MSK PROTOCOL COVER SHEET

A Pilot Protocol Evaluating Safety of Using the Medtronic Pump and Codman Catheter for the Delivery of Hepatic Arterial Infusion (HAI) Chemotherapy in patients with Colorectal Carcinoma or Cholangiocarcinoma

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Objective
The primary objective of this protocol is to determine the safety of using the Medtronic pump with the Codman catheter for hepatic arterial infusion (HAI) to deliver chemotherapy to patients with colorectal cancer that is metastatic (unresectable or resectable) and cholangiocarcioma.

The secondary objective is to measure overall survival (OS) and progression free survival. Overall survival is defined as the time from treatment initiation till the day of death or last follow-up whichever occurs first. Progression free survival is defined as the time from treatment initiation till the day of progression or death whichever occurs first. Patients that are alive without progression at the end of the study will be censored. OS and PFS will be estimated using the Kaplan-Meier method separately for each of the three groups.

Study Population
The study population will consist of 3 groups of patients: 1) unresectable liver metastases from colorectal cancer, 2) resectable liver metastases from colorectal cancer, and 3) unresectable cholangiocarcinoma.

Number of Patients
30

Study Design
Pilot non- randomized safety study.

Therapeutic Intervention
The Medtronic Pump is attached to a Codman catheter and implanted using routine procedures for HAI. Systemic chemotherapy depends on patient cohort and follows standard MSK practice.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

This pilot study aims to assess the safety of using the Medtronic Pump with the Codman catheter to administer HAI using standard guidelines. The primary objective of this study is to assess safety.Safety will be determined by: 1) serious adverse events related to pump or catheter malfunction such as catheter disconnects, 2) requirement of stent placement, and 3) % usual toxicities (alkaline phosphatase, serum bilirubin). The secondary objective will be to asses overall survival and progression free survival.

3.0 BACKGROUND AND RATIONALE

3.1 Introduction

In the United States, it is estimated that 134,490 people will be diagnosed with colorectal cancer and that 49,190 people will die from this cancer in 2016.[1] Approximately 50% of colorectal cancer deaths are due to liver metastases.[2] Venous drainage from the colon and rectum allow metastases 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. Approximately 15% of patients present with de-novo metastatic disease to the liver and up to 60% of patients treated with definitive surgery for colorectal cancer who develop metastatic disease will have liver metastases.[3]

Systemic chemotherapy without surgical resection is generally non-curative and requires continuous therapy. This treatment approach alone rarely yields long-term survivors with a 2-

year survival rate of approximately 40%. A number of liver-directed therapeutic options now exist beyond systemic chemotherapy as adjunctive therapy to surgical resection for the management of patients with liver confined metastatic colorectal cancer. These therapies are delivered with the intention of converting patients to resectable disease, reducing the risk of recurrence, treating recurrent disease and most importantly to improve overall survival.

3.2 General Information

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. This anatomical difference together with pharmacologic factors provide the rationale for liver directed HAI therapy in the management of colorectal cancer liver metastases. The liver predominantly metabolizes certain drugs during the first pass through the hepatic arterial circulation, which results in high local concentrations of the 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. They facilitate the delivery of high concentrations of chemotherapy directly to liver metastases while minimizing toxicity to the remaining liver and body.[4,5] FUDR, a prodrug of fluorouracil (5-FU), is a more suitable 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.

Toxicity from HAI FUDR therapy includes biliary toxicity and gastric ulceration. 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. The biliary system derives its blood supply almost exclusively from the hepatic artery. Biliary toxicity, due to the perfusion of the bile duct by the hepatic artery therapy, manifests clinically as elevations of aspartate transaminase (AST), alkaline phosphatase and bilirubin. In the setting of jaundice, obstruction due to malignant or surgical stricture must be out-ruled prior to concluding that liver dysfunction is due to HAI therapy. An endoscopic retrograde cholangiopancreatogram (ERCP) may demonstrate an idiopathic sclerosis secondary to HAI therapy which, if focal may be alleviated with interventional biliary stent insertion and drainage. A randomized study of HAI therapy with FUDR with or without dexamethasone in patients with metastatic colorectal cancer liver metastases highlighted that hyperbilirubinemia occurs in about one third of patients treated with FUDR therapy alone. The addition of decadron reduced the incidence of hyperbilirubinemia from 30% to 9%. FUDR in combination with dexamethasone also improved response rate.[6]

3.3 HAI Used to Convert Unresectable, Liver Metastases to Resection

In the absence of extra-hepatic disease, surgery for colorectal liver metastases is a potentially curative, therapeutic option that has been shown to positively impact overall survival in this patient group.[7-11,] The majority of patients who achieve a complete response with systemic chemotherapy alone, harbor residual disease.[12,13,] Decisions regarding the management of liver-confined, metastatic, colorectal cancer should ideally be made in the setting of a hepatobiliary multi-disciplinary meeting.[14] Only 10-20% of patients with colorectal liver metastases are deemed suitable candidates for surgical resection.[15] In light of the improved outcomes observed in patients who undergo surgery for colorectal liver metastases the goal of therapy for those with unresectable liver metastases should focus on optimizing the

response rate to facilitate surgery. The correlation between response rate and resection rate is high in the setting of liver-confined colorectal metastases (r =0.96, P = .002).[16]

With major improvements in systemic chemotherapy, options available for the management of colorectal cancer patients with unresectable liver confined metastatic disease can be downstaged from unresectable to resectable with conversion rates ranging from 3.3% to 37%.[17-21]

However, in the era of modern systemic chemotherapy, no significant improvement in prognosis has been observed among patients that received perioperative chemotherapy alone and underwent resection of extensive CLM (≥4 metastases) [22] or < 4 metastases. [23] New liver directed strategies to improve prognosis amongst patients with higher volume liver limited metastatic colorectal cancer are warranted.

The definition of resectability is complex. It involves biological and technical elements that results in variability between institutions and may explain the variation in conversion rates evident amongst these studies. Studies also differ in their definition of resection, which makes it difficult to compare the data. Most of these studies documented that resected patients have outcomes similar to those patients with initially resectable colorectal liver metastases and that long-term survival is possible. Lam et al, demonstrated in a systematic, retrospective review of 1,886 patients with initially unresectable colorectal liver metastases, 22.5% underwent resection following response to systemic chemotherapy. In this group the median overall survival was 45 (range, 36-60) months with 19% of patients alive and recurrence-free.[24]

HAI therapy in combination with systemic chemotherapy represents an effective therapeutic approach to convert patients with unresectable colorectal liver metastases to resectable disease. In the first line setting, initial randomized studies comparing HAI of FUDR alone to systemic 5FU in patients with unresectable CLM revealed overall response rates between 42-47% for the HAI arms compared to 9-24% for the systemic chemotherapy arms.[25-27] Subsequently, phase I/II studies of HAI in combination with modern systemic chemotherapy deemed this combination strategy to be safe and effective, responses of 64 to 100% amongst patients with previously untreated, liver limited, unresectable disease. In previously treated patients with CLM response rates of 74-85% have been observed with combination HAI and modern systemic chemotherapies.

In 49 patients treated with HAI floxuridine and dexamethasone plus systemic chemotherapy with oxaliplatin and irinotecan, the overall response rate was 92% (complete - 8%; partial - 84%). The conversion rate to surgical resection was 47% (n=23) even though the patients had extensive disease (73% with > five liver lesions, 98% with bilobar disease, 86% with ≥ six segments involved). The median survival from the start of HAI therapy was 50.8 in the treatment naïve group and 35 months in the group that previously received chemotherapy, respectively.[28] Using HAI of oxaliplatin in 28 patients combined with systemic 5-FU, a response rate was 64% was obtained and a median overall and DFS of 27 and 27 months, respectively.[29]

A retrospective review of 87 patients with unresectable liver metastases treated with HAI of oxaliplatin and systemic 5-FU/LV revealed a conversion rate to curative resection +/- ablation of 24%. A higher conversion rate was observed amongst patients who received HAI therapy in the first line setting compared to those receiving HAI therapy following failure of systemic

therapy alone (53% vs 19%, p=0.008). Five-year overall survival was 56% in the surgery group versus none in the non-resectable group (p<0.001). The median overall survival in the resected group was 41.9 months, while the 1- and 2- disease free survival rates were 28% and 10%, respectively. [30] Subsequent studies evaluated the addition of biologics such as bevacizumab to liver-directed and combination systemic chemotherapy. Biliary toxicity increased in the setting of concurrent administration of systemic bevacizumab. The addition of bevacizumab did not improve response rates or conversion rates to liver resection.[31]

A prospective study of 49 patients with advanced, unresectable liver-limited colorectal cancer treated with HAI and best systemic chemotherapy yielded a response rate of 76%. The conversion rate to liver resection was 47% and of note, 65% of the study population had been previously treated with systemic chemotherapy. Notably, significant surgical complications post liver resection was low with only one individual experiencing a grade 3 adverse event (a biloma requiring percutaneous drainage). A high degree of biliary complications were noted in the first 24 patients who also received concurrent systemic bevacizumab. Bevacizumab was discontinued for the following 25 patients who were enrolled. The conversion to resection was the only factor associated with longer overall and PFS. A landmark analysis, confirmed a higher 3-year overall survival among patients who underwent liver resection compared to those that remained unresectable, (80% versus 26%). At a median follow up of 39 months (32–65 months), 10 of the 49 patients (20%) had no evidence of disease.[32]

A French study investigated the conversion to resection with intravenous cetuximab in addition to triplet HAI chemotherapy (5-Fluorouracil, oxaliplatin and irinotecan) in 64 patients with KRAS wild type, unresectable colorectal liver metastases who progressed on 1-3 lines of systemic chemotherapy. The disease control rate was 84.4%, with a liver resection rate of 29.7%. When this chemotherapy strategy was delivered in the second line setting liver resection was achieved in 46.4% (13/28) patients. Comparatively, liver resection was achieved in only 16.7% (n=6/36) of patients that received chemotherapy in the 3rd line setting and beyond, (p=0.014). Overall survival was significantly longer among patients completing the chemotherapy +/- liver resection therapeutic strategy as second rather than third to fourth treatment protocol, despite similar other characteristics. The respective median survival times were 31.8 months (26.0–37.6) compared with 15.7 months (10.1–21.2) (*P* = 0.001). [33]

3.4 Adjuvant therapy following liver resection using HAI

The recurrence rate following liver resection for colorectal cancer metastases is in the order of 60-70%. The liver represents the site of recurrence in two thirds of these relapses. [34] Adjuv ant liver-directed therapy as a strategy to reduce the risk of recurrence to the liver 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 significant decrease in hepatic disease-free survival (DFS) as well as overall survival. [7, 35-38]

A recent report from MSKCC, 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. [39] Another recent publication from MSKCC looked at 2368 consecutive patients who underwent liver resection of colorectal metastases. 785 had HAI and 1583 did not. The HAI group of patients had significantly increased 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). [40]

Primary intrahepatic cholangiocarcinoma (ICC) is the second most common primary hepatic malignancy. Epidemiology and End Results (SEER) data showed a 9% annual percentage increase in incidence of ICC, and a 10-fold increase in ICC-related mortality since 1973[41]

Patients with unresectable primary liver cancer have a median survival of less than 12 months. Multiple systemic regimens have been evaluated and shown to have limited efficacy. A recent study using systemic gemcitabine and cisplatin versus gemcitabine alone in advanced biliary tract cancer produced a median DFS of 8 and 5 months (p,0.001), respectively, with an overall survival difference of 3.6 months (11.7 versus 8.1 months, respectively, p=0.001). [42]

Recently, the results of a phase II study, conducted at MSKCC (IRB #02-120) and evaluating the efficacy of HAI floxuridine (FUDR) (with no systemic component) in patients with primary liver cancer were reported. [43] This study included 34 patients, 26 with ICC and 8 with hepatocellular carcinoma (HCC). The response rate was 47% and the median 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 ICC appeared to derive more 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, suggesting an important role for regional chemotherapeutic strategies in the treatment of unresectable ICC. However, since most initial treatment failures occurred in the liver, improving drug deliver to the liver appeared to be a means of enhancing the results of regional therapy. [43]

Building on these initial results, a second study was initiated and completed at MSKCC (IRB#06-114), evaluating the efficacy of HAI FUDR combined with systemic bevacizumab in patients with liver-only disease. The rationale for this study was that bevacizumab would ‘normalize’ the tumor vasculature and improve FUDR delivery. Twenty-two patients were enrolled, 18 with ICC and 4 with HCC. The overall response rate was 32%, and the median TTP was 8.8 months. [44]

The combined results of these two prospective trials demonstrated the potential utility of hepatic arterial chemotherapy for providing prolonged control of the hepatic disease in advanced ICC.

3.5 Current Shortage of HAI Pumps Preliminary Work

The manufacturer of the C3000 Codman Pump has announced that it will terminate production in 2018. The design of the pump contains many unique and individual 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. The use of the Medtronic Pump with a Codman Catheter has previously been successfully employed (see

below) and if safety is demonstrated in a larger patient population would provide an option for appropriate patients to receive HAI.

3.6 Preliminary Data Using Alternate Pump and Catheter Configurations

Historically, there were three patients who were treated with the Medtronic pump connected to the Codman catheter at MSK. Patients 1 and 2 were enrolled in an MSK clinical trial that was studying the effectiveness of HAI chemotherapy in colon and colorectal patients. Codman pumps were being used for study HAI therapy until a production shortage left the pumps unavailable while the study was still accruing patients. After being escalated to the MSK IRB, it was determined that it was safe and still within study guidelines to use the Medtronic pumps with the Codman catheters for the remaining patients. The combination of the Medtroninc pump and the Codman catheter was deemed “off-label” use.

Patient 1: 36-year-old with an (mucinous) ascending colon lesion diagnosed in 12/2013 with right and left liver mets at baseline (CEA 998). She was started on FOLFOX-4 and then pump therapy on 5/14/2014 with Medtronic pump (Codman catheter). She tolerated treatment well. She received 4 full doses without change in liver function and then subsequent elevation prompted a reduction in dose. Tumor continued to regress and she went on to have a resection of liver tumor on 12/15/2014.

Patient 2: 59 year-old who had a sigmoid colon lesion resected followed by adjuvant therapy with FOLFOX. She then recurred in the liver. She underwent a liver resection and was started on HAI with Medtronic pump (Codman catheter) in the adjuvant setting. She received two full doses of FUDR and then had elevation in alkaline phosphatase and required dose reduction which she tolerated. Her initial pump placement was 6/4/2014, and she was off therapy from 8/27/2014 to 1/15/2015 when she had progression in lymph nodes and did not want further chemotherapy. On the March 2015 scan, she had progression in the liver as well as nodes off therapy. She had no clinically significant abnormalities with liver function on follow up tests.

After having the success with patients 1 and 2, the same pump and catheter combination was used in a cholangiocarcinoma patient for “off-label” use due to the Codman pumps still being unavailable.

Patient 3: 59 year-old who had intra-hepatic cholangiocarcinoma. Initially, she had systemic chemotherapy. In January 1996, she had a sarcoma resected and was given radiation. Nine years later she had masses in the liver. On 11/2012, she had a left hepatectomy which showed an intra hepatic cholangiocarcinoma. In 10/2013, she had recurrence of the cholangiocarcinoma then received systemic chemotherapy with gemcitabine and cisplatin. She had an increase in disease and she started on HAI with Medtronic pump and Codman catheter on 6/2014. She required dose reduction after two treatments but continued with the lower dose and tumor responded. The liver was still responding on last follow-up in 2/2015.

After the Codman pumps stopped being manufactured in April of 2018, a group of surgeons and medical oncologists at MSK discussed using Medtronic pumps in an “off-label” capacity as a replacement for the Codman pumps based on previous experience. Pump function, capability, size, and risks were all weighed before it was decided that patients needing pump implantation surgery to receive HAI therapy would receive Medtronic pumps and Codman tapered catheters that MSK already had. The tapered catheters had previously been used with the Codman pumps for patients with narrow arterial openings where the standard

catheter could not be used. The same connection method that was used with the Codman pump and Codman tapered catheter would be used for threading together the Medtronic pump and Codman tapered catheter.

Between May 30, 2018 and July 1, 2018, ten patients ages 26 - 73 have successfully received pump implantation surgery with the Medtronic pump and tapered Codman catherter. None of the 10 patients have undergone surgical or pump complications such as infection or disconnection.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

A total of 30 patients with unresectable liver mets, or adjuvant therapy after resection, or cholangiocarcinoma can be enrolled. Toxicities with the Medtronic pump and Codman catheter will be monitored and recurrence and survival will be reported. We estimate an acrcrual rate of 4-5 patients a month.

Cycle Schema for Cycle 1	
Cycle 1 Day 1***	***Cycle 1 Day 15***
Pump Therapy* FUDR + Dexamethasone (14 day infusion)	**Pump Emptied** Heparin and saline placed in the pump **Systemic Therapy**** mCRC: FOLFIRI, FOLFOX, Irinotecan, or Irinotecan/oxaliplatin (anti-EGFR agent may be added to any of the systemic treatments) Cholangio: Gemcitabine/Oxaliplatin or Gemcitabine alone
Cycle Schema for All Subsequent Cycles	
All subsequent Cycles on Day 1	***All subsequent Cycles on Day 15***

Pump Therapy*	**Pump Emptied**
FUDR + Dexamethasone (14 day infusion)	Heparin and saline placed in the pump
Systemic Therapy**	**Systemic Therapy****
mCRC: FOLFIRI, FOLFOX, Irinotecan, or Irinotecan/oxaliplatin (anti-EGFR agent may be added to any of the systemic treatments) Cholangio: Gemcitabine/Oxaliplatin or Gemcitabine alone	mCRC: FOLFIRI, FOLFOX, Irinotecan, or Irinotecan/oxaliplatin (anti-EGFR agent may be added to any of the systemic treatments) Cholangio: Gemcitabine/Oxaliplatin or Gemcitabine alone

*patients with colon cancer will receive systemic chemotherapy that will consist of either FOLFIRI, FOLFOX, Irinotecan, or Irinotecan/oxaliplatin (anti-EGFR agent may be added to any of the systemic treatments).

*patients with cholangiocarcinoma will receive Gemcitabline/Oxaliplatin or Gemcitabine alone
The following pump dose will be used:
HAI FUDR [(0.12 mg/kg/day) x wt (kg) x (20ml) X 0.9)/ pump flow rate (1ml/day)]
Dexamethasone [1 mg/day * 20] / pump flow rate

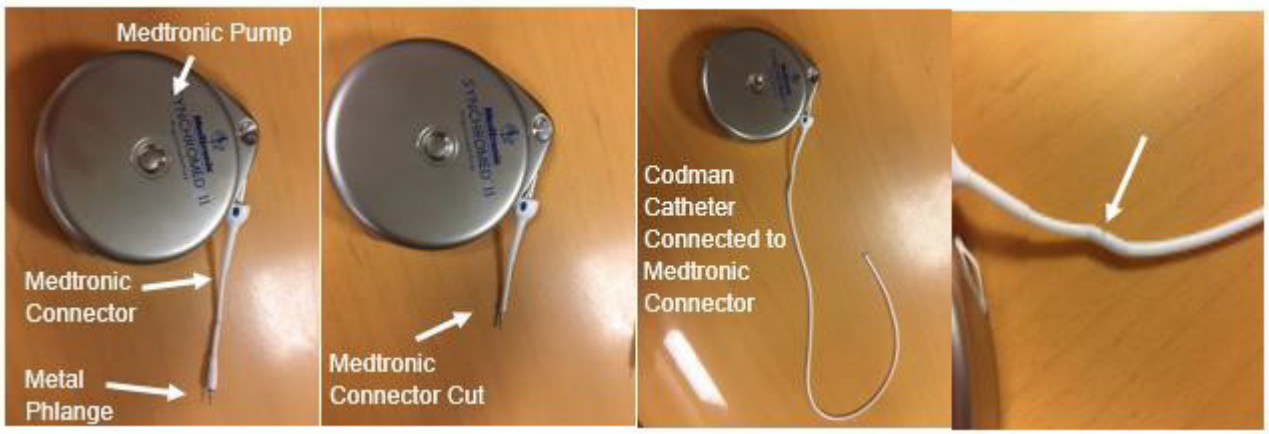
** All systemic chemotherapy dosing for patients on this study will follow the HAI dosing guidelines that have been previously established.

*** *On Cycle 1 Day 1 systemic chemotherapy will be held*
If patients are allergic to heparin, they will receive Fondaparinux in the pump instead along with saline.

4.2 Intervention

All patients will undergo surgery to have the Medtronic pump and Codman straight catheter placed appropriately before HAI therapy can begin. During the surgical 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 phlange at the end of the connector so the Codman straight catheter can then be connected to the cut end of the Medtronic connector (Figure 3). Silk ties will be used on both ends of the catheter to ensure the fit to the connecton is secure (Figure 4).

Figure1: Figure 2: Figure 3: Figure 4:



Chemotherapy with HAI FUDR/Dex will commence approximately 14 days post surgical placement of HAI pump for unresected patients and approximately 28 days post surgical placement of HAI pump for resected patients. All patients will receive HAI FUDR [(0.12 mg/kg/day) x wt (kg) x (20ml) X 0.9)/ pump flow rate (1ml/day)] and dexamethasone ([1 mg/day *20] / pump flow rate) on Day 1 of each cycle (1 Cycle = 28 days).

Group 1 unresectable liver metastases from colorectal cancer

- Patients will receive either FOLFIRI, FOLFOX, Irinotecan, or Irinotecan/oxaliplatin (anti-EGFR agent may be added to any of the systemic treatments) on Days 1 and 15 of each cycle, however initiation with systemic chemotherapy will not take place until approximately 4 weeks post-surgery for pump placement, so the first doses of systemic chemotherapy will be given on Cycle 1, Day 15, and then every 2 weeks thereafter.
- CT C/A/P every 2 months. A window of +/- 3 weeks for scans is allowed in order to accommodate patient schedules.

Group 2 resectable liver metastases from colorectal cancer

- Patients will receive either FOLFIRI, FOLFOX, Irinotecan or Irinotecan/oxaliplatin on Days 1 and 15 of each cycle, however initiation with systemic chemotherapy will not take place until approximately 6 weeks post-surgery for pump placement, so the first doses of systemic chemotherapy will be given on Cycle 1, Day 15, and then every 2 weeks thereafter. Protocol treatment will continue for 6 months in the absence of toxicity or patient withdrawal.
- CT C/A/P every 3 months. A window of +/- 3 weeks for scans is allowed in order to accommodate patient schedules.

Group 3 unresectable cholangiocarcinoma

- Patients will receive Gemcitabine (800 mg/m^2 IV over 30 minutes) and Oxaliplatin (85 mg/ m^2 IV over 120 minutes) or Gemcitabine (1000 mg/m^2 IV over 30 minutes) alone on Days 1 and 15 of each cycle, however initiation with systemic chemotherapy will not

take place until approximately 4 weeks post-surgery for pump placement, so the first doses of systemic chemotherapy will be given on Cycle 1, Day 15, and then every 2 weeks thereafter.

- A CT C/A/P every 2 months during treatment. A window of +/- 3 weeks for scans is allowed in order to accommodate patient schedules.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 FUDR

5.1.1 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.

5.1.2 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.

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5.2 DEXAMETHASONE

5.2.1 Dexamethasone is an adrenocortical steroid, used for chronic inflammation, neoplastic and autoimmune diseases; used in HAI treatment as an agent to prevent liver damage.

5.3 GEMCITABINE

5.3.1 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.

5.3.2 The drug is supplied as either a 200mg or 1 gram lyophilized powder in a 50 mL sterile single vial for reconstitution.

5.3.3 The drug is administered via a freely-running intravenous catheter per institutional guidelines.

5.4 OXALIPLATIN

5.4.1 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.

5.4.2 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.

5.4.3 Do not combine with alkaline medications or media (such as basic solutions of 5FU, 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).

5.4.4 The compound may be stored (in the form of freeze-dried powder for two years at room temperature protected from light. *Reconstituted solution:* In 5% glucose solution or water for injection in the original vial, the solution may be stored for 24 to 48 hours at +2° /+8° C.

5.5 IRINOTECAN

5.5.1 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.

5.5.2 CPT-11 will be diluted with 250 ml of 5% Dextrose (D5W) and infused intravenously over 30 min to an hour. Nothing else should be added to the infusate. No other diluent is to be used.

5.5.3 CPT-11 vials must be stored in a cool, dry place, protected from light in a locked cabinet accessible only to authorized individuals. CPT-11 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. CPT-11 is stable for at least 24 hours in glass bottles or plastic bags when mixed with D5W.

5.6 FLUOROURACIL

5.6.1 Antimetabolite that will be administered by MSKCC guidelines.

5.7 LEUCOVORIN CALCIUM (FOLINIC ACID)

5.7.1 Leucovorin calcium is a stable reduced formyl derivative and the active form of folic acid.

5.8 Anti-EGFR (Panitumumab or Cetuximab)

5.8.1 Panitumumaba and Cetuximab are antibodies against EGFR. These are recombinant, human IgG2 kappa monoclonal antibodies that bind specifically to the human Epidermal Growth Factor Receptor (EGFR) to inhibit the binding of ligands for EGFR. This results in inhibition of cell growth, induction of apoptosis, decreased pro-inflammatory cytokine and vascular growth factor production

5.9 CATHETER AND PUMP

5.9.1 **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 will be

supplied with a connector. The straight catheter connector ends are designed to be connected into the pump catheter and silicone extension tubing from the drug delivery system.

Specifications: IP-38000 Codman straight silicone rubber catheter. Length= 72.6 cm. Volume= 0.003 mL/cm

5.9.2 Medtronic SynchroMed Pump is a programmable drug delivery system that stores and delivers infusion treatment. This device is implanted under the skin and is indicated for chronic intravascular infusion of floxuridine (FUDR) or doxorubicin hydrochloride (Adriamycin) and, when required bacteriostatic water, physiological saline and/or heparin.

Indications:

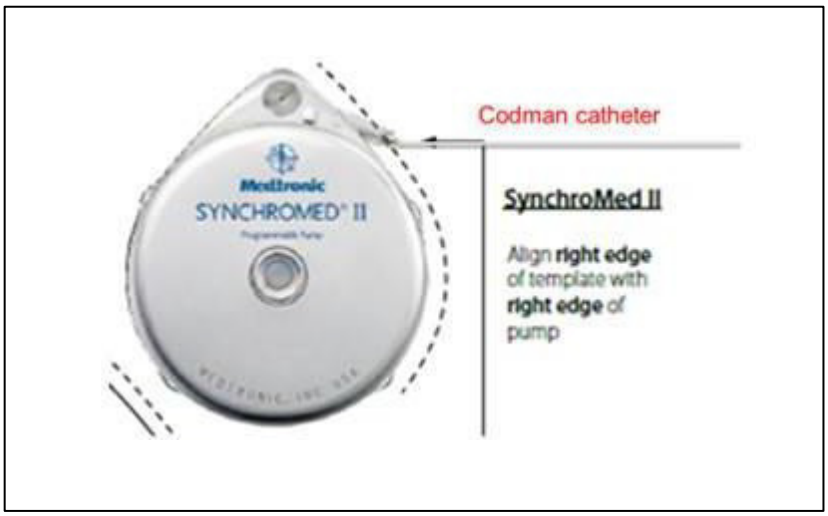
- Chronic infusion of Lioresal Intrathecal (baclofen injection) for the management of severe spasticity of spinal or cerebral origin.
- Chronic intrathecal or epidural infusion of sterile, preservative-free morphine sulfate for chronic, intractable pain of malignant and/or non-malignant origin.
- Chronic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

Specifications: 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 criticial memory error.

5.9.3 Connecting the pump & catheter: The Medtronic pump catheter will be sharply cut and the metal Codman connector will be used to splice the Codman straight 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.

Medtronic Pump



6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- History of histologically confirmed colorectal adenocarcinoma metastatic to the liver with no clinically or radiographically confirmed extrahepatic disease
  (or) Histologically confirmed cholangiocarcinoma (Clinical or radiographic evidence of metastatic disease that has been resected is allowed, provided there is no recurrence in that area prior to protocol consent)

- Confirmation of diagnosis must be performed at MSKCC

- Patient may have completely resected hepatic metastases without current evidence of other metastatic disease

- Lab values ≤14 days prior to registration
  - WBC ≥2.5 K/uL
  - Platelets ≥100,000/uL
  - Creatinine <1.7mg/dL
  - HGB ≥ 8.5 gm/dL
  - Total Bilirubin
    - ≤1.5 mg/dl (Colorectal patients)
    - ≤ 2 mg/dl (Cholangiocarcinoma patients)

- Prior chemotherapy is acceptable if last dose of oxaliplatin or irinotecan is given ≥3 weeks prior to planned first dosing on this protocol. 5-FU or 5-FU leucovorin may be given ≥2 weeks prior to planned first dosing on this protocol. [Note: no chemotherapy to be given after resection of liver lesions prior to treatment on this study]

- Any investigation agent is acceptable if administered ≥3 months before planned first dose on this protocol

- KPS ≥ 60% or ECOG ≤ 2
- Patients ≥18 years of age

6.2 Subject Exclusion Criteria

- Prior radiation to the liver (prior radiation therapy to the pelvis is acceptable if competed at least 4 weeks prior tothe planned first dose of treatment on protocol))
- Active infection, ascites, hepatic encephalopathy
- 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 ≤72 hours beforetreatment start)
- If in the opinion of the treating investigator a patient has any serious medical problems which may preclude receiving this type of treatment
- Patients with current evidence of hepatitis A, B, C (i.e., active hepatitis)
- Patients with history or known presence of primary CNS tumors, seizures not well-controlled with standard medical therapy, or history of stroke will also be excluded
- Serious or non-healing active wound, ulcer, or bone fracture
- History of other malignancy, except:
    1. Malignancy treated with curative intent and with no known active disease present for ≥3 years prior to registration and felt to be at low risk for recurrence by the treating physician
    2. Adequately treated non-melanomatous skin cancer or lentigo maligna without evidence of disease
    3. Adequately treated cervical carcinoma in situ without evidence of disease
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

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.

7.0 RECRUITMENT PLAN

We will make every effort to include women and minorities. Patients will be recruited from medical and surgical oncology clinics based on their eligibility criteria. The consenting professional will explain in detail the study to the patient and will review the informed consent with the patient. Patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. Upon signing the requisite copies of the informed consent, a copy is provided to them.

8.0 PRETREATMENT EVALUATION

Prior to treatment start, patients will undergo the following procedures:

- CT Angiogram or liver triphasic to determine arterial structures
- Perfusion flow scan (TcMAA): to be done after surgery, and before the patient is discharged from the hospital.
    - MRI or CT scan of chest, abdomen, pelvis: within 3 weeks prior to treatment start. *Please Note: Pursuant to literature received from the Medtronic pump brochure, an MRI examination of the entire body may be safely performed under the following conditions:*
        - 1.5-Tesla (T) and 3T horizational closed bore;
        - Maxiumum gradient of 19T/m (1900 gauss/cm);
        - Maximum gradient slew rate: 200 T/m/s
        - Maximum RF field intensity: First level controlled operating mode defined in IEC 60601-2 33.
        - At this time, Medtronic pump performance has not been established using other types of MRI scanners such as open-sided or standing MRI. Although MRIS temporarily stall pump operation, the Medtronic pump is able to reciver and continue normal perfusion rates.
-
- MediPort placement: any time prior to systemic treatment start
- Medical history, Physical Exam, Blood Pressure, Weight: within 2 weeks prior to treatment start
- Height: any time prior to treatment start
- Urine pregnancy test (female of child-bearing potential): 72 hours prior to treatment start
- KPS/ECOG, CBC with diff/plts, albumin, LDH, BUN, creatinine, alk phos, AST, ALT, bilirubin,: within 48 hours prior to treatment start
- CEA, if colorectal cancer
- CA 19-9, if Cholangiocarcinoma

9.0 TREATMENT/INTERVENTION PLAN

9.1 Surgical Treatment Plan

Prior to the patient going into the Operating Room (OR) for surgery, the patient's oncologist will place an order for the Medtronic pump into the MSKCC CIS ordering system to ensure the patient gets the correct pump. Additionally, the oncologist or a member of their team, will also be relaying this information to the OR staff, surgeon, and nuclear medicine staff via email.

The surgery to implant the Medtronic pump will be done at Memorial Hospital, and is a same day procedure. The same surgical techniques used to implant the Codman pump into 1000+

patients at MSK will be used for the Medtronic pump implantation in this study. Patients will undergo general anesthesia. The pump implantation is usually an open procedure requiring a laparotomy, but depending on the patient, surgeon, and any other surgeries happening concurrently, it can be done non-invasively. Pump implantation can be done at the same time as a liver or colon resection.

The Medtronic pump will be sutured to the anterior abdominal fascia. The Codman catheter is inserted into the gastroduodenal artery. The Medtronic pump catheter will be cut 15cm distance from the Medtronic pump. 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. Post-operatively, the perfusion flow scan will be done to further ensure there are no leaks between the Medtronic pump and the Codman catheter.

Intra-abdominal bleeding during and after pump implantation surgery is a rare complication. If this was to occur, it's likely that 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 MSK, they have a Medtronic pump implanted in their liver, and it also gives study contact information so external providers can contact the MSK treating physician at any time if they have questions or concerns.

9.2 Medical 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.

Dose calculation:

$$\text{FUDR: } \frac{0.12 \text{ mg/kg} \times \text{kg (patient weight)} \times \text{pump volume (20)} \times 0.9}{\text{pump flow rate 1 ml/day}}$$

Overweight patients:
If a patient is 35% above ideal weight, dose of FUDR chemotherapy will be calculated as follows:

To calculate Ideal Body Weight (kg):

Males: 50 kg + (2.3 x height in inches above 5 ft)
(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

To calculate Ideal Average Weight (kg):

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

Using the male example from above:
106 = 75.3 = 181.3/2 = 90.65 is the Ideal Average Weight

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.

Heparin: 25,000 units total dose

Normal saline: quantity sufficient to make total reservoir volume of 20 ml.

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.

9.3 On Day 15, the pump will be emptied and then filled with 25,000 units of heparin in normal saline (q.s. 20cc) 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.

9.4 Patients must meet all hematologic and blood chemistry criteria before beginning the first cycle of therapy:

WBC	≥2.5 K/uL
ANC	≥1.0 K/uL
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, therapy will be delayed one to two weeks or at the discretion of the treating physician.

Parameters for treatment with FUDR via intrahepatic pump are outlined in Section 11.4.2.

9.5 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.

Once pump is filled with drug, it must be emptied in 14 days or less because exceeding the 14 day window would pose a serious safety risk to the patient.

9.6 Patients receiving HAI therapy in an adjuvant setting typically stay on treatment for approximately 6 months. Because there is a higher risk of disease recurrence within the first two years of treatmend end, the pump will remain in the patient for an additional 2 years. During that time the patient may no longer be receiving HAI therapy but will continue to receive flush with heparin and saline to keep Pump open in case there is a recurrenceWe like them to be recurrence free for at least 2 years before romoving pump.. If the patient is still disease free at the 2 year mark, the pump can then be removed if the patient agreesThe pump may be left in longer depending on patient preference or clinical judgement. Even in cases where the pump can be removed from the patient, the catheter remains inside the patient because it is sewn in to the gastrintestinal artery at the time of pump implantation.

9.7 HAI therapy responses in metastatic (colorectal carcinoma and cholangiocarcinoma) patients typically show response in the first 3-4 months. These patients can be removed from protocol for the following reasons, but a number will continue with pump treatment at the investigator's discretion:

1. Their disease shrinks to a size that qualifies them for resection
2. Their disease progresses, and a new treatment regimen needs to be started, which may include some further FUDR treatment.
3. The patient decides to no longer receive protocol treatment for their cancer
4. If the patient wants to continue pump treatment, but does not want to travel to MSKCC every two weeks for pump flush, and has found a doctor who is well-trained to empty the pump and use heparin/saline with decadron or heparin/saline alone. The patient should be allowed to continue protocol.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Day 1 each Cycle (or w/in 48 hrs prior to Day 1)	**Days of systemic chemotherapy** (or w/in 72 hrs prior to Day 15)
Interval History, Physical Exam, MD or NP visit	X	
Interval History, Nurse visit		X
Toxicity assessment	X	
Weight	X	
KPS/ECOG	X	
CBC, Plts	X	X
BUN, Creat	X	X
Bili, AST, ALT	X	X
Alk phos, LDH	X	X
CEA/Ca 19-9*	X	X

MRI or CT Chest/abdomen/pelvis**	Q3 or Q2 months depending on cohort	
Documentation of pump residual	X	X

**CEA if colorectal or CA 19-9 if Cholangiocarcinoma*

*** CT windows of +/- 3 weeks will be acceptable. Resectable patients will have CT scans every 3 months. Unresectable patients will have CT scans every 2 months.*

- *Please Note: Pursuant to literature received from the Medtronic pump brochure, an MRI examination of the entire body may be safely performed under the following conditions:*
  - 1.5-Tesla (T) and 3T horizational closed bore;
  - Maxiumum gradient of 19T/m (1900 gauss/cm);
  - Maximum gradient slew rate: 200 T/m/s
  - Maximum RF field intensity: First level controlled operating mode defined in IEC 60601-2 33.
  - At this time, Medtronic pump performance has not been established using other types of MRI scanners such as open-sided or standing MRI. Although MRIS temporarily stall pump operation, the Medtronic pump is able to reciver and continue normal perfusion rates.

10.1 While being treated with protocol therapy, patients will be seen at or prior to the first day of each cycle by their medical oncologist. During the treatment phase, participants may receive standard systemic IV infusions at facilities outside MSKCC as long as they are still being seen for toxicity assessments at a study site at least every two weeks. During this time, all pump intervention will occur at MSKCC. Standard scans may also be done at an outside facility as long as they are read at MSKCC.

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

10.3 Patients will have an end of study treatment assessment for toxicity.

10.4 Patients will transition to the follow-up phase for safety and survival monitoring when:

- the patient's disease shrinks to a size that qualifies them for resection;
- the treating physician determines disease progression requiring a new treatment regimen off protocol;
- the patient decides to no longer receive protocol treatment for their cancer; or
- the patient is no longer amenable to pump treatment per protocol.

11.0 TOXICITIES/SIDE EFFECTS

All toxicities will be rated as per the NCI Common Toxicity Criteria version 5. Hepatic enzyme toxicities will also be captured according to the schema on 11.4.3 as well (see FUDR Dose Modifications and Table I).

11.1 Catheter and Pump

Possible risks associated with the catheter and pump are infection, hepatic artery thrombosis, pump malfunction, catheter occlusion and intra-abdominal bleed. If drug is not emptied from the pump in 14 days or less, there is a of risk becoming toxic.

The clinical management of patients with documented or confirmed pump pocket infections is based on our past experience with this problem, and includes intravenous antibiotics and washout of the operative site. In our extensive experience using hepatic artery pumps, such an approach eradicates most infections and salvages the pumps, which are subsequently used without incident. In a small fraction of patients with infections, replacement of the pump and relocation to a new site is necessary. If a pump catheter is infected, the pump and catheter must be removed.

When a patient comes off study or terminates protocol treatment, the device may remain implanted and must continue to be flushed at least every two weeks to maintain implant integrity. During this time, it may be used in accordance with standard pump treatments.

Sudden persistent changes in altitude (due to flying in an airplane, scuba diving, etc.) or temperature can affect the way the pump works. Altitude changes alter the pressure inside the pump, that can cause it to not work as programmed. Patients should always tell their study doctor before exposing themselves to prolonged altitude or temperature changes so the settings within the pump can be adjusted accordingly. If patients experience a persistent high fever, they should contact their study doctor immediately to ensure the pump is continuing to function as programmed. In rare cases, these types of changes could lead to serious injury or death. The rate of pump failure is less than 1%. Patients will receive standard systemic therapy alone if the pump is unusable.

If there is a stricture of a bile duct and the bilirubin goes up and does not come down after holding treatment and using decadron in the pump a biliary stent will have to be placed to the stricture.

11. 1. 2 FUDR

Toxicities associated with the intrahepatic administration of FUDR include biliary sclerosis, hepatic enzyme elevation, gastric ulcers

11.1.3 Dexamethasone

Common potential side effects include anxiety, mood alteration/lability, hyperglycemia, insomnia, peripheral edema, myopathy (with chronic use), acne, and hirsutism.

11.1.4 Gemcitabine

Common potential side effects include nausea, vomiting, alopecia, stomatitis, anorexia, fatigue, elevations of hepatic transaminases, reversible myelosuppression, rash, flu-like symptoms, edema, constipation, paresthesia, hypersensitivity reactions, phlebitis, proteinuria, hematuria, and rarely interstitial pneumonitis, ARDS and hemolytic uremic syndrome.

11.1. 5 Oxaliplatin

Toxicities associated with intravenous administration of Oxaliplatin include neuropathy, paresthesias/dysesthesias, neutropenia, thrombocytopenia, and diarrhea.

11.1.6 Irinotecan

Phase I and II studies of CPT-11 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.

11.1.7 Fluorouracil

Toxicity: Nausea, vomiting, stomatitis, diarrhea, dermatitis, alopecia, leukopenia, and thrombocytopenia.

11.1.8 Leucovorin Calcium (Folinic Acid)

The only adverse reaction reported for Leucovorin has been rare cases of allergic sensitization.

11.1.9 Combination of FUDR, Dexamthasone, Systemic Chemotherapy, Heparin and Saline

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

11.1.10 Anti-EGFR (panitumumab or cetuximab)

Toxicity: diarrhea, nausea, vomiting, stomatitis, and fatigue.

Dermatologic Toxicity: Dermatologic toxicities occurred in 89% of patients and were severe (NCI-CTC grade 3 and higher) in 12% of patients receiving Panitumumab monotherapy. The clinical symptoms include, but are not limited to, dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures. In some cases, it may cause infected sores requiring medical and/or surgical treatment, or cause severe skin infections that could be fatal. Subsequent to the development of severe dermatologic

11.2 Dose Modifications

Protocol treatment dosing regimens may be modified at the investigators discretion.

11.2.1 Systemic Chemotherapy Dose Modifications

If patients have delays in treatments due to hospitalization or other reasons, 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 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 heparin saline.

Guidelines for re-starting systemic therapy are listed in the tables below:

Hematologic Toxicities

Patients must meet all hematologic criteria outlined in Section 6.0 before beginning the systemic therapy. Pump therapy can start regardless of this bloodwork. For subsequent systemic therapy, patients must meet the following criteria for the full doses of systemic therapy:

- WBC $\geq$2000 cells/mm^3
- ANC $\geq$ 1000 cells/mm^3
- Platelets $\geq$ 75,000/mm^3
- Creatinine $\leq$ 1.8 mg/dL
- Bilirubin $\leq$ 1.5 mg/dL

If counts are outside these levels on date of scheduled treatment, therapy will be delayed by no less than one week. 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.

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

Non-Hematologic Toxicities

Dose Reduction for Non-Hematologic Toxicities

CTCAE Grade	Toxicity	Irinotecan	5FU Infusion	Leucovorin	Gemcitabine	Oxaliplatin

3	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	20% decrease	20% decrease	20% decrease	20% decrease	20% decrease
3	Diarrhea despite premedication with an effective antidiarrheal therapy	20% decrease	20% decrease	20% decrease	20% decrease	20% decrease
4	Nausea and/or vomiting despite premedication with an effective antiemetic therapy	30% decrease	30% decrease	30% decrease	30% decrease	30% decrease
4	Diarrhea despite premedication with an effective antidiarrheal therapy	30% decrease	30% decrease	30% decrease	30% decrease	30% decrease
3	Stomatitis	No dose reduction	20% decrease	20% decrease	No dose reduction	No dose reduction
4	Stomatitis	No dose reduction	30% decrease	30% decrease	No dose reduction	No dose reduction
≥2	Cardiac toxicity	No dose reduction	Stop treatment	Stop treatment	No dose reduction	No dose reduction
3 or 4	Hand/foot skin reaction	No dose reduction	20% decrease	20% decrease	No dose reduction	No dose reduction

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, symptoms of dehydration, fever, inability to take liquids by mouth, inability to control diarrhea (return to baseline) within 24 hours. Subjects with diarrhea should be evaluated frequently by a nurse or physician until resolution of diarrhea.

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 2nd time: 25% decrease	Stop
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 0).

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.

11.2.2 Gemcitabine/Oxaliplatin Dose Modification Considerations In 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 serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemzar 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.

11.3.3 Anti-EGFR (panitumumab or cetuximab) For subjects who experience toxicities while on study, one or more doses of panitumumab or cetuximab may need to be withheld, reduced, or delayed. On resolution of toxicity, a limited number of attempts to re-escalate reduced panitumumab doses will be allowed. Dose escalations above **6 mg/kg** starting dose are not allowed. ati-EGFR dose reductions are listed in the table below.

Symptomatic skin- or nail-related toxicity felt to be intolerable by the subject can have a reduction in dose according to the table below.

Table 1. anti-EGR Dose Reductions

	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Percentage (%)	100	80	60
mg/kg	6	4.8	3.6

11.3.4 FUDR Dose Modifications for Liver Toxicity

"Reference value" is defined as the value obtained on the first day of the most recent FUDR dose. 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. Percentages listed under "FUDR Dose" refer to percentage of last dose of FUDR administered.

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 < 3 x reference value	50%
	> 4 x reference value	Hold[A]
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 reference value	Hold[B]
TOT 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 reference value	Hold[C]

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 "Recommencing FUDR Treatment After Hold."

[A]AST elevation, [B]Alkaline Phosphatase elevation, [C]Total bilirubin elevation

* *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 u 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 H_2 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 1) 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 12 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.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients will be assessed for the following:

1) Serious adverse events related to pump or catheter malfunction such as catheter disconnects
2) Requirement of stent placement
3) Patients will be assessed for the usual toxicities (alkaline phosphatase, serum bilirubin).
4) Response (when measurable disease is present) will be recorded per standard scan report
5) Survival and progression free survival: the study team may make phone calls and review scans performed as part of standard of care to determine OS and PFS.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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 to determine if the pump is will 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.

Patients will be removed from HAI treatment if any of the following occur:

- Development of clear-cut progression or recurence of colorectal cancer compared to the baseline postoperative CT scan, Patient is unable to resume hepatic arterial FUDR due to hepatic toxicity.
- Unacceptable toxicity that does not respond to the dosage modification.
- Changes in a patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator.

Patients will be removed from the study if any of the following occur:

- Patient decides to withdraw from participating in the study.

Patients will be removed from the study and replaced if any of the following occur:

- Patients needs to have the Medtronic pump and Codman catheter removed due to post-operative infection prior to meeting the 3 month timpoint for evaluability
- 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
- Extrahepatic disease is found at the time of surgery and a pump is not placed
- Patient has extensive liver disfunction from the surgery and cannot get HAI treatment

Results will be released on Clinicaltrials.gov within one month of the conclusion of study interventions (after followup is completed of final patient accrued). If the study is stopped early, data will be posted within two weeks of termination

14.0 BIOSTATISTICS

We plan to enroll 30 evaluable patients in this study to characterize the toxicity profile of Medtronic pump with the Codman Catheter. Safety and tolerability will be summarized using descriptive statistics. Proportions will be estimated using binomial distribution along with 95% exact confidence intervals. Of primary interest is to estimate the incidence of liver toxicity in particular that of alkaline phosphates, bilirubin, and stent placement. With 30 patients we can estimate these proportions to within +/-18% margins of errors with 95% confidence. In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive liver toxicity within the first 3 months after pump placement. The stopping rules are derived using repeated significance testing are are given in the table below.

Toxicity	# of toxicities needed to stop the study	Toxicity rate	Probability boundary is crossed
Alk phos grade≥3(NCI)	6 within the first 10 patients 10 within the first 20 patients 13 within 30 patients	.30	.12
		.55	.94
Bili grade≥3(NCI)	4 within the first 10 patients 6 within the first 20 patients 8 within 30 patients	.15	.12
		.40	.97
Stent	5 within the first 10 patients 7 within the first 20 patients 9 within 30 patients	.19	.13
		.44	.97

For example, if the true probability of alkaline phosphates is 0.30 (considered acceptable based on prior studies on pump) then the probability the boundary will be crossed is 0.12, however if the probability of alkaline phosphates is 0.55 (unacceptable), then the boundary crossing probability if 0.94.

Since the catheter will be connected to the pump we will also monitor the incidence of a disconnect between the catheter and the pump. This is a serious event and if one such event occurs we will stop further enrollment onto the protocol and investigate this occurrence. Patients that already had the pump and catheter implanted will be allowed to continue use, if clinically appropriate. A sample size of 30 patients will provide 79% probability to observe one or more disconnects if the true incidence of this event in the population is 5% or more. This probability is 60% if the true underlying disconnect rate is 3%, it is 45% if the true underlying rate is 2%, and it is 26% if the true underlying rate is as rare as 1%.

If patient does not reach the 3 month point at the time they develop a recurrence they may not be able to be assessed for toxicity. Patient developing recurrence within the first 3 months will be replaced because they will require other chemotherapy which may affect toxicity.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study.

Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

This study is not randomized.

16.0 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into MSK Medidata. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: https://deainfo.nci.nih.gov/grantspolicies/datasafety.pdf.The DSM Plans at MSKCC were established and are monitored by the Clinical Research Administration. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: https://one.mskcc.org/sites/pub/rtm/GC%20Documents/Proposal%20Development%20Assistance/Data%20and%20Safety%20Monitoring%20Plan.pdf There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e. g. protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees:

Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institution Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g. NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

17.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event. The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

If appropriate, the report will be forwarded to the FDA by the IND Office

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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