed onto the other side of the metal Codman catheter connector. A permanent type tie using silk ties will be placed around the Codman catheter and the Medtronic catheter to add additional security to ensure both catheters are securely fastened to the Codman catheter connector. Finally, the pump will be flushed with dye once to demonstrate patency across the connection. The dye will allow any leaks in the connection to be visualized and corrected. The same technique has been used when connecting the Codman pumps and catheter with success.

If the patient has an AXIOS™ stent or similar in place (connecting the small intestine to the gastric remnant after a prior gastric bypass for access to the biliary tree for ERCP/stent in the setting of biliary obstruction), if this has not been removed prior to HAIP implantation, the entirety of the Codman catheter must be placed away from the AXIOS™ stent by at least 5cm in order to prevent catheter erosion into the bowel from pressure related to the AXIOS™ stent. The method for securing the catheter away from the stent will be at the discretion of the operating surgeon, but may including implantation of the pump on the right side of the abdominal wall, or by securing the catheter with sutures keeping the catheter away from the stent.

Post-operatively, the perfusion flow scan will be done to further ensure there are no leaks between the Medtronic pump and the Codman catheter and that perfusion is appropriate (liver only; no perfusion to stomach, duodenum, or other organs). Intra-abdominal bleeding during and after pump implantation surgery is a rare complication. If this were to occur, usually the bleeding would be able to be treated angiographically. After the patient‘s pump implantation surgery is deemed successful, the patient will be given a participant identification card. The patient will be instructed to keep this card with them at all times, and to present it to any external healthcare providers. The card states that the patient is participating in a clinical trial at the University of Kentucky, they have a Medtronic pump implanted in their liver, and it also gives study contact information so external providers can contact the UK treating physician at any time if they have questions or concerns.

### 6.4 HAI Chemotherapeutic Treatment Plan

For the first cycle, the dose of FUDR will be calculated based on the predetermined flow rate provided by the pump manufacturer. Thereafter, doses will be adjusted (lowered, if necessary, but never increased) based on actual observed flow rate. The pump will be filled with FUDR, Dexamethasone, heparin, and saline, prepared by the Investigational Drug Service (IDS).

**Dose calculation**:

**Heparin:** 25,000 units total dose
**Normal saline:** quantity sufficient to make total reservoir volume of either 20 mL or 40 mL, depending on which reservoir is implanted.

**FUDR**: $\frac{\textbf{0.12 mg/kg X kg (patient weight) X pump volume (20 or 40mL) x 0.9}}{\textbf{pump flow rate 1 ml/day}}$

***Overweight patients:*** If patient is 35% above ideal body weight, the dose of FUDR will be based on Ideal Average Weight, derived from Ideal weight (calculated) and actual measured/observed weight, as follows:

Calculate ideal weight (kg) with these formulas:

*Males*: 50 kg + (2.3 x height in inches above 5 ft) = ideal weight
*(i.e., for a patient who is 5‘10‘‘, use 10)*

*Females*: 45.5 kg + (2.3 x height in inches above 5 ft)

Example: An overweight male is 106 kg and 5‘11‘‘:
50 kg + (2.3 x 11) = 50 + 25.3 = 75.3 kg is the Ideal Body Weight
An overweight female is 80 kg and 5’8
45.5 kg + (2.3 x 8) = 45.5 + 18.4 = 63.9 kg is the Ideal Body Weight

Use calculated Ideal Weight to calculate Ideal Average Weight (kg) as follows:

$$\frac{\text{Actual weight + Ideal Body Weight}}{2}$$

Using the overweight male example, 106 kg and 5’11’ his Ideal Average Weight is 90.65 kg
106 kg + 75.3 = 181.3 181.3/2 = 90.65 kg
Using the overweight female example, 80 kg and 5’8’ her Ideal Average Weight is 71.95 kg
80 kg + 63.9 = 143.9 143.9/2 = 71.95 kg

Use the Ideal Average Weight to calculate the FUDR dose in patients who are overweight. If the PI feels the patient is an appropriate weight, the Ideal Average Weight equation should not be used and patients can have the regular dose calculation of FUDR.

**Pump Flow Rate:** 1 ml/day. The pump will be filled with FUDR, Dexamethasone, heparin, and saline on Day 1 of each Cycle. The pump will be filled with heparin and saline on Day 15 of each Cycle. One Cycle of treatment is equal to 28 days.

On Day 15, the pump will be emptied and then filled with 25,000 units of heparin in normal saline (q.s. 20-40cc depending on reservoir size) for 14 days. In the event that there is an unexpected amount (more or less) of the FUDR mixture left in the pump on Day 15, it could be an indication that the connection is leaking. If this is suspected, the patient will undergo further evaluation immediately.

## 6.5 Laboratory Criteria for Treatment

Before beginning the first cycle of therapy, patients must meet all hematologic and blood chemistry criteria outlined in Section 3.0.

Once a patient is on-study, for all subsequent cycles of therapy, the following criteria apply:

- ANC ≥ 1.0 K/uL
- AST/ALT < 5 x ULN
- Platelet count ≥ 75 K/uL
- Creatinine ≤ 1.8 mg/dL
- Bilirubin < 1.5 mg/dL

If counts are outside these levels on date of scheduled treatment for ANC, platelet count and creatinine, therapy will be delayed until the value meets the listed parameter at the discretion of the treating physician (Section 7.2). For elevations in AST, ALT or bilirubin, a hold of at least 1 week must take place with Dose Modifications delineated in Section **7**. Note that standard of care systemic chemotherapy regimens also have dose modification/hold parameters based on laboratory values, which in some cases are more stringent.
Parameters for treatment with FUDR via intrahepatic pump are outlined below.

## 6.6 Evaluation during Treatment, Adherence to Treatment and Long-Term Follow-up and Pump Management

While being treated with protocol therapy, patients will be seen at or prior to the first day of each cycle by their medical oncologist, and additionally as clinically indicated, in the case of abnormal liver function tests necessitating alterations in the treatment plan.

Patients will be assessed for adverse events prior to administration of systemic chemotherapy or HAI.

Patients will have an end-of-treatment assessment for toxicity, 30-days after the last dose of chemotherapy (be it systemic or HAI FUDR).

6.6.1 All reasonable efforts will be made to adhere to treatment and evaluation schedules, however minor infrequent variations to accommodate holidays, transportation issues, or patient‘s personal schedule will be permitted if these do not, in the opinion of the investigator, constitute a major safety or compliance issue. Such variations, assuming they do not occur with unreasonable frequency or regularity, will not be considered protocol deviations. The only exception to this is emptying the pump in 14 days or less (with a window of +/- 3 days). Once pump is filled with drug, it must be emptied in 14 days or less because exceeding this window would pose a serious safety risk to the patient.

6.6.2 If patients are treated on trial and eventually undergo complete resection to no evidence of disease, there remains high risk for recurrence, and the pump should typically remain in place for 2 years. During the time when a patient is no longer receiving HAI therapy, and waiting to be declared disease-free at 2 years, the patient will need to come to clinic once every 2 weeks to have the 20mL pump filled with heparinized saline (this is once every 4 weeks if the 40mL pump was placed). If the patient is still disease-free at the 2-year mark, the pump can then be removed (outpatient surgery). Even in cases where the pump can be removed from the patient, the catheter remains inside the patient just underneath the abdominal wall. If a patient progresses on pump therapy, and the pump is no longer deemed useful, it will be removed. This requires an outpatient surgery. The subcutaneous pump pocket is opened. The catheter is tied and cut, leaving the catheter under the abdominal wall fascia. The pump is then removed.

6.6.3 HAI therapy responses in unresectable CLM and IHC patients typically show response in the first 3-4 months. These patients will stay on treatment until the completion of the study period (6 months). At this point there are three possibilities:

- Their disease has shrunk to a size that qualifies them for resection
- Their disease has progressed, and a new treatment regimen needs to be started
- The patient decides to no longer receive treatment for their cancer

Should a patient become resectable during the long-term follow-up period, surgical resection may be considered if deemed appropriate by multi-disciplinary tumor board and at the treating surgical oncologist’s discretion.

### 6.7 General Concomitant Medication and Supportive Care Guidelines

At the start of therapy, an assessment of all medications (e.g., concurrent use of other drugs, over-the-counter medications or alternative therapies) is conducted for interactions, coordinated by pharmacy per standard of care. At subsequent clinic visits, medication reconciliation is conducted (i.e., new medications will be reviewed if started) per standard of care.

## 6.8 Duration of Therapy

In the absence of treatment delays due to adverse event(s), HAI/systemic chemotherapy treatment will continue for 6 cycles (6 months) or until one of the following criteria applies:

- Disease progression, assessed by standard of care, and defined as
    - progression of liver lesions from baseline by RECIST v1.1 criteria
    - development of new metastatic lesions

  Patients will be discontinued from HAI treatment only after multi-disciplinary tumor board review consensus that HAI is no longer beneficial
- Intercurrent illness that prevents further administration of treatment including inability to resume hepatic arterial FUDR due to hepatic toxicity or unacceptable toxicity that does not respond to the dosage modification.
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

The reason(s) for discontinuation of protocol therapy, and the corresponding dates must be documented in the Case Report Form (CRF).

All patients will be followed for both toxicity and safety of the Medtronic pump and Codman catheter. Once patients discontinue standard systemic chemotherapy as listed in this protocol, they will only be followed for safety of the Medtronic pump and Codman catheter. Monitoring for safety will include a record of pump residual every 2 weeks for 20 mL pump (every 4 weeks for 40 mL pump) to determine if the pump is still working and surveillance of routine scan reports for any sign of a pump catheter disconnect. This is to ensure that toxicities of future treatments are not captured as a part of this study. Patients will continue to be monitored for the safety of the pump/catheter combinations as long as the pump remains implanted in the patient.

## 6.9 Duration of Follow-Up

Patients will be followed for safety of the pump/catheter and survival status up to three years post-therapy initiation or until death, whichever occurs first.

Patients removed from the study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients who have their HAI pump removed will also be followed for survival for up to three years post-therapy initiation.

# 7. DOSING DELAYS/DOSE MODIFICATIONS

## 7.1 Systemic Chemotherapy Dose Modifications

If patients have delays in treatments due to hospitalization or other reasons, once recovered they should proceed with treatment as scheduled.

Patients who experience *grade 3 or 4 toxicity* may continue treatment at a lower dosage level once toxicities have fully resolved (refer to tables below). Toxicity should typically resolve within two weeks. If the physician feels the patient cannot tolerate systemic therapy, they can hold therapy for one week. If the patient has elevated liver function tests in the PI's discretion, systemic therapy can be held and Decadron can be placed in the pump with heparinized saline.
Guidelines for re-starting systemic therapy are listed in the tables below.

## 7.2 Hematologic Toxicities

**Section 3.0** details standard hematologic criteria for study eligibility before beginning the systemic therapy.

For subsequent systemic therapy, patients must meet criteria in **Section 6.5** for the full doses of systemic therapy:
If counts are outside these levels on the date of scheduled treatment, therapy will be held until counts are within the range specified in Section 6.5 and resumed at the discretion of the treating investigator with the appropriate dose modifications as listed below (hematologic parameters only).

Bloodwork should be monitored at subsequent cycles, and if necessary, doses should be reduced according to the table below. Patients will continue on reduced dose and can be reduced further according to the treating investigator. Once patient has been reduced they do not need further reduction unless the treating investigator feels the patient cannot tolerate therapy without further reduction.

### 7.2.1 Dose Reduction for Hematologic Toxicities:

| CTCAE Grade | Toxicity | Irinotecan, 5FU, or Leucovorin | Gemcitabine or Oxaliplatin |
|---|---|---|---|
| 3 | Neutropenia | 20% decrease | 25% decrease |
| 4 | Neutropenia | 30% decrease | 40% decrease |
| 3 | Febrile Neutropenia [a] | 20% decrease | |
| 4 | Febrile Neutropenia [a] | 30% decrease | |
| 3 | Thrombocytopenia | 20% decrease | |
| 4 | Thrombocytopenia | 30% decrease | |

[a] Febrile Neutropenia = ANC, 1.0 X $10^9$/L with fever ≥ 38.5°C

### 7.3 Dose Reduction for Non-Hematologic Toxicities

| CTCAE Grade | Toxicity | Irinotecan | 5FU Infusion | Leucovorin | Gemcitabine | Oxaliplatin |
|---|---|---|---|---|---|---|
| **≥ 2** | **Cardiac toxicity** | No dose reduction | Stop Rx | Stop Rx | See below | See below |
| 3 | **Nausea and/or vomiting** despite pre-medication w/ an effective antiemetic | 20% Decrease | 20% decrease | 20% decrease | see below | see below |
| 3 | **Diarrhea** despite pre-medication w/ an effective antidiarrheal | 20% Decrease | 20% decrease | 20% decrease | see below | see below |
| 4 | **Nausea and/or vomiting** despite pre-medication w/ an effective antiemetic | 30% Decrease | 30% decrease | 30% decrease | see below | see below |
| 4 | **Diarrhea** despite premedication w/an effective antidiarrheal | 30% Decrease | 30% decrease | 30% decrease | see below | see below |
| 3 | **Stomatitis** | No dose Reduction | 20% decrease | 20% decrease | see below | see below |
| 4 | **Stomatitis** | No dose Reduction | 30% decrease | 30% decrease | see below | see below |
| 3 *or* 4 | **Hand/foot skin reaction** | No dose reduction | 20% decrease | 20% decrease | see below | see below |
| 3 *or* 4 | **Any non- hematologic toxicity** | N/A | N/A | N/A | 25% decrease to 600 mg/m$^2$ for 1$^{st}$ occurrence and subsequently, reduce to 400 mg/m$^2$ for 2$^{nd}$ occurrence | 25% decrease to 64 mg/m$^2$ |

#### 7.3.1 Guidelines for Diarrhea Management

- Symptoms of diarrhea and/or abdominal cramping may occur at any time and should be managed according to standard institutional practice.
- Subjects should also be instructed to notify the investigator or nurse for the occurrence of bloody or black stools
- Subjects should notify the investigator or nurse for symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline or Grade 1) within 24 hours.
- Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.

7.3.2 Oxaliplatin Dose Modification for Neurological Toxicities

| **Symptom** | **< 7 Days** | **Persistent for 2 weeks** |
|---|---|---|
| Dysesthesias with cold | No change | No change |
| Paresthesias | No change | 25% decrease |
| Paresthesias with numbness | 1st time: 25% decrease<br>2nd time: 25% decrease | Stop Discontinue permanently |
| Paresthesias with functional impairment | Stop | Stop |

***Note:*** If pseudo-laryngopharyngeal dysesthesia occurs, the next dose of oxaliplatin should be administered as a six-hour infusion. Subsequent oxaliplatin infusions should be administered as six-hour infusions, or shorter as tolerated.
Patients who experience grade 3 or 4 toxicity may, at the discretion of the investigator, continue treatment at a lower dosage level once toxicities have fully resolved (Grade 1 or baseline).
At the discretion of the investigator, patients may start with oxaliplatin and, if necessary, discontinue the drug (because of neuropathy or other oxaliplatin related toxicities) and continue with systemic Gemcitabine alone. This will not remove the patient from protocol and is intended to avoid significant ongoing neuropathy.

7.3.3 Gemcitabine/Oxaliplatin Dose Modification Considerations

At the discretion of the investigator, patients can be held 1 week and resume at reduced dose as per the tables above. Laboratory evaluation of renal and hepatic function, including transaminases and creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine should be administered with caution in patients with evidence of significant renal or hepatic impairment (as determined by the treating investigator) as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

7.3.4 Dose Adjustments for EGFR Inhibitors (e.g., Panitumumab)

Dosing: Renal Impairment: Adult
There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Hepatic Impairment: Adult
There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).

Dosing: Adjustment for Toxicity: Adult
Infusion reactions, mild-to-moderate (grade 1 or 2):
Reduce the infusion rate by 50% for the duration of infusion.
Infusion reactions, severe (grade 3 or 4):
Stop infusion; consider permanent discontinuation (depending on severity or persistence of reaction).

Dermatologic toxicity:

Grade 3 toxicity (first occurrence):

Withhold 1 to 2 doses; if reaction improves to <grade 3, resume therapy at initial dose.

Grade 3 toxicity (second occurrence):

Withhold 1 to 2 doses; if reaction improves to <grade 3, resume therapy at 80% of initial dose.

Grade 3 toxicity (third occurrence):

Withhold 1 to 2 doses; if reaction improves to <grade 3, resume therapy at 60% of initial dose.

Grade 3 toxicity (fourth occurrence), grade 3 toxicity that does not recover to <grade 3 after withholding 1 or 2 doses, or grade 4 toxicity: Permanently discontinue.

Ocular toxicity (acute or worsening keratitis): Interrupt or discontinue treatment.

Pulmonary toxicity:

Acute onset or worsening pulmonary symptoms: Interrupt treatment.

Interstitial lung disease: Permanently discontinue treatment.

### 7.4 FUDR Dose Modifications for Liver Toxicity

To determine if a FUDR dose modification is necessary, compare reference value to either the value obtained on the day pump was emptied (e.g., day 14) or the value obtained on the day of planned pump filling (e.g., day 28), whichever is higher.

| **FUDR DOSE MODIFICATION SCHEMA:** | | |
|---|---|---|
| ***Toxicity*** | ***Reference Value **** | ***% FUDR dose ***** |
| **AST** (*at pump emptying or day of planned retreatment, whichever is higher*) | 0 to < 2 x reference value | 100% |
| | 2 to < 3 x reference value | 80% |
| | 3 to < 4 x reference value | 50% |
| | ≥ 4 x reference value | **Hold** |
| **ALK PHOS ***** (*at pump emptying or day of planned retreatment, whichever is higher)* | 0 to < 1.2 x reference value | 100% |
| | 1.2 to < 1.5 x reference value | 50% |
| | ≥ 1.5 x reference value | **Hold ***** |
| **TOTAL BILI ***** *(at pump emptying or day of planned retreatment, whichever is higher)* | 0 to < 1.2 x reference value | 100% |
| | 1.2 to < 1.5 x reference value | 50% |
| | ≥ 1.5 x reference value | **Hold ***** |

* Reference Value: defined as the value obtained on the first day of the most recent FUDR dose. For laboratory values below the upper limit of normal (ULN), fold change should be calculated only once the reference value is above the ULN, i.e. changes that occur and remain within the normal range should not result in dose reductions/holds. If the prior value is below the ULN and the new value is above, fold change should be calculated from the ULN.

** FUDR Dose: percentage of last dose of FUDR administered.

If AST ≥ 4X reference value, alkaline phosphatase ≥1.5X reference value, total bilirubin ≥ 1.5X reference value, then treatment will be held and will not be reinstituted until values come down to more normal levels, as indicated in section below, 'Recommencing FUDR Treatment After Hold.'

*** If a patient's Alkaline Phosphatase or Total Bilirubin shows a continual rise from Day 1 of treatment, then the Day 1 value will be used as the reference value for that patient when determining whether to hold treatment, and time of re-treatment after hold.

| **RECOMMENCING TREATMENT AFTER HOLD** | | |
|---|---|---|
| **Reason for treatment delay** | **Chemotherapy resumed when value has returned to:** | **% FUDR dose** |
| AST elevation | 3 X reference value | 25% of last dose |
| Alkaline Phosphatase elevation | 1.2 X reference value | 25% of last dose |
| Total bilirubin elevation | 1.2 X reference value | 25% of last dose |

If patient develops a **total bilirubin ≥3.0 mg/dl**, the pump should be emptied and Dexamethasone 20 mg plus heparin 25,000 units and saline 20 cc placed in the pump every 14 days. Once there is no longer evidence of toxicity, Dexamethasone dose should be tapered in increments of 5 mg every 14 days. Tapering will continue unless enzymes increase.

FUDR should be permanently discontinued unless there is evidence of disease progression (increasing CEA, worsening CT scan, worsening clinical status) AND bilirubin has returned to ≤1.5 mg/dl. In this case, FUDR can be restarted as follows: Use 25% of the last FUDR dose given with Dexamethasone, heparin and saline in the pump for 7 days. Pump should be emptied after 7 days, and patients given a 3-week rest period. This treatment and treatment schedule should continue as long as bilirubin remains ≤1.5 mg/dl and liver enzyme values do not increase.

If a patient **presents with abdominal pain**, HAI FUDR should not be given and, if the pump is already filled with FUDR, the FUDR should be emptied immediately. Epigastric pain unresponsive to oral H2 blocker use is suggestive of gastroduodenal irritation or ulcer. Severe pain should prompt workup with an upper gastrointestinal endoscopy. Serum amylase should be checked along with the routine blood (screening profile, creatinine, and CBC) in patients with abdominal pain. If an ulcer or gastroduodenitis is documented, therapy should be held for one month to allow healing. If abdominal pain is severe, the pump should be emptied of FUDR until results of workup are available.

If patients have **delays in FUDR treatment**, the cycle numbering will go as follows:

- 2 systemic treatments = 1 cycle
- If patients return for FUDR and the liver function tests (AST, alkaline phosphatase and/or bilirubin are too elevated, as in table 10.4.4) patients will wait one to two weeks. If they are still elevated, patients will start the next cycle with systemic and not with FUDR. During that cycle if the liver function tests come down enough (according to Table *Recommencing Treatment After Hold*), patients will be able to receive FUDR again at a lower dose. In that case, they can receive the FUDR, then two weeks later they will receive systemic once afterwards and then move onto the next cycle.

- If liver function tests are too high for a patient to receive FUDR, they may continue on study treatment with systemic chemotherapy for a total of 11 systemic treatments. In this case, the patient will be treated with systemic treatment on Day 1 and on Day 15, then move onto the next cycle starting with Day 1.

If any of the following occur, patients will not receive HAI but will be monitored as below:

- Patient needs to have the Medtronic pump and Codman catheter removed due to post-operative infection. These patients will be monitored until resolution of the infection. These patients will be counted as failure to meet the primary endpoint of the study if they do not receive first cycle of HAI.
- HAI implantation fails due to technical issues such as inadequate artery for implantation found at time of surgery. These patients will be monitored for post-operative recovery and resolution of any complications. These patients will NOT be counted as failure to meet the primary endpoint of the study and will be replaced.
- Patient experiences complications during surgery that does not allow the pump to be implanted or experiences a complication at surgery that does not allow HAI treatment to begin. Patient will be monitored through routine recovery from surgery and resolution of any postoperative complications. These will be evaluated on a case-by-case basis by the investigator as to whether to consider as failures to meet the primary endpoint. For example, an unavoidable complication such as an enterotomy with spillage (resulting in non-placement of pump) from adhesions from prior surgery should not be counted as a failure related to pump safety, whereas technical safety issues related to the implantation of the device combination such as intraoperative catheter complications may be (such as arterial dissection caused by catheter).
- Patient has extensive liver dysfunction from the HAI implantation surgery and cannot get HAI treatment. Patient will be monitored through routine recovery from surgery and resolution of any postoperative complications. These patients will be counted as failure to meet the primary endpoint of the study.
- Extrahepatic disease is found at the time of surgery and a pump is not placed. Patient will be monitored through routine recovery from surgery and resolution of any postoperative complications. These patients will NOT be counted as failure to meet the primary endpoint of the study and will be replaced.

## 8. DEVICE AND PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial devices and agents administered in this study can be found in Section 10.1.

### 8.1 Drug Ordering and Accountability

*8.1.1 Procurement of medications:*

Prescriptions for medications will be written by the site PI, treating physician, preferably the medical oncologist, using study-approved standardized Markey Cancer Center chemotherapy order sets. The University of Kentucky Investigational Drug Service will review and approve

these orders per published polices. IDS will order and dispense FUDR during the treatment phase of this trial. All commercial agents will be dispensed as per routine institutional guidelines.

*8.1.2 Storage & Drug Accountability:*
All commercial agents used in this study will be stored per package insert and institutional guidelines.

## 8.2 Infusion Pump and Catheter

### 8.2.1 Codman Tapered Pump Catheter

The Codman Pump Catheter originally approved as a component of the Codman 3000 Infusion Pump (P890055), is designed to be connected to the Codman 3000 Implantable Pump. The pump catheter is made of medical-grade silicone elastomer impregnated with a radiopaque material. The catheter has a length of 30 inches; the inner diameter is 0.025 inches; the outer diameter is 0.090 inches. The catheter is supplied with a connector. The straight catheter connector ends are designed to be connected into the pump catheter and silicone extension tubing from the pump.

Specifications: IP-37957 Codman 3000 series tapered silicone rubber catheter (radiopaque) with connector. Length= 51.7 cm. Volume= 0.003 mL/cm.

### 8.2.2 Medtronic SynchroMed II Programmable Implantable Infusion Pump

Medtronic SynchroMed II Pump is a programmable drug delivery system that stores and delivers infusion treatment. This pump device/reservoir is placed subcutaneously with the catheter implanted in the target organ. This pump is currently used predominantly for pain indications, with the catheter tip in the intrathecal space. A previous generation of the pump had FDA indicated for HAI, but the manufacturer has not sought indication for the current model due to lack of market share when the Codman pump was available.

Current FDA Indications:

- Chronic infusion of Lioresal Intrathecal (baclofen injection) for the management of severe spasticity of spinal or cerebral origin
- Chronic intrathecal or epidural infusion of sterile, preservative-free morphine sulfate for chronic, intractable pain of malignant and/or non-malignant origin.
- Chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain

Specifications: Medtronic Model 8637 Synchromed II programmable implantable infusion pump (20 mL and 40 mL reservoirs); 8578, Sutureless pump connector revision kit. Length= 7.6 cm. Volume=0.0022 mL/cm.

Safety features that the pump includes is smart software that helps guide the clinician through programming the system via informational and warning screens. The pump has critical alarms that are triggered if the reservoir is empty, the pump is at the end of service, the motor stalls or if the pump has a critical memory error.

### 8.2.3 Connecting the pump & catheter:

The Medtronic pump catheter will be sharply cut and the metal Codman connector will be used to splice the Codman catheter to the Medtronic catheter. This connector and splicing technique has been used extensively (>20 years) at MSKCC with the previous Medtronic pumps. Two ties will be used to ensure the splicing technique is durable.

## 8.3 Commercial Chemotherapeutic Agents

### 8.3.1 Floxuridine (FUDR)

Floxuridine (FUDR) is an antimetabolite that blocks the methylation of deoxyuridylic acid, interfering with the synthesis of DNA. It is also incorporated into RNA and interferes with its functions. The drug is metabolized in the liver, and will be delivered via HAI.
FUDR is commercially available from Roche and Adria Laboratories in 500mg/10cc ampules.
It is stable (protected from light) and is a colorless aqueous solution. Store at room temperature.

### 8.3.2 DEXAMETHASONE

Dexamethasone is an adrenocortical steroid, used for chronic inflammation, neoplastic and autoimmune diseases; used in HAI treatment as an agent to prevent biliary toxicity.
Dexamethasone is commercially available in various concentrations as a solution for injection: 4 mg/mL (1 mL); 20 mg/5 mL (5 mL); 120 mg/30 mL (30 mL); 10 mg/mL (1 mL); 100 mg/10 mL (10 mL). The solution must be protected from light, heat, and freezing. It should be stored at room temperature.

### 8.3.3 GEMCITABINE

Gemcitabine is a pyrimidine analogue of deoxycytidine in which the deoxyribose moiety contains 2 fluorine atoms at the 2‘-position. The drug acts as an inhibitor to ribonucleotide reductase and inhibition of DNA synthesis may result in perturbations of deoxynucleotide pools and interference with DNA chain elongation. The drug is cell-cycle specific and blocks cells in the G1/S interface. Cytotoxicity is schedule-dependent and increases with duration of exposure. The drug is rapidly eliminated from plasma, owing mainly to deamination. Renal clearance of drug is less than 10% of parent drug.
The drug is commercially available and supplied as either a 200mg or 1 gram lyophilized powder in a 50 mL sterile single vial for reconstitution. The drug is administered via a freely-running intravenous catheter per institutional guidelines. Solutions prepared/diluted for infusion in NS are stable for 24 hours at room temperature. Do not refrigerate (may result in crystallization). Prolongation of the infusion time > 60 minutes has been shown to increase toxicity. For labeled indications, infuse over 30 minutes.

### 8.3.4 OXALIPLATIN

Oxaliplatin functions as an antineoplastic agent by forming platinum-DNA adducts which, if not excised, will prevent further DNA synthesis and/or transcription and thereby lead to cell death. Oxaliplatin is commercially available from the manufacturer.

The freeze-dried powder is reconstituted by adding 10 to 20 mL (for the 50-mg vials) or 20-40 mL

(for the 100-mg vials) of water for injection or 5% glucose solution and then by diluting in an infusion solution of 250 mL or 500 mL of 5% glucose solution. The reconstitution or final dilution must never be performed with a sodium chloride solution.

Do not combine with alkaline medications or media (such as basic solutions of 5-FU, trometamol) which cause Oxaliplatin to degrade. Do not use for the preparation of administration needles or intravenous infusion sets containing aluminum items (risk of degradation of Oxaliplatin upon contact with aluminum).

The compound may be stored (in the form of freeze-dried powder for two years at room temperature protected from light. Reconstituted solution: Solutions diluted in D5W for infusion are stable up to 6 hours at room temperature of 20°C to 25°C (68°F to 77°F) or up to 24 hours under refrigeration at 2°C to 8°C (36°F to 46°F).

Administer as IV infusion over 2 hours; extend infusion time to 6 hours for acute toxicities. Flush infusion line with D5W prior to administration of any concomitant medication. Avoid ice chips, exposure to cold temperatures, or consumption of cold food/beverages during or within hours after oxaliplatin infusion (may exacerbate acute neurological symptoms). Do not use needles or administration sets containing aluminum. When used in combination with a fluoropyrimidine (e.g., 5-FU), infuse oxaliplatin first.

### 8.3.5 IRINOTECAN

Irinotecan (CPT-11) is a semi-synthetic derivative of camptothecin that possesses greater aqueous solubility, greater in vitro and in vivo activity, and is associated with less severe and more predictable toxicity than camptothecin. Both camptothecin and CPT-11 are potent inhibitors of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription.

Irinotecan is commercially available and will be diluted with 250 ml of 5% Dextrose (D5W) and infused intravenously over 90 minutes. Nothing else should be added to the infusate. No other diluent is to be used.

Irinotecan vials must be stored in a cool, dry place, protected from light. Irinotecan is relatively stable against heat and light but becomes slightly unstable against light in aqueous solution. It is stable for at least three years at room temperature. Irinotecan is stable for at least 24 hours in glass bottles or plastic bags when mixed with D5W.

### 8.3.6 FLUOROURACIL

An antimetabolite and pyrimidine analog which acts as thymidylate synthase inhibitor and interrupts the actions of enzyme by blocking synthesis of thymidine, required in DNA replication. It will be administered by MCC guidelines.

Fluorouracil is commercially available as a 1g/20mL solution for reconstitution. Store intact vials at room temperature. Do not freeze. Protect from light.

Syringes and solutions diluted for infusion may be stored for up to 4 hours (at room temperature) prior to administration (according to the manufacturer). Fluorouracil 50 mg/mL in NS was stable in polypropylene infusion pump syringes for 7 days when stored at room temperature. Stability of fluorouracil 1 mg/mL or 10 mg/mL in NS or D5W in PVC bags was demonstrated for up to 14

days at 4°C (39.2°F) and 21°C (69.8°F).

Stability of undiluted fluorouracil (50 mg/mL) in ethylene-vinyl acetate ambulatory pump reservoirs was demonstrated for 3 days at 4°C (39.2°F) (precipitate formed after 3 days) and for 14 days at 33°C (91.4°F). Stability of undiluted fluorouracil (50 mg/mL) in PVC ambulatory pump reservoirs was demonstrated for 5 days at 4°C (39.2°F) (precipitate formed after 5 days) and for 14 days at 33°C (91.4°F). Follow USP 797 recommendations for beyond use dates based on the level of risk for preparation.

### 8.3.7 LEUCOVORIN CALCIUM (FOLINIC ACID)

Leucovorin calcium is a stable reduced formyl derivative of tetrahydrofolic acid and the active form of folic acid. It aids in the binding of fluorouracil to enzyme thus enhancing its activity profile.

Leucovorin is commercially available as a 350mg, 200mg, 100mg, and 50mg vials for reconstitution.

Reconstitute with sterile water and dilute in D5W or NS for infusion.

Due to calcium content, do not administer IV solutions at a rate >160 mg/minute; not intended for intrathecal use. Fluorouracil is usually given after, or at the midpoint, of the leucovorin infusion. Leucovorin is usually administered by IV bolus injection or short (10-120 minutes) IV infusion. Other administration schedules have been used; refer to individual protocols.

### 8.3.8 Panitumumab

Panitumumab is a recombinant human IgG2 monoclonal antibody which competitively inhibits EGFR. EGFR is a transmembrane glycoprotein that is constitutively expressed in normal epithelial tissues but is over-expressed in colorectal cancer. When bound by its normal ligands there is a cascade of intracellular protein activation that ultimately leads to transcription of genes involved with cellular growth, survival, motility, and proliferation. Binding of panitumumab prevents receptor autophosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, decreased proinflammatory cytokine and vascular growth factor production, and internalization of the EGFR. Normal signal transduction in the EGFR pathway results in activation of the wild-type KRAS and NRAS proteins. However, in cells with activating *KRAS* and *NRAS* mutations, the mutant proteins are constitutively active independent of EGFR regulation; therefore, panitumumab is only indicated in patients with *KRAS* and *NRAS* wild-type disease.

Panitumumab is commercially available as a 100g/5mL and 400mg/20mL vial. It will be diluted with 100mL of NS and infused over 60 minutes for the first dose and 30 minutes for subsequent doses through a 0.22 micron filter. Flush line with NS before and after infusion; do not mix or administer with other medications. Reduce infusion rate by 50% for mild to moderate infusion reactions (grades 1 and 2); stop infusion for severe infusion reactions (grades 3 and 4) and consider permanent discontinuation

Store intact vials in the original carton at 2°C to 8°C (36°F to 46°F) until the time of use. Do not

freeze; do not shake. Protect from direct sunlight. Solutions diluted in NS for infusion should be used within 6 hours of preparation if stored at room temperature or within 24 hours of dilution if stored at 2°C to 8°C (36°F to 46°F); do not freeze.

# 9. STATISTICAL CONSIDERATIONS

## 9.1 Study Design

A one-arm, Phase 1 pilot trial is proposed to estimate the primary endpoint of safety (defined as successful completion of one full cycle of HAI chemotherapy (FUDR) via the combination of the Codman tapered vascular catheter with the Medtronic SynchroMed II implantable infusion pump). The operational definition of safety is described in Section 1.1 (Primary Objective).

## 9.2 Sample Size Justification

A sample of 34 patients provides an exact, two-sided 90% confidence interval with a width equal to 0.25 when the success rate of completion is assumed to be 80%. The lower and upper limits of the 90% confidence interval for successful completion rate are 0.65 and 0.90, respectively.

## 9.3 Accrual Rate

The accrual rate is estimated to be one patient per month. Based on this enrollment rate, we will complete the accrual of 34 patients in about 36 months. The upper limit of accrual is 34 evaluable patients, and lower limit of accrual is 10 evaluable patients (See Interim Monitoring Section 9.4).

## 9.4 Interim Monitoring for Safety

Interim analysis to assess futility will be performed based on the Bayesian posterior probability. Two interim analyses after 10 and 20 patients will be performed for safety. Assuming a successful completion rate at 80%, a probability threshold for futility stopping of 80% and a non-informative prior for a beta distribution for success rate, the following stopping bounds will be utilized.
Early stopping for futility will occur if ≤6/10 and ≤14/20 patients fail to exhibit successful completion of one cycle of HAI. Otherwise, enrollment will continue until a total of 34 evaluable patients have been enrolled.

Futility Early Stopping Boundaries

Table SB1: Futility Early Stopping Boundaries

| # Patients (inclusive) | # Responses (inclusive) are considered futile | Actions |
|---|---|---|
| 10 | 0 \| 1 \| 2 \| 3 \| 4 \| 5 \| 6 | Early stopping |
| 20 | 0 \| 1 \| 2 \| 3 \| 4 \| 5 \| 6 \| 7 \| 8 \| 9 \| 10 \| 11 \| 12 \| 13 \| 14 | Early stopping |

## 9.5 Data Analysis Plans

For the primary objective defined as safety based on successful completion rate, the proportion will be calculated along with exact 90% binomial confidence interval.

For secondary endpoints, feasibility including percent pump loss attributable to missed pump fills, therapy completion at 3 and 6 months will be summarized descriptively using proportions and exact binomial confidence intervals. The mSIPAT will be completed during screening by the treating investigators; the mSIPAT yields a rating for each potentially eligible patient regarding candidacy status for pump implantation. As described in Section 12.2, mSIPAT scores will be associated with factors indicating treatment adherence (e.g., number of missed clinic visits during the study) using two sample t-tests or Spearman correlation coefficients. Other psychosocial, lifestyle factors, mSIPAT will be summarized and correlated using correlation coefficients while changes over time will be assessed using paired t-tests or longitudinal mixed models. Association of these endpoints with successful completion rate, feasibility, clinical response will be assessed using linear models.

All patients who received HAI intervention will be included in the safety analysis of this study. Adverse event (AE) data and corresponding toxicity grades during each cycle of treatment will be summarized. Treatment-related toxicity will be monitored by usual clinical grading and laboratory parameters such serum alkaline phosphatase, bilirubin. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific adverse event, incidence of adverse events causing withdrawal (from study treatment) and incidence of serious adverse events. The total number of episodes for each event reported (Frequency Table), the severity and attribution to study therapy of each episode reported (Severity Table and Attribution Table) will also be displayed. Listings of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal (from study treatment). Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5). Other safety assessments such as rate of 30-day catheter malfunction, requirement for additional postop intervention will also be summarized as proportions and 90% exact binomial confidence intervals.

Overall Response Rate based on RECIST will also be summarized with confidence intervals.

Pharmacokinetic model will be performed to estimate PK parameters (AUC, half-life, clearance) using descriptive statistics of each of these measures for all patients.

## 9.6 Early study closure due to FDA approval of the Intera 3000 pump

As described in section 2.13, the study was closed on 5/17/2022 prior to completing accrual goal of 34 participants. At the time of closure to accrual, there were 21 subjects enrolled. The last patient completed the primary endpoint in December 2021 and finished the study treatment in June 2022. Long-term follow-up will be completed as planned. Statistical analysis will proceed with the enrolled subjects as described above.

### 9.7 Clinical Trial Registration with NIH

All clinical treatment trials have to be registered into clinicaltrials.gov before opening to accrual and trial results have to be published. The MCC-CRO Regulatory unit (mccreg@uky.edu) supports investigators in completing registration and renewal of their trials to NIH system in conjunction with a representative from UKHC. Results of this trial will be released on Clinicaltrials.gov within 12 months after follow-up is completed (of final patient accrued). If the trial is stopped early, data will be posted within six months of the study's termination.

## 10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting to Overall PI and DSMC via the OnCore **in addition** to routine reporting.

All toxicities will be rated as per the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5). **Hepatic enzyme toxicities** will also be captured according to the schema on 6.4, 6.5, and 7.0 as well (see Section 7.8 for FUDR Dose Modifications and Table I).

### 10.1 Surgery for Pump implantation

Risks of HAI pump implantation surgery are overall low but include bleeding, infection including abscess, wound infection, pneumonia, urinary tract infection; injury to other structures including pancreas, bowel, liver, biliary tree; postoperative ileus or bowel obstruction; hernia; venous thromboembolism; cardiopulmonary complications; stroke; very low risk of death.

### 10.2 Catheter and Pump

Possible risks associated with the catheter and pump are infection requiring antibiotics and possibly pump removal, hepatic artery thrombosis, pump malfunction, catheter occlusion and intra-abdominal bleeding. If drug is not emptied from the pump in 14 days or less, there is a risk of becoming toxic from extended chemotherapy. If the pump is not filled and runs dry, thrombosis/pump failure will occur, which is usually unsalvageable.

The rate of pump failure is less than 1%. If this occurs, patients will receive standard systemic therapy alone if the pump is unusable. If the bilirubin goes up and does not come down after holding treatment and using dexamethasone in the pump, an ERCP (endoscopic retrograde cholangiopancreatography) will be done to evaluate for a focal biliary stricture, which would require an endoscopic biliary stent.

### 10.3 Toxicities and Side Effects of Chemotherapeutic Agents in this Study

### 10.3.1 FUDR

Toxicities associated with the intrahepatic administration of FUDR include biliary sclerosis (5%), hepatic enzyme elevation, and gastric ulcers. Toxicities seen with systemic administration such as bone marrow suppression are not typically seen with intrahepatic administration.

### 10.3.2 Dexamethasone

Common potential side effects of systemic administration include anxiety, mood alteration/lability, hyperglycemia, insomnia, peripheral edema, myopathy (with chronic use), acne, and hirsutism. However, expected toxicity from intrahepatic administration is minimal.

### 10.3.3 Gemcitabine

Frequency of adverse reactions reported for single-agent gemcitabine only.

**>10%:**

*Cardiovascular*: Peripheral edema (20%), edema (≤13%)
*Central nervous system*: Drowsiness (11%)
*Dermatologic*: Skin rash (30%), alopecia (15%)
*Gastrointestinal*: Nausea and vomiting (69%), diarrhea (19%), stomatitis (11%; grade 3: <1%)
*Genitourinary*: Proteinuria (45%), hematuria (35%)
*Hematologic & oncologic*: Anemia (68%; grade 3: 7%; grade 4: 1%), neutropenia (63%; grade 3: 19%; grade 4: 6%), thrombocytopenia (24%; grade 3: 4%; grade 4: 1%), hemorrhage (17%; grade 3: <1%; grade 4: <1%)
*Hepatic*: Increased serum alanine aminotransferase (68%), increased serum aspartate aminotransferase (67%), increased serum alkaline phosphatase (55%), hyperbilirubinemia (13%)
*Infection*: Infection (16%)
*Renal*: Increased blood urea nitrogen (16%)
*Respiratory*: Dyspnea (23%), flu-like symptoms (19%)
*Miscellaneous*: Fever (41%)

**1% to 10%:**

*Central nervous system*: Paresthesia (10%)
*Local*: Injection site reaction (4%)
*Renal*: Increased serum creatinine (8%)
*Respiratory*: Bronchospasm (<2%)

**<1%:**postmarketing, and/or case reports (reported with single-agent use or with combination therapy): Acute respiratory distress syndrome, anaphylactoid shock, bullous skin disease, capillary leak syndrome, cardiac arrhythmia, cardiac failure, cellulitis (including pseudocellulitis), cerebrovascular accident (Kuenen 2002), desquamation, gangrene of skin and/or subcutaneous tissues, hemolytic-uremic syndrome, hepatic failure, hepatic sinusoidal obstruction syndrome, hepatotoxicity, interstitial pneumonitis, myocardial infarction, petechia (Nishijima 2013; Zupancic 2007), pruritus (Curtis 2016), pulmonary edema, pulmonary fibrosis, radiation recall phenomenon, renal failure syndrome

### 10.3.4 Oxaliplatin Percentages reported with monotherapy.

Frequency of adverse reactions reported for single-agent oxaliplatin only.

**>10%:**

*Central nervous system*: Peripheral neuropathy (may be dose limiting; 76% to 92%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), fatigue (61%), pain (14%), headache (13%),

insomnia (11%)
*Gastrointestinal*: Nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%)
*Hematologic & oncologic*: Anemia (64%; grades 3/4: 1%), thrombocytopenia (30%; grades 3/4: 3%), leukopenia (13%)
*Hepatic*: Increased serum AST (54%; grades 3/4: 4%), increased serum ALT (36%; grades 3/4: 1%), increased serum bilirubin (13%; grades 3/4: 5%)
*Neuromuscular & skeletal*: Back pain (11%)
*Respiratory*: Dyspnea (13%), cough (11%)
*Miscellaneous*: Fever (25%)

**1% to 10%:**
*Cardiovascular*: Edema (10%), chest pain (5%), peripheral edema (5%), flushing (3%), thromboembolism (2%)
*Central nervous system*: Rigors (9%), dizziness (7%)
*Dermatologic*: Skin rash (5%), alopecia (3%), palmar-plantar erythrodysesthesia (1%)
*Endocrine & metabolic*: Dehydration (5%), hypokalemia (3%)
*Gastrointestinal*: Dyspepsia (7%), dysgeusia (5%), flatulence (3%), hiccups (2%), mucositis (2%), dysphagia (acute 1% to 2%), gastroesophageal reflux disease (1%)
*Genitourinary*: Dysuria (1%)
*Hematologic & oncologic*: Neutropenia (7%)
*Hypersensitivity*: Hypersensitivity reaction (3%; includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope: grades 3/4: 2% to 3%)
*Local*: Injection site reaction (9%; redness, swelling, pain)
*Neuromuscular & skeletal*: Arthralgia (7%)
*Ocular*: Abnormal lacrimation (1%)
*Renal*: Increased serum creatinine (5% to 10%)
*Respiratory*: Upper respiratory tract infection (7%), rhinitis (6%), epistaxis (2%), pharyngitis (2%), pharyngolaryngeal dysesthesia (grades 3/4: 1% to 2%)

**<1%:** postmarketing, and/or case reports (reported with mono- and combination therapy): Abnormal gait, acute renal failure, anaphylaxis, anaphylactic shock, anaphylactoid reaction, angioedema, aphonia, ataxia, blepharoptosis, cerebral hemorrhage, colitis, cranial nerve palsy, decreased deep tendon reflex, deafness, decreased visual acuity, diplopia, dysarthria, eosinophilic pneumonitis, fasciculations, febrile neutropenia, hematuria, hemolysis, hemolytic anemia (immuno-allergic), hemolytic-uremic syndrome, hemorrhage, hepatic failure, hepatic fibrosis (perisinusoidal), hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive disease), hepatitis, hepatotoxicity, hypertension, hypomagnesemia, hypoxia, idiopathic noncirrhotic portal hypertension (nodular regenerative hyperplasia), increased INR, increased serum alkaline phosphatase, infusion related reaction (extravasation [including necrosis]), interstitial nephritis (acute), interstitial pulmonary disease, intestinal obstruction, laryngospasm, Lhermittes' sign, metabolic acidosis, muscle spasm, myoclonus, neutropenic enterocolitis, neutropenic infection (sepsis), optic neuritis, pancreatitis, prolonged Q-T interval on ECG, prolonged prothrombin time, pulmonary fibrosis, purpura, rectal hemorrhage, renal tubular necrosis, reversible posterior leukoencephalopathy syndrome, rhabdomyolysis, seizure, sepsis, septic shock, temporary vision loss, thrombocytopenia (immuno-allergic), torsades de pointes, trigeminal neuralgia, ventricular arrhythmia, visual field loss, voice disorder

### 10.3.5 Irinotecan

Phase I and II studies of irinotecan have reported neutropenia and diarrhea as the dose-limiting toxicities. **It is expected that these toxicities will also be encountered in this trial.** Other Grade 2-3 toxicities seen in phase I trials include nausea and vomiting, anorexia, abdominal cramping, cumulative asthenia,

thrombocytopenia, renal insufficiency, increase in transaminase level and hair loss.

Frequency of adverse reactions reported for single-agent use of irinotecan only.

**>10%:**

Cardiovascular: Vasodilatation (9% to 11%)
Central nervous system: Cholinergic syndrome (47%; includes diaphoresis, flushing, increased peristalsis, lacrimation, miosis, rhinitis, sialorrhea), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)
Dermatologic: Alopecia (46% to 72%), diaphoresis (16%), skin rash (13% to 14%)
Endocrine & metabolic: Weight loss (30%), dehydration (15%)
Gastrointestinal: Diarrhea (late: 83% to 88%, grades 3/4: 14% to 31%; early: 43% to 51%, grades 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), abdominal cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), mucositis (30%), flatulence (12%), stomatitis (12%)
Hematologic & oncologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), leukopenia (63% to 96%, grades 3/4: 14% to 28%), thrombocytopenia (96%, grades 3/4: 1% to 4%), neutropenia (30% to 96%; grades 3/4: 14% to 31%)
Hepatic: Increased serum bilirubin (84%), increased serum alkaline phosphatase (13%)
Infection: Infection (14%)
Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)
Respiratory: Dyspnea (22%), cough (17% to 20%), rhinitis (16%)
Miscellaneous: Fever (44% to 45%)

**1% to 10%:**

Cardiovascular: Edema (10%), hypotension (6%), thromboembolism (5%)
Central nervous system: Drowsiness (9%), confusion (3%)
Gastrointestinal: Abdominal distention (10%), dyspepsia (10%)
Hematologic & oncologic: Febrile neutropenia (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (grades 3/4: 1% to 2%)
Hepatic: Increased serum AST (10%), ascites (grades 3/4: ≤9%), jaundice (grades 3/4: ≤9%)
Respiratory: Pneumonia (4%)

**<1%** postmarketing, and/or case reports: Acute renal failure, anaphylactoid reaction, anaphylaxis, angina pectoris, arterial thrombosis, bradycardia, cardiac arrhythmia, cerebral infarction, cerebrovascular accident, circulatory shock, colitis, deep vein thrombophlebitis, dysarthria, embolism, gastrointestinal hemorrhage, gastrointestinal obstruction, hepatomegaly, hiccups, hyperglycemia, hypersensitivity reaction, hyponatremia, immune thrombocytopenia, increased amylase, increased serum ALT, increased serum lipase, interstitial pulmonary disease, intestinal obstruction, intestinal perforation, ischemic colitis, ischemic heart disease, lymphocytopenia, megacolon, muscle cramps, myocardial infarction, pancreatitis, paresthesia, peripheral vascular disease, pulmonary embolism; pulmonary toxicity (includes dyspnea, fever, reticulonodular infiltrates on chest x-ray), renal insufficiency, syncope, thrombophlebitis, thrombosis, typhlitis (including neutropenic typhlitis), ulcer, ulcerative colitis, vertigo

### 10.3.6 Fluorouracil (5-FU)

Frequency not defined. Toxicity depends on duration of treatment and/or rate of administration.
*Cardiovascular*: Angina pectoris, cardiac arrhythmia, cardiac failure, cerebrovascular accident, ischemic heart disease, local thrombophlebitis, myocardial infarction, vasospasm, ventricular ectopy
*Central nervous system*: Cerebellar syndrome (acute), confusion, disorientation, euphoria, headache

*Dermatologic*: Alopecia, changes in nails (including nail loss), dermatitis, hyperpigmentation (supravenous), maculopapular rash (pruritic), palmar-plantar erythrodysesthesia, skin fissure, skin photosensitivity, Stevens-Johnson syndrome, toxic epidermal necrolysis, xeroderma
*Gastrointestinal*: Anorexia, diarrhea, esophagopharyngitis, gastrointestinal hemorrhage, gastrointestinal ulcer, mesenteric ischemia (acute), nausea, stomatitis, tissue sloughing (gastrointestinal), vomiting
*Hematologic & oncologic*: Agranulocytosis, anemia, leukopenia (nadir: days 9 to 14; recovery by day 30), pancytopenia, thrombocytopenia
*Hypersensitivity*: Anaphylaxis, hypersensitivity reaction (generalized)
*Ophthalmic*: Lacrimal stenosis, lacrimation, nystagmus, photophobia, visual disturbance
*Respiratory:* Epistaxis
**<1%,** postmarketing, and/or case reports: Dysgeusia

### 10.3.7 Leucovorin Calcium (Folinic Acid)

Frequency not defined.
Toxicities (especially gastrointestinal toxicity) of fluorouracil are enhanced when used in combination with leucovorin.

Dermatologic: Erythema, pruritus, skin rash, urticaria
Hematologic & oncologic: Thrombocythemia
Hypersensitivity: Anaphylactoid reaction, hypersensitivity reaction
Respiratory: Wheezing

### 10.3.8 Panitumumab

#### 10.3.8.1 Adverse Events of Panitumumab in combination with FOLFOX:

**>10%:**

Dermatologic: Skin rash (56%; grades 3/4: 17% to 26%), acneiform eruption (32%; grades 3/4: 10%), pruritus (23%; grades 3/4: <1%), paronychia (21%; grades 3/4: 3%), xeroderma (21%; grades 3/4: 2%), erythema (16%; grades 3/4: 2%), skin fissure (16%; grades 3/4: <1%), alopecia (15%), acne vulgaris (14%; grades 3/4: 3%)
Endocrine & metabolic: Hypomagnesemia (30%), hypokalemia (21%), weight loss (18%)
Gastrointestinal: Diarrhea (62%), anorexia (36%), abdominal pain (28%), stomatitis (27%), mucosal inflammation (25%)
Neuromuscular & skeletal: Weakness (25%)
Ophthalmic: Conjunctivitis (18%)
Respiratory: Epistaxis (14%)

**1% to 10%:**

Cardiovascular: Deep vein thrombosis (5%)
Central nervous system: Fatigue (≥1%), paresthesia (≥1%)
Dermatologic: Nail disorder (10%; grades 3/4: 1%), palmar-plantar erythrodysesthesia (9%; grades 3/4: 1%), cellulitis (3%)
Endocrine & metabolic: Dehydration (8%), hypocalcemia (6%)
Hypersensitivity: Hypersensitivity (≥1%)

Local: Localized infection (4%)

**<1%:** Antibody development

**Postmarketing and/or case reports (mono- and combination therapy):** Abscess, angioedema, bullous skin disease (mucocutaneous), corneal ulcer, keratitis, necrotizing fasciitis, sepsis, skin necrosis, Stevens-Johnson syndrome, toxic epidermal necrolysis

10.3.8.2 Adverse Events of Panitumumab, *monotherapy*

**>10%:**
Central nervous system: Fatigue (26%)
Dermatologic: Skin toxicity (90%; grades 3/4: 15%), erythema (66%; grades 3/4: 6%), pruritus (58%; grades 3/4: 3%), acneiform eruption (57%; grades 3/4: 7%), paronychia (25%; grades 3/4: 2%), rash (22%; grades 3/4: 1%), skin fissure (20%; grades 3/4: 1%), exfoliative dermatitis (18%; grades 3/4: 2%), acne vulgaris (14%; grades 3/4: 1%)
Endocrine & metabolic: Hypomagnesemia (grades 3/4: 7%)
Gastrointestinal: Nausea (23%), diarrhea (21%; grades 3/4: 2%), vomiting (19%)
Ophthalmic: Ocular toxicity (16%)
Respiratory: Dyspnea (18%), cough (15%)
Miscellaneous: Fever (17%)

**1% to 10%:**
Cardiovascular: Pulmonary embolism (1%)
Central nervous system: Chills (3%)
Dermatologic: Nail toxicity (10%), xeroderma (10%), desquamation (9%; grades 3/4: <1%), dermal ulcer (6%; grades 3/4: <1%), pustular rash (4%), papular rash (2%)
Endocrine & metabolic: Dehydration (3%)
Gastrointestinal: Mucositis (7%), stomatitis (7%), xerostomia (5%)
Immunologic: Antibody formation (≤5%)
Ophthalmic: Abnormal eyelash growth (6%), conjunctivitis (5%)
Respiratory: Epistaxis (4%), interstitial pulmonary disease (1%)
Miscellaneous: Infusion related reaction (3%; grades 3/4: <1%)

**<1%:** Hypersensitivity reaction, pulmonary fibrosis

### 10.3.9 Combination of FUDR, Dexamethasone, Systemic Chemotherapy, Heparin and

**Saline**

Potential side effects from the *combination of all the medications and devices* used in this study include abdominal pain, anemia, increased AST and/or ALT, and an increase in bilirubin.

### 10.4 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

- Clavien-Dindo Classification will be utilized for surgical complications [44] **Appendix C**

- **For expedited reporting purposes only:**

AEs for chemotherapy (FUDR, 5-FU, oxaliplatin, irinotecan, gemcitabine) and dexamethasone noted in Section 10.0) should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information, which is provided. Other AEs that do not require expedited reporting are outlined below.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

### 10.5 MCC Expedited Adverse Event Reporting Guidelines

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy, as specified in the table in below. Use the MCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

**Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.**

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

For MCC Investigator-Initiated Trials (IITs), study investigators and staff must report to the Overall PI any serious adverse event (SAE) per the specific categories below that occur after the initial surgery, during study treatment, and within 30 days of the last dose of study drug on the SAE form. This applies only to the following categories:

- Grade 2 or greater cardiac toxicity changes – any changes, regardless of attribution to the Medtronic pump and Codman catheter
- Grade 3 (severe) *Medical* Events – Only events that are Unexpected and Possibly, Probably or Definitely Related / Associated with the Medtronic pump and Codman catheter
- ALL Grade 4 (life threatening or disabling) *Medical* Events – Unless expected AND specifically listed in protocol as not requiring reporting.
- ALL Grade 5 (fatal) Events regardless of study phase or attribution.

**Note:** If subject is in Long-Term Follow-Up, death is reported at continuing review.
**Note: Abnormal laboratory values are not considered medical events**, unless determined to be causative of the SAE by the investigator or are a grade 5.

The following table outlines the required forms and reporting structure for clinical trials.

| **Expedited Reporting to MCC, to external agencies, Non-Expedited AEs and to IRB** | | | | | |
|---|---|---|---|---|---|
| **Study type** | **Expedited reporting to MCC** | **Expedited reporting to External Agency** | **Non-expedited AE** | **Form** | **IRB** |
| IIT by MCC investigator of HAI FUDR combined with systemic chemo-therapy | **Catheter disconnects, pump failures, or loss of pump due to failure to fill on time**<br><br>Grade 2 or greater **cardiac toxicity** – any changes regardless of attribution to Medtronic pump or Codman catheter<br><br>Grade 3 – Unexpected AE PLUS Possibly, Probably or Definitely Related with Medtronic pump and Codman catheter<br><br>ALL Grade 4 Unless expected AND listed specifically in protocol as not requiring reporting.<br><br>ALL Grade 5 events (fatal) | FDA: Suspected AE that is serious and unanticipated (not listed in IDB or in the consent) | OnCore and DSMC reporting only | Voluntary Medwatch 3500 for Serious and Unanticipated<br><br>OnCore for all AEs, including SAEs | Yes if it meets the IRB reporting requirements: Unanticipated Problem and/or Serious AE<br><br>(use IRB AE reporting form for all correspondence with IRB) |
| IDB = Investigational Device Brochure | | | | | |

### 10.6 MCC Expedited Reporting Guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy.

| Attribution | MCC Reportable AEs | | | | |
|---|---|---|---|---|---|
| | **Gr. 2 AE (expected or unexpected); Grade 3 AE expected** | **Gr. 3 AE Unexpected** | **Gr. 4 AE Expected** | **Gr. 4 AE Unexpected** | **Gr. 5 AE Expected or Unexpected** |
| Unrelated Unlikely | Not required except for **cardiac** | Not required except for **cardiac** | 5 calendar days[#] | 5 calendar days | 24 hours* |
| Possible Probable Definite | Not required except for **cardiac** | 5 calendar days | 5 calendar days[#] | 5 calendar days | 24 hours* |
| # If listed in protocol as Expected and not requiring expedited reporting, the adverse event does not need to be reported. | | | | | |
| * For participants enrolled and actively participating in the study ***or*** for SAEs occurring within 30 days of the last study intervention, the SAE should be reported within 24 business hours of learning of the event. | | | | | |

### 10.7 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the MCC DSMC, however, they still must be reported through the routine reporting mechanism (i.e., case report form) and UK IRB as outlined in IRB SOP: C2.0350.

| CTCAE SOC | Adverse Event | Grade(s) | Attribution | ≥24h Hospitalization[a] |
|---|---|---|---|---|
| | Alopecia | All | All causes | |
| | Lymphopenia | 1 - 4 | All causes | |
| | Laboratory abnormalities | 1 - 2 | deemed not clinically significant by treating physician | |
| [a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient. | | | | |

### 10.8 Expedited Reporting to External Agencies

Overall PI will comply with the policies of all external funding agencies and the UK IRB regarding expedited reporting, as per the UK IRB's Mandated Reporting to External Agencies SOP C4.0150.

### 10.9 Expedited Reporting to the Food and Drug Administration (FDA)

Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

### 10.10 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

### 10.11 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions with the exception of those listed in Section 10.7. **AEs reported expeditiously to the Overall PI and DSMC via OnCore must <u>also</u> be reported in routine study data submissions.**

### 10.12 Pregnancy

Pregnancy is considered an unanticipated events and pregnancy as well as its outcome must be documented and reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

### 10.13 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported to overall PI, DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Three options available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

## 10.14 Second Malignancy

A *second* malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

## 11. STUDY CALENDAR

Baseline evaluations and scans are to be conducted per protocol (**Section 4**). In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

| | PRE-STUDY | Surgery | Chemotherapy Cycle | | | | Last visit on treatment | Off-Treatment [19] | Follow-Up | | | Off-Study |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 1 | | 2 - 6 | | | | | | | |
| | Enrollment Day – 30 to Day – 1 | | HAI Only (D1-14) | Systemic Chemo Only (D15-28) | HAI + Systemic Chemo (D1-14) | Systemic Chemo Only (D15-28) | | | Year 1 | Year 2 | Year 3 | |
| mSIPAT [1] | R(T) | | | | | | | | | | | |
| Informed Consent | R(T) | | | | | | | | | | | |
| Demographics | R(T) | | | | | | | | | | | |
| Concomitant Meds (D1,15) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | | | | |
| Performance Status (D1,15) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | | | | |
| Adverse Event review | | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | | | | |
| Beta-HCG-urine [2] | B [2] | | | | | | | | | | | |
| EKG [2] | B [2] | | | | | | | | | | | |
| HAI Pump Surgery [3] | | B | | | | | | | | | | |
| PT/PTT [4] | B | | | | | | | | | | | |
| Perfusion flow scan [5] | | B | | | | | | | | | | |
| Record HAI pump residual (D1,15) | | | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | | | | |
| FUDR (floxuridine) administered via HAI pump [6] | | | B | | B | | B [18] | B [18] | | | | |
| Heparinized saline via HAI pump [6] | | | | B [6] | | B [6] | B [19] | B [19] | | | | |
| Systemic chemotherapy [7] | | | | B | B | B | B [19] | B [19] | | | | |
| Venipuncture | | | B | B | B | B | B | B | | | | |
| Interval H&P including Vital Signs, Weight, Height | B [2] | | B | B | B | B | B | B | | | | |
| Staff-to-patient contacts [8] | R(T) | R(T) | R(T) | R(T) | R(T) | R(T) | | | | | | |
| CBC w/ diff and CMP [2, 20] | B | | B (D1) | B (D15) | B (D1) | B (D15) | B | | | | | |
| LDH [9, 20] | B | | B (D1) | | B (D1) | | B | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Viral Serologies (Hepatitis status) [10] | B | | | | | | | | | | | |
| HIV status [10] | B | | | | | | | | | | | |
| CEA [11, 20] or CA 19-9 [11, 20] | B | | B (D1) | | B (D1) | | B | | | | | |
| Pharmacokinetics [12] | | | R (D1) | R (D15) | | | | | | | | |
| Gene polymorphisms [13] | | | R (D1) | | | | | | | | | |
| CT C/A/P [14] | B [14] | | | | | | | | | | | |
| CT angiogram of the liver [14] (or a recent triphasic CT C/A/P) | B [14] | | | | | | | | | | | |
| CT C/A/P triphasic liver protocol [15, 16] | B [15] | | | | | B [16] | | | | | | |
| Assessment of disease progression [17] | | | | | | R(T) | | | | | | |
| Survival Status [18] | | | | | | | | X | X | X | X | X |

**LEGEND FOR STUDY CALENDAR**

**B=** billable to insurance as routine care **R=** research **R(T) =** research time (staff time, not a billable procedure/test/scan)

**1** mSIPAT (modified Stanford Integrated Psychosocial Assessment for Transplant [1]): mSIPAT will be completed by the treating investigator in consultation with the treatment team, see Appendix B. Potentially eligible patients will receive a rating of their candidacy for HAIP treatment based on the presence of psychosocial risk factors associated with poor medical outcomes. Ratings on the mSIPAT scores are as follows: "Excellent Candidate", "Good Candidate", "Minimally Acceptable Candidate", to "Poor / High Risk Candidate."

**2** Note specific requirements of individual tests at baseline and/or study enrollment (Section 4):
History/physical (H&P), vital signs, height, weight (all within 2 weeks of surgery; height is only measured once);
EKG within 4 weeks of surgery
Labs within 2 weeks of surgery
Urine pregnancy test only in females of child-bearing potential at the pre-operative visit (before surgery)

**3** HAI pump and catheter implantation for all patients

**4** PT/PTT is part of standard pre-operative work-up before surgery (i.e., pump implantation procedure) in order to assess bleeding risk. INR is calculated from the results of the PT blood test.

**5** Perfusion flow scan: (Tc-99 mass aggregated albumin, TcMAA) prior to hospital discharge after pump implantation

**6** At first post-operative visit (no earlier than post-operative **day 14),** if patient is deemed appropriately recovered, HAI chemo will commence. If additional recovery is required, a new postoperative clinical visit will be scheduled in q1-2 weeks to reassess. If the pump is not filled with chemotherapy at post-op visit #1, it will be filled with heparinized saline, which must be repeated every 14 days until HAI chemotherapy starts.

**7** If HAI chemo (FUDR) deemed appropriate at post-op visit, this becomes Chemotherapy Cycle 1 D1. No systemic chemo is given for the first 2 weeks of HAI chemotherapy, but it is given q14d afterwards, per standard of care.
**- For patients with CLM,** FOLFOX or FOLFIRI or irinotecan/oxaliplatin (choice by medical oncologist preference, per standard of care); CLM patients with driver mutations may also receive EGFR inhibitors concurrent with chemotherapy per current SOC guidelines (e.g., panitumumab for RAS wildtype, etc.). For patients who receive panitumumab, magnesium levels will be monitored per SOC.
**-For patients with IHC**, Gemcitabine/oxaliplatin or Gemcitabine only, per standard of care.
All systemic chemotherapy regimens are standard of care.

**8** For the feasibility portion of the study, any contacts by study staff to assure follow-up must be recorded in a tracking log. This will be tabulated during the chemotherapy visits. Study staff will record missed appointments and patient contact attempts outside normal clinic visits and interventions required to maintain follow-up while the patient is on study treatment.

**9 LDH** (lactate dehydrogenase) is a serum test of liver enzymes, distinct from ALT/AST. LDH will be tested, as clinically indicated, at baseline and at other clinic visits when signs or symptoms of liver damage indicate it is medically necessary.

**10 Viral serologies** (hepatitis, HIV) will be conducted as clinically indicated. IHC and colorectal liver metastases harm liver function. Thus, at pre-study:
-For patients with known or suspected HBV and HCV: Disease status will be checked as clinically indicated to determine eligibility.
-For patients with known or suspected HIV: Disease status will be checked as clinically indicated to determine eligibility.

**11 Tumor markers:** Current best practice in routine care includes assessing disease response via blood tests of tumor markers. Assessed at pre-study, and again on Day 1 of each cycle of chemotherapy (CEA in CLM; for IHC patients, CA19-9).

**12 Pharmacokinetic studies**: At each timepoint collect 10mL EDTA tube. FUDR plasma levels and metabolites will be measured at three timepoints:
- on Cycle 1 Day 1: 2 hours after initiation of HAI infusion
- on Cycle 1 Day 15: 2 samples collected. The first tube is collected prior to pump empty and commencing systemic chemotherapy. The 2nd tube is collected immediately after a systemic bolus of 5-FU, or 2 hours after starting a systemic continuous infusion during the systemic chemotherapy only portion of the cycle.

**13 Polymorphism studies**: A baseline analysis by Kolesar lab of polymorphisms in 5-FU metabolism genes (DYPD, TYMS and GSTP1). Study staff will collect blood sample (8.5mL in a DNA PAXgene tube) at Cycle 1 Day 1, and collaborate with Biospecimen Core for processing per lab manual.

**14, 15 Pre-study Imaging**: Pre-operative imaging to evaluate suitability for HAI comprises assessment of liver's arterial anatomy AND extent of disease and liver involvement. Imaging to assess arterial anatomy (CT angiogram or triphasic liver CT) must have been completed within 6 months of surgery, provided no surgical intervention has taken place on the liver in the interim. Imaging to assess extent of disease must include a C/A/P with IV contrast. This must be completed with 4 weeks of surgery. CT C/A/P with IV contrast performed with a triphasic liver protocol or CT angiogram protocol will suffice for both purposes if done within 4 weeks of surgery.

**16 Imaging During Study Treatment**: Post-operative imaging involves CT C/A/P (triphasic with IV contrast) completed every 2 months during study treatment (i.e., D28 of C2, C4, & C6; +/-14 days window for scans). Assessment of disease progression for imaging will use RECIST v1.1. Clear cut progression of disease at 2 and 4 months will prompt consideration for removal from HAI therapy, based on multi-disciplinary tumor board review to confirm no residual benefit of maintaining HAI therapy.

**17 Assessment of disease progression**: Study staff will enter tumor markers (CEA, CA 19-9) and results of routine scans per RECIST v1.1 into OnCore study database, along with disease status (CR, PR, PD, etc.) for the duration of time the patient is on-study.

**18 Survival Status**: staff will record survival status into the OnCore study database of all participants at indicated timepoints as well as at the off-study visit, whenever it occurs (see X's to the right on this row). Survival status may be ascertained by checking the patient chart or the National Death Index.

**19** Patients will be evaluated for adverse events 30 days after completion of therapy. Continuation of HAI and/or systemic therapy as clinically deemed appropriate by multi-disciplinary tumor board and oncologist discretion. Patients will be assessed for resectability, and if resectable, plans are made to pursue this; otherwise, therapy is typically continued (if responding) or changed (if not responding). Patients going off continuous pump therapy will need to continue pump fills with heparinized saline q2 weeks.

**20** Labs after the Pre-Study/Baseline timepoint can be drawn up to 2 days prior to treatment administration.

# 12. MEASUREMENT OF EFFECT

## 12.1 Safety analysis

12.1.1 Primary endpoint:

We will tabulate the number of patients who do not meet the primary safety endpoint (completion of the first cycle of HAI).

12.1.2 30-day adverse events:

We will generate a frequency table showing 30-day adverse events related to pump implantation, i.e. re-admission, wound infection, urinary tract infection, etc. We will use the Clavien-Dindo (44) classification for surgical complications (**Appendix C**). This will be stratified by all patients, CLM, and IHC.

12.1.3 Interventions required to achieve primary function of pump:

We will generate a frequency table showing secondary interventions such as interventional radiology embolization or stents to control extrahepatic perfusion. This will be stratified by all patients, CLM, and IHC

12.1.4 Chemotherapy-related toxicity:

We will tabulate laboratory toxicities (hematologic and non-hematologic) using the NCI Common Terminology Criteria for Adverse Events (CTCAE version 5) grading system. Notation will be made of dose changes and delays (see section 11). This will be stratified by all patients, CLM, and IHC.

## 12.2 Feasibility

12.2.1 Feasibility as pre-treatment screening for patient selection:

To augment the medical evaluation for HAI therapy, we are also implementing a standardized tool to screen for the presence of psychosocial risk factors (known to predict treatment non-adherence). In considering patients' candidacy for HAI administration, we will adapt and implement the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT [1]) measure, slightly modified to reflect HAI pump/catheter implantation, rather than solid organ transplantation).

SIPAT scores of enrolled patients will be recorded and grouped into 4 ratings categories, "Excellent Candidate", "Good Candidate", "Minimally Acceptable Candidate" and "Poor/High Risk Candidate". Patients with a rating of "Excellent" or "Good" are considered optimal for

enrollment, while a rating of "Minimally Acceptable" requires a remediation plan for risk factors before being deemed acceptable to the primary investigator for enrollment. A patient whose mSIPAT score corresponds to a rating of "Poor / High Risk Candidate" will excluded from trial enrollment.

- Feasibility as treatment initiation and adherence:
  - Pre-study mSIPAT score (numeric and categorical) will be correlated to therapy initiation
  - Pre-Study mSIPAT score (numeric and categorical) will be correlated to therapy adherence:
    i. percent remaining on therapy at 3 and 6 months
    ii. number of missed/re-scheduled appointments
    iii. number of phone calls/interventions required to maintain appointment schedule
    iv. pump loss during therapy due to failure to keep follow-up appointments (pump thrombosis due to failure to fill on time)
  - These factors will be correlated to distance of patient's primary residence from the Markey Cancer Center (numeric and categorical as <50 miles, 50-100, >100)

### 12.3 Treatment Response Rate

12.3.1 Patients will undergo evaluation of treatment response by CT scan and tumor markers. Analysis will be completed as all patients and stratified by CLM vs IHC.

- Imaging response will be assessed on CT scans, which will be done at 2, 4, and 6 months of treatment. Response will be categorized using the RECIST v1.1 criteria as progressive disease, stable disease, partial response, and complete response. We anticipate at 70% partial response in previously treated CLM patients, and 80% in chemotherapy-naïve [3]. We anticipate a 50% partial response rate in IHC patients [4].
- Treatment response will be also measured by tumor markers (CEA for CLM and CA 19-9 for IHC).

12.3.2 Conversion to resectability: Patients who are tolerating therapy will continue HAI combined with systemic therapy for the full 6 months. At that point, restaging scans will be discussed in a multidisciplinary tumor board to determine if the patient is a candidate to undergo resection vs. continued HAI/systemic therapy vs. change or discontinuation of therapy. Resectability status is assessed at day 28 of Cycle 6, where the patient will be presented to multi-disciplinary tumor board for evaluation.

- We anticipate approximately half of CLM will convert to resectability [3]. Less data is available for IHC but based on retrospective data we anticipate 10% will become resectable [5].
- We will correlate conversion to resection to disease burden measured by Clinical Risk Score [43] and number of lesions.
- We will tabulate latency to resection, margins from resection (R0, R1, R2) and recurrence status at 3 years of follow-up.

### 12.4 Assessment of Pharmacokinetics (Correlatives)

12.4.1 We will build a population model for the pharmacokinetics of 5-FU, FUDR and FdUMP during systemic 5-FU combined with HAI FUDR:

- In order to assess the relative contribution of HAI and systemic therapy:
    - For HAI treatment: On Cycle 1 Day 1 Plasma levels of FUDR, the active metabolite of 5-FU, will be measured at 2h starting an infusion of HAI. FUDR plasma levels will be measured again at the end of HAI treatment on Day 15 of Cycle 1 (just prior to administration of systemic chemotherapy). At each timepoint, collect 10mL whole blood into EDTA tube.
    - Systemic chemotherapy: Plasma levels of FUDR will be measured immediately after a systemic bolus of 5FU or 2 hours after starting a systemic continuous infusion of 5-FU (Cycle 1 Day 15). Collect 10mL whole blood into EDTA tube.
- Levels will be correlated to gene polymorphisms in 5-FU drug metabolism genes (DYPD, TYMS and GSTP1) drawn prior to initiation of treatment on Cycle 1 Day 1

12.4.2 FUDR levels and polymorphisms will be correlated to treatment response by RECIST, and toxicity. 5-FU, FUDR and FdUMP plasma concentrations will be evaluated in with a validated LC-MS/MS assay as previously described[8]. Data will be analyzed by a nonlinear mixed-effects modeling approach using the NONMEM system (Version VI, NONMEM Project Group, UCSF/Globomax and PDx-Pop Version 3.1). Xpose4 and S-PLUS (Insightful Corp, Seattle, Washington) are used for goodness-of-fit assessment and model evaluation. Both intrahepatic and plasma administration will be simultaneously analyzed in the single model. In addition, polymorphisms in DYPD, TYMS and GSTP1 will be evaluated for association with adverse effects (toxicity) and clinical outcome (treatment response, conversion to resection).

## 13. STUDY APPROVAL, OVERSIGHTAND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

### 13.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

## 13.2 Quality Assurance

The MCC places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translation research. The MCC Quality Assurance (QA) Office oversees the maintenance of quality standards in clinical cancer research through clinical data monitoring of Investigator Initiated Trials (IITs) and routine audits.

### 13.2.1 Data Monitoring

The MCC QA Office will collaborate with the PI, Biostatisticians and Lead OnCore® Data Management Specialist in creating a Clinical Data Monitoring Plan (CDMP) using a risk-based approach. The CDMP will describe the scope, communication plan, and frequency of monitoring visits. In addition, describe query submissions and resolutions, action items and monitoring reports.

The QA monitor assigned to the trial will perform the monitoring tasks in accordance with the protocol specified CDMP. The monitoring process will provide research staff and PI with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of the case report forms, assure that all protocol requirements, including applicable regulations and investigator's obligations are being fulfilled, and prompt resolution of any inconsistencies in the study records.

### 13.2.2 Audit

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the MCC Audit Committee will conduct a quality assurance audit. A minimum of 25% of patients enrolled in the study may be selected for review. The purpose of a MCC audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

## 13.3 Data and Safety Monitoring Committee

The MCC Data and Safety Monitoring Committee (DSMC) will oversee the conduct of this trial. The MCC DSMC performs routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs). The MCC DSMC will conduct review of the trial on a schedule determined the MCC Protocol Review & Monitoring Committee (PRMC). The MCC DSMC will monitor the following elements of the trial: adverse event analysis, serious adverse events, protocol deviations/violations, and accrual. In addition, when applicable will review QA audits and monitoring reports, previous reviews by the DSMC, suggested actions by other committees, such as the IRB, UK Risk Management Committee, and other parameters and outcomes as determined by the DSMC. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The MCC DSMC has the authority to amend, temporarily suspend, or terminate the trial based upon patient safety or compliance matters.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

## 13.4 Data Reporting

### 13.4.1 Method

This study will require data submission and reporting via the OnCore Enterprise Research Clinical Trials Management System, which is the official database of the Markey Cancer Center. Instructions for submitting data is listed in study-specific guidance documents authored by a member of the MCC Data Management Team. These guidance documents may include any of the following, as appropriate for the scope of the study: eCRF Completion Guidelines, Data Management Specifications, Subject Console Guide, and Query Resolution Guide. These guidance documents will be approved and housed within OnCore to ensure access to approved versions to facilitate data submission.

### 13.4.2 Responsibility for Data Submission

This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. Study staff are responsible for submitting study data and/or data forms to OnCore as per the Markey Cancer Center SOPs. Study staff are responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

## 13.5 Data Management

Data management will be performed by cross-team members at MCC. These team members will include representatives from the Data Management Team, Biostatistics and Bioinformatics SRF, and the Quality Assurance Office. They will work closely with study staff to ensure timely and accurate data submission. A protocol specific Data Management Plan (DMP) will be authored by a senior data manager in collaboration with the biostatistician and Principal Investigator with each expected to review and approve the finalization of the DMP. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol specific DMP will additionally define the schedule at which data will be accessed by data management and study statistician to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, annual reports, interim analysis and final data analysis.

### 13.6 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities. The Markey DSMC will review all adverse events of this IIT as per its SOP.

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## APPENDIX A.ECOG PERFORMANCE STATUS CRITERIA

| **ECOG Performance Status Scale** | |
|---|---|
| Grade | Descriptions |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work). |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

## APPENDIX B. PSYCHOSOCIAL ASSESSMENT SCREENERS

RATIONALE:
HAI pump chemotherapy requires strict adherence to every 2-week clinic visit schedule, similar to post-transplant regimens. If the cancer patient misses the biweekly scheduled appointment, the implantable chemotherapy infusion pump ceases to function. Consequently, assessment of psychosocial status (social support, treatment compliance, presence of cognitive or psychiatric dysfunction) in addition to medical status is a crucial component in the selection of appropriate candidates for HAIP treatment. Unlike medical risk factors, the evaluation of psychosocial vulnerabilities and risk factors is less established, standardized.

Given the demand of biweekly clinic visits, baseline assessment of psychosocial risk factors was added to our clinical trial in hepatic arterial pump infusion for patients with colorectal liver metastases and intrahepatic cholangiocarcinoma. Thus, in this trial, we adapt an instrument evaluating psychosocial risk factors in transplant populations for current use in HAIP treatment.

The Stanford Integrated Psychosocial Assessment for Transplant (SIPAT tool, created in 2012 and updated in 2015) comprises a standardized approach for assessment of patients being considered as a potential organ transplant recipient. [1, 2] Assessment of both medical and psychosocial status are required under UNOS (United Network for Organ Sharing) guidelines for the transplant listing criteria. Minimal medical listing criteria are well established for organ transplant, however psychosocial listing criteria are less standardized. Psychosocial assessment for transplant listing focuses on identifying potential risk factors that may result in increased risk of post-operative noncompliance and morbidity. Data indicates that pre-transplant psychosocial problems continue post-transplant, and are strongly associated with transplant failure (rejection episodes), mortality and higher risk of infections, hospital readmissions and higher medical costs.

**On the following pages**, you will find

Appendix B.1 – Kentucky Psychosocial Assessment for Hepatic Arterial Infusion Chemotherapy (K-PAHC)

*This is screening questionnaire we developed, via adaptation of the SIPAT, for use in hepatic arterial infusion therapy. Primary edits comprise alteration of language ("transplant" term changed to HAIP) and omission of certain items that are highly liver-transplant-specific and as such, not as salient to cancer populations (e.g., knowledge of medical illness that caused organ failure, risk for recidivism of alcohol abuse, truthfulness vs. deceptive behavior and personality disorders*).

Appendix B.2 original SIPAT screener (version 2.0 PMID: 26517474)

**APPENDIX B.1 KENTUCKY PSYCHOSOCIAL ASSESSMENT FOR HEPATIC ARTERIAL INFUSION CHEMOTHERAPY**

K-PAHC

Patient MRN #: _____

Patient Initials: _____

Patient DOB: _____ / _____ / _____

Today's Date: _____ / _____ / ___202_____

## INSTRUCTIONS for Completing the K-PAHC:

- For Questions I – VIII (on pages 2 – 4), CIRCLE one rating for this patient per question
  - Each question has different response options.
  - Each response rating has a specific numeric score ranging from 0 up to 8
  - Note the numeric score of your selected rating in the Subtotals box, found at the bottom of the page.
  - Sum the subtotals for each page (pages 2-4 only).

## RESULTS: *(this section is filled in after the ratings are completed)*

**K-PAHC Total Raw Score = _____**

**K-PAHC Category regarding candidacy for HAIP Chemotherapy treatment:**

(Please circle one, corresponding to instructions on Page 6)

Excellent Good Minimally Acceptable High Risk / Poor

**I.Availability of Social Support System**

**0) Excellent:** Multiple family, significant others &/or friends have been identified and ARE actively engaged as part of the support system. Excellent back-up system in place.

**2) Good:** Various individuals (e.g., minimum of two people) have been identified and are actively engaged in the patient's care. A back-up system, albeit limited, seems feasible

**4) Moderate:** A back-up system has not been confirmed or appears limited / tentative.

**6) Limited:** The patient's identified support system appears tentative, inconsistent, unreliable, conflicted, uncertain or uncommitted. Identified back-up system's reliability is questionable.

**8) Poor:** Patient unable to identify reliable support system, or identified caregiver has failed to present to clinic. No reasonable back-up support system is in place.

**II.Functionality of Social Support System**

**0) Excellent:** Members of the patient's support team have demonstrated initiative in learning and are already committed to and actively and effectively engaged in the patient's care

**2) Good:** A limited support system has already committed to and has had effective engagement in the patient's care. Or, they are not involved yet, but appear ready to help.

**4) Moderate:** Members of the patient's identified support system may themselves need some support before ready for HAIP treatment process.

**6) Limited:** Members of the identified support system themselves have problems (e.g., medical or psychosocial) which may impair or limit their ability to reliably assist the patient– **OR –** The identified person(s) have expressed doubts/hesitation/conflict.

**8) Poor:** Patient has suffered due to unreliable support system **–OR–** the HAIP team has not been able to work effectively with the patient's support members.

**III.Treatment Compliance/Adherence (Pertinent to medical issues)**

**0) Excellent:** Patient is fully compliant and is an effective partner with medical staff.

**1) Good:** Patient is mostly compliant; requires redirection or reeducation; but no significant negative outcomes are documented.

**4) Moderate:** Only partially compliant or excessive self-management; requires multiple efforts and persuasion from the HAIP team and/or family **– OR –** A patient who just found out about his/her condition and has not received HAIP chemotherapy education.

**6) Limited:** Only compliant after the development of complications or side effects.

**8) Poor:** Evidence of significant treatment non-adherence with negative impact to patient's health (e.g., treatment non-adherence/compliance)

| | |
|---|---|
| Question I = (0, 2, 4, 6, or 8) | |
| Question II = (0, 2, 4, 6, or 8) | |
| Question III = (0, 1, 4, 6, or 8) | |
| *Subtotal, Page 2* | |

**IV. Knowledge & Understanding of the Process of Hepatic Arterial Infusion Chemotherapy**

**0) Excellent Understanding:** High degree of self-directed learning and excellent knowledge of treatment risks & benefits.

**1) Good Understanding:** Patient & support have studied & understood provided literature**.**

**2)Moderate Understanding:** Patient has modest knowledge despite teaching/material provided **– OR –** A patient who just found out about his/her condition and has not received HAIP chemotherapy education.

**4) Limited / Poor Understanding:** Patient only has only rudimentary knowledge despite intensive teaching by providers.

**V. Presence of Psychopathology**

**0) None:** No history of psychiatric problems.

**1) Mild Psychopathology:** Present or History **of mild psychopathology** (e.g., Adjustment Disorder). Usually a self-limited problem without significant negative impact on level of functioning. No hospitalization needed. **No History of SI/SA** (suicidal ideation/attempts)**.**

**4) Moderate Psychopathology:** Present or history of moderate psychopathology (e.g., depressive or anxiety disorder)**.** Treatment, if needed, has been/was effective, good compliance. No SI/SA at present; although **possible history SI/SA in past**.

**6) Severe Psychopathology: Present or** history of severe psychopathology (e.g., severe mood anxiety or psychotic disorder with significant impairment of psychosocial functioning)**.** Patient has needed **psychiatric hospitalization(s) in the past or "+" history of SI/SA**.

**8) Extreme Psychopathology:** Present or history of severe psychopathology (e.g., as above) usually associated with repeated episodes of psychosis or suicidality; and associated with a history of multiple psychiatric hospitalizations and/or treatment with ECT; or history of multiple SI/SA).

**VI. Assessment of Current Cognitive Functioning (use clinical judgment or MMSE)**

0) Cognitive Functioning within Normal Limits: (MMSE ≥ 26)
2) Borderline Level of Cognitive Functioning: (MMSE = 22 – 25)
4) Impaired Cognitive Functioning: (MMSE < 22)

| | |
|---|---|
| Question IV = (0, 1, 2, or 4) | |
| Question V = (0, 1, 4, 6 or 8) | |
| Question VI = (0, 2, or 4) | |
| *Subtotal, Page 3* | |

**VII. Alcohol Use/Abuse/Dependence**

**0) None:** No history of alcohol use.

**1) Alcohol Use – No Abuse:** History of minimal alcohol use which has caused no social or medical problems (i.e., no abuse). If requested by the team the patient promptly discontinued all alcohol use.

**4) Moderate Alcohol Abuse:** History of moderate alcohol abuse evidenced by excessive drinking and possible deleterious bodily or social effects. Patient quit use as soon as patient learned of disease or when first told by MD. Patient may have required treatment/intervention in order to achieve sobriety.

**8) Dependence *OR* Severe/Extreme Abuse:** History of severe alcohol abuse or dependence. Patient required treatment/ intervention in order to achieve sobriety (or refused treatment); or continued to use after disease progressed, developing medical complications. **– OR --** History of extreme alcohol abuse & multiple relapses despite warning and/or treatment. Patient continued to drink until just prior to presentation or only quit drinking when too sick to continue.

**VIII. Substance Use/Abuse/Dependence – Including Prescribed & Illicit Substances**

(Use clinical judgment)

**0) None:** No history of illicit substance use; or abuse of prescribed substances.

**2)** History of **minimal** substance abuse (illicit or prescribed substances). Quit use as soon as patient learned of disease or when first told by MD.

**4) Moderate Substance Abuse:** History of moderate substance abuse (illicit or prescribed substances), but quit use as soon as patient learned of disease or when first told by MD. Patient may have required treatment/intervention in order to achieve remission.

**8) Dependence *OR* Severe/Extreme Abuse:** History of dependence or severe abuse (illicit or prescribed substances). Patient required treatment/intervention in order to achieve sobriety (or refused treatment/intervention); or continued to use after medical complications**. – OR--** History of multiple relapses despite warning and/or treatment. Patient continued to use until just prior to presentation or only quit when too sick to continue.

| | |
|---|---|
| Question VII = (0, 1, 4, or 8) | |
| Question VIII = (0, 2, 4, or 8) | |
| *Subtotal, Page 4* | |

## ABSOLUTE CONTRAINDICATIONS –

**Place an "X" by the presence of any of the following seven risk factors.**

___ Inadequate social support system

___ Major Non-adherence with treatment (e.g., long periods of no follow-up and missed appointments, noncompliance with medications, etc.)

___ Active severe/extreme illicit substance use

___ Active severe/extreme alcohol dependence/abuse

___ Active manic or psychotic symptoms that may impair adherence with treatment

___ Current suicidal ideation (in a patient with a history of multiple suicidal attempts)

___ Severe Dementia

**Total number of Risk Factors (RF) / Contraindications =** _____
*(this will be between 0 – 7)*

## SCORING INSTRUCTIONS for 8 ITEMS on the K-PAHC:

On each of the EIGHT questions (I – VIII), CIRCLE one rating for the patient.

- Each rating option has a numeric score ranging from 0 up to 8
- Note the numeric score of your selection in the Subtotals box.
- Sum these, and enter that total in the bottom row of the Subtotals box
- In the table below, Enter the subtotals of the raw scores from Pages 2 – 4. Sum these subtotals to arrive at the total score.

| | |
|---|---|
| *Subtotal, Page 2 (questions 1-3)* | |
| *Subtotal, Page 3 (questions 4-6)* | |
| *Subtotal, Page 4 (questions 7-8)* | |
| ***K-PAHC total score:*** | |

## ABSOLUTE CONTRAINDICATIONS –

**Place an "X" by the presence of any of the following seven risk factors.**

___ Inadequate social support system

___ Major Non-adherence with treatment (e.g., long periods of no follow-up and missed appointments, noncompliance with medications, etc.)

___ Active severe/extreme illicit substance use

___ Active severe/extreme alcohol dependence/abuse

___ Active manic or psychotic symptoms that may impair adherence with treatment

___ Current suicidal ideation (in a patient with a history of multiple suicidal attempts)

___ Severe Dementia

**Total number of Risk Factors (RF) / Contraindications =** _____
*(this will be between 0 – 7)*

## SCORING INSTRUCTIONS for 8 ITEMS on the K-PAHC:

On each of the EIGHT questions (I – VIII), CIRCLE one rating for the patient.

- Each rating option has a numeric score ranging from 0 up to 8
- Note the numeric score of your selection in the Subtotals box.
- Sum these, and enter that total in the bottom row of the Subtotals box
- In the table below, Enter the subtotals of the raw scores from Pages 2 – 4. Sum these subtotals to arrive at the total score.

| | |
|---|---|
| *Subtotal, Page 2 (questions 1-3)* | |
| *Subtotal, Page 3 (questions 4-6)* | |
| *Subtotal, Page 4 (questions 7-8)* | |
| ***K-PAHC total score:*** | |

# HAIP Candidacy:
# Interpreting the K-PAHC score and risk factors

K-PAHC TOTAL Score = _____

## K-PAHC Score Interpretation

**0 – 5** **Excellent Candidate**

- Recommend without reservations

**6 – 10** Good Candidate

- Recommend in the absence of any absolute contraindication – monitoring of identified risk factors may be required.

---

**11 – 28** **Minimally Acceptable Candidate**

- Candidacy for HAIP treatment is at the discretion of the HAIP team. Identified risk factors must be carefully considered.

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**29 – 56** **Poor / High Risk Candidate**

- HAIP treatment is not recommended.

Please note the score and category of candidacy for this patient on Page 1.

**APPENDIX B.2 STANFORD INTEGRATED PSYCHOSOCIAL ASSESSMENT FOR TRANSPLANT (2015 VERSION)**

***Adapted for use with Hepatic Arterial Infusion Pump Chemotherapy***

**Patient Name: _____**

**Date: _____**

**EMR #: _____**

**SIPAT Total Score: _____**

**SIPAT Category regarding candidacy for HAIP treatment:**

(please circle one)

| Excellent | Good | Minimally Acceptable | High Risk / Poor |
|---|---|---|---|

### *A. PATIENT'S READINESS LEVEL*

I.Knowledge & Understanding of Medical Illness Process (that caused specific organ failure)

0) **Excellent Understanding:** Patient & support system are fully aware of the cause(s) of illness leading to organ failure and need for transplantation. Both patient and support system demonstrate a high degree of self-directed learning.
1) **Good Understanding:** Patient & support system are mostly aware of the cause(s) of the illness process and contribution to current health status.
2) **Moderate Understanding:** Patient has modest knowledge despite teaching/material provided **– Or –** A patient who just found out about his/her condition and has not received transplant-related education.
3) **Limited Understanding:** Patient has only rudimentary knowledge despite of years of illness and/or extensive teaching by providers.
4) **Poor Understanding:** Extreme denial or indifference is evident.

II.Knowledge & Understanding of the Process of Transplantation

5) **Excellent Understanding:** High degree of self-directed learning and excellent knowledge of treatment risks & benefits.
6) **Good Understanding:** Patient & support have studied & understood provided literature**.**
7) **Moderate Understanding:** Patient has modest knowledge despite teaching/material provided **– Or –** A patient who just found out about his/her condition and has not received transplant-related education.
8) **Limited Understanding:** Patient only has only rudimentary knowledge despite of intensive teaching by providers.
9) **Poor Understanding:** Extreme denial or indifference evident.

III.Willingness/Desire for Treatment (Transplant)

10) **Excellent:** Patient is highly motivated and proactively involved in his/her medical care.
11) **Good:** Patient expresses interest and is actively involved in his/her care
12) **Moderate:** Patient appears ambivalent; only passively involved in process; actions are only acceptable at best. **– Or –** A patient who just found out about his/her condition and has not received transplant-related education.
13) **Limited: Patient who has limited involvement in his/her care.** Family member or medical team appears more interested in the transplant process than patient.
14) **Poor:** Family member or MD pushing patient to participate in the transplantation evaluation process; the patient is uninterested or mostly unengaged.

**II.** Treatment Compliance/Adherence (Pertinent to medical issues)

**0) Excellent:** Patient is fully compliant and is an effective partner with medical staff.

**2) Good:** Patient is mostly compliant; requires redirection or reeducation; but no significant negative outcomes are documented.

**4) Moderate:** Only partially compliant or excessive self-management; requires multiple efforts and persuasion from the Transplant team and/or family **– Or –** A patient who just found out about his/her condition and has not received transplant-related education.

**6) Limited:** Only compliant after the development of complications or side effects.

**8) Poor:** Evidence of significant treatment non-adherence with negative impact to patient's health (e.g., treatment non-adherence/compliance; continued substance use after learning of illness).

V.Lifestyle Factors (Including diet, exercise, fluid restrictions; and habits according to organ)

**0)** Able to modify & sustain needed changes- self initiated.

**1)** Patient is responsive to recommended changes.

**2)** Patient is reluctant, but compliant with recommended changes, after much prompting and encouragement from support & transplant team.

**3)** Patient complies with recommended changes only after the development of complications.

**4)** Unhealthy diet & sedentary lifestyle. Reluctant to change despite efforts from treatment team and support system (e.g., non-adherence with recommended restrictions; continued substance use after learning of illness).

***B. SOCIAL SUPPORT SYSTEM***

VI.Availability of Social Support System

**0) Excellent:** Multiple family, significant others &/or friends have been identified and ARE actively engaged as part of the support system. Excellent back-up system in place.

**2) Good:** Various individuals (e.g., minimum of two people) have been identified and are actively engaged in the patient's care. A back-up system, albeit limited, seems feasible.

**4) Moderate:** A back-up system has not been confirmed or appears limited / tentative.

6) **Limited:** The patient's identified support system appears tentative, inconsistent, unreliable, conflicted, uncertain or uncommitted. Identified backup system's reliability is questionable..

**8) Poor:** Patient unable to identify reliable support system, or identified caregiver has failed to present to clinic. No reasonable back-up support system is in place.

VII.Functionality of Social Support System

**0) Excellent: Members of the** support team have demonstrated initiative in learning and are already committed to and actively and effectively engaged in the patient's care.

**2) Good:** A limited support system has already committed to and has had effective engagement in the patient's care. Or, they are not involved yet, but appear ready to help.

**4) Moderate: Members of the** patient's identified support system may themselves need some psychosocial work before they are ready for transplantation.

**6) Limited:** Member of the identified support system themselves have problems (e.g., medical or psychosocial) which may impair or limit their ability to reliably assist the patient

– **OR –** The identified person(s) have expressed doubts/hesitation/conflict.

**8) Poor:** Patient has suffered due to unreliable support system **–OR–** the transplant team has not been able to effectively work with the support team.

VIII. Appropriateness of physical living space & environment

**0) Excellent:** Patient has excellent, long-term, permanent and adequate housing.
**1) Good:** Patient has some stable housing arrangement, albeit not optimal.
**2) Adequate:** Reported arrangement is only temporary and/or tenuous.
**3) Limited:** Unable to confirm reported arrangement or perceived to be inappropriate.
**4) Poor:** Non-existent; patient has no stable living arrangements **–OR–** lives in environment that doesn't promote Transplant health.

### *C. PSYCHOLOGICAL STABILITY & PSYCHOPATHOLOGY*

IX.Presence of Psychopathology (mood, anxiety, psychosis & others)

**(Other than organic psychopathology [Q.X] & personality disorders [Q.XI]) (Use clinical judgment. If the patient demonstrates clinical signs of psychopathology please follow up with appropriate diagnostic exam (e.g., depression (Q.IXa] or anxiety [QIXb])**

**0) None:** No history of psychiatric problems.
**2) Mild Psychopathology** – Present or History **of mild psychopathology** (e.g., Adjustment disorder). Usually a self-limited problem without significant negative impact on level of functioning. No hospitalization needed. **No History of SI/SA.**
**4) Moderate Psychopathology** – Present or history of moderate psychopathology (e.g., depressive or anxiety disorder)**.** Treatment, if needed, has been/was effective, good compliance. No SI/SA at present; although **possible history SI/SA in past**.
**6) Severe psychopathology. Present or** history of severe psychopathology (e.g., severe mood, anxiety or psychotic disorder with significant impairment of psychosocial functioning)**.** Patient has needed **psychiatric hospitalization(s) in the past or "+" history of SI/SA.**
**8) Extreme psychopathology.** Present or history of severe psychopathology (e.g., as above) usually associated with repeated episodes of psychosis or suicidality; and associated with a history of multiple psychiatric hospitalizations and/or treatment with ECT; or history of multiple SI/SA). Patient may be in need of acute psychiatric intervention before proceeding.

IXa. Assessment of Depression (Use clinical judgment; Patient Health Questionnaire [PHQ] or Beck Depression Inventory [BDI], if available)

**0) No** Clinical Depression; or PHQ < 5; or BDI= 0 – 13.
**1) Mild** Clinical Depression; or PHQ = 5 – 9; or BDI= 14 – 19.
**2) Moderate** Clinical Depression; or PHQ = 10 – 19; or BDI= 20 – 28.
**3) Severe** Clinical Depression (includes psychosis and/or suicidality); or PHQ ≥ 20; or BDI = 29 – 63.

IXb. Assessment of Anxiety (Use clinical judgment; Generalized Anxiety Disorder questionnaire [GAD-7] or Beck Anxiety Inventory [BAI], if available)

**0) No** Clinical Anxiety; or GAD-7 < 5; or BAI = 0 – 7.
**1) Mild** Clinical Anxiety; or GAD-7 = 5 – 9; or BAI = 8 – 15.
**2) Moderate** Clinical Anxiety; or GAD-7 = 10 – 14; or BAI = 16 – 25.
**3) Severe** Clinical Anxiety; or GAD-7 ≥ 15; or BAI = 26 – 63.

X.History of Organic Psychopathology or Neurocognitive Impairment:

**Illness or medication induced psychopathology (e.g., encephalopathy, Rx-induced psychosis)**

**0) None:** No history of disease or treatment induced psychiatric problem.
**1) Mild Organic Psychopathology:** history or at present.
**3) Moderate Organic Psychopathology:** history or at present.
**5) Severe Organic Psychopathology:** history or at present.

Xa. Assessment of Current Cognitive Functioning (Use clinical judgment or MoCA or MMSE, if available)

**0) Cognitive Functioning Within Normal Limits;** or MoCA / MMSE ≥26.
**1) Borderline** Level of Cognitive Functioning; or MoCA / MMSE = 22 –25.
**2) Impaired** Cognitive Functioning; or MoCA / MMSE < 22.

XI. Influence of Personality Traits vs. Disorder

**0) None:** No history of significant personality disorder or psychopathology/traits.
**1) Minimal:** History of some personality traits or mild psychopathology only in response to illness, medical treatment or psychosocial stressors (i.e., none at baseline). No characterological interference with medical treatment. No history of SI/SA.
**2) Mild:** History of minimal personality traits or psychopathology at baseline, or in response to illness, medical treatment or psychosocial stressors. Treatment, if needed, has been effective. Patient with good compliance and no characterological interference with medical treatment. No history of SI/SA.
**3) Moderate:** History of moderate personality psychopathology or traits, at baseline; evidence of exacerbation & poor coping in response to illness, medical treatment or psychosocial stressors. "+" need for multiple psychiatric hospitalizations in the past. Some characterological interference with medical treatment. "+"/"-" History of SI/SA.
**4) Severe:** History of very severe character pathology present at baseline; evidence of significant exacerbation & poor coping in response to illness, medical treatment or psychosocial stressors. Significant characterological interference with medical treatment. Patient is in need for acute psychiatric intervention before proceeding, or history "+" need for multiple psychiatric hospitalizations and/or SI/SA in the past

X11. Effect of Truthfulness vs. Deceptive Behavior in Presentation

**0)** No evidence of deceptive behavior in history or at present.

**2)** Patient has not volunteered some negative information, but truthfully answered on direct questioning.

**4)** Patient has not been fully forthcoming with negative information, but provides it on confrontation.

**6)** Patient has not been fully forthcoming with negative information. Information obtained only from external sources.

**8)** There is clear evidence of deceptive behavior as evidence by records, collateral information or testing.

XIII. Overall Risk for Psychopathology (including items IX – XII)

**0) None:** No history of personal or familial psychiatric problems; no psychiatric complications in response to illness, medical treatment or psychosocial stressors**.**

**1) Minimal:** History of acceptable coping with current or previous medical challenges or psychosocial stressors. No psychiatric complications in response to illness, medical treatment or psychosocial stressors**.**

**2) Mild:** History of poor coping with current or previous medical challenges or psychosocial stressors. Only minimal, if any, psychiatric complications in response to illness, medical treatment or psychosocial stressors**.**

**3) Moderate:** History of problematic coping with current or previous medical challenges or psychosocial stressors. Patient has experienced some psychiatric complications to medical illness, interventions or treatment **–OR–** Presence of moderate psychopathology in family of origin.

**4) Severe:** History of significant problems with coping in response to current or previous medical challenges or psychosocial stressors. **–OR–** History of significant psychopathology present in family of origin**.**

### *D. LIFESTYLE & EFFECT OF SUBSTANCE USE*

XIV. Alcohol Use/Abuse/Dependence

**0) None:** No history of alcohol use.

**2) ALCOHOL USE – NO ABUSE:** History of minimal alcohol use which has caused no social or medical problems (i.e., no abuse). If requested by the team the patient promptly discontinued all alcohol use.

**4) MODERATE ALCOHOL ABUSE:** History of moderate alcohol abuse evidenced by excessive drinking and possible deleterious bodily or social effects. Patient quit use as soon as patient learned of disease or when first told by MD. Patient may have required treatment/intervention in order to achieve sobriety.

**6) DEPENDENCE OR SEVERE ABUSE:** History of severe alcohol abuse or dependence. Patient required treatment/ intervention in order to achieve sobriety (or refused treatment); or continued to use after disease progressed, developing medical complications.

**8) DEPENDENCE OR EXTREME ABUSE:** History of extreme alcohol abuse & multiple relapses despite warning and/or treatment. Patient continued to drink until just prior to presentation or only quit drinking when too sick to continue.

XV. Alcohol Use/Abuse/Dependence - Risk for Recidivism (Use clinical judgment or use AUDIT, if available)

**0) None:** No history of Alcohol use (Audit = 0).

**1) Low Risk:** (AUDIT 1 – 7).

**2) Moderate Risk:** (AUDIT 8 – 15).
**3) High Risk:** (AUDIT 16 – 19).
**4) Extreme Risk:** History of recidivism after prior treatment or after an extended period of sobriety (AUDIT > 20).

XVI. Substance Use/Abuse/Dependence – Including Prescribed & Illicit Substances (Use clinical judgment or use DAST, if available)

**0) None:** No history of illicit substance use; or abuse of prescribed substances.

**2)** History of **minimal** substance abuse (illicit or prescribed substances). Quit use as soon as patient learned of disease or when first told by MD.

**4) MODERATE SUBSTANCE ABUSE:** History of moderate substance abuse (illicit or prescribed substances), but quit use as soon as patient learned of disease or when first told by MD. Patient may have required treatment/intervention in order to achieve remission.

**6) DEPENDENCE OR SEVERE ABUSE:** History of dependence or severe abuse (illicit or prescribed substances). Patient required treatment/intervention in order to achieve sobriety (or refused treatment/intervention); or continued to use after disease progressed, developing medical complications.

**8) DEPENDENCE OR EXTREME ABUSE:** History of dependence or extreme substance (illicit or prescribed substances); History of multiple relapses despite warning and/or treatment. Patient continued to use until just prior to presentation or only quit when too sick to continue.

XVI. Substance Use/Abuse/Dependence – Including Prescribed & Illicit Substances - Risk for Recidivism

**0) None:** No history of illicit substance Use; or abuse of prescribed substances (DAST = 0).
**1) Low Risk:** (DAST 1 – 2).
**2) Moderate Risk:** (DAST 3 – 5).
**3) High Risk:** (DAST 6 -8).
**4) Extreme Risk:** History of recidivism after prior treatment or after an extended period of sobriety (DAST 9 – 10).

XVIII. Nicotine Use/Abuse/Dependence

**0) None:** Never used tobacco in any form. No history of Nicotine Use/Abuse.
**1) Past use:** Quit > 6 months ( " – " nicotine test).
**3) Recent use:** Quit <6 months ( " – " nicotine test).
**6) Active use:** Still currently smoking (per admission, accessory source report, or "+" test).

## SIPAT TOTAL Score:

**SIPAT Score Interpretation**

| | |
|---|---|
| 0 – 6 | Excellent candidate<br>Recommend to list without reservations. |
| 7 – 20 | Good candidate<br>Recommend to list – although monitoring of identified risk factors may be required. |
| 21 – 39 | Minimally Acceptable Candidate<br>Consider Listing. Identified risk factors must be satisfactorily addressed before representing for consideration. |
| 40 – 69 | Poor Candidate<br>Recommend deferral while identified risks are satisfactorily addressed. |
| > 70 | High Risk candidate, significant risks identified<br>Surgery is not recommended while identified risk factors continue to be present. |

**CONSIDERATIONS FOR FINAL PSYCHOSOCIAL RECOMMENDATIONS:**

**The following contraindications or risk factors were identified:**

**ABSOLUTE CONTRAINDICATIONS:**

_____ Inadequate social support system

_____ Active illicit substance use

_____ Active alcohol dependence/abuse

_____ Active nicotine abuse

_____ Active manic or psychotic symptoms that may impair adherence with treatment

_____ Current suicidal ideation (in a patient with a history of multiple suicidal attempts)

_____ Dementia (requires a formal diagnosis by psychiatrist, neurologist or geriatrician)

_____ Non-adherence with treatment ⌖

_____ History of recidivism of substance abuse after previous organ transplantation ⌖

⌖= in the case of a re-transplant candidate.

**RELATIVE CONTRAINDICATIONS**

**A. High Risk:**

___ Active alcohol use (suspected to be directly causative/exacerbating medical problem)

_____ Active abuse of prescribed substances

_____ Limited adherence with treatment (e.g., self-management with interference with care)

_____ Deceptive behavior

_____ Current suicidal ideation (in a patient with no prior history of multiple suicidal attempts)

_____ High degree of denial or ambivalence regarding transplantation

_____ Personality disorders

- Cluster A (i.e., Paranoid, Schizotypal)
- Cluster B (i.e., Antisocial, Borderline, Narcissistic)

**B. Moderate Risk:**

_____ Alcohol use (not directly causative of medical problem)

_____ Prescribed ("medical") marijuana use

_____ Inability to understand relevant information and poor receptiveness to education

_____ Reluctance to relocate near care center

_____ Absence of adequate living environment –OR– Reluctance to relocate to a more appropriate housing environment

_____ Limited or restricted access to resources

_____ Controlled major psychiatric disorder

- History of suicidal attempts
- Mood disorders
- Psychotic disorders
- Severe anxiety disorders
- Mental retardation

**C. Lower Risk:**

_____ Obesity: BMI > 30 – 40kg/m2

_____ Limited literacy

_____ Cognitive disorders

## APPENDIX C. CLAVIEN-DINDO CLASSIFICATION OF SURGICAL COMPLICATIONS

Clavien P, Barkun J, doe Oliveria M, et al. The Clavien-Dindo Classification of Surgical Complications: Five-Year Experience. Annals Surgery. 2009; 250(2): 187-96. PMID: 19638912

| **Clavien-Dindo Classification for Surgical Complications** | |
|---|---|
| **Grades** | **Definition** |
| **Grade I:** | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. |
| | Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside. |
| **Grade II:** | Requiring pharmacological treatment with drugs other than such allowed for Grade I complications. |
| | Blood transfusions and total parenteral nutrition are also included. |
| **Grade III:** | Requiring surgical, endoscopic or radiological intervention |
| **Grade III-a**: | intervention not under general anesthesia |
| **Grade III-b:** | intervention under general anesthesia |
| **Grade IV:** | Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management |
| **Grade IV-a:** | single organ dysfunction (including dialysis) |
| **Grade IV-b:** | multi organ dysfunction |
| **Grade V:** | Death of a patient |
| **Suffix 'd':** | If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication. |
| ‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA);<br>IC: Intermediate care;<br>ICU: Intensive care unit<br>**www.surgicalcomplication.info** | |

## APPENDIX D. RECIST V1.1

Response and disease progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). 42

RECIST v1.1:
Eisenhauer EZ, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-47, 2009. PMID: 19097774

## APPENDIX E. MEDTRONIC SYNCHROMED II IMPLANTABLE INFUSION PUMP MANUALS

### Manuals for Implantation and Pump Refills

(these manuals will be inserted once this protocol is converted to a pdf)

IRB Approval
2/3/2020
IRB # 55664
IRB1

**KEY INFORMATION FOR MCC-19-GI-109 (CAVNAR PUMP): FEASIBILITY PILOT OF HEPATIC ARTERIAL INFUSION (HAI) CHEMOTHERAPY IN A RURAL CATCHMENT AREA, USING THE CODMAN TAPERED VASCULAR CATHETER WITH THE SYNCHROMED II PUMP, FOR PATIENTS WITH UNRESECTABLE COLORECTAL CANCER LIVER METASTASES (CLM) OR UNRESECTABLE INTRAHEPATIC CHOLANGIOCARCINOMA (ICC)**

We are asking you to choose whether or not to volunteer for a research study about cancers that involve the liver. We are asking you because have a colorectal cancer that has spread to your liver or a cancer that is located in the bile ducts within the liver that cannot be removed by surgery. This page is to give you key information to help you decide whether to participate. We have included detailed information after this page. Ask the research team questions. If you have questions later, the contact information for the research investigator in charge of the study is below.

## WHAT IS THE STUDY ABOUT AND HOW LONG WILL IT LAST?

Hepatic arterial infusion (HAI) therapy is a procedure in which chemotherapy drugs are directly delivered to the liver through a pump that is surgically implanted into the liver. This approach can produce higher local concentrations of the infused drug with few systemic side effects. The manufacturer of the C3000 Codman Pump, the main device used for HAI, terminated production of the pump in April 2018. Thus, alternate means of employing HAI need to be devised in order to continue to offer this therapy. This study will use a similar pump, the Synchromed II, made by Medtronic that has been approved by the FDA for chronic intravascular infusion of floxuridine (FUDR), physiological saline and/or heparin. The Medtronic pump combined with a Codman vascular catheter (still being manufactured and FDA approved) have previously been successfully used off label at other cancer centers. If safety is demonstrated in a larger population, this would provide an option for appropriate patients to receive HAI therapy.

By doing this study we hope to learn about the safety of using the Medtronic Synchromed II pump connected to the Codman vascular catheter combined with standard of care systemic therapy. The combined systemic therapies used include FOLFOX, FOLFIRI, or irinotecan/oxaliplatin for colorectal cancer, and gemcitabine/cisplatin or gemcitabine alone for intrahepatic cholangiocarcinoma.

Your participation in this research will last about 3 and a half years. The first 6 months will be for treatment. After that, you will be followed for up to 3 additional years. You may not receive treatment for the full 6 months if your disease progresses (worsens) during therapy.

## WHAT ARE KEY REASONS YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

Taking part in this study may or may not make your health better. We do know that the information from this study will help doctors learn more about the safety of using the Synchromed II hepatic artery infusion pump and the Codman catheter together for the administration of standard chemotherapy in patients with your condition. This approach may result in higher concentrations of drug getting to the tumor site(s) and as a result be more effective in treating patients with these conditions. For a complete description of benefits, refer to the Detailed Consent.

## WHAT ARE KEY REASONS YOU MIGHT CHOOSE NOT TO VOLUNTEER FOR THIS STUDY?

We do not know if HAI therapy via the Medtronic pump and Codman vascular catheter will help your cancer. The standard treatment for your condition is to receive systemic treatment without the addition of HAI therapy. For a complete description of alternate treatment/procedures, refer to the Detailed Consent and/or Appendix.

## DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any services, benefits or rights you would normally have if you choose not to volunteer.

## WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS OR CONCERNS?

If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study contact Michael Cavnar, MD of the University of Kentucky, Department of Surgical Oncology at 859-323-8920.

If you have any concerns or questions about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

**DETAILED CONSENT:**

**ARE THERE REASONS WHY YOU WOULD NOT QUALIFY FOR THIS STUDY?**

You should not participate in this study if you are:

- Under the age of 18
- Pregnant or breastfeeding
- You are currently taking any other investigational agents
- You are unwilling/unable to commit to the amount of time needed to take part in this study
- There are other criteria that must be met to take part in this study that your study doctor will review with you.

**WHERE WILL THE STUDY TAKE PLACE AND WHAT IS THE TOTAL AMOUNT OF TIME INVOLVED?**

The research procedures will be conducted at University of Kentucky Medical Center and Markey Cancer Center facilities. The duration of your participation and the number of visits you will be asked to make may vary according to how you respond to treatment. You will need to come about 24 times during the study. The length of each visit will depend upon which trial period you are taking part in. Below is a table summarizing the number of visits and their duration.

| **Trial Period** | **Number of Visits** | **Duration** |
|---|---|---|
| Pre-Study/Screening (up to 30 days prior to surgery) | 1 | 2 hours |
| Surgery/Device implantation | 1 | 4 hours plus your recovery will be monitored for an additional 5 days in the hospital after surgery |
| Chemotherapy Cycle 1 | 4 (Day 1, 15, 28) | 5-6 hours/visit plus an additional continuous infusion at home for next 48 hours if receiving FOLFOX and FOLFIRI + 5FU.<br>4 hours/visit if receiving Gemcitabine infusion. |
| Chemotherapy Cycles 2-6 | 4 per cycle (Day 1, 15, 28) | 5-6 hours/visit plus an additional continuous infusion at home for next 48 hours if receiving FOLFOX and FOLFIRI + 5FU.<br>4 hours/visit if receiving Gemcitabine infusion. |
| Last visit on treatment | 1 | 2 hours |
| Off Treatment visit (within 30 days after last dose of chemotherapy) | 1 | 2 hours |
| Follow up at years 1, 2 & 3 | 1 visit/phone call each year | 20 minutes per call |
| Off study | 1 phone call | 20 minutes per call |

**WHAT WILL YOU BE ASKED TO DO?**

**Pre-Study/Screening Visit (up to 30 days prior to starting study treatment)**

In order to find out if you can take part in the study, the following procedures will be done:

The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken in the last 90 days or are taking now. The study doctor will ask you questions to determine whether you are a good candidate for HAI treatment and to learn more about your ability to perform daily tasks.

The study doctor will collect demographic information.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also have an Electrocardiogram (EKG) to evaluate your heart's functioning.

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) via venipuncture and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample for correlative research studies.

If you are a woman who might be able to get pregnant, you will be required to have a urine test to check for pregnancy before you start the study. If you are currently pregnant or have immediate plans to become pregnant, you may not take part in this study. Both men and women of childbearing potential who take part in the study must agree to use an effective form of birth control (such as an intrauterine device (women only) and/or condoms) during the study, as well as 90 days after the last dose of study treatment. You should discuss birth control options for you and your partner with your study doctor prior to starting the study.

All lab tests and radiographic (imaging) studies should be completed within 4 weeks prior to registration/initiation of treatment.

You may be asked to undergo a computed tomography (CT) scan of your liver if you have not had a scan in the last 6 months or if you had one but later had a surgical intervention on the liver. A CT scan combines a series of X-ray images taken from different angles around your body and uses computer processing to create cross-sectional images (slices) of the bones, blood vessels and soft tissues inside your body.

You may be asked to undergo a computed tomography (CT) scan of your chest, abdomen, pelvis within 4 weeks of starting treatment (surgery).

**During the study…**

**On the day of your surgery the following procedures will occur:**

You will undergo surgery to implant the HAI pump and catheter.

After the pump has been implanted you will be ask to undergo a Perfusion flow scan. This is a type of CT scan that is done to evaluate the flow of blood to the liver.

**Chemotherapy Cycles**

HAI only (Cycle 1, Day 1- Day 15

On Day 1, the study doctor will monitor the amount of drug that is still in the pump to ensure it is working properly. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other

over-the-counter (e.g., aspirin) items that you have taken. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also be asked about any side effects you have experienced since your last visit.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample for correlative research studies.

During your first visit after surgery (no earlier than 14 days after surgery), you will be evaluated to determine if you are appropriately recovered. If so HAI chemo will begin with FUDR. If you need more time to recover, you may be asked to come back within 1-2 weeks to be reassessed. If you are not able to begin HAI on your first visit after surgery, your pump will be filled with heparinized saline, which must be repeated every 14 days until therapy starts. Heparin is an anticoagulant (blood thinner) that prevents the formation of blood clots. Saline is a solution of salt in water.

Systemic Chemotherapy only (Cycle 1, Day 15- Day 28)

On Day 15, the study doctor will monitor the amount of drug that is still in the pump to ensure it is working properly. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also be asked about any side effects you have experienced since your last visit.

Once you have been able to complete 2 weeks of HAI chemotherapy with FUDR, you will begin systemic chemotherapy. If you are being treated for CLM you will receive FOLFOX, FOLFIRI or Irinotecan/oxaliplatin every 2 weeks. If you are being treated for ICC you will receive Gemcitabine/cisplatin or Gemcitabine only every 2 weeks. Each of these are standard treatment plans. During this time, your pump will be emptied and refilled with heparin and saline.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) and urine to check your heart, blood, liver, thyroid, and kidney functions. On day 15, you will also be asked to provide a blood sample for correlative research studies.

HAI with Systemic chemotherapy (Cycles 2-6, Day 1- Day 15

The study doctor will monitor the amount of drug that is still in the pump to ensure it is working properly. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also be asked about any side effects you have experienced since your last visit.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample for correlative research studies.

You will receive FUDR via the HAI pump and standard systemic chemotherapy based on your disease type (CLM or ICC) as discussed above.

Systemic chemotherapy only (Cycles 2-6, Day 15-28)
The study doctor will monitor the amount of drug that is still in the pump to ensure it is working properly. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken. You will also be asked about any side effects you have experienced since your last visit.

You will have a full physical examination performed by a medical doctor to check your health status. He or will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) and urine to check your heart, blood, liver, thyroid, and kidney functions.

You will receive standard systemic chemotherapy based on your disease type (CLM or ICC) as discussed above. During this time, your pump will be emptied and refilled with heparin and saline.

Last visit on treatment

During your last treatment visit the study doctor will monitor the amount of drug that is still in the pump. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also be asked about any side effects you have experienced for 30 days after completing therapy.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

You will be asked to provide a sample of your blood (about 3 tablespoons, or 45 milliliters) and urine to check your heart, blood, liver, thyroid, and kidney functions. You will also be asked to provide a blood sample for correlative research studies.

Off-Treatment visit
During your last treatment visit the study doctor will monitor the amount of drug that is still in the pump. The study doctor will ask you about your medical history, including any medicines, herbal/natural remedies, vitamins, or other over-the-counter (e.g., aspirin) items that you have taken. Your blood pressure, heart rate, the number of times you breathe per minute, your body temperature (known as vital signs), and your height and weight will be measured. You will also be asked about any side effects you have experienced for 30 days after completing therapy.

You will have a full physical examination performed by a medical doctor to check your health status. He or she will evaluate your performance status (a measure of your general well-being and your abilities to carry out activities of daily life)

Follow up/Off study
The study doctor will follow you for up to 3 years after completion of treatment. During this time, the study doctor or team may see you during your standard of care visits or you may be contacted via phone to check on your health status. This call should take no more than 20 minutes.

**WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?**

Surgery for Pump implantation

Risk of HAI pump implantation surgery are overall low but include bleeding, infection including abscess (a swollen area within body tissue containing pus), wound infection, pneumonia, urinary tract infection; injury to other structures including pancreas, bowel, liver, biliary tree; postoperative ileus or bowel obstruction (blockage); hernia; venous thromboembolism

(blockage caused by a blood clot that has dislodged from another part of the body); complications relating to heart and lungs; stroke; very low risk of death.

Catheter and Pump

Possible risks associated with the catheter and pump are infection requiring antibiotics and possibly pump removal, blood clot in an artery in the liver, pump malfunction, catheter blockage and intra-abdominal bleeding. If the drug is not emptied from the pump in 14 days or less, there is a risk of becoming toxic from extended chemotherapy. If the pump is not filled and runs dry, thrombosis/pump failure will occur, which is usually unsalvageable. The rate of pump failure is less than 1%. If this occurs, you will receive standard systemic therapy alone if the pump is unusable. If your bilirubin goes up and does not come down after holding treatment and using dexamethasone in the pump, an ERCP (endoscopic retrograde cholangiopancreatography) will be done to evaluate for a narrowing of the bile duct, which would require an endoscopic biliary stent.

You should not have an MRI while participating in this study as the pump is not compatible with MRIs.

**Side Effects of Agents in this Study**

FUDR
Toxicities seen with systemic administration such as bone marrow suppression are not typically seen with intrahepatic administration. Adverse reactions to the arterial infusion of FUDR are generally related to the procedural complications of regional arterial infusion.

The more common adverse reactions to the drug are nausea, vomiting, diarrhea, inflammation of the intestine, inflammation of the mouth and lips and localized, superficial reddening of the skin. The more common laboratory abnormalities are anemia, low white blood cell count, low blood platelet count and elevations of alkaline phosphatase, serum transaminase, serum bilirubin and lactic dehydrogenase (liver function studies).

Other adverse reactions are:

- Gastrointestinal: ulcer of the small intestines, inflammation of the duodenum (a part of the small intestine), inflammation of the protective lining of the stomach and intestines, bleeding, inflammation of the tongue, sore throat, anorexia, cramps, abdominal pain; possible intra- and extrahepatic biliary sclerosis (an autoimmune disease of the liver), as well as acalculous cholecystitis (inflammatory disease of the gallbladder).
- Dermatologic: hair loss, dermatitis, nonspecific skin toxicity, rash.
- Cardiovascular: myocardial ischemia (decreased blood and oxygen flow to the heart).
- Miscellaneous Clinical Reactions: fever, lethargy, malaise, weakness.
- Laboratory Abnormalities: BSP, prothrombin, total proteins, sedimentation rate and low level of platelets (the blood clotting component of your blood).
- Procedural Complications of Regional Arterial Infusion: arterial aneurysm (weakening of artery wall); arterial ischemia (decreased blood flow of the artery); arterial blood clot; blood clot; fibromyositis (chronic inflammation of a muscle); thrombophlebitis (inflammation that may lead to a blockage of one or more veins); hepatic necrosis; abscesses; infection at catheter site; bleeding at catheter site; catheter blocked, displaced or leaking.

Dexamethasone
Common potential side effects of systemic administration include anxiety, mood alteration/lability, high blood sugar, insomnia, peripheral edema, muscle weakness (with chronic use), acne, and excessive growth of dark or coarse hair on the face, chest and back. However, expected toxicity from intrahepatic administration is minimal.

Gemcitabine (when used on its own)

In 100 people receiving Gemcitabine, more than 10 and up to 100 may have:

- Cardiovascular: Peripheral edema (swelling) (20%), edema (≤13%)
- Central nervous system: Drowsiness (11%)
- Dermatologic: Skin rash (30%), alopecia (hair loss) (15%)
- Gastrointestinal: Nausea and vomiting (69%), diarrhea (19%), stomatitis (inflammation of the mouth and lips) (11%; grade 3: <1%)

- Genitourinary: Protein in the urine (45%), presence of blood in the urine (35%)
- Hematologic & oncologic: Anemia (68%; grade 3: 7%; grade 4: 1%), low level of white blood cells (that fight infection) (63%; grade 3: 19%; grade 4: 6%), low level of platelets (the blood clotting component of your blood) (24%; grade 3: 4%; grade 4: 1%), hemorrhage (17%; grade 3: <1%; grade 4: <1%)
- Hepatic: Increased liver functions tests including: serum alanine aminotransferase (68%), increased serum aspartate aminotransferase (67%), increased serum alkaline phosphatase (55%), hyperbilirubinemia (13%)
- Infection (16%)
- Renal: Increased blood urea nitrogen (16%)
- Respiratory: Dyspnea (shortness of breath) (23%), flu-like symptoms (19%)
- Miscellaneous: Fever (41%)

In 100 people receiving Gemcitabine from 1 to 10 may have:

- Central nervous system: Paresthesia (a tingling, pricking, chilling, burning, or numb sensation on the skin) (10%)
- Local: Injection site reaction (4%)
- Renal: Increased serum creatinine (8%)
- Respiratory: Bronchospasm (tightening of the muscles that line the airways) (<2%)

Cisplatin (when used on its own)

In 100 people receiving Cisplatin, more than 10 and up to 100 may have:

- Central nervous system: Neurotoxicity (peripheral neuropathy is dose and duration dependent)
- Gastrointestinal: Nausea and vomiting (76% to 100%)
- Genitourinary: Nephrotoxicity (28% to 36%; acute renal failure and chronic renal insufficiency)
- Hematologic & oncologic: Anemia (≤40%), leukopenia (25% to 30%; nadir: Day 18 to 23; recovery: By day 39; dose related), low level of platelets (the blood clotting component of your blood) (25% to 30%; nadir: Day 18 to 23; recovery: By day 39; dose related)
- Hepatic: Increased liver enzymes
- Otic: Ototoxicity (children 40% to 60%; adults 10% to 31%; as tinnitus, high frequency hearing loss)

In 100 people receiving Cisplatin, from 1 to 10 may have:

- Local irritation (burning, redness or swelling at injection site)

Oxaliplatin (when used on its own)

In 100 people receiving, Oxaliplatin more than 10 and up to 100 may have:

- Central nervous system: Peripheral neuropathy (may be dose limiting; 76% to 92%; acute 65%; grades 3/4: 5%; persistent 43%; grades 3/4: 3%), fatigue (61%), pain (14%), headache (13%), insomnia (11%)
- Gastrointestinal: Nausea (64%), diarrhea (46%), vomiting (37%), abdominal pain (31%), constipation (31%), anorexia (20%), stomatitis (14%)
- Hematologic & oncologic: Anemia (64%; grades 3/4: 1%), low level of platelets (the blood clotting component of your blood) (30%; grades 3/4: 3%), leukopenia (13%)
- Hepatic: Increased serum AST (54%; grades 3/4: 4%), increased serum ALT (36%; grades 3/4: 1%), increased serum bilirubin (13%; grades 3/4: 5%)
- Neuromuscular & skeletal: Back pain (11%)
- Respiratory: Dyspnea (13%), cough (11%)
- Miscellaneous: Fever (25%)

In 100 people receiving, Oxaliplatin from 1 to 10 may have:

- Cardiovascular: Edema (10%), chest pain (5%), peripheral edema (5%), flushing (3%), (blockage caused by a blood clot that has dislodged from another part of the body) (2%)
- Central nervous system: Rigors (9%), dizziness (7%)
- Dermatologic: Skin rash (5%), hair loss (3%), palmar-plantar erythrodysesthesia (redness, swelling, and pain on the palms of the hands and/or the soles of the feet) (1%)
- Endocrine & metabolic: Dehydration (5%), hypokalemia (3%)

- Gastrointestinal: Indigestion (7%), distorted sense of taste (5%), flatulence (3%), hiccups (2%), inflammation of the lining of the mouth (2%), difficulty swallowing (acute 1% to 2%), gastroesophageal reflux disease (1%)
- Genitourinary: Painful urination (1%)
- Hematologic & oncologic: low level of white blood cells (that fight infection) (7%)
- Hypersensitivity: Hypersensitivity reaction (3%; includes hives, itchy skin, facial flushing, shortness of breath, bronchospasm, excessive sweating, hypotension (low blood pressure), fainting: grades 3/4: 2% to 3%)
- Local: Injection site reaction (9%; redness, swelling, pain)
- Neuromuscular & skeletal: Joint pain (7%)
- Ocular: Abnormal lacrimation (increased tear production) (1%)
- Renal: Increased serum creatinine (5% to 10%)
- Respiratory: Upper respiratory tract infection (7%), rhinitis (6%), nosebleed (2%), sore throat (2%), pharyngolaryngeal dysesthesia (abnormal sensation in the back of the throat when swallowing) (grades 3/4: 1% to 2%)

Irinotecan (when used on its own)

In 100 people receiving, Irinotecan more than 10 and up to 100 may have:

- Cardiovascular: Vasodilatation (widening of blood vessels which decreases blood pressure) (9% to 11%)
- Central nervous system: Cholinergic syndrome (47%; includes excessive sweating, flushing, increased peristalsis, increased tear production, excessive constriction of the pupil, stuffy nose, drooling), pain (23% to 24%), dizziness (15% to 21%), insomnia (19%), headache (17%), chills (14%)
- Dermatologic: hair loss (46% to 72%), excessive sweating (16%), skin rash (13% to 14%)
- Endocrine & metabolic: Weight loss (30%), dehydration (15%)
- Gastrointestinal: Diarrhea (late: 83% to 88%, grades 3/4: 14% to 31%; early: 43% to 51%, grades 3/4: 7% to 22%), nausea (70% to 86%), abdominal pain (57% to 68%), vomiting (62% to 67%), abdominal cramps (57%), anorexia (44% to 55%), constipation (30% to 32%), inflammation of the lining of the mouth (30%), flatulence (12%), inflammation of mouth and lips (12%)
- Hematologic & oncologic: Anemia (60% to 97%; grades 3/4: 5% to 7%), low white blood cells (63% to 96%, grades 3/4: 14% to 28%), low blood platelet count (96%, grades 3/4: 1% to 4%), low levels of neutrophils (30% to 96%; grades 3/4: 14% to 31%)
- Hepatic: Increased serum bilirubin (84%), increased serum alkaline phosphatase (13%)
- Infection: Infection (14%)
- Neuromuscular & skeletal: Weakness (69% to 76%), back pain (14%)
- Respiratory: shortness of breath (22%), cough (17% to 20%), stuffy nose (16%)
- Miscellaneous: Fever (44% to 45%)

In 100 people receiving, Irinotecan from 1 to 10 may have:

- Cardiovascular: Edema (swelling) (10%), low blood pressure (6%), (blockage caused by a blood clot that has dislodged from another part of the body) (5%)
- Central nervous system: Drowsiness (9%), confusion (3%)
- Gastrointestinal: Abdominal distention (10%), indigestion (10%)
- Hematologic & oncologic: Febrile neutropenia (fever resulting from a low level of white blood cells) (grades 3/4: 2% to 6%), hemorrhage (grades 3/4: 1% to 5%), neutropenic infection (infection resulting from low white blood cell levels) (grades 3/4: 1% to 2%)
- Hepatic: Increased serum AST (10%), ascites (the accumulation of fluid in the peritoneal cavity, causing abdominal swelling) (grades 3/4: ≤9%), jaundice (grades 3/4: ≤9%)
- Respiratory: Pneumonia (4%)

Fluorouracil (5-FU)

The side effects for 5-FU depends on duration of treatment and/or rate of administration.

- Cardiovascular: Angina pectoris, cardiac arrhythmia, cardiac failure, cerebrovascular accident, ischemic heart disease, local thrombophlebitis (inflammation and pain caused by a blood clot), myocardial infarction, vasospasm, ventricular ectopy (irregular heartbeat)
- Central nervous system: Cerebellar syndrome (acute), confusion, disorientation, euphoria, headache

- Dermatologic: Hair loss, changes in nails (including nail loss), dermatitis, discoloration of the skin over the veins that the drug was administered through,
  red raised itchy rash on the skin, palmar-plantar erythrodysesthesia (redness, swelling, and pain on the palms of the hands and/or the soles of the feet), skin fissure, skin sensitivity to sunlight,
  Stevens-Johnson syndrome, toxic epidermal necrolysis (a type of severe skin reaction), dry skin
- Gastrointestinal: Anorexia, diarrhea, esophagopharyngitis, gastrointestinal hemorrhage, gastrointestinal ulcer, mesenteric ischemia (acute), nausea, stomatitis, tissue sloughing (gastrointestinal), vomiting
- Hematologic & oncologic: Agranulocytosis, anemia, leukopenia (nadir: days 9 to 14; recovery by day 30), Pancytopenia (decreased blood hemoglobin, the cells that fight infection and blood platelets), low blood platelet count
- Hypersensitivity: Anaphylaxis (severe allergic reaction), hypersensitivity reaction (generalized)
- Ophthalmic: Hardening of the tear ducts, increased tear production, nystagmus, photophobia, visual disturbance
- Respiratory: nose bleed

Leucovorin Calcium (Folinic Acid)

Toxicities (especially gastrointestinal toxicity) of fluorouracil are enhanced when used in combination with leucovorin.

- Dermatologic: Redness and itching of the skin, skin rash, hives
- Hematologic & oncologic: low blood platelet count
- Hypersensitivity: Anaphylactoid reaction, hypersensitivity reaction
- Respiratory: Wheezing

Combination of FUDR, Dexamethasone, Systemic Chemotherapy, Heparin and Saline

Potential side effects from the combination of all the medications and devices used in this study include abdominal pain, anemia, increased AST and/or ALT (liver enzymes), and an increase in bilirubin.

Reproductive risks:
You should not become pregnant or father a baby while on this study because the drug in this study could affect an unborn child. It is not known if the drugs used in this study are harmful to an unborn or breastfed baby. If you are a female subject and you become pregnant while receiving these drugs, potential risks could include complications such as miscarriage or birth defects. It is not known if the study drugs are transferred to breast milk. Potential subjects who are breastfeeding will be required to discontinue nursing during treatment and for an additional 30 days following treatment.

The drugs used in this study may cause fetal harm when administered to pregnant women. Animal studies have revealed evidence of harm to an unborn baby as well as birth defects. There are no controlled data in human pregnancy. If you are a female subject and you become pregnant while receiving this drug, potential risks could include complications such as miscarriage or birth defects.

If you are of childbearing potential, you must use contraception during and for 30 days after the last dose of study drug. Examples of contraceptive methods with a failure rate of less than 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be combined to achieve a failure rate of less than 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

If you are a male subject who has had a vasectomy and testing has shown that there is no sperm present in the semen, the use of birth control method in this study is not required. Otherwise, male subjects must:

- Let their female partner know he is participating in this study.
- Practice abstinence or use a condom during treatment in addition to 90 days following final treatment with the study drugs.

Male subjects must not donate sperm during treatment and for an additional 90 days following their last treatment. To prevent exposure of the unborn child through semen, the male subject must agree to the use of a condom during vaginal sex.

For more information about risks and side effects, ask your study doctor.

CT scan risks:
Each CT scan will give a radiation dose greater than that from typical natural background exposure, but less than the limit for radiation workers and well below the levels that are considered to be a significant risk of any harmful effects.

EKG risks:
With the echocardiogram, you may feel some discomfort when the technician pulls the electrodes off your chest similar to a Band-Aid.

Blood Tests
For most people, needle punctures for blood tests do not cause any serious problems. However, they may cause fainting, bleeding, bruising, soreness, discomfort, dizziness, infections and/or pain at the injection site. There can be mild pain, soreness or some bleeding or bruising when blood is drawn. Rarely, an infection can happen where the needle was placed. Feeling dizzy or fainting can also happen, but may only last a few minutes after blood is drawn. If you take the blood thinner warfarin or Coumadin, you may have an increased risk of bleeding from the needle used to draw your blood.

There is always a chance that any medical treatment can harm you. The research treatments/procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect.

**WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?**

We do not know if you will get any benefit from taking part in this study. However, some patients with your condition have experienced longer overall survival and lessened side effects compared to systemic chemotherapy alone. Your willingness to take part in this study may lead to information that may help others with your condition.

**IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?**
Other treatments available for your condition include:

- Getting treatment or care for your cancer without being in a study. Standard of care for your cancer may include systemic chemotherapy;
- Taking part in another study of an investigational drug;
- Getting no treatment;
- Getting comfort care, also known as palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by cancer. It does not treat the cancer directly but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

**WHAT WILL IT COST YOU TO PARTICIPATE?**

You and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you would normally receive for any conditions you may have. These are costs that are considered medically necessary and will be part of the care you receive even if you do not take part in this study.

The study intervention of hepatic artery infusion pump placement will only done after insurance pre-approval. Similarly, chemotherapy drugs will only be administered after insurance pre-approval. However, you or your insurance may be charged for the costs associated with study treatments or medications.

Your insurer, Medicare, or Medicaid, may agree to pay for the costs. However, a co-payment or deductible may be needed from you. The amount of this co-payment or deductible may be costly.

The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.

Therefore, the sponsor, Markey Cancer Center, will pay for the following:

- FUDR administration via pump

- Blood testing for Pharmacokinetic and genetic analysis
- Monitoring of pump drug levels

**WHO WILL SEE THE INFORMATION THAT YOU GIVE?**
When we write about or share the results from the study, we will write about the combined information. We will keep your name and other identifying information private.

We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. At the University of Kentucky, data is stored at the Markey Cancer Center in locked facilities, and with limited access to records by designated research staff. The study doctor will assign you a unique code consisting of a series of numbers and only your unique code and your initials, and nothing that could identify you personally, will be entered into the study report forms.

You should know that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to share your information with:

- a court or agencies, if you have a reportable disease/condition;
- authorities, if you report information about a child being abused, or if you pose a danger to yourself or someone else.

Officials of the Food and Drug Administration, the National Cancer Institute, the University of Kentucky or its agents may look at or copy pertinent portions of records that identify you.

**CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?**

You can choose to leave the study at any time. You will not be treated differently if you decide to stop taking part in the study.

If you choose to leave the study early, data collected until that point will remain in the study database and may not be removed.

The investigators conducting the study may need to remove you from the study. You may be removed from the study if:

- you are not able to follow the directions,
- we find that your participation in the study is more risk than benefit to you, or
- the study is stopped early for a number of scientific reasons.

If that occurs, the study intervention or medication will no longer be provided to you and may not be available for purchase. This may occur for a number of reasons.

If you withdraw from the study are or removed early for any reason, it is important for your own safety that you complete the final check-up examinations. This is to make sure any potential side effects from the study drugs are identified and properly treated.

**ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?**

You may not take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should discuss this with the investigator/your doctor before you agree to participate in another research study while you are in this study.

**WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?**
If you believe you are hurt or if you get sick because of something that is due to the study, you should call Michael Cavnar, MD 859-323-8920 (Days) or 859-323-5321 (Evenings & Weekends) immediately.

Dr. Cavnar will determine what type of treatment, if any, is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study.

Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

Medical costs related to your care and treatment because of study-related harm will be your responsibility or may be paid by Medicare or Medicaid if you are covered by Medicare or Medicaid (If you have any questions regarding Medicare/Medicaid coverage you should contact Medicare by calling 1-800-Medicare (1-800-633-4227) or Medicaid 1-800-635-2570).

A co-payment/deductible may be needed by your insurer or Medicare/Medicaid even if your insurer or Medicare/Medicaid has agreed to pay the costs. The amount of this co-payment/deductible may be costly.

You do not give up your legal rights by signing this form.

**WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?**

If you go on-study, you will receive a small travel stipend (i.e., two gas/petrol gift cards) to offset travel expenses for study participation.

You may receive up to $100 for travel reimbursement for taking part in this study. One gift card of $50 will be provided to you at the baseline visit and a second gift card of the same value will be provided at a visit occurring approximately mid-study.

**WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?**

We will tell you if we learn new information that could change your mind about staying in the study. We may ask you to sign a new consent form if the information is provided to you after you have joined the study.

**WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?**

Do you give permission for us to contact you about research results or incidental findings that are determined to be important to you/your family's health? (Incidental findings are unforeseen findings discovered during the course of the research that may affect you or your family's health).

☐ Yes ☐ No _____Initials

You may also withdraw your consent to be contacted with information about research results or incidental findings by sending a written request to Michael Cavnar, MD c/o Markey Cancer Center CRO Room C-1
Pavilion H, 800 Rose Street, Lexington, KY 40536.

**WHAT ELSE DO YOU NEED TO KNOW?**

If you volunteer to take part in this study, you will be one of about 30 to do so at the University of Kentucky.

The Markey Cancer Center is providing financial support and/or material for this study.

The information that you are providing will no longer belong to you. The research may lead to new clinical or educational knowledge, tests, treatments, or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives if this occurs.

A description of this clinical trial will be available on ClinicalTrials.gov as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

All identifiable information (e.g., your name, medical record number, or date of birth) will be removed from the information or tissue samples collected in this study. After we remove all identifiers, the information or tissue samples may be used for future research or shared with other researchers without your additional informed consent.

**WILL YOUR INFORMATION (OR SPECIMEN SAMPLES) BE USED FOR FUTURE RESEARCH?**

Your information or samples collected for this study will NOT be used or shared for future research studies, even if we remove the identifiable information like your name, medical record number, or date of birth.

**AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION**

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

**Your health information that may be accessed, used and/or released includes:**

- Demographic Information (your name, sex, race & age.)
- Your social security number
- History and diagnosis of your disease
- Specific information about treatments you have received
- Past and present medical records pertaining to your health condition
- Your entire research record
- Your medical records held at the University of Kentucky that pertain to your health condition
- Information about other medical conditions that may affect your treatment
- Medical data, including physical examinations, laboratory test results, pathology results, and pregnancy test results
- Information on side effects (adverse events) you may experience, and how these were treated
- Long-term information about your general health status and the status of your disease
- Tissue and/or blood samples, associated data related to the analysis of the samples

**The Researchers may use and share your health information with:**

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- Authorized representatives of the University of Kentucky, UK Hospital, and Markey Cancer Center
- Representatives of the Kentucky Cancer Registry
- Representatives of the U.S. Food and Drug Administration (FDA)
- The National Institutes of Health and its affiliates including the for Human Research Protections (OHRP) and the NCI (National Cancer Institute) and their affiliates
- If necessary, your other healthcare providers who are not part of the study

If you become pregnant anytime during the study or within 30 days after stopping the study drug, you must inform the study doctor. The study doctor must then report the outcome of your pregnancy to the Sponsor (and/or the FDA).

The researchers agree to only share your health information with the people listed in this document.

Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign this form, it will not affect your:

- Current or future healthcare at the University of Kentucky;
- Current or future payments to the University of Kentucky;
- Ability to enroll in any health plans (if applicable); or
- Eligibility for benefits (if applicable).

**After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:**

- Send a written letter to: Michael Cavnar, MD c/o Markey Cancer Center CRO Room C-1, Pavilion H, 800 Rose Street, Lexington, KY 40536. to inform him of your decision.
- Researchers may use and release your health information **already** collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

The use and sharing of your information has no time limit.

**If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Monday-Friday at (859) 323-1184.**

## INFORMED CONSENT SIGNATURES

**This consent includes the following:**

- **Key Information Page**
- **Detailed Consent**
- **Authorization to Use or Disclose Your Identifiable Health Information**

**You will receive a copy of this consent form after it has been signed.**

_____ _____
**Signature of research subject** Date

_____
**Printed name of research subject**

_____ _____
Printed name of [authorized] person obtaining informed consent and HIPAA authorization Date

_____
Signature of Principal Investigator or Sub/Co-Investigator