A randomized trial of endoscopic biliary co-axial stent placement plus/minus use of radiofrequency ablation (RFA) for clearance of occluded self expandable metal stents (SEMS) in patients with distal biliary obstruction from unresectable biliary-pancreatic malignancies

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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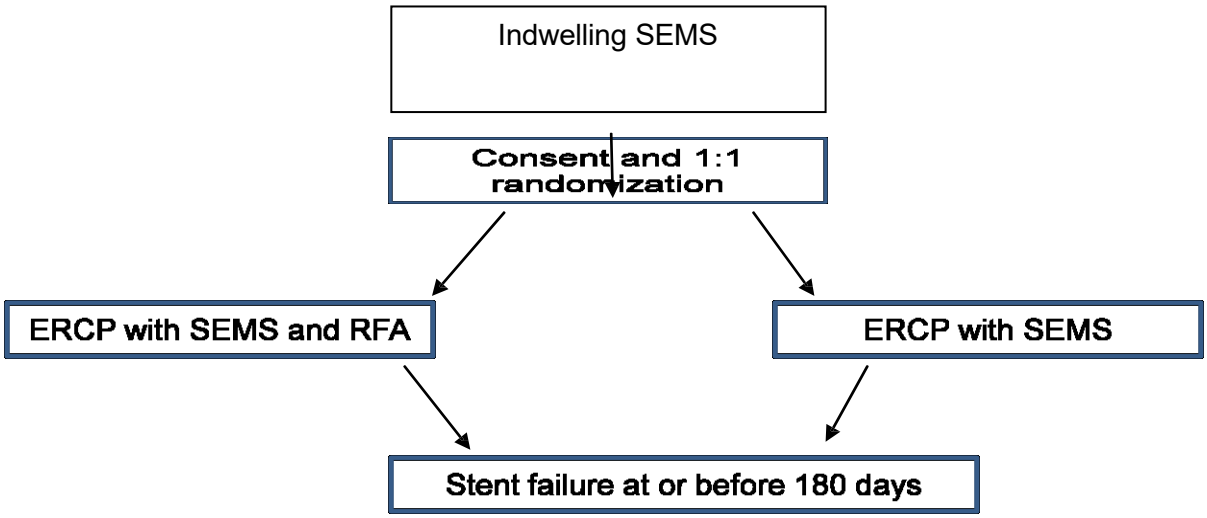
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

While advances in oncological treatments have improved survival for patients with distal cholangiocarcinomas and pancreatic cancers, progress in the management of malignant biliary obstruction and occluded SEMS has been limited. Recently, RFA, an ablative treatment modality for dysplastic Barrett's esophagus and hepatocellular carcinoma, has been applied to malignant biliary obstruction and occluded SEMS with encouraging results. The efficacy and safety of this endoscopic technique however have been reported largely in pilot studies, case series, and retrospective reviews. The primary objective of this prospective randomized controlled trial is to compare, in patients with unresectable tumors obstructing the distal bile duct presenting with an episode of SEMS occlusion, the rate of failure after instent RFA followed by SEMS placement versus SEMS placement alone coaxially within the existing occluded SEMS. As co-axial stent placement is the current standard of managing an existing occluded SEMS, and to study the potential additive effect of RFA, the study treatment arm will consist of RFA followed by SEMS placement. Secondary outcomes on stent patency, as well as safety and adverse events will be monitored.



2.1 OBJECTIVES AND SCIENTIFIC AIMS

To study the efficacy and safety of endoscopic biliary radiofrequency ablation (RFA) for clearance of occluded self expandable metal stents (SEMS) in unresectable malignant distal biliary obstruction.

Primary outcome:

- Rate of failure at or before 180 days from date of on-study procedure (co-axial stent placement +/- RFA)

- Failure is defined as:
  Imaging findings supportive of stent occlusion (loss of stent patency, debris within stent, loss of or excessive pneumobilia) with one or more of the following:
  - Development of jaundice
  - Clinical cholangitis (fever, elevated white blood cell count, clinical impression of biliary infection)
  - Development of bilirubin rise to greater than 3.0 mg/dl in patients who had achieved a normal bilirubin after the on-study procedure
  - Rise in bilirubin of 2.0 mg/dl above post-procedure bilirubin nadir in patients who did not achieve a normal bilirubin level post procedure
- There is no mandatory imaging; all imaging will be triggered by symptoms therefore any patient who does not have imaging by 180 days will be considered to hav e a patent stent and be counted as a success.

Secondary outcomes:

- Rate of technical success for endoscopic biliary RFA
  - Technical success for endoscopic biliary RFA will be defined as:
    - the ability to position the RFA catheter and deliver the prescribed energy.
  - Technical failure of RFA would not impact on the ability to place a co-axial stent. These patients would still be followed for the stent occlusion primary endpoint.
- Rate of stent patency one month and three months post procedure
- Median duration of stent patency post procedure
- Radiographic evidence of local disease progression
- Median survival post procedure
- Incidence of procedure related complications
- Incidence of adverse events within one month post procedure
- Rates of 30 day and 90 day mortality

3.0 BACKGROUND AND RATIONALE

Malignant biliary obstruction from intraductal disease or extrinsic compression by tumor, adenopathy or metastasis can occur at presentation or with progression of disease. Consequences of biliary obstruction include risk of cholangitis, need for hospitalization, procedural risks associated with decompression, interruption of chemotherapy regimen, and associated health care costs. Management of biliary obstruction ranges from percutaneous or endoscopic placement of plastic or self expandable metal biliary stents (SEMS) to potentially curative surgical resection, and is influenced by the stage and resectability of the disease, patient performance status, and the need and response to neoadjuvant treatment. SEMS are the treatment of choice for palliation in unresectable disease, and are superior to plastic stents and surgical bypass. Mean SEMS patency ranges between 6 months to under 1 year, but as patient survival lengthens with improved

oncological care, stent occlusion from benign epithelial hyperplasia, sludge, tumor ingrowth or overgrowth often necessitates stent clearance.

Recently, radiofrequency ablation (RFA), an established endoscopic modality for treatment of dysplastic Barrett's esophagus and hepatocellular carcinoma, has been applied for management of malignant biliary obstruction. Using a 2.6mm bipolar wire guided catheter (Habib™ EndoHBP catheter from EMcision, London, United Kingdom) inserted through the working channel of a standard side viewing endoscope, contact coagulative necrosis is cylindrically delivered via two ring electrodes along a length of 2.5cm across the malignant stricture. In 2009, this device received FDA approval to assist in the coagulation of tissue during endoscopic surgical procedures in the gastrointestinal tract, and has in turn been applied to the treatment of biliary tumors and SEMS occlusion. There are six published case series evaluating efficacy and safety of RFA for treating malignant biliary strictures. The most recent study included 58 patients from 11 Austrian centers with predominantly Klatskin tumor (78% of patients) undergoing 84 RFA procedures.[1] The intervention provided was heterogeneous with 44/58 patients undergoing a single RFA, 13/58 patients having multiple sessions, 15/84 RFAs performed within a SEMS. 31/58 patients underwent other treatment modalities prior to RFA. After RFA, 35/58 patients had placement of SEMS, 19/58 patients had a plastic stent deployed and 4/58 patients had no stent placement. Median stent patency from the last RFA procedure was 170 days, with no difference between the SEMS and plastic stent groups. 21/58 patients required re-intervention after RFA. Median survival from the first RFA was 10.6 months. The most serious complication was partial liver infarction in a Bismuth IV Klatskin tumor who had RFA applied at 6 sites along the biliary tree. The patient was managed conservatively, and recovered. Other complications included cholangitis, cholangiosepsis, hemobilia, and gallbladder empyema requiring cholecystectomy. The only North American study prospectively included 20 patients, 11 of which had cholangiocarcinoma and 7 with pancreatic cancer.[2] RFA significantly increased biliary stricture diameter by 3.5mm. All patients had placement of either a SEMS or plastic stent after RFA, with all stents patent at 30 days post procedure. Pain was the most common complication occurring in 5/20 patients, 1 from cholecystitis requiring percutaneous drainage, and 1 due to post ERCP pancreatitis managed conservatively. Earlier studies concentrating exclusively on Bismuth I hilar and distal cholangiocarcinomas showed intraductal RFA followed by SEMS had a median stent patency rate of 9 months (range 6-15 months).[3] Finally, the original human study on biliary RFA reported in Gastrointestinal Endoscopy in 2011 described successful deployment of the RFA catheter in 21/22 patents (16/21 with pancreatic cancer) followed by successful SEMS placement in all patients, maintenance of 30 day patency and no 30 day mortality.[4] Overall, over 100 patients have undergone endoscopic biliary RFA with a technical success rate of over 99%, with the most common complications as cholangitis (5%), cholecystitis (<4%), and post ERCP pancreatitis (<3%), which is within the recognized range of 5% for the procedure.

The efficacy of percutaneous intraductal biliary RFA through an existing blocked metal stent was prospectively assessed in a 9 patient study in 2014 by Pai *et al*.[5] 6/9 patients had cholangiocarcinoma with indwelling blocked metal stent. After external biliary drainage

with an internal-external catheter, RFA was performed percutaneously across the blocked stent. All patients had stent patency restored without use of secondary stents, a median stent patency of 102 days and no 30 day mortality. A larger retrospective study with 39 patients, predominantly cholangiocarcinomas, who underwent percutaneous intraductal RFA followed by SEMS placement yielded similar median stent patency durations. All but one patient had patent stents at the time of last follow up or death.[6]

A six month review of Memorial Sloan Kettering Cancer Center's endoscopy database identified 94 endoscopic retrograde cholangiopancreatograms (ERCPs) were performed for malignant biliary obstruction, of which 41 patients had an existing SEMS. In 17 patients, a SEMS was placed coaxially. 12 patients had the SEMS sweeped with an extraction balloon. 7 patients had a plastic biliary stent placed coaxially. In 2 patients, a SEMS replaced the existing stent. No changes were made to 3 SEMS.

Despite changes in biliary stent design, maintaining long term biliary drainage represents a management challenge, especially as advances in oncological treatments improve patient survival. The efficacy and safety of endoscopic biliary RFA have been demonstrated largely in pilot studies, case series, and retrospective reviews, involving small numbers of patients. A prospective randomized controlled trial comparing endoscopic biliary RFA followed by coaxial SEMS placement versus standard of care to rigorously evaluate this novel technique could potentially establish a treatment for occluded SEMS.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

In this single center study at Memorial Sloan Kettering Cancer Center, patients with any unresectable tumor obstructing the distal bile duct causing an indwelling biliary SEMS with symptoms, biochemical, radiographic and endoscopic findings supportive of an episode of stent occlusion are prospectively randomized to endoscopic RFA followed by SEMS deployment versus coaxial placement of a SEMS alone, which represents standard of care. The primary and secondary outcomes listed in section 2.0 will be compared between the two groups to determine the efficacy and safety of endoscopic biliary RFA for clearance of occluded SEMS in malignant biliary obstruction.

4.3 Intervention

Endoscopic retrograde cholangiopancreatogram (ERCP) is performed under standard conditions with cannuation of the bile duct, and demonstration on a cholangiogram the location, diameter and length of the biliary stricture. The Habib^{TM} EndoHBP probe (EMcision, London, United Kingdom) is advanced through the working channel of a side viewing endoscope over a 0.035in guidewire, and positioned across the occluded SEMS under fluoroscopy. 7-10W are usually delivered for 90 seconds with a standard high frequency generator, followed by a 1 minute resting period. Sequential applications of RFA are applied along the entire length of the stricture with an overlap of 1cm. After RFA, a SEMS the size determined by the endoscopist is placed.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The Habib™ EndoHBP probe (EMcision, London, United Kingdom) is a commercially available FDA approved device for the coagulation of tissue in the gastrointestinal tract, and has been used for the treatment of biliary tumors and SEMS occlusion. It is a 8Fr (2.6mm) bipolar 0.035in wire guided catheter which is inserted through the working channel of a standard side viewing endoscope. Contact coagulative necrosis is cylindrically delivered via two radiologically marked ring electrodes along a length of 2.5cm across the occluded SEMS under fluoroscopic guidance. 7-10W are usually delivered for 90 seconds with a standard high frequency generator, followed by a 1 minute resting period. The Habib™ EndoHBP probe (EMcision, London, United Kingdom) has been used at Memorial Sloan Kettering Cancer Center.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

Patients meeting all of the following criteria are eligible for study participation.

- Patients with any tumor obstructing the distal bile duct and causing an indwelling biliary SEMS
- Patients with jaundice or clinical cholangitis, with new elevation of alkaline phosphatase, total bilirubin, and imaging findings supportive of stent occlusion (loss of stent patency, debris within stent, loss of or excessive pneumobilia)
- Age ≥ 18 years

6.3 Subject Exclusion Criteria

Patients meeting the above inclusion criteria, but having any one of the following criteria will be excluded. Patients who:

- Have altered gastro-duodenal or hepatobiliary anatomy such that ERCP is felt to be unacceptably technically difficult or unsafe
- Have additional sites of biliary strictures (intrahepatic/hilar) such that ERCP stenting is felt to be unlikely to provide adequate clinical benefit
- Have cardiac pacemakers
- Have Child B/C cirrhosis
- Are pregnant
- Are unsuitable for endoscopy (either because of hemodynamic instability, respiratory distress or unsafe hematological parameters such as refractory anemia <7g/dL, thrombocytopenia <50K/mcL, or coagulopathy with INR >2.0)
- Have biliary strictures not technically amenable to endoscopic therapy

7.0 RECRUITMENT PLAN

Inpatients and outpatients of Memorial Sloan Kettering Cancer Center fitting the inclusion criteria in section 6.1 will be approached for the study. Eligible patients will be provided

with the IRB approved study informed consent form at the time of their consultation by the gastroenterology service. This consultation is completed at least one day prior to the procedure. A consenting professional on this study will review and have a consenting discussion with the participant, detailing all sections of the consent form. Participants will also be asked to sign a procedural consent form, detailing standard of care risks. Those who consent for study participation will be provided with a copy of the consent form. Patients will then be registered and randomized by study research staff by use of CRDB. Patients' clinical details will become part of an outcomes database for future analysis. No reimbursements will be provided to study participants.

8.0 PRETREATMENT EVALUATION

Evaluation of SEMS occlusion will be based on symptoms (abdominal pain, jaundice, pruritus, changes in urine/stool color, fever, chills), bloodwork (elevated white blood cell count, liver enzymes), imaging findings of biliary obstruction, including loss of stent patency, debris within stent, loss of or excessive pneumobilia, within the 2 weeks before study enrollment. Complete blood count, comprehensive profile and coagulation parameters will be obtained within 24 hours prior to the procedure.

9.0 TREATMENT/INTERVENTION PLAN

Patients meeting the inclusion criteria outlined in section 6.1 will be randomized to two treatment arms: endoscopic biliary RFA followed by SEMS deployment (study arm) versus coaxial placement of SEMS alone (standard of care). Existing studies outlining safety and efficacy of RFA for management of malignant biliary obstruction and occluded SEMS are outlined in section 3.0. The procedural details of endoscopic biliary RFA are described in section 4.2. Primary and secondary outcomes defined in section 2.0 will be monitored.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

At the time of endoscopy, the occluded SEMS position, length and diameter will be documented prior to intervention, as will the number, duration and total energy delivered during RFA for the study arm. Characteristics of the SEMS deployed will be recorded. Post procedure complications will be evaluated and managed according to standard clinical practice. Patients without adverse events will be discharged within 48hours after procedure, and followed to monitor primary and secondary outcomes. All additional imaging and laboratory studies will be conducted as clinically indicated and recorded.

11.0 TOXICITIES/SIDE EFFECTS

Among published studies, over 100 patients have undergone endoscopic biliary RFA with a technical success rate of over 99%, with the most common complications as cholangitis (5%) all treated conservatively, cholecystitis (<4%) requiring either percutaneous drainage or cholecystectomy, hemobilia (<3%), and post ERCP pancreatitis (<3%) all treated conservatively, and which is within the recognized 5% incidence post ERCP in general. Other complications occurring at less than 1% include: liver infarction managed

conservatively, and left bundle branch block managed conservatively. All cases of cholangitis, hemobilia, liver infarction, left bundle branch block were reported from a single study where 78% of the study group consisted of Klatskin tumor, a disease site which is excluded from this study. All procedural related adverse events on study will be captured by the Research Study Assistant (RSA) and reported to the IRB if serious.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Rate of failure for biliary stent obstruction after randomization to either instent RFA or coaxial SEMS placement alone serves as the primary objective to assess treatment efficacy. SEMS re-occlusion will be based on symptoms (jaundice or cholangitis), bloodwork (elevation of total bilirubin), imaging findings of biliary obstruction, including loss of stent patency, debris within stent, loss of or excessive pneumobilia. Study participants will be instructed to contact study physicians with any of the above symptoms of biliary stent occlusion for further evaluation. Please see section 2.0 for secondary outcomes.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Enrolled patients who withdraw consent for continued study participation, and patients who do not achieve clearance of occluded SEMS by the intended randomized treatment will be removed from the study, and will be managed based on standard of care.

Any patient who withdraws consent prior to randomization will be replaced in the study. Any patient who withdraws consent after randomization will not be replaced.

14.1 BIOSTATISTICS

This is a prospective randomized study comparing RFA followed by SEMS deployment versus placement of a SEMS alone. Patients with unresectable cancers of the distal bile duct or head of the pancreas with symptoms, biochemical, radiographic and endoscopic findings supportive of biliary obstruction will be randomized to one of these two arms and the primary endpoint, rate failure 180 days, will be compared across the two arms. Based on a review of internal data, rate of failure at 180 days is anticipated to be 60% with SEMS alone. Randomizing a total of 170 patients will give us approximately 80% power to detect an odds ratio of 2.5(i.e. a rate of 37% in the RFA+SEMS group) while controlling the Type I error at 5%. This sample size also allows for one interim analysis halfway through the trial (after 85 patients are randomized) using the O'Brien-Fleming boundary. If the p-value at the interim analysis is less than 0.003, the study will stop early for efficacy and if p>0.712 it will stop for futility. If the study does not stop early, final analysis will use a p-value threshold of 0.048 for significance.

Primary analysis will follow the intent-to-treat principle, with each patient analyzed in its randomized group even if the patient received another treatment or was not treated at all. Patients who do not receive any treatment or who die before 6 months will be counted as events regardless of whether their stents failed.

Rate of technical success for the endoscopic RFA group will be reported. All other secondary endpoints will be presented with summary statistics or contingency tables as appropriate and compared across the two groups with the tests listed next to them.:

- Rate of stent patency one month and three months post procedure: chi-square test
- Median duration of stent patency post procedure: log-rank test
- Median survival post procedure: log-rank test
- Incidence of procedure related complications: chi-square test
- Incidence of adverse events within one month post procedure: chi-square test
- Rates of 30-day and 90-day mortality: chi-square test.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

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

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

After consent and prior to the procedure, patients will be randomized into either the intervention or control group on a 1:1 ratio. Patients will be assigned to either group by the institutional Clinical Research Database (CRDB).

16.1 DATA MANAGEMENT ISSUES

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

The RSA will track and collect all the information gathered by the study clinicians and enter the data into the institutional Clinical Research Database (CRDB).

16.2 Quality Assurance

Throughout the life of the study, the study team comprising of the PI, research fellows, RSA, and CRC will meet regularly. During these meetings, they will address accrual rates, review adverse events, and discuss any challenges with using the device in this population. Weekly registration reports will be generated to monitor patient accruals and completeness of data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the PI and CRM for discussion and action.

Random sample data quality audits will be performed on a recurring basis and evaluated at the study team meetings.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

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

17.1 PROTECTION OF HUMAN SUBJECTS

Participants will be informed that information collected during their participation in this study is considered confidential. All data gathered will be kept in a secured location and available only to members of the research study team. Findings will be presented in aggregate form only - with no references made to the individual participant's data. Confidentiality of each participant's data will be protected with utmost care; data will be identified solely by a code number. A list matching participant's names and code numbers will be maintained on a secure and password protected database in MSKCC servers. Participation in this study is entirely voluntary. All participants will be required to sign a statement of informed consent that adheres to MSKCC guidelines. Should a patient decide not to participate in this study or to withdraw their consent to participate at any time during the study, their treatment at MSKCC or participating institutions will in no way be compromised.

17.2 Privacy

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

17.3 Serious Adverse Event (SAE) Reporting

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

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

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

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

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

The PI's signature and the date it was signed are required on the completed report.

17.2.1

Not applicable.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to

withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

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

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

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

19.0 REFERENCES

[1]Dolak W, Schreiber F, Schwaighofer H et al. Endoscopic radiofrequency ablation for malignant biliary obstruction: a nationwide retrospective study of 84 consecutive applications. Surg Endosc. 2014 Mar;28(3):854-60

[2]Figueroa-Barojas P, Bakhru MR, Habib NA et al. Safety and efficacy of radiofrequency ablation in the management of unresectable bile duct and pancreatic cancer: a novel palliation technique. J Oncol. 2013 doi: 10.1155/2013/910897

[3] Alis H, Sengoz C, Gonenc M et al. Endobiliary radiofrequency ablation for malignant biliary obstruction. Hepatobiliary Pancreat Dis Int. 2013 12(4):423-7

[4] Steel A, Postgate AJ, Khorsandi S et al. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. Gastrointest Endosc. 2011 73(1):149-53

[5] Pai M, Valek V, Tomas A et al. Percutaneous intraductal radiofrequency ablation for clearance of occluded metal stent in malignant biliary obstruction: Feasibility and early results. Cardiovasc Intervent Radiol. 2014 Feb;37(1):235-40

[6] Mizandari M, Pai M, Xi F et al. Percutaneous intraductal radiofrequency ablation is a safe treatment for malignant biliary obstruction: Feasibility and early results. Cardiovasc Intervent Radiol. 2013 Jun;36(3):814-9.

20.0 APPENDICES

None.