

PROTOCOL SUBMISSION FORM Amendment Form	PROTOCOL NO. 11C0099-E	PRINCIPAL INVESTIGATOR (NIH Employee Name, Inst/Br, Telephone and e-mail): Udo Rudloff NCI SB 301.496.3098 Udo.Rudloff@nih.gov
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PROTOCOL TITLE: Regional Chemotherapy in Locally Advanced Pancreatic Cancer: RECLAP Trial

ABBREVIATED TITLE: Regional Chemo in Pancreas ca

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Amendment Letter: e

The Following revisions were incorporated into this protocol and approved by:

- ☒ Expedited Review (risk/ benefit ratio not changed)
☐ Full Board Review (meeting date)

Amendment includes changes required by:

- | | |
|---|---|
| <input checked="" type="checkbox"/> N/A | <input type="checkbox"/> Other Sponsor |
| <input type="checkbox"/> NCI IRB (CCR) | <input type="checkbox"/> FDA |
| <input type="checkbox"/> CTEP | <input type="checkbox"/> Special Studies IRB (DCEG) |
| <input type="checkbox"/> Other | |

If Other, list:

Amendment required Scientific Review?

- ☐ Yes ☒ No

ADMINISTRATIVE CHANGES

- ☐ Protocol Title/ Abbreviated Title
☐ New Principal Investigator
☐ NIH Personnel Change
☒ Non-NIH Personnel Change
☐ Converting to multi-institutional trial
 DEC clearance required? ☒ Yes ☒ No

Date submitted to IC DEC: N/A

Date cleared by IC DEC: N/A

PROTOCOL CONTENT CHANGES

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| <input type="checkbox"/> Precis | <input type="checkbox"/> Data Collection/Evaluation |
| <input type="checkbox"/> Study Objectives | <input type="checkbox"/> Human Subject Protections |
| <input type="checkbox"/> Background and Rationale | <input checked="" type="checkbox"/> Data Reporting |
| <input checked="" type="checkbox"/> Eligibility Assessment and Enrollment | <input type="checkbox"/> Ionizing Radiation Use |
| <input type="checkbox"/> Implementation of Study Design | <input type="checkbox"/> Pharmaceutical Information |
| <input type="checkbox"/> Supportive Care | <input type="checkbox"/> Appendices |
| <input type="checkbox"/> Accrual Ceiling Changed to: N/A | <input type="checkbox"/> Transfer of Materials/Data (DCEG Only) |

Does the amendment impact the risk/benefit assessment?

- ☐ Yes ☒ No

INFORMED CONSENT DOCUMENTATION

- ☒ Text Revisions to Consent(s)
☐ Investigator Contact Information on Consent(s)
☐ No Changes to Consent Form

SIGNATURE	Udo Rudloff - applied signature on 11/09/2012 7:13 AM EST New and Old Principal Investigators - electronic signature and date
APPROVALS	Steve Rosenberg - applied signature on 11/13/2012 11:57 AM EST Branch Chief - electronic signature and date Not Applicable Branch Scientific Review Committee Chair - electronic signature and date William Dahut - applied signature on 11/15/2012 10:38 AM EST Clinical Director- electronic signature and date Michael Hamilton - applied signature on 11/15/2012 9:42 PM EST Chair, IRB Review - electronic signature and date

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IRB Meeting Date:

Abbreviated Title: Regional Chemo in Pancreatic Ca

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Regional Chemotherapy in Locally Advanced Pancreatic Cancer: RECLAP Trial

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PRECIS

Background:

- Pancreatic cancer is the fourth leading cause of cancer death in the United States.
- Surgery offers the only chance at cure; however, less than 20% of patients are considered resectable at initial presentation.
- A common reason for being classified as unresectable is loco-regional advanced disease.
- Several phase I studies of regional administration of chemotherapy have proven safe.
- The main advantage of pancreatic cancer targeted arterial perfusion of Gemcitabine is achievement of higher local bio-available active drug levels at the tumor bed.
- The RECLAP trial is a phase I trial offering highly selective 24-hour intra-arterial administration of Gemcitabine via a subcutaneous port for patients with unresectable locally-advanced pancreatic cancer.

Objectives:

Primary Objective:

- To evaluate feasibility and toxicity of intra-arterial gemcitabine therapy (DLT).
- To establish the maximum tolerated dose (MTD)

Secondary Objectives:

- To evaluate response rate using RECIST, PET, MRI and CT perfusion criteria (EASL)¹
- To determine progression free and overall survival.
- To evaluate the conversion rate from unresectable or borderline resectable to potentially resectable pancreatic cancer.
- To determine progression-free and overall survival.
- To analyze potential selection criteria to be used in future studies for patients who present with marginally unresectable or unresectable locally-advanced pancreatic cancer that might benefit from this approach.

Eligibility:

- Unresectable locally-advanced pancreatic cancer.
- 18 years old or greater with an ECOG 0-2
- Laboratory and physical examination parameters within acceptable limits by standard of practice guidelines prior to surgery or chemotherapy.
- No extra-pancreatic disease except regional lymph nodes.

Design:

- This is a dose escalation phase-I study.
- Patients considered unresectable due to locally-advanced pancreatic cancer will receive selective arterial perfusion of gemcitabine over 24 hours via a subcutaneous indwelling port.
- Treatment will be given on Days 1 and 14. One cycle = 4 weeks for up to six cycles.
- Three to six patients will be enrolled per dose cohort.
- 18 to 36 patients in 7 cohorts will be accrued plus 6 more patients at the MTD over 36 months. Patients will be evaluated every 2 cycles (8 weeks). Upon progression patients will be taken off study. If no PD, patients will continue up to 6 cycles.

- Chemotherapy naïve patients and patients who received previously chemotherapy including gemcitabine will be allowed, as this mode of administration has better bioavailability, offer potential for better biological effect and less systemic toxicity profiles.

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1. Introduction:

1.1. Study Objectives

1.1.1. Primary Objective:

- To evaluate feasibility and DLT (dose limiting toxicity).
- To establish the MTD (maximal tolerated dose)

1.1.2. Secondary Objectives:

- To evaluate response rate using RECIST, PET, MRI and CT perfusion criteria (EASL)¹
- To evaluate the conversion rate from unresectable or borderline resectable to potentially resectable pancreatic cancer.
- To determine progression-free and overall survival
- To analyze potential selection criteria to be used in future studies for patients who present with unresectable locally-advanced pancreatic cancer that might benefit from this approach.

1.2. Background and Rationale

In 2009 there were an estimated 42,470 new cases and 35,240 deaths attributed to pancreatic cancer in the United States.² Overall, survival is poor, with approximately 23% of patients living 12 months after diagnosis. Overall 5-year survival is approximately 5% at best.³ Prolonged survival is possible for patients that undergo complete resection and approximates a median of 18 to 20 months in large series, with or without the addition of single-agent chemotherapy.⁴ Unfortunately, less than 20% of patients with pancreatic cancer are considered resectable at the time of diagnosis (in the USA only 8% are deemed resectable), most often due to locally advanced or metastatic disease. For patients with inoperable pancreatic cancer chemotherapy may prolong survival and improve quality of life. Yet it must be considered palliative in patients without a surgical treatment option.⁵

The optimal treatment for pancreatic cancer is complete resection followed by adjuvant systemic chemotherapy. Due to late-stage diagnosis most patients have limited chance for curative resection, thus novel approaches for early detection and effective treatment must be explored. In addition, new approaches that will convert unresectable locally advanced pancreatic cancer into a resectable state might result in better outcome as surgical extirpation provide the only chance to survive 5 years. One such approach is suggested here: Regional perfusion. In cases which tumors are detected early enough to allow resection, the choice of adjuvant chemotherapy is based on the results of a randomized clinical trial that demonstrated significant improvement in median overall survival favoring Gemcitabine over observation alone.⁴ Overall-survival was demonstrated and subsequently Gemcitabine supplanted 5-fluorouracil (5-FU) as the single-agent treatment of choice for patients with pancreatic cancer. However, a well designed phase-3 study testing Gemcitabine versus 5-FU is yet to demonstrate a significant advantage favoring Gemcitabine. The addition of targeted molecular agents or cytotoxic drugs to gemcitabine adds little or no clinical benefit to patients with this disease to date.^{6, 7} Likewise, although encouraging, current data are not definitive regarding the benefit of adjuvant chemoradiotherapy. Therefore, increasing the

rate of resection for patients with pancreatic cancer may represent a practical approach to improve survival for patients currently without a surgical treatment option. Achieving this goal requires neoadjuvant therapy that mediates substantial tumor regression, potentially allowing for complete resection in previously unresectable patients. This trial will offer patients such a potential approach.

We hypothesize that neoadjuvant regional chemotherapy may improve resectability rates in cases of locally advanced pancreatic cancer. Progressive surgical techniques combined with current neoadjuvant chemoradiotherapy strategies have already yielded emerging support for a multimodality approach to treatment of advanced pancreatic cancer.⁸

Regional therapy for locally advanced solid organ cancer

Since the 1950s, regional administration of chemotherapy has been evaluated in many cancers and in some cases proven an effective therapy for local and regional disease. The pharmacologic rationale for regional drug delivery is to increase drug concentrations at tumor sites and limit systemic drug exposure and its sequelae.⁹ In 1958 Creech et al described the use of regional isolation perfusion with nitrogen mustard compounds in the treatment of 24 patients with a variety of cancers.¹⁰ This report was the first to employ the use of an extracorporeal circuit in the administration of regional chemotherapy. Since that time, the role of regional chemotherapy administration as an adjunctive therapy in patients with locally advanced or regional disease has been well established. Regional administration of chemotherapy is used to treat local-regional and metastatic disease for many cancer histologies. Examples of effective regional therapy include isolated limb perfusion, hyperthermic intraperitoneal chemotherapy, intrathecal, and intravesicular chemotherapy.¹¹⁻¹⁵ The surgery branch accumulated significant experience over the years with limb perfusion, peritoneal perfusion, and liver perfusion.

Regional chemotherapy for pancreatic cancer

Reports published between 1995 and January 2010, described 895 patients with pancreatic cancer treated with regional chemotherapy. The majority of these studies were small series or sequential, uncontrolled trials. The majority of the patients (>95%) were diagnosed with pancreatic ductal adenocarcinoma (Table 1). Virtually all patients were described as having locally advanced (stage III) or metastatic cancer (stage IV) at the time of treatment. In over half of reports (11/21) patients were allowed to have undergone prior curative or palliative surgery and, in studies in which it was reported, 11% of patients (59/543) received radiation or chemotherapy prior to receiving regional chemotherapy. One year survival rates approximated those seen with systemic chemotherapy. However, analysis of heterogeneous reports of a non-standardized treatment strategy is limited not only by the inherent bias associated with each study, but also the retrospective nature of any such review. Despite these limitations, a review of the existing literature on an experimental method of treating this lethal disease is necessary for the advancement of future investigation.

Regional chemotherapy techniques used included arterial infusion and perfusion, with or without hemofiltration. Celiac axis infusion (CAI) was used in a majority of studies (57.1%) whereas selective arterial infusion (SAI; 23.8%) and hypoxic abdominal perfusion (HAP; 28.6%) were used less often. In two studies, HAP and CAI were utilized sequentially. In an attempt to direct blood flow to tumor or pancreas only, three studies utilized selective arterial embolization prior to arterial infusion. Variations to arterial catheterization, including percutaneous versus open surgical approach, appeared to reflect changes in experience or the use of newer technologies over time. A variety of chemotherapeutic agents were used alone or in combination; 5-FU was used most often (57.1%) followed by mitomycin-C (MMC; 47.6%), cisplatin (CDDP; 38.1%), gemcitabine (23.8%), mitoxantrone (19%), epirubicin and carboplatin (14.3%), methotrexate (4.8%) and melphalan (4.8%). Three studies also included adjuncts to chemotherapy: warfarin, angiotensin-II, and degradable starch microspheres.

Selective arterial infusion (SAI) with gemcitabine as a continuous infusion (30-minutes infusion) has been reported in 2 separate occasions^{16 17}. Shamseddine et al. performed a comparative pharmacokinetic profile of gemcitabine infusion delivered as intravenous and intra-arterial infusions in patients with unresectable pancreatic cancer¹⁶. Seven patients with unresectable pancreatic cancer received escalating IA doses of gemcitabine ranging from 800 to 1400 mg/m², after selective embolization of all pancreatic blood supply, except for the tumor-feeding arteries. Four patients received similar doses of IV gemcitabine (control). The pharmacokinetic data revealed differences in plasma concentrations between intra-arterial and intravenous delivery routes. The area under the curve (AUC) for gemcitabine during and after intra-arterial administration via the proximal splenic artery was 29.0 vs. 331.0 ng.ml/min ($p < 0.0001$) for intravenous administration. Additionally, the peak plasma concentration of gemcitabine was significantly lower than that for the corresponding systemic intravenous route (intra-arterial 1.1 vs. intravenous 7.6 ng/ml; $p < 0.0001$). The median overall survival in this very small trial was 5 months with median time to progression of 4 months. No patients reported grade 3 or 4 toxicity.

A significant concern with any regional therapy is local toxicity. Miyanishi et al. recently demonstrated safe effective delivery of 1000 mg/m² of intra-arterial gemcitabine following selective embolization of pancreatic blood supply in 12 patients with pancreatic cancer¹⁷. They report an overall response rate of 33% with median survival time of 22.7 (95% CI; 9.5-24.5) months with 1- and 2- year overall survival rates of 83 and 25% respectively. The side effect profile associated with intra-arterial infusion were very slight including grade 3 anemia in only 1 patient and no grade 3 or 4 leucopenia, thrombocytopenia or neutropenia. Grade 1 fatigue was seen in 5 patients while grade 1 anorexia, nausea and vomiting were observed in only 2 patients. During arterial infusion of chemotherapy, no case required administration of insulin or oral hypoglycemic agents. Additionally, there was no evidence of exocrine or endocrine pancreatic insufficiency in this cohort. The most common complication related to the indwelling catheter was dislocation of the catheter tip in 2 patients and skin abscess around the embedded port in 2 patients. All catheter related complications were treated and neither resulted in discontinuation of treatment. No patients had pancreas specific complications related to delivery of regional arterial chemotherapy. Clinically 10 patients had elevated carcinoembryonic antigen (CEA) prior to therapy and 7

demonstrated greater than 50% reduction in CEA levels following treatment. Three patients demonstrated complete normalization of CEA values. The median time to progression was 9.1 (95% CI; 5.4-12.8) months. This study, while small and limited, does suggest that regional gemcitabine can be delivered safely at high doses in the setting of pancreatic cancer.

The primary endpoints reported in most of the studies described above were tumor response and survival. World Health Organization (WHO) criteria for objective tumor response were used by 71% (15/21) of studies, while 19% (4/21) cited no objective criteria. The average response rate reported was 25.9% (n=19 studies). The average 1-year survival was 38.9% (n=10), with an average median survival of 9 months (n=18). The most commonly reported toxicities were hematologic and gastrointestinal, however 7 studies that reported toxicity did not use standardized reporting criteria. In total, there were 199 cases of grade 1-2, and 47 cases of grade 3-4 gastrointestinal toxicity; 142 cases of grade 1-2 and 70 cases of grade 3-4 hematologic toxicity. At least two studies reported instances of duodenal ulceration while others reported complications including arterial dissection, catheter dislocation, inguinal hematoma, lymphatic fistula, and deep vein thrombosis. Based on radiographic responses to therapy, 78 out of 277 patients (28%) were taken to surgery following regional chemotherapy administration; thirty-two (41%) of those patients were amenable to pancreatectomy or necrosectomy. There were no complete responses to regional chemotherapy reported. No studies performed analyses to identify factors predicting response to regional chemotherapy. Also, no studies compared survival of responding patients versus non-responding patients.

Pancreatic cancer patients with unresectable primary tumors have approximately 20% chance of surviving one year following diagnosis and treatment with single agent chemotherapy.¹⁸ For those patients with tumors amenable to resection, the most common sites of recurrence include the local resection bed, liver and peritoneum. For this reason, the application of local-regional chemotherapy for advanced pancreatic cancer has been posited not only as a method of treating recurrent disease, but also as prevention in the adjuvant and neoadjuvant settings.

Pancreatic circulation

In general, the arterial system in the head of the pancreas consists of the anterior and posterior superior pancreaticoduodenal artery (ASPD and PSPD) that arise from the gastroduodenal artery (GDA) and the inferior pancreaticoduodenal artery (IPA) which branches from the superior mesenteric artery (SMA). These arteries combine to form the pancreaticoduodenal arcade surrounding the head of the pancreas. The body and tail of the pancreas receive blood flow from the dorsal pancreatic artery (DPA), the great pancreatic artery (GPA) and the caudal pancreatic artery (CPA) which all arise from the splenic artery (Figure 1). It is assumed that blood flow to pancreatic head neoplasm is supplied from the ASPD, PSPD and IPA while body and tail neoplasm are supplied by the DPA, GPA and CPA. Super selective arterial embolization of main branches combined with selective catheter directed chemotherapy infusion represents a novel combined therapy which will simultaneously increase the concentration of bio-available drug within the local tumor bed and lower the systemic concentration of drug, thus reducing toxicity.

Gemcitabine

Gemcitabine is a pro-drug that requires intracellular phosphorylation for conversion to the active difluorodeoxycytidine disphosphate (dFdCDP) and triphosphate (dFdCTP) metabolites. dFdCTP competes with dCTP for incorporation into DNA by DNA polymerase; once incorporated into DNA, dFdCTP is resistant to removal within the DNA strand by DNA polymerase resulting in DNA fragmentation and apoptosis. Additionally, dFdCTP competitively inhibits DNA polymerase resulting in a decrease in intracellular dCTP and preferential incorporation of dFdCTP into DNA (referred to as self-potential). The pharmacokinetics of dFdCTP are linear; however, the phosphorylation and metabolism of dFdCTP are saturable at dose rates above 10 mg/m²/min.¹⁹ This observation suggests that perhaps smaller doses given over longer period of time may potentiate the cytotoxic effect of gemcitabine. Indeed providing proof of this principle, Tempero et al. reported improved median survival (5.0 vs. 8.0 mo; p=0.013) and 2-yr survival rates (2.2% vs. 18.3%; p=0.007) when comparing the recommended dose of single agent gemcitabine 1000 mg/m² given as a 30-min infusion weekly, compared with a fixed dose rate (FDR) infusion given at 10 mg/m²/min (1500 mg/m² over 150 minutes).^{20, 21}

Prolonged intravenous administration of Gemcitabine

Based on the pharmacology of Gemcitabine described above, two studies reported on prolonged administration of Gemcitabine. Anderson et al. reported on a phase-I study of a 24 hour infusion of Gemcitabine in previously untreated patients with inoperable non-small-cell lung cancer. A total of 24 patients were studied. Gemcitabine was administered as a 24 hour infusion on days 0, 7 and 14 every 28 days. Dose levels were 10, 20, 40, 80, 120, 180, and 210mg/m²/24hr. The MTD was 180mg/m²/24hr and the DLT was neutropenia and lethargy.²² Rajdev et al. reported on a phase-I trial of gemcitabine administered as a 96 hour continuous intravenous infusion in patients with advanced carcinoma and lymphoma. Gemcitabine was initially given at 1mg/m²/24hr for 48 hours, then 72 hours and finally 96 hours.²³ The dose was then increased to 2, 4, 6, 10, 15, 20 and 25mg/m²/24hr for 96 hours. Subsequently, dose modification was added: 7, 8, and 9mg/m²/24hr for 96 hours. Patients received initially an every 3 week schedule and later an every 2 week schedule, and then weekly every 3 weeks of 4 week cycle schedule was amended to the protocol. Thirty four patients were treated with a variety of tumors. The MTD was 8mg/m²/24hr for 96 hours every 3 weeks and 6mg/m²/24hr for 96 hours every 2 weeks. The most common grade 2 or higher toxicity at all dose levels included: Fever (n=14), dyspnea (n=7), mucositis (n=6), hypotension (n=6), nausea/vomiting (n=6) and fatigue (n=5). Neutropenia and thrombocytopenia were uncommon.

Pancreatic Arterial Port Catheter for Chemotherapy Infusion

A recently published article by Deschamps et al** described in detail a series of 84 patients who received hepatic arterial infusions using an arterial port system²⁴. The patients underwent hepatic angiography, embolization as indicated, and insertion of the arterial port catheter. Patients received the first course of intraarterial chemotherapy on the day of catheter insertion. The mean number of courses was 7.3 (range 0–25) per patient; of these patients, 73% (61 of 84) received at least 4 courses of therapy. Intraarterial chemotherapy was discontinued due to catheter malfunction in 24% (20 of 84) of the patients. This included infection, femoral artery thrombosis, infusion hole migration, catheter occlusion,

and gastroduodenal ulceration. The mean number of courses these patients received prior to discontinuation of treatment was 3.6. Intraarterial chemotherapy was discontinued despite functional catheters for: tumor progression or death 56%, chemotherapy induced toxicity in 6%, a response that allowed hepatic surgery or radiofrequency ablation in 10%, or completion of the planned adjuvant treatment in 5%.

The proposed trial will offer an innovative approach for locally advanced unresectable pancreatic cancer: A 24 hour highly selective intra-arterial gemcitabine administration. This approach offer two advantages: First, based on the pharmacodynamics and pharmacokinetics of gemcitabine, a lower dose infused over prolonged time will optimally saturate the enzyme responsible for the conversion of gemcitabine into its two active metabolites resulting in higher concentrations of intracellular active gemcitabine, and second, selective intra-arterial delivery of gemcitabine will avoid systemic toxicity and first pass degradation of gemcitabine by the small-bowel and the liver. Local administration of gemcitabine to the pancreas has been shown to be safe with low morbidity.

2. Eligibility Assessment and Enrollment:

2.1. Eligibility Criteria

2.1.1. Inclusion Criteria

- a. Histologically or cytologically confirmed locally advanced pancreatic adenocarcinoma or clinical and radiographic evidence of pancreatic cancer
Note: Patients with a limited disease burden outside the pancreas, who have undergone systemic chemotherapy for metastatic disease and have achieved a complete response in the metastatic lesions of ≥ 6 months, and have no evidence of disease outside the pancreas at time of enrollment, are eligible.
- b. Disease must be evaluable
- c. Disease should be deemed unresectable by the MD Anderson criteria ²¹ (Table 2)
- d. Patients may be chemo naive or have received prior chemotherapy (including Gemcitabine) and/or radiation
- e. Greater than or equal to 18 years of age
- f. Must be able to understand and sign the Informed Consent Document
- g. Clinical performance status of ECOG ≤ 2
- h. Life expectancy of greater than three months
- i. Patients of both genders must be willing to practice birth control during and for four months after receiving chemotherapy
- j. Hematology:
 - Absolute neutrophil count greater than $1300/\text{mm}^3$ without the support of Filgrastim.
 - Platelet count greater than $75,000/\text{mm}^3$.
 - Hemoglobin greater than 8.0 g/dl.
- k. Chemistry:
 - Serum ALT/AST less or equal to 3 times the upper limit of normal, unless patient carries a biliary stent. For these patients, to account for

asymptomatic, transient elevations in transaminases ('transaminitis'), serum ALT/AST may be less than or equal to 5 times the upper limit of normal provided all other eligibility parameters are met.

- Serum creatinine less than or equal to 1.8 mg/dl unless the measured creatinine clearance is greater than 60 mL/min/1.73 m²
 - Total bilirubin less than or equal to 2 mg/dl,
 - PT within 2 seconds of the upper limit of normal or INR≤1.8
- l. No history of prior/other malignancies within the 2 years prior to enrollment with the exception of basal cell carcinoma

2.1.2. Exclusion Criteria

- a. Metastatic disease including malignant ascities
- b. Women of child-bearing potential who are pregnant or breastfeeding because of the potentially dangerous effects of the chemotherapy on the fetus or infant.
- c. Active systemic infections, coagulation disorders or other major medical illnesses of the cardiovascular, respiratory or immune system, myocardial infarction, heart failure
- d. Childs B or C cirrhosis or with evidence of severe portal hypertension by history, endoscopy, or radiologic studies
- e. Weight less than 40 kg
- f. Significant ascites, greater than 1000cc in the absence of peritoneal disease
- g. Concomitant medical problems that would place the patient at an unacceptable risk for the procedure
- h. Need for concurrent chemotherapy
- i. Discretion of the PI

2.2. Research Eligibility Evaluation

2.2.1. Within 4 weeks prior to treatment:

- Complete physical examination including vital signs, height and weight as well as ECOG assessment.
- HIV, Hepatitis B surface antigen and Hepatitis C antibody {may be completed anytime within 8 weeks prior to 2 weeks prior to enrollment}
- 12 lead EKG
- Pathology slides will be reviewed by the NCI Laboratory of Pathology if available. {may occur at any time prior to enrollment}
- Diagnostic laparoscopy as clinically indicated to confirm local advanced disease
- Baseline imaging
 - CT scan of chest, abdomen and pelvis (CT C/A/P) with triphasic 1mm cuts as per the pancreas protocol.
 - MRI/MRCP – pancreas, if medically indicated
 - FDG PET - as feasible
 - Radionuclide bone scan, when clinically indicated.
 - MRI Brain when clinically indicated.

- Laboratory evaluation
 - CBC with platelets
 - Chemistries (Sodium (Na), Potassium (K), Chloride (Cl), total CO₂ (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, total CK, Uric acid
 - Lipase, amylase and CRP
 - PT/PTT & INR,
 - Urinalysis
 - CA19-9 and CEA

2.2.2. Within 2-3 days prior to therapy

- Brief physical examination of the lungs, heart and abdomen as well as vital signs measurements, weight and ECOG assessment
- PT/PTT & INR
- Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin
- Serum beta-HCG on all females of child bearing potential or urine pregnancy test
- Medical consult as indicated
- Anesthesia evaluation

2.3. Patient Registration

Registration of patients onto this study will take place within 7 days of the patient signing the consent by faxing a completed eligibility checklist to the Central Registration Office (CRO) at 301-480-0757 between 9:00 and 5:00 Monday through Friday.

3. Study Implementation:

Study Design (See appendix 1 for trial schema)

This is a phase 1 trial with inter-patient and intra-patient dose-escalation scheme in which cohorts of patients will be treated with increasing doses of gemcitabine administered as a super-selective continuous arterial infusion over approximately 24 hours.

The initial treatment will start in the Interventional Radiology (IR) Suite after placement of the subcutaneous port in the presence of the PI and an anesthesiologist. Subsequent treatments may be administered in the Intensive Care Unit or on 3NW as will be determined by the PI (Section 3.6).

Treatment will be administered (+/- 3 days) on days 1 (C1D1) and 15 (C1D15) every 28 days (one cycle). Two cycles will constitute one course.

Patients who enroll and are willing to have specimens collected for research purposes will be enrolled on protocol 09-C-0079. No specimens will be collected for research purposes on this protocol.

3.1. Inter-patient Dose – escalation rules

The starting dose for cohort-1 (3 patients) will be 18 mg/m²/24 hours (10% of the similarly administered 24-hr infusion of gemcitabine I.V. dose);

3.1.1. MTD

- The MTD is the highest dose that induces DLT in no more than 2 patients among a cohort of 6 patients.
- Patients will be divided into 7 cohorts and will begin dosing at successively higher doses until MTD is established or up to 165 mg/m²/24 hours.
 - Cohort-1 will start on 18 mg/m²/24 hr
 - Cohort 2 at 36 mg /m²/24 hr
 - Cohort 3 at 72 mg /m²/24 hr
 - Cohort 4 at 96 mg /m²/24 hr
 - Cohort 5 at 115 mg /m²/24 hr
 - Cohort 6 at 138 mg /m²/24 hr
 - Cohort 7 at 165 mg /m²/24 hr
- Only DLTs that occur during Cycle 1 of each dose level will be used to determine MTD. DLTs that occur during the intra patient dose escalation will not be used to determine MTD.

3.1.2. Escalation of dose in successive cohorts will be as specified below:

- At least 3 patients will be entered to each cohort. Escalation to the next higher dose cohort may occur if none of the three patients have dose-limiting toxicity (DLT) or if no more than 1 out of 6 patients experienced DLTs at that dose level.
- If multiple patients are contemporaneously enrolled in a cohort, no patient may be dosed until the preceding patient has undergone the day 2 toxicity evaluation.
- Dose escalation may proceed after the third patient in each cohort has shown no DLTs at the day 14+/-2days toxicity evaluation provided no DLT's occurred at that dose level.
- If 1 of 3 patients in a given cohort has a DLT, then an additional 3 patients will be treated at that dose level. Escalation to the next higher cohort may occur if only one of six patients develops a DLT.
- If only 3 patients were treated in the cohort below which the MTD was exceeded, up to an additional 3 patients will be treated at that dose level
- If no additional DLTs are seen, then up to an additional 6 patients may be treated at a dose that is the average between the DLT-dose and the dose given prior to the DLT-dose in order to further define the MTD.
- If fewer than 2 in 6 patients experience a DLT at this dose level, then this will be the MTD. If 2 or more patients experience DLT then the previously identified level will be considered MTD.
- Escalation of a dose level in successive cohorts of 3 to 6 patients will be based on toxicity until an MTD is determined.
- The maximum permitted dose limit will be set at 165 mg/m². All toxicities occurring during the first cycle will be used to determine MTD.
- If the MTD has been exceeded in the first cohort, the dose will be de-escalated as described in appendix 2
- Up to an additional 6 patients (beyond the 6 entered to determine the safety of the dose level) may be treated at the MTD to establish further data concerning the biologic aspects of this route of administration.

3.2. Intra patient dose escalation

Patients who complete the first cycle of a course without experiencing any DLTs may escalate to the next dose level for subsequent cycles. Patients who escalate to higher dose levels will not count towards accrual to the higher cohort but will remain in their initial cohort. The rationale for using intra-patient dose escalation is as follows: Unresectable locally advanced pancreatic cancer is a deadly disease without effective therapy; if toxicity is not exhibited by any particular patient, it is reasonable to assume that dose escalation is safe and potentially beneficial. We do not want to prevent patients from experiencing a potential benefit from this treatment when other treatments clearly have little impact and result always in death within 8-10 months.

- At each cycle the dose will be increased to the next dose level by 100%, 100%, 33%, 20%, and 20% respectively (18, 36, 72, 96, 115 and 138mg /m² /24hr) unless DLT is observed
- Patients who experience DLT, will continue treatment at the previous dose level once toxicities have resolved to grade 1 or baseline
- Patients who meet any of the off treatment or off study criteria will not continue the dose escalation

3.3. Definition of Dose-limiting Toxicity

Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE version 4.0)

3.3.1. DLT is defined as follows:

All grade 3 or greater toxicities with the exception of

- Grade 3 constitutional symptoms that persist for less than 72 hours.
- Grade 3 and 4 myelosuppression (neutrophils and thrombocytopenia) of less than 5 days duration.
- Grade 3 metabolic/laboratory events that are correctable within 24 hours

3.3.2. Events that are assessed by the PI as clearly unrelated to the agent will not be considered DLTs (e.g., events directly related to catheter insertion, pain related to underlying disease)

3.3.3. Only DLTs that occur during the first cycle of the first course in a given cohort will be used in the determination of MTD. DLTs that occur during intra patient dose escalations will not be used to determine MTD.

3.4. Protocol Stopping Rules

Accrual will be suspended, the IRB will be notified, and the dose escalation regimen will be reassessed if any of the following criteria are met during the first course (8 weeks) of treatment

- Any treatment related deaths within 30 days of treatment
- If 2 of the first 5, or 3 of the first 10, 4 of the first 15, or 5 of the first 20 patients are taken off treatment due to treatment related toxicity

3.5. Pancreatic Arterial Infusion Catheter Placement Procedure:

3.5.1. Patient Management

Patients will be admitted prior to scheduled procedure. Patients will be put on generous IV fluids for hydration in preparation for contrast angiography. Cefazolin or ciprofloxacin (PCN allergy) or any other appropriate antibiotics deemed in the best interest of a particular patient will be administered approximately 1 hour prior to incision. All patients will be maintained on proton pump inhibitors approximately 24 hours prior to first treatment and for the duration of the trial. Catheter placement will be performed in the Interventional Radiology Section under conscious sedation or anesthesia (as determined by condition) by interventional radiologists as associate investigators. Vital Signs (including continuous pulse oximetry and ECG) will be monitored during the procedure. Patients will be managed by the GI and hepatobiliary surgical oncology section fellow (Ward) in conjunction with the PI.

3.5.2. Catheterization Strategy

The catheterization procedure will be performed as per routine and according to a three-step strategy; 1) arterial redistribution will be performed as necessary, 2) percutaneous placement of the indwelling infusion catheter and port, and 3) evaluation of catheter position and patency and management of drug distribution.

- **Arterial Redistribution**

The purpose of arterial redistribution procedures is to 1) reduce pancreatic arterial supply from multiple branches to a single (or few) feeding artery(s) for infusion purposes, and 2) occlude non-target arteries that arise from the chemoinfusion site which supply non-target intraabdominal organs.

In general, pancreatic head neoplasms will be supplied by the anterior and posterior pancreaticoduodenal arteries and inferior pancreaticoduodenal arteries, whereas the pancreatic body and cauda tumors would be supplied by the dorsal pancreatic artery, the great pancreatic artery, and the caudal pancreatic artery, all branches of the splenic artery. Homma et al.¹ developed a strategy in which pancreatic arterial branches are superselectively embolized, leaving the great and caudal pancreatic arteries alone arising from the splenic artery as the chemoinfusion source for any tumor in the entire pancreas.²⁵

- **Superior Mesenteric Arteriography**

The patient will be placed in the supine position and sterile preparation of the right or left femoral area will be performed. Following selective catheterization of the superior mesenteric artery, superior mesenteric arteriography will be performed to identify accessory or replaced hepatic vasculature, as well as to assess the patency of the inferior pancreaticoduodenal arcade. If the pancreaticoduodenal branches from the gastroduodenal artery are stenotic or encased by tumor, coil embolization of

the inferior pancreaticoduodenal artery/arcade will be performed through the origin of this vessel from the superior mesenteric artery.

- **Celiac Arteriography**

Celiac Arteriography will then be performed to identify hepatic and splenic arterial anatomy, followed by selective gastroduodenal and splenic arteriography to recognize pancreatic supply as well as non-target vessels supplying the duodenum, or stomach. The anterior and posterior superior pancreaticoduodenal arteries and the gastroduodenal arteries will then undergo coil embolization. If CT-angiography or similar study previously demonstrated supply to the target pancreatic tumor from the dorsal pancreatic artery (splenic artery origin), then this vessel will be embolized as well. As a result of the embolization steps, the only remaining arterial supply to the pancreatic tumor will be the great pancreatic and caudal pancreatic artery branches of the splenic artery¹⁷. The above described maneuvers will be done however, it is not always possible to perform in all patients due to vascular variation. In these cases a selective infusion will be done via the most prominent artery supplying the tumor.

3.5.3. Pancreatic Chemoinfusion catheter placement

Following the selective embolization steps described above, the tip of the infusion catheter (3.3F or 5F polyurethane catheter with a hydrophilic heparinized polymer such as the Anthron PU catheter (Toray Medical Company, Tokyo, Japan) will be placed in the splenic artery proximal to the great and caudal pancreatic arteries. If a different diagnostic catheter is used for the selective angiography and embolization, catheter exchange will be performed for the infusion catheter in routine fashion. Cone bead CT arteriography will be performed with iodinated contrast injection through the infusion catheter to confirm opacification of the entire pancreas. Preferentially, a subcutaneous pocket will be created in the lower abdominal or lateral thigh soft tissues, and the trailing end of the infusion catheter will be pulled subcutaneously into the pocket for port attachment. Other access sites (e.g. subclavian) may be used as indicated depending upon patient anatomy. A Celsite access port (Toray Medical Company) or similar device (Cook Corporation or Bard Access) will serve as the subcutaneous infusion port.

- **Treatment modification- Splenic Artery Occlusion**

In the event that the splenic artery is severely encased or occluded, chemoinfusion treatment may be possible via the gastroduodenal artery following selective embolization of the right gastric artery, anterior superior pancreaticoduodenal artery, and gastroepiploic artery. More proximal celiac chemoinfusion may be performed with or without selective embolization at the discretion of the PI.

3.6. Post procedure care

- Patients will be admitted to the Intensive Care Unit of the NIH Clinical Center and will be monitored for approximately 48 hours in the ICU.
- Patients will receive routine post-procedure care.

- Abdominal X-ray or CT to confirm catheter placement the evening and the morning following the procedure. Subsequent to the port implantation patient will receive prophylactic Lovenox® 1.5mg/kg s.c. daily for the duration of the study. (Note: dose will be rounded to the nearest 10, 20, or 30 mg in order allow unit dosing with prefilled syringes.)

3.7. Pancreatic Chemotherapy Infusion

- Initial treatment may begin the morning following embolization (\pm 14 days) or when all procedure related toxicities have resolved and X-ray and or angiography confirms correct placement of the catheter
- The first hour of the first infusion will be given in the Interventional Radiology Department; subsequent treatments will be given in the ICU. After the patient has completed 2 treatments, additional treatments may be given on 3NW.
- Gemcitabine will be administered in 100 ml of 0.9% Sodium Chloride over approximately 24 hours via infusion pump every 14 days \pm 3 days (as per the dose escalation described in Section 3.1)
- During each treatment patients will be monitored for:
 - Pancreatic-related complications i.e. amylase, lipase,
 - Fever
 - leukocytosis
 - any other gastrointestinal, metabolic and constitutional symptoms
- Prior to discharge, patients will receive instructions on
 - Catheter care
 - Lovenox injection
 - Completion of the patient diary
 - Potential toxicities

3.8. Evaluation During Treatment

- Laboratory evaluation days 1,2,3, 8, 14, 21 and 28 (\pm 2 days - **Note:** day 8 & 21 labs may be performed by the patient's local oncologist with the results faxed to 301- 480 - 3838)
 - CBC with differential
 - Chemistries: (Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid).
 - Lipase, Amylase
- Within approximately 48 hours of each treatment
 - Abdominal X-ray or CT to confirm catheter placement and/or angiography
 - Toxicity evaluation, review of patient diary
 - Vital signs, weight, and ECOG assessment

3.9. Prior to each treatment

- Angiography via the port to ascertain the location of the catheter.
- All non- hematological toxicities must resolve to grade 2 or less with the following exceptions:
 - Serum ALT/AST must be less or equal to 3 times the upper limit of normal, unless patient carries a biliary stent. For those patients, serum ALT/AST may be less than or equal to 5 times the upper limit of normal.
 - Serum creatinine must be less than or equal to 1.8 mg/dl unless the measured creatinine clearance is greater than 60 mL/min/1.73 m²
 - Total bilirubin must be less than or equal to 2 mg/dl,
 - INR ≤ 1.8
- Hematological toxicities must resolve to:
 - Absolute neutrophil count greater than or equal to 1300/mm³
 - Platelet count greater than or equal to 75,000/mm³.
 - Hemoglobin greater than or equal to 8.0 g/dl.
- Endoscopy as clinically indicated in patients who present with GI symptoms following treatment
- Treatments may be held up to 2 weeks, patients who do not meet retreatment criteria at this time point will be taken off treatment.

3.10. Dose Reduction

Patients who experience DLT during any cycle will be treated at the next lowest dose level; patients may only undergo one dose reduction

3.11. Evaluation Following Each Course

- Patients will undergo evaluation for response at the end of each course (every 8 weeks +/- 1 week) as follows:
 - CT scan of chest, abdomen and pelvis (CT C/A/P) with triphasic 1mm cuts as per the pancreas protocol.
 - MRI – pancreas if indicated
 - FDG PET- if indicated
- Response will be determined using RECIST criteria and EASL
- Patients who meet PR or SD may receive a total of 3 courses (24 weeks) of treatment if they continue to respond or remain stable
- Patients who meet criteria for surgical resection will be offered this option

3.12. Criteria for Surgical Resection

- Potential resectability will be determined as per the MD Anderson resectability criteria (Table 2) However, in cases where controversy will exist, resectability status will be determined by the investigator and/or PI discretion.
- Patients must be off chemotherapy for at least 4 weeks and all toxicities must resolve to grade 1 or less prior to surgery

3.13. Off Treatment Criteria

- Completion of treatment regimen
- Voluntary withdrawal from treatment

- Inability to follow the treatment regimen
- Toxicities that do not resolve within 4 weeks of treatment as described in Section 3.9
- Unacceptable toxicity
- Clinical disease progression e.g., decrease in performance status, increase in ascities
- Radiographic or clinical disease progression
- Surgical resection
- If the physician deems it is in the patient's best interest not to receive further treatment

3.14. Follow up evaluation

- Following treatment, scans will be performed every 12 weeks (+/-2 weeks) for the first 2 years and every 6 months thereafter. At each evaluation patients will undergo:
 - Physical examination to include weight, vital signs and ECOG assessment
 - Laboratory tests to include CBC with differential and Chemistry panel (Section 3.7) , lipase and amylase
 - Tumor markers as appropriate
 - CT scan of chest, abdomen and pelvis (CT C/A/P) with triphasic Imm cuts as per the pancreas protocol.
 - MRI – pancreas
 - FDG PET- if indicated
- Patients who are unable or unwilling to travel to the NIH Clinical Center for follow up evaluation will be followed via phone contact.

3.15. Off Study Criteria

- Death
- Unwillingness to participate in study specified follow up (including phone contact)
- If the physician deems it is no longer in the best interest of the patient to remain on study

Patients will be officially taken off study by contacting the CRO.

4. Supportive Care:

- During the post-procedure period patients will receive standard of care supportive measures including analgesics, antiemetics and fluid hydration and all other medically necessary interventions as needed when in the best interest of the patient.
- Patients will be placed on proton pump inhibitors approximately 24 hours prior to the first treatment until the completion of therapy
- During the administration of chemotherapy patients will receive all necessary supportive care. This may include:

- Blood transfusions and growth factor support as necessary for the management of myelosuppression. Filgrastim 5 mcg/kg/day subcutaneously may be administered for ANC less than 1000 mm³ or as per the guidelines of the treating institution. Note: Filgrastim will not be administered prophylactically during systemic chemotherapy.
- Neutropenic fever will be treated with broad-spectrum antibiotics pending culture results.
- Premedication with antiemetics, including 5-HT3 blockers with or without dexamethasone.
- Port Care
 - The patients will receive routine VAD care as per NIH Clinical Center Guidelines

5. Data Collection and Evaluation:

5.1. Data Collection

Data will be collected using the NCI C3D web based data collection system.

5.2. RECIST Response Criteria

Lesions will be evaluated using the RECIST criteria 1.1 as described below. In addition, tumors will be evaluated by the EASL criteria to further assess response (see below).

5.2.1. Evaluation of target lesions*

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters.
- Progression (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) or the appearance of one or more new lesions.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

* All measurable lesions up to a maximum of 5 lesions (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all organs involved, and be suitable for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

5.2.2. Evaluation of non-target lesions^{**}

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or maintenance of tumour marker level above the normal limits.
- Progression (PD): Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions

^{**} All other lesions (or sites of disease), including pathological lymph nodes should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression.”

5.2.3. Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Nor all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

5.2.4. Confirmatory Measurement/Duration of Response Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-8 weeks.

5.3. EASL Evaluation of target lesions

(EASL- European Association for the Study of the Liver- Criteria)

EASL criteria are a variation on the WHO criteria (change in sum of the products of largest diameter and greatest perpendicular diameter i.e. a surrogate of an area) but accounting for a change in the diameter of the viable tumor area (overall diameter minus percent necrosis), instead of the overall diameter of the measured tumors.^{1 26}

Complete Response	Complete disappearance of all known disease and no new lesions
Partial Response	50% reduction in viable tumoral area of all measurable lesions via uptake of contrast in the arterial phase of a triphasic CT scan
Progressive disease	25% increase in size of one or more lesions or the appearance of new lesions
Stable Disease	All other cases
Objective Response	Complete Response and Partial Response

5.3.1. Duration of Overall Response

The duration of overall response is measured from the time of measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

5.3.2. Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

5.4. Toxicity Criteria

This study will utilize the CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov>). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

5.5. Statistical Section

The primary objective of the trial is to determine feasibility, toxicity and tolerability of this treatment after super-selective continuous arterial infusion of gemcitabine in patients with locally-advanced unresectable pancreatic cancer. The secondary objectives include: Conversion rate from unresectable to potentially resectable pancreatic cancer, progression free and overall survival, tumor response rate and to analyze potential selection criteria for patients who present with locally advanced pancreatic cancer that might benefit from this approach.

It is expected that a maximum of 15 patients per year can be accrued onto this trial, and thus accrual will be completed in approximately 3 years. Allowing for a very small number of inevaluable patients, the accrual ceiling will be set at 50 patients.

5.6. Safety and Monitoring Plan

Careful evaluation to ascertain the toxicity and clinical response will be performed. The principal investigator will monitor the data and toxicities to identify trends quarterly. The

principal investigator will be responsible for revising the protocol as needed to maintain safety. The NCI IRB will review submitted adverse events monthly to also evaluate trends and will require a follow up plan from the principal investigator whenever a trend is identified. A CCR Safety Monitoring Committee will monitor toxicity trends on this study on at least an annual basis and report any trends to the NCI IRB and Principal Investigator.

5.7. Clinical Trial Monitoring Plan

This trial will be monitored by personnel employed by Harris Technical Services on contract to the NCI, NIH. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

At least 25% of enrolled patients' will be randomly selected and monitored at least quarterly, base on accrual rate. The patients selected will have 100% source document verification done. Additional monitoring activities will include: adherence to protocol specified study eligibility, treatment plans, data collection for safety and efficacy, reporting and time frames of adverse events to the NCI IRB and FDA, and informed consent requirements. Written reports will be generated in response to the monitoring activities and submitted to the Principal investigator and Clinical Director or Deputy Clinical Director, CCR, NCI.

6. Human Subject Protection:

6.1. Rational for Subject Selection

The patients to be entered in this protocol have locally advanced unresectable pancreatic cancer and have limited life expectancies.

Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in drug metabolism or disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

6.2. Evaluation of Potential Benefits and Risks

The ideal benefit to patients undergoing this therapy would be inducing direct tumor necrosis and ideally shrinkage allowing for a surgical resection. Alternatively, a less dramatic outcome of this therapy is palliation in terms of preventing or delaying tumor progression and metastases elsewhere which can be a devastating and painful source of symptoms and cause for demise. In addition, significant tumor response may extend

progression free and overall survival. This treatment can also result in a significant palliation of symptoms due to local tumor progression which are major source of morbidity of patients with pancreatic cancer.

The possible risks for this regional therapy include those associated with prolonged infusion of gemcitabine intra-arterially (pancreatitis, leucopenia and fatigue) although previously very mild local (pancreatic) symptoms were described with this methodology, and complications associated with having an indwelling vascular catheter in the pancreatic vasculature (migration and thrombosis) as well as local complications of the indwelling subcutaneous access port.

In the review of 84 patients with arterial port catheters in place described in the background section, major complications occurred in 5% of patients and included catheter port infection in 3 patients and femoral artery thrombosis in 1 patient. Minor complications occurred in 31% of patients and included minimal bleeding at the site, and delay in wound healing. Catheter dysfunction occurred in 52% of patients and included catheter occlusion and extra hepatic perfusion; however, in most cases these events did not result in the discontinuation of treatment. Although extra hepatic perfusion can be serious, we feel that our extensive experience with abdominal angiography will enable us to accurately visualize and embolize the vasculature and avoid this complication.

6.3. Risk Benefit Analysis

Percutaneous placement of continuous infusion catheters with subcutaneous ports allowing inter-vascular access has long been utilized for chemotherapy delivery in cancer patients with minimal morbidity reported.

Selective intra-arterial delivery of cytotoxic chemotherapy has been shown to be safe with low morbidity. Selective embolization of pancreatic arterial inflow has also been performed with minimal pancreas specific toxicity. Systemic chemotherapy for Stage IV pancreatic cancer offers low rates of durable response with minimal chance of disease cure. Surgical resection, when possible, remains the only therapy with a chance at long term survival. Distant metastases and advanced local regional disease are the principle determinants of surgical versus alternative treatment options. The risks associated with this phase I study of regional chemotherapy using intra-arterial gemcitabine delivered selectively to the pancreatic tumor bed for patients with locally advanced and borderline resectable pancreatic cancer are all within the accepted standard of clinical practice. Recognizing that multimodality therapy including surgical resection offers the only opportunity for long term survival for pancreatic cancer, the ability to increase the proportion of patients who are eligible for surgical therapy is an important objective. For patients who are increasingly being diagnosed with advanced loco-regional disease, regional treatment strategies may offer symptom control and mediate tumor regression that may then allow systemic therapy or surgical resection to be more effective. The potential benefit is great for these patients if a regional response is obtained. Therefore, this protocol involves greater than minimal risk, but presents the prospect of direct benefit to individual subjects.

6.4. Consent Process

All patients are thoroughly screened prior to initial consultation at the NIH. During the initial consultation the patient, along with family members, is presented a forthright and detailed overview of the treatment option available to them at the NIH. The experimental nature of the treatment, its theoretical advantages and disadvantages, and an overview of the treatment schema is presented and the likelihood of serious or potentially life-threatening complications are presented. The Informed Consent document is given to the patient and they are asked to review it, make notes and follow-up with a phone call to the physician or nurse investigator to have any additional questions answered prior to considering treatment on protocol.

When the patient is admitted to the Clinical Center for treatment, an associate physician investigator responsible for the care of the patient presents the previously described information in detail. The research nurse or Principal Investigator, or designee is responsible for obtaining consent from the patient upon admission. The patient is reassured that participation on the trial is entirely voluntary and that they can withdraw or decide against treatment at any time without adverse consequences.

7. Data Reporting:

7.1. Definitions

- **Adverse Event**

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 7.3

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

- **Suspected adverse reaction**

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

- **Unexpected adverse reaction**

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has

been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

- **Serious**

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **Disability**

A substantial disruption of a person's ability to conduct normal life functions.

- **Life-threatening adverse drug experience**

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

- **Protocol Deviation (NIH Definition)**

Any change, divergence, or departure from the IRB approved study procedures in a research protocol that does not have a major impact on the subject's rights, safety or well-being, or the completeness, accuracy and reliability of the study data.

- **Protocol Violation (NIH Definition)**

Any change, divergence, or departure from the IRB-approved study procedures in a research protocol that does have a major impact on the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data.

- **Unanticipated Problem**

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
(b) the characteristics of the subject population being studied; AND
- Is related or possibly related to participation in the research; AND

- o Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2. Routine Data Reporting

Following registration, all adverse events will be described in the source documents, reviewed by the designated research nurse, and captured in C3D.

- o During hospitalization, only the admission labs, first morning labs drawn after 4 am, and labs that support the diagnosis of a reportable event will be uploaded into C3D.
- o During chemotherapy regimen, for laboratory values obtained at sites other than the NIH Clinical Center: only the following values (highest grade per cycle) will be captured in C3D:
 - Hemoglobin, total white blood cell count, absolute neutrophil count, platelet count
 - PTT, PT or INR
 - Creatinine, ALT, AST, Bilirubin (total and direct), lipase and amylase
 - Any unexpected laboratory abnormality \geq grade 2 possibly, probably or definitely related to the research
- o All chemotherapy dose reductions and the reason for the reduction will be captured in C3D
- o During the follow up period (more than 30 days following the last treatment), only those events that are serious, unexpected, and related to the treatment will be captured in C3D.
- o All toxicities occurring within 30 days of treatment will be followed until resolution or return to baseline

7.3. Exclusions to Routine Data Reporting:

The following Adverse Events will be captured only in the source documents and will not be reported in C3D

For the duration of the study:

- o Laboratory values that do not support the diagnosis of a reportable event
- o All grade 1 events
- o Grade 2 and 3 events which resolve during the first 72 hours following catheter insertion

Note: Events that result in a hospitalization for convenience will not be reported.

Concomitant medications: Only those medications that the patient is taking at baseline on a routine basis or medications that cause an AE will be captured in C3D. (Thus onetime medications, PRN medications, and medications given to treat adverse events will not be captured in C3D.)

7.4. NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

The Protocol PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Violations or Deviations
- All Unanticipated Problems

Reports must be received by the NCI IRB within 7 days of notification of the event via the NCI-IRB iRIS Application for Serious Adverse Event Reporting @ <https://iris.nci.nih.gov/iMedris/>

7.5. Adverse Event Reporting in the Continuing Review Report

The protocol PI will report to the NCI-IRB:

- All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

The following table is an example of the report to be used in the continuing Review Report

CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious Yes/no	Unexpected Yes/no
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8. Pharmaceutical Information:

8.1. Gemcitabine

8.1.1. Source:

Gemcitabine will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

8.1.2. Toxicities:

The most common adverse reactions for the single-agent ($\geq 20\%$) are nausea and vomiting, anemia, ALT, AST, neutropenia, leukopenia, alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea.

8.1.3. Formulation and Preparation:

The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar® contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

The recommended diluent for reconstitution of Gemzar® is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar® upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL.

8.1.4. Stability/Storage:

Reconstituted Gemzar® is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar® solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Discard unused portion. Solutions of reconstituted Gemzar® should not be refrigerated, as crystallization may occur.

8.1.5. Administration:

Gemzar® will be administered as described in Section 3.7 Dose escalation.

8.2. Lovenox®:

8.2.1. Source:

Lovenox® will be purchased from commercial sources by the NIH Clinical Center Pharmacy Department.

8.2.2. Toxicities:

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea

8.2.3. Formulation and Preparation:

Lovenox® is supplied as prefilled syringes: 30 mg, 40 mg, 60mg, 80mg, 100mg, 120mg, and 150mg

8.2.4. Stability/Storage:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)

8.2.5. Administration:

Lovenox® will be given daily at a dose of 1.5 mg/kg body weight given via subcutaneous injection. The dose will be rounded to the nearest amount available in the prefilled syringe and will be given as long as the catheter is in place.

9. **References**

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Table 1 Summary of Trials using Regional Therapy

Table 1. Summary of Trials of Regional Therapy for Advanced Pancreatic Adenocarcinoma

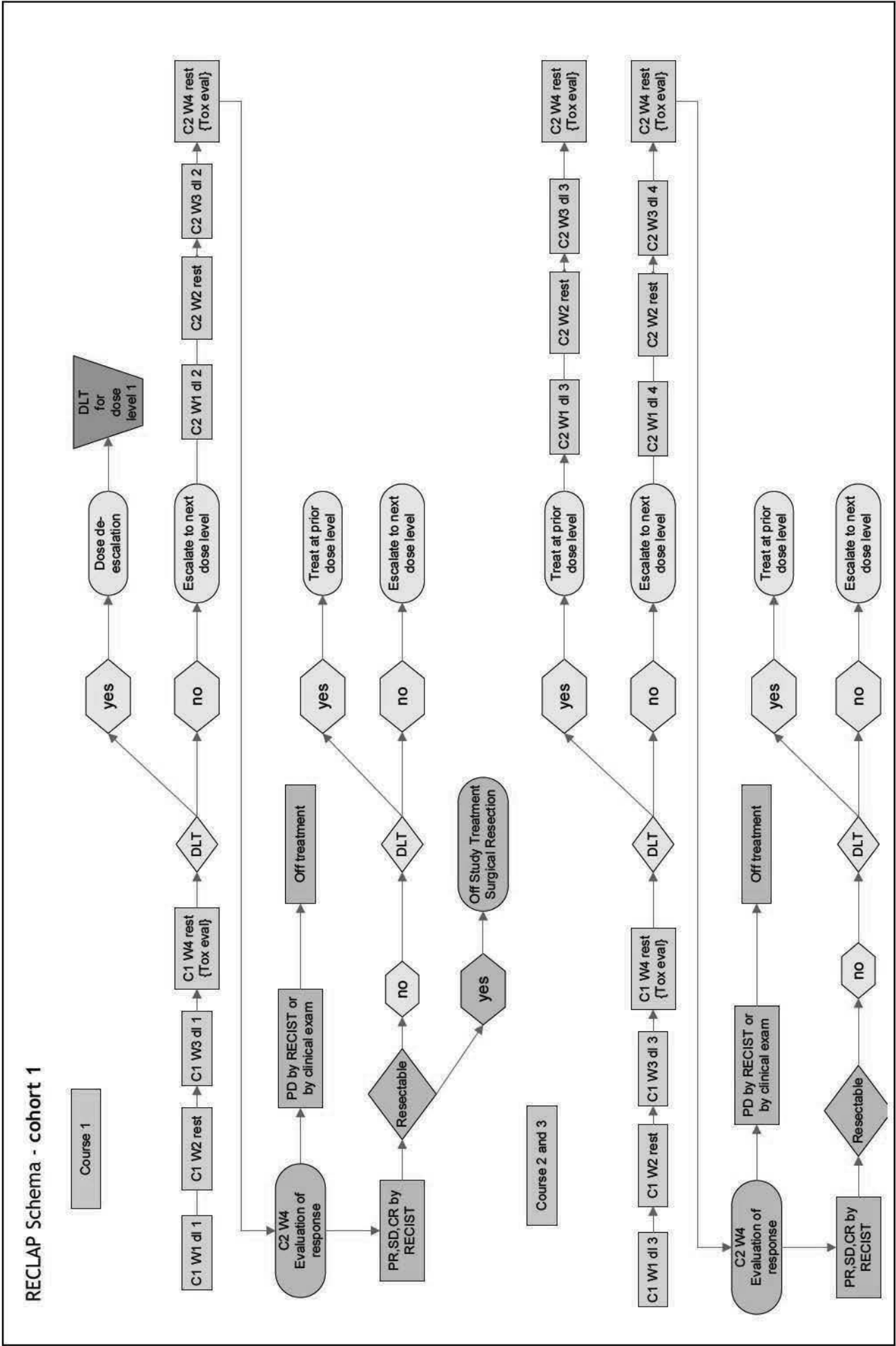
Author (Year)	Patients (n)	Mean/Median Age (yr)	Stage	Procedure	Chemotherapeutic agents	Response rate	1-year survival	Median survival	Treatment schedule	Toxicity	GI Toxicity I-II	GI Toxicity III-IV	Heme Toxicity I-II	Heme Toxicity III-IV	Technical complications
Fiorentini (1996)	20	NR	III, IV	HAP (no filtration?)	MMC 25mg/m ²	50%	NR	NR	NR	6 cases Gr 3 leukopenia, 3 cases Gr 3					
Muchmore (1996)	12	59 (mean)	II, III	CAI with hemofiltration	MMC 20-24mg/m ² , 5-FU 500-700mg/m ² , (+Mitoxantrone 20-25mg/m ²)*	45.5%	NR	NR	Every 4 weeks	NR	NR	NR	NR	NR	NR
Link (1997)	32	60 (mean)	III, IV	CAI	Mitoxantrone 10mg/m ² on day 1; 5-FU 600mg/m ² + folinic acid days 2-4; CDDP 60mg/m ² on day 5	19%*	NR	12 mo. (Stage III), 4 mo.	Every 4 weeks		54%**	10%**	9%**	1%**	2% intimal artery tear, 1% hematoma/pseudoaneurysm
Lorenz (1998)	17	61 (median)	I-IV	HAP (no filtration)	MMC 40mg	0%	NR	4.2 mo.	NR	DVT in 5 patients	28	5	22	2	
Maurer (1998)	12	59.9 (mean)	III, IV	CAI	mitoxantrone 10mg/m ² day 1, 5-FU 600mg/m ² days 2-4, folinic acid 170mg/m ² days 2-4, CDDP 60mg/m ² day 5	8%	NR	6 mo.	Every 6 weeks	33% Grade 3 (Heme & GI)	12	1	10	2	1 groin hematoma
Klapdor (1999)	28	NR	III, IV	CAI	MMC 10-15mg, gemcitabine 800mg i.d. day 1, gemcitabine 800mg i.v. day 8 & 15	46%	NR	9 mo.	Every 3 weeks	4 GI, 1 Resp, 1 thrombosis	3	1			
Homma (2000)	31	61.5 (mean)	IV	SAI*	5-FU 500mg/m ² day 1-7; CDDP 20mg/m ² on days 1, 3 & 5	58%	66.7%	NR	Every 2 weeks		22	0	11	0	4 cases of catheter dislodgement
Bayar (2003)	14	55 (median)	III, IV	CAI	5-FU 600mg/m ² x 3 days, MMC 10mg/m ² x 1 day, CDDP 60mg/m ² x 1 day	36%	NR	8 mo.	Every 4 weeks	36% Heme (No Gr.)					
Ohigashi (2003)	32	60 (mean)	III	SAI*	methotrexate 50mg/m ² , angiotensin-II 10ug, 5-FU 500mg/m ² , oral folinic acid 30mg	6%**	56%	13 mo.	Weekly or biweekly		5	3	1	0	
van Ijken (2004)	21	59 (mean)	III, IV	HAP (no filtration) followed by CAI*	MMC 10-20mg/m ² *, melphalan 10mg/m ²	5%#	NR	6 mo.		25% Gr. 3/4 Heme	1	2	4	5	
Aigner (2005)	265	NR	III, IV	CAI + HAP*	MMC, mitoxantrone, CDDP, Spherox**	NR	NR	9 mo.	CAI for 3 cycles, HAP	NR	NR	NR	"did not exceed GrII"	NR	NR
Takamori (2005)	24	62.6 (median)	III, IV	CAI*	gemcitabine 1000mg weekly x 3 weeks; 5-FU 250mg/m ² days 1-5 every week	20.8%	50.9%	14 mo.	Every 4 weeks		19	0	51	18	One case of catheter dislodgement
Barletta (2006)	32	62 (median)	III, IV	CAI	5-FU 1000mg/m ² , folinic acid 100mg/m ² , epirubicin 60mg/m ² , carboplatin 300mg/m ²	22%	50%	6.1 mo.	Every 3 weeks	53% Gr. 3/4 Heme					

Table 1. Summary of Trials of Regional Therapy for Advanced Pancreatic Adenocarcinoma															
Author (Year)	Patients (n)	Mean/Median Age (yr)	Stage	Procedure	Chemotherapeutic agents	Response rate	1-year survival	Median survival	Treatment schedule	Toxicity	GI Toxicity I-II	GI Toxicity III-IV	Heme Toxicity I-II	Heme Toxicity III-IV	Technical complications
Mambrini (2006)	211	61 (median)	III, IV	CAI	5-FU 1000mg/m ² , folinic acid 100mg/m ² , epirubicin 60mg/m ² , carboplatin 300mg/m ²	7.6%	NR	9.2 mo.	Every 3 weeks	24% Gr. 3/4 Heme toxicity	*	*	*	24%	3 patients with iliac artery dissection
Meyer (2006)	17	54.5 (mean)	III, IV	HAP (no filtration)	MMC 20mg/m ²	17.6%	6%	4.1 mo.	NR	50% Gr. 3/4	26	23	11	12	
Guadagni (2007)	22	66 (median)	III, IV	HAP (with filtration)	MMC 30mg/m ² , CDDP 60mg/m ²	18%*	9%	6 mo.	Every 4 weeks	6 groin lymphatic fistulae	2	1	6	0	
Ikeda (2007)	33	60 (mean)	IV	SAI + systemic chemotherapy	5-FU 250mg/day ia day 1-5, gemcitabine 1000mg iv weekly for 3 weeks	24%	NR	13 mo.	NR	15% GI (No Gr.)	**				1 dislocation of infusion catheter
Ishikawa (2007)	20	63.7 (median)	IV	CAI*	gemcitabine 1000mg/m ² + A-II 10ug bolus, 5-FU 500mg/m ² + A-II 24-hr infusion, CDDP 10mg bolus	25%	45%	12 mo.	3 weekly treatments repeated every 4 weeks	No Gr. 3/4	7	0	NR	0	
Milandri (2007)	19	62 (median)	III, IV	SAI	5-FU 1000mg/m ² , folinic acid 100mg/m ² , epirubicin 60mg/m ² , carboplatin 300mg/m ²	25%*	16%	6 mo.	Every 3 weeks	5% Gr. 3/4	17	0	14	1	
Nakchbandi (2008)	17	65.7 (mean)	II - IV	CAI	gemcitabine 800mg/m ² on day 1, MMC 8mg/m ² on day 2, gemcitabine 800mg.m ² iv on day 14, warfarin 1.25mg orally daily	NR	6%	6.8 mo.	Every 4 weeks				1	3	
Sasada (2008)	16	61.2 (mean)	III, IV	SAI	5-FU 250mg/m ² continuous days 1-7; CDDP 5mg/m ² bolus days 1-5;	58%**	83%	22 mo.	Every 2 weeks	2 Gr. IV heme toxicities; 1 Gr. III hepatic	3	1	2	2	2 port (reservoir) site leaks; 1 catheter occlusion

Table 2: M.D.Anderson Criteria for Resectability of Pancreatic Cancer

TABLE 2. M. D. Anderson criteria for resectability of pancreatic cancer			
Vessel	Resectable	Borderline resectable	Locally advanced
SMA	No extension; normal fat plane between the tumor and the artery	Tumor abutment $\leq 180^\circ$ (one half or less) of the circumference of the artery; periarterial stranding and tumor points of contact forming a convexity against the vessel improve chances of resection	Encased ($> 180^\circ$)
Celiac axis/hepatic artery	No extension	Short-segment encasement/abutment of the common hepatic artery (typically at the gastroduodenal origin); the surgeon should be prepared for vascular resection/interposition grafting	Encased and no technical option for reconstruction usually because of extension to the celiac axis/splenic/left gastric junction or the celiac origin
SMV/PV	Patent	Short-segment occlusion with suitable vessel above and below; segmental venous occlusion alone without SMA involvement is rare and should be apparent on CT images	Occluded and no technical option for reconstruction
SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein; CT, computed tomography.			

Appendix 1: Trial Schema:



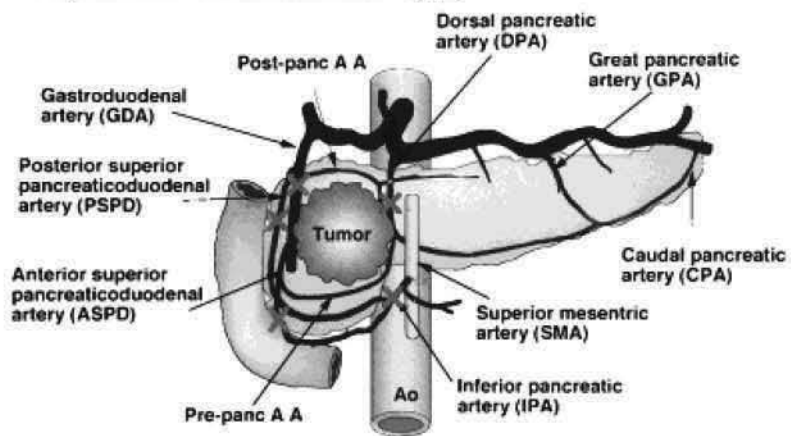
Appendix: 2 Dose de-escalation:

Patients will be treated in the same manner as described in Section 3.1.

- Patients will begin in cohorts of 3-6 patients dosing at successively lower doses until MTD is established or to a dose of 11.5 mg/m²/24 hours.
 - Cohort 1d will start on 16.5 mg/m²/24 hr
 - Cohort 2d at 13.8 mg /m²/24 hr
 - Cohort 3d at 11.5 mg /m²/24 hr
- If one of the first three patients experiences a DLT then a total of 6 patients will be enrolled. If more than 1 of 6 patients experiences a DLT then patients will be enrolled at the next lower dose level.
- If 1 or fewer patients experience DLT then the dose level will define the MTD.

Figure 1

Peri pancreatic arterial blood supply



INSTITUTE: National Cancer Institute

STUDY NUMBER: 11-C-0099

PRINCIPAL INVESTIGATOR: Udo Rudloff, M.D

STUDY TITLE: Regional Chemotherapy in Locally Advanced Pancreatic Cancer: RECLAP Trial

Continuing Review Approved by the IRB on 10/15/12

Amendment Approved by the IRB on 11/15/12 (E)

Date Posted to Web: 11/20/12

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Pancreas cancer is the fourth leading cause of cancer death in the United States. Surgery offers the only chance at cure however, by the time most patients are diagnosed with pancreas cancer their tumors are too large to be removed. Standard intravenous chemotherapy may shrink some of the tumor, but even with chemotherapy, only about 25% of patients will live for one year following diagnosis. Researchers have been studying different ways of giving chemotherapy which will be more effective at shrinking the cancer so that it is small enough to be surgically removed. Several phase 1 studies have shown that administration

**STUDY
MEDICAL RECORD**

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH

• Adult Patient or • Parent, for Minor Patient

STUDY NUMBER: 11-C-0099

CONTINUATION: Page 2 of 9

of chemotherapy directly into the pancreas in the area of the tumor is safe. Studies have also shown that giving gemcitabine over a longer period of time increases the amount of drug that is available to the tumor. In this study, we plan to give gemcitabine (a chemotherapy approved to treat pancreas cancer) directly into the pancreas in the area of the cancer and at a slow rate of infusion. Giving the gemcitabine directly to the tumor and at a slow rate of infusion is an experimental treatment and we are looking to find the safest dose of gemcitabine to give patients and also to see how well patients tolerate the drug given in this manner.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have pancreas cancer which is currently too large to be removed but has not yet spread to other organs that are not near your pancreas.

How many people will take part in this Study?

Up to 46 subjects will be enrolled here at the National Institutes of Health for this initial study.

Description of Research Study

This is an intra-inter patient dose escalation study (see below*) of gemcitabine given at a slow rate of infusion through a catheter which is threaded into one of the blood vessels in the pancreas and connected to a conventional vascular access device (port). Subjects who meet the eligibility criteria will undergo pancreatic angiography and embolization (see *During the Study* for a description of angiography and embolization) as necessary to isolate the blood vessels supplying the tumor. Subjects will receive up to 3 courses (6 months) of Gemcitabine given through this catheter directly into the pancreatic circulation. The dose for each subject will be increased at the beginning of each cycle until the maximum dose is reached provided no dose limiting toxicities were experienced. Subjects will be assessed every 8 weeks to see if the tumor is shrinking.

*intra-inter patient dose escalation study – a study where each group (cohort) of 3-6 patients enrolled in the study receives a higher dose of medication than the previous group unless 2 of 6 patients have a dose limiting toxicity (DLT – a specified list of side effects.) In addition, patients in each cohort who do not experience a DLT, will receive a higher dose with each cycle of chemotherapy until the maximum dose is reached.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for six (6)

PATIENT IDENTIFICATION

**CONSENT TO PARTICIPATE IN A CLINICAL
RESEARCH STUDY (Continuation Sheet)**

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (07-09)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

**STUDY
MEDICAL RECORD**

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH

• Adult Patient or • Parent, for Minor Patient

STUDY NUMBER: 11-C-0099

CONTINUATION: Page 3 of 9

months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

What will happen if you take part in this research study?

Before you begin the study

You will have a history and physical examination, and your recent lab work and imaging studies will be reviewed to see if you are eligible for the study and to see if it is safe for you to be in this study. If you haven't had recent blood work or imaging studies, they will be repeated. If the exact size and location of your tumor is not clear on the MRI or CT scan, you will have a laparoscopy performed to be sure that you are eligible for the study. This is a minor surgical procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen. A laparoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

During the study

Within about two weeks following your initial evaluation visit, you will be admitted to the NIH Clinical Center patient care unit and will undergo pancreatic angiography and embolization. This procedure is performed in the Interventional Radiology (IR) Suite by a radiologist while you are under either general or local anesthesia with sedation. The radiologist will thread a catheter (long thin flexible plastic tube) through the femoral artery (in your groin) to the blood vessels supplying the pancreas. He will then inject dye into the catheter and take x-rays in order to see the blood circulation to the tumor, the pancreas and other nearby organs (angiogram). In order to separate the blood flow to the tumor from the blood flow to the other organs, he will embolize or close off, vessels that supply both the tumor and the other organs. He will then thread another catheter into the main vessel that supplies the tumor. The other end of the catheter will then be tunneled under your skin and attached to a conventional "port" under the skin in your hip. This will allow the medication to be given into the catheter throughout the course of treatment. If the catheter cannot be placed through the femoral artery due to the location of your tumor and/or the shape of your blood vessels, then the catheter may be placed through one of the blood vessels in your neck or arm and the port will be placed in your chest – like a conventional port. After you have completed treatment the port will be removed. The whole procedure takes approximately 2 hours to complete. The principle investigator will review the procedure with you and you will be asked to sign an additional consent for the treatment.

PATIENT IDENTIFICATION

**CONSENT TO PARTICIPATE IN A CLINICAL
RESEARCH STUDY (Continuation Sheet)**

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (07-09)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

**STUDY
MEDICAL RECORD**

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH

• Adult Patient or • Parent, for Minor Patient

STUDY NUMBER: 11-C-0099

CONTINUATION: Page 4 of 9

After the catheter has been inserted, you will be monitored over night in the intensive care unit (ICU). The following morning, you will return to the IR suite to start your first dose of chemotherapy. The radiologist will inject dye and take x-rays to be sure the catheter is in the correct place. If it is not – he will re position it. A special needle will be inserted into the port and the gemcitabine infusion will be started. Once the physicians are certain you are tolerating the infusion, you will return to the ICU for the rest of the infusion – 24 hours total. During the infusion you will be monitored, have blood drawn at least once daily and received routine care. In order to prevent blood clots from forming in or around the catheter you will be placed on a blood thinner given by injection. The nurses on the patient care unit will instruct you on how to give the injections before you are discharged.

Once you are discharged, you will need to have blood drawn weekly (this may be done by your home oncologist) and we will give you a diary to record any side effects from the treatment and your blood thinner doses. If you do not return to the Clinical Center to have blood drawn, the research nurse will contact you and ask you about any side effects you may be having.

Two weeks after the first infusion, you will return to the Clinical Center every two weeks to receive your second, third and fourth infusions. Prior to each infusion the research nurse or physician will review your diary, you will have a physical exam, lab work and another angiogram, CT, or x-ray performed to check the placement of the catheter. You may receive the second (and subsequent) infusions in the ICU or on the patient care unit. You will be monitored during the infusions and have labs drawn and receive standard care as needed. If you tolerated the second infusion without experiencing any DLTs your dose will be increased for the third and fourth infusions. Once you are discharged you will have blood drawn and complete your diary as noted above. If you have abdominal pain or other GI symptoms following your treatments, you will have an endoscopy prior to your next treatment to be certain that it is safe for you to continue treatment. An endoscopy is similar to a laparoscopy except that a flexible tube is inserted through your esophagus and into your stomach to look for signs of bleeding or irritation.

Two weeks after the fourth treatment (course 1) you will return to the Clinical Center for imaging studies, a physical examination and lab work. If your tumor is shrinking you will continue with treatment for 2 more courses. If at any time your tumor becomes small enough to be surgically removed, your physician will discuss this option with you.

When you are finished taking the treatments

You will be seen in the clinic every 3 months for 2 years following your last treatment and then every 6 months. At each evaluation you will have a physical examination, blood work drawn and imaging studies. If you are unable or un-willing to return to the Clinical Center for follow up visits, the research nurse will contact you by phone.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options:

PATIENT IDENTIFICATION

**CONSENT TO PARTICIPATE IN A CLINICAL
RESEARCH STUDY (Continuation Sheet)**

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (07-09)

P.A.: 09-25-0099

File in Section 4: Protocol Consent

**STUDY
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- Getting chemotherapy or surgery for your cancer without being in a study
- Taking part in another experimental study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation: What side effects or risks can I expect from being in this study?

The risks involved in participating in this study have been summarized below according to each part of the experimental treatment. Because gemcitabine has not been given in this way before, there may be additional risks that we do not know about.

Pancreatic Angiography and Embolization

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Abdominal Pain (12-24 hours) • Fever (99-102 degrees F) • Nausea and/or Vomiting 	<ul style="list-style-type: none"> • Abdominal Fluid Buildup (Ascites) • Bleeding (at catheter insertion site) • Infection (at catheter insertion site) • Allergy to Iodine Contrast agent • Mild pancreatitis 	<ul style="list-style-type: none"> • Liver Failure • Kidney Failure • Liver Abscess Formation • Stomach or Duodenal Ulcer • Pancreatitis - severe • Cholecystitis • Arterial Injury at catheter insertion site

Gemcitabine

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none"> • Fatigue, may be due to due to low red blood cell counts • Increased risk of infection due to low white blood cell counts • Bleeding due to low platelet counts • Mucositis (mouth sores) • Nausea and vomiting 	<ul style="list-style-type: none"> • Diarrhea • Rash • Change in lab values that may not cause any symptoms and may not require treatment 	<ul style="list-style-type: none"> • Liver damage • Kidney damage

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Indwelling catheter

Likely	Less Likely	Rare but Serious
<ul style="list-style-type: none">Mild Pain (12-24 hours)	<ul style="list-style-type: none">InfectionFormation of blood clots which could break off and travel to your legs and other organs	<ul style="list-style-type: none">PancreatitisBleeding

lovenox

Likely – at the site of injection	Less Likely	Rare but Serious
<ul style="list-style-type: none">Mild irritationPainBruisingRedness	<ul style="list-style-type: none">Change in lab values that may not cause any symptoms and may not require treatment	<ul style="list-style-type: none">Hemorrhage or bleeding

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinkage of your tumor(s), possibly making your tumors small enough to be removed, lessening of your symptoms, such as pain, that are caused by the cancer or slowing the growth of your cancer. Because there is little information about the giving gemcitabine at a slow rate directly to pancreas tumors, we do not know if you will benefit from taking part in this study (improved survival), although the knowledge gained from this study may help others in the future who have pancreas cancer.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

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There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs even if they are not covered by your insurance company.

Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Stopping Study Participation

Your doctor may decide to take you off of the study if he/she believes that it is in your best interest, if your disease does not respond to the treatment, if you have side effects that are too severe, or if new information shows that another treatment may be better for you. In this case, you will be informed of the reason therapy is being stopped. You will also be counseled regarding other treatment options as in "Alternative Approaches or Treatments."

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

A description of this clinical trial will be available on <http://www.Clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process: [://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide](http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide). You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to \$15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

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OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Udo Rudloff, M.D., Building 10, Room 4-5940, Telephone: 301-496-3098.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

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COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/
Legal Representative

Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian

Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian

Date

Print Name

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE
FROM OCTOBER 15, 2012 THROUGH OCTOBER 14, 2013.**

Signature of Investigator

Date

Signature of Witness

Date

Print Name

Print Name

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