Phase I-II Clinical Trial of the Safety and preliminary efficacy of Hydroxychloroquine Combined with Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma

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Study Product: *Hydroxychloroquine Sulfate*

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List of Abbreviations

HCQ – Hydroxychloroquine
TACE – transarterial chemoembolization
HCC – hepatocellular carcinoma
OLT – Orthotopic liver transplantation
MTD – Maximum tolerated dose
DLT – Dose limiting toxicity
LFT – Liver Function test
CBC – Complete Blood count
BMP – basic metabolic panel
AFP – alpha fetoprotein
CR – Complete response
PR – partial response
SD – stable disease
PD – progression of disease
CQ – Chloroquine
HCV – Hepatitis C virus
MSR – metabolic stress response
HIF – hypoxia inducible factor
PFS – progression free survival
LPFS – local progression free survival
OS – overall survival

Study Summary

Title	Phase I-II Clinical Trial of the Safety and Preliminary Efficacy of Hydroxychloroquine combined with Transarterial Chemoembolization in Unresectable Hepatocellular carcinoma
Short Title	Phase 1-2 Trial HCQ plus TACE in Unresectable HCC
Protocol Number	UPCC 22213
Phase	Phase 1-2
Methodology	Single arm, unblinded, dose escalation
Study Duration	5 years
Study Center(s)	Hospital of the University of Pennsylvania
Objectives	Primary Phase I: To determine dose limiting toxicities and maximum tolerated dose (MTD) of the oral administration of hydroxychloroquine (HCQ) in conjunction with transarterial chemoembolization (TACE) in treating hepatocellular carcinoma (HCC) Primary Phase II: To evaluate the tumor necrosis rate in a cohort of patients treated at the MTD
Number of Subjects	Maximum 58 [18 patients maximum (6 patients at 3 dose levels) to define maximum tolerated dose (MTD) and total of 46 patients as expansion of cohort at the MTD, which includes 6 patients at MTD from Phase I]
Diagnosis and Main Inclusion Criteria	≥18yo, unresectable HCC, outside transplant criteria Candidate for TACE for palliative therapy Exclusions: HCQ allergy, porphyria, uncontrolled psoriasis, and existing retinopathy
Study Product, Dose, Route, Regimen	Hydroxychloroquine: Initial Dose 400mg PO daily for 28 days prior to TACE and continued until 8 weeks (2mo) following initial TACE. Doses will be escalated to, 400 mg BID (9AM/9PM), and 600 mg BID (9AM/9PM) to define MTD. Phase I: Dose escalation will be performed to define dose limiting toxicities and maximum tolerated dose (MTD) using 3+3 cohort expansion design. Phase II: Expansion of cohort at MTD using Simon's optimal Two Stage design to define complete response rate as determined by mRECIST imaging criteria. Study will be powered to detect a 20% increase in complete response rate (i.e. complete necrosis) from 40% to 60%.
Duration of administration	12-15 weeks
Reference therapy	TACE without HCQ
Statistical Methodology	Phase I: To determine dose limiting toxicity and maximum tolerated dose of HCQ in combination with TACE. Basic statistical analysis will include tabulation of graded toxicities by dose level. Phase II: Using Simon's optimal Two Stage design, we evaluate the efficacy of the combination of HCQ and TACE at the MTD to induce complete response as determined by mRECIST imaging criteria. Study is powered to detect a 20% increase in complete response rate (i.e. complete necrosis) from 40% to 60%.

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1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Background

Epidemiology of Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the third leading cause of cancer death worldwide(1). Between 2001 and 2006, the annual incidence of HCC increased an average of 3.5% per year. The incidence of HCC is expected to continue to rise in the United States secondary to the aging cohort of patients with chronic hepatitis C infection and the rising incidence of cirrhosis from non-alcoholic steatohepatitis related to the obesity epidemic(2,3).

Rationale for TACE to treat HCC

The difference in blood supply to the normal liver parenchyma, dual from the portal vein and hepatic artery, compared to the predominantly hepatic arterial blood supply to HCC, as well as metastatic lesions, allows transarterial chemoembolization (TACE) to be performed with low risk of liver failure or other serious complications(4). TACE is performed by administering high doses of chemotherapeutic agents, most commonly doxorubicin with or without cisplatin and mitomycin-C, into the hepatic artery branches supplying the HCC along with embolic material to slow washout of the chemotherapeutic agents and induce ischemia to the tumor(4). Following chemoembolization, transient elevations in liver function tests (LFTs) can be observed from interruption of hepatic arterial supply to normal parenchyma adjacent to the tumors; however, the majority of studies have shown these effects normalize by one week following therapy without permanent effect(5,6).

Typically, HCC arises in the setting of cirrhosis, and thus orthotopic liver transplant (OLT) is often regarded as the only curative option in patients with localized HCC(3,7). However, the majority of patients with HCC will be outside the criteria for liver transplant to treat HCC and will be of unacceptably high risk for local recurrence or metastatic disease following OLT(3,7). In patients with HCC regardless of stage of disease, TACE has been shown to delay HCC progression, improve local tumor control, and allow downstaging (4,8-11). Two randomized trials demonstrated improved survival among Childs A patients compared to best supportive care(4,12).

Deficiencies of TACE in treating HCC

Effectiveness of TACE as a bridging therapy to OLT or definitive therapy depends on tumor necrosis(13,14). TACE can, but often fails, to cause complete necrosis of HCC with rates of complete response (CR), defined as a 100% decrease in the amount of enhancing tissue in target lesion or complete necrosis, ranging from 29-43% even after repeated TACE(9,13,15-20). Georgiades, et al., studied the radiologic responses of 116 patients who underwent TACE(21). After a second TACE, the complete radiologic response rate increased from 14 to 38%. However, still over 25% of the patients did not respond at all to two TACE treatments, and 62% of patients did not have a complete response by imaging (see Imaging Assessment of Response under Section 3.3)(21).

Complete imaging response to TACE correlates well with pathological analysis and impacts patient outcome. In an analysis of patients exceeding transplant criteria down-staged with TACE, Bargellini et al. found a complete tumor response (CR) in 55% of patients which corresponded to a complete pathologic response rate of 61%(13). Progression free survival rates were higher in patients with complete response following TACE compared to those with a partial response or stable disease following TACE(13). Thus, improving the rate of complete tumor response following TACE is likely to result in improved progression free and overall survival.

Autophagy and HCC

Emerging data has demonstrated HCC can survive the post-TACE microenvironment by activating the autophagy pathway to degrade non-vital intracellular proteins and organelles to derive energy and replicate (see preliminary data in Section 1.2 Preclinical Data)(22,23). Our preclinical data suggests the addition of the autophagy inhibitor hydroxychloroquine as a complementary therapy to TACE could prevent cells from evading the cytotoxic and ischemic micro-environment post-TACE. Hydroxychloroquine (HCQ), a commercially available, FDA approved drug used to treat malaria and connective tissue disorders, has been identified as a potent inhibitor of autophagy. Several phase I studies establishing the safety of combining HCQ with various chemotherapies have been conducted at UPENN and other partner institutions. Phase II clinical trials evaluating the addition of HCQ to chemotherapeutic regimens for treatment of pancreatic and metastatic colon cancer are currently underway(24). Given its long history of safe use in humans and known side-effect profile, HCQ is an ideal drug to combine with TACE to inhibit the autophagy pathway of cell survival.

1.2 Investigational Agent

Hydroxychloroquine (HCQ) Sulfate, known by the trade name Plaquenil, is a colorless crystalline solid with the chemical structure 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino] ethanol sulfate. HCQ sulfate tablets come in 200mg doses, equivalent to 155 mg of the free HCQ base, for oral administration.
Inactive Ingredients contained in HCQ Sulfate tablets include: Dibasic Calcium Phosphate, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polyethylene glycol 400, Polysorbate 80, Corn Starch, Titanium Dioxide.

HCQ is FDA approved drug, which possesses anti-malarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or systemic) and acute or chronic rheumatoid arthritis. HCQ is a derivative of the drug chloroquine (CQ) which had been used for 60 years in humans to prevent and treat malaria and rheumatoid arthritis(25,26). CQ is an inexpensive oral medication with a large therapeutic index. The most predictable toxicity is retinopathy, which is related to cumulative dose and can be prevented by discontinuation of CQ(27). This toxicity and worldwide malarial resistance to CQ lead to the discontinuation of research into non-malarial applications of CQ.

The structure of HCQ allows it to serve as a weak base becoming trapped in acidic cellular compartments(28). Thus, HCQ deacidifies the lysosomal contents resulting in inhibition of the last step in autophagy. With this inhibition, cells reliant on autophagy will increase the generation of autophagosomes and eventually undergo apoptotic or non-apoptotic cell death. The significant anti-tumor activity of HCQ by inhibition of autophagy has been validated in various animal models and cancer cell lines and multiple clinical trials in humans are now underway (24,29).

Overall, HCQ has been shown to have a low incidence of hepatotoxicity with rates as low as 1% in prospective randomized trials studying rheumatoid arthritis(30). HCQ has been used in patients with cirrhosis with concomitant rheumatoid arthritis as well as to treat hepatitis C virus associated arthritis(31,32). Although studies suggest the incidence of elevation of LFTs above 1.5 times the upper limit of normal is increased in patients with chronic HCV taking HCQ for rheumatoid arthritis compared to those without HCV, the mean duration of use in these patients was 1.9 years(33). Similarly in this retrospective series, the incidence of hepatic dysfunction was higher in patients with pre-existing abnormalities in LFTs prior to initiating therapy(33).

1.3 Preclinical Data

TACE induces ischemia
Other investigators have demonstrated that HCC cells are able to survive under severe, TACE-like ischemia(22,23). Furthermore, preliminary data generated at the Hospital of the University of Pennsylvania supports this observation (Fig.1A-D, unpublished data courtesy of Dr. Terence Gade). Moreover, HCC cells able to survive under severe ischemia demonstrate an increased propensity for metastasis as well as an advanced growth kinetic following reintroduction of normoxia and complete media to mimic reperfusion after TACE (Fig.1E). The current standard TACE protocols utilize cell cycle specific agents, most commonly doxorubicin, mitomycin and cisplatin, which target proliferating cells; however, our preliminary data demonstrates that cells capable of surviving under TACE-like ischemia

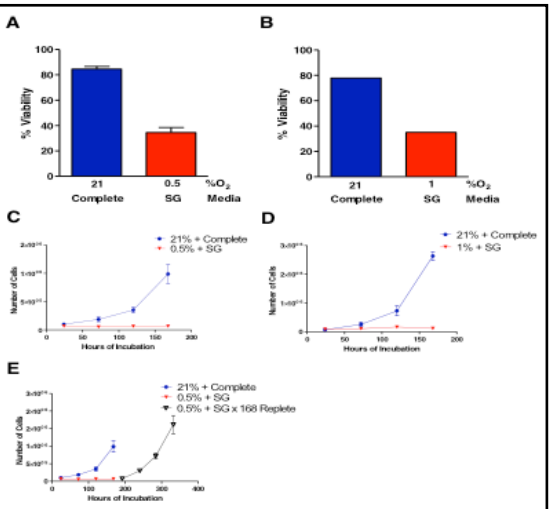


Figure 1: HCC Cells survive under TACE-like ischemia. (A,B) FACS assay reveals significant proportion of HCC cells are viable after 48 hrs of incubation at ischemia (SG) as compared to cells incubated under normoxia (21% O2). **(C,D)** HCC cells were able to survive for up to 1 wk under severe ischemia. **(E)** HCC demonstrate an advanced growth kinetic when ischemia is reversed.

demonstrate a significant reduction in proliferative fraction (S-phase cells, Fig 2A). In cytotoxicity assays, cells grown under ischemia were more resistant to the commonly used TACE agent doxorubicin relative to cells incubated under standard conditions (Fig.2B). These data suggest that the currently used TACE agents fail to target those cells surviving the embolic effects of TACE, underscoring the importance of identifying the molecular mechanisms through which these cells persist under these cytotoxic conditions.

TACE-induced hypoxia activates cytoprotective autophagy

Cancer cells undergo metabolic reprogramming to enable survival under ischemia via pathways collectively known as the metabolic stress response (MSR) including hypoxia inducible factors (HIFs) and autophagy. HIF-1α plays a critical role in the adaptation of proliferating cells to hypoxia by modulating metabolism, angiogenesis, growth, and metastasis(34). TACE is associated with increased expression of HIF-1α in viable tumor cells in vivo, and a preclinical study demonstrated that antisense HIF-1α augmented the response to TACE in HCC(35-37). Autophagy, the process by which cellular components are captured, degraded and recycled, has been shown to enable survival of HCC under TACE-like ischemia(23). In our preclinical data, HCC cells grown under ischemic conditions have demonstrated activation of the MSR with increased expression of HIFs and mediators of autophagy (Fig.2D). Thus, our preliminary data demonstrates targeted inhibition of autophagy with HCQ is likely to enhance cell death when combined with the hypoxic and ischemic conditions created by TACE (Fig.2C). Given the results of our pre-clinical data combining HCQ with TACE and the safety of both therapies, translation of this novel combined therapy into clinical practice offers the promise of improved tumor necrosis and progression free survival.

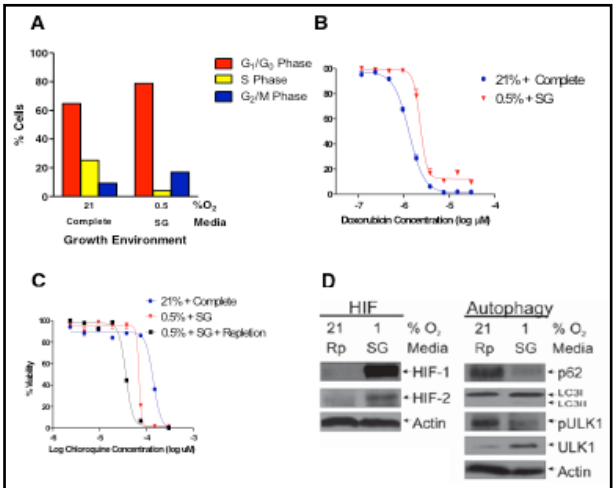


Figure 2: HCC cells under TACE-like ischemia demonstrate are more sensitive to autophagy inhibition compared to doxorubicin. (A) HCC under ischemic have reduced S-phase fraction. **(B)** Ischemia induces resistantance doxorubicin with a 44% increase IC50 **(C)** Cell death via inhibition of autophagy with chloroquine was potentiated under ischemia with a 50% reduction in the IC50. Upon reversal of ischemia, IC50 was further decreased. **(D)** Ischemia activates MSR pathways including HIFS and autophagy.

1.4 Clinical Data to Date

No studies regarding the use of HCQ in HCC in humans have been published. Currently, no clinical trials are underway utilizing the combination of HCQ and TACE. Currently, multiple Phase II clinical trials (including two at the Hospital of the University of Pennsylvania) investigating the addition of HCQ to intravenous chemotherapeutics for a variety of locally advanced and/or metastatic gastrointestinal and solid organ malignancies(24). The addition of CQ as anticancer therapy has already been tested in a randomized clinical trial which demonstrated an improvement in overall survival in patients receiving standard of care plus CQ compared to standard therapy only(38).

1.5 Dose Rationale and Risk/Benefits

The present clinical trial is a Phase I-II clinical trial investigating the safety of HCQ as an autophagy inhibitor in combination with TACE using a dose escalation strategy to identify DLT and MTD, with sufficient cohort size to explore the impact of the MTD of HCQ on tumor necrosis rate and PFS. The initial dose of 400mg has been chosen as this is the standard daily maintenance dose used to treat systemic lupus erythematosus and rheumatoid arthritis in adults with acceptable side effect profile A pharmacokinetic/pharmacodynamic study of escalating doses of HCQ at 400 mg, 800 mg, and 1200 mg PO daily in patients with rheumatoid arthritis followed by maintenance doses of 400 mg PO daily found doses up to 1200 mg daily were well tolerated. Dose limiting toxicities were nausea, vomiting and abdominal pain were observed at 800 and 1200 mg PO daily(39).

Retinopathy is predictable toxicity associated with cumulative dose of CQ, which would limit its use clinically. While a link between HCQ and retinopathy has also been made, the incidence is infrequent and only occurring after prolonged usage. A study using multifocal electroretinography to detect early pre-clinical retinal changes in long-term HCQ users, found that 10 out of 11 patients that developed early pre-clinical changes had been taking HCQ at doses of 400 mg PO daily for greater than 5 years(40). No overt clinical signs of retinopathy occurred in the 19 patients followed suggesting the risk of retinopathy does not increase until a cumulative dose of 730 g is reached. However, if implemented as a long-term therapeutic agent, techniques such as multifocal electroretinography could be used to detect preclinical retinal changes from HCQ and prevent overt visual loss.

Currently, multiple trials involving HCQ combinations in cancer patients are either enrolling patients at UPENN or have completed enrollment(24). In all except one, no dose limiting toxicities have been identified and the maximal administered dose of 1200 mg HCQ daily in combination with different anticancer agents was easily achieved. In most trials grade 2 anorexia, nausea, fatigue, and diarrhea were the most common side effects attributable to high dose HCQ. No hepatic toxicity has been observed. Some these clinical trials have produced encouraging results. The most encouraging HCQ trial as far as antitumor activity is a phase I trial of temsirolimus and HCQ in advanced melanoma patients. We have observed a 75% stable disease rate in contrast to a 0% stable disease rate observed with temsirolimus alone in previous phase II trial. Based on these promising results in other clinical trials in conjunction with out pre-clinical data, potential benefits of inhibition of autophagy with HCQ when added to TACE are improved tumor necrosis, progression free survival, and possibly overall survival following TACE.

2 Study Objectives

Primary Objective Phase I
Determine the dose limiting toxicities and maximum tolerated dose of HCQ in combination with TACE

Secondary Objective Phase I
Determine rate of late grade 1 or higher LFT abnormalities after continuation of HCQ for 8 weeks post TACE (ie after day 56 of treatment)

Primary Objective Phase II
Assess effect of combined HCQ and TACE on the complete response rate to therapy

Secondary Objectives Phase II
Assess local progression free survival (LPFS)
Assess overall survival of patients receiving combination therapy

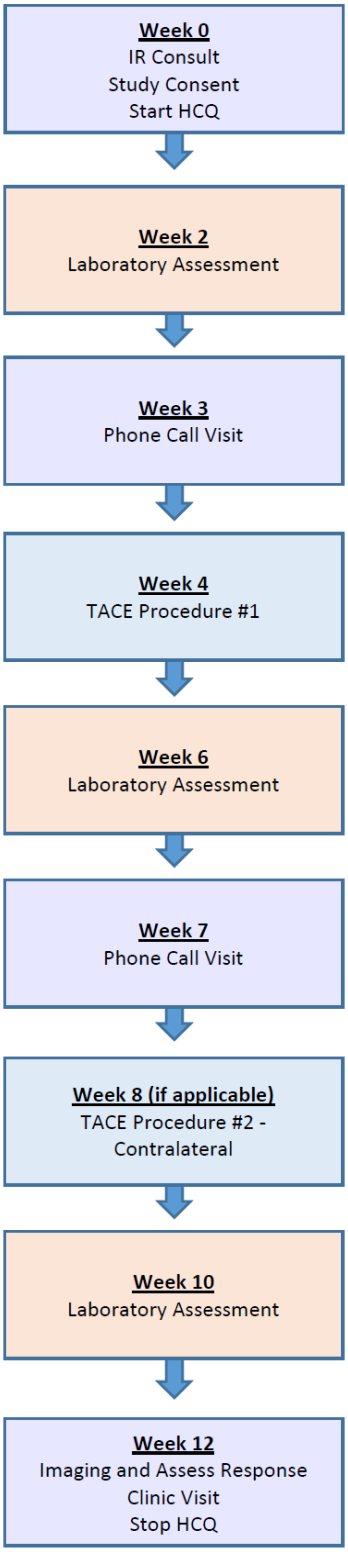
3 Study Design

3.1 General Design

Time Course of Procedures, HCQ Dosing, and Patient Follow-up

Phase I-II non-randomized, unblinded dose escalation study of the safety and toxicity of the combination of HCQ and TACE for the treatment of unresectable HCC outside of transplant criteria. A conventional phase I “3+3” cohort expansion design will be utilized with an initial dose of 400mg HCQ PO daily (see chart below). The timeline for clinical follow up and response assessment will differ slightly for patients with bilobar and unilobar HCC.

Time Line: Phase I Bilobar Disease



Timeline Bilobar HCC
Patients will be unblinded to the dose of HCQ that they have been prescribed. Patients will take the prescribed dose of HCQ once or twice daily for 4 weeks, prior to chemoembolization to achieve peak serum concentrations of HCQ prior to initial TACE. After initial TACE, the patient will undergo a second session of TACE , if necessary, to treat all of the patients HCC. The patient will continue the use of the same prescribed dose of HCQ for approximately 8 weeks following initial TACE (approximately 12 total). Upon enrollment, patients will be provided with a comprehensive list of symptoms/side effects of HCQ therapy and TACE as well as contact information for the research time to report any concerns.

Patients will have baseline laboratory levels including CBC, CMP, and PT/INR, checked $\leq$ 30 days prior to enrollment and the start of HCQ. Approximately two weeks after starting HCQ, the patient will have CBC, CMP and PT/INR repeated to identify hepatoxicity or nephrotoxicity. The patient will be contacted the week after receiving these laboratory results to assess for toxicity/AEs.

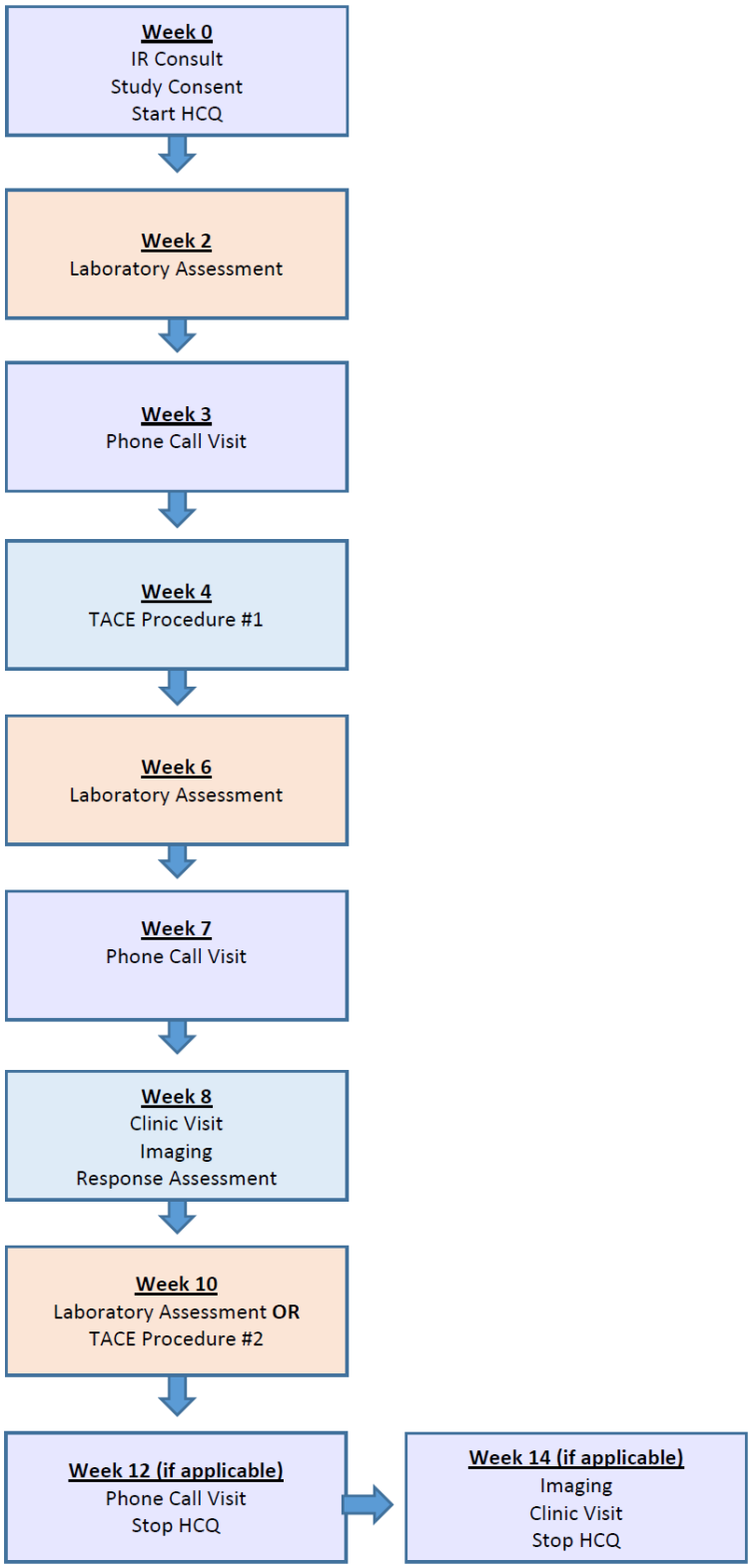
TACE will be performed using standard method currently employed by IR at HUP(41). In brief, following access to the arterial system, selective diagnostic arteriography of the superior mesenteric and celiac arteries will be performed to define the hepatic vasculature. Selective catheterization of arteries supplying the HCC will be performed, and a chemoembolic emulsion consisting of 50 mg of doxorubicin (Adriamycin; Pharmacia-Upjohn, Kalamazoo, MI) and 10 mg of mitomycin C (Bedford Laboratories, Bedford, Ohio) dissolved in 10 mL of water-soluble contrast material emulsified with ethiodized oil (Lipiodol, Guerbet Laboratories) will be administered. This is followed by embolization with 100-300 micron Embospheres (Merit Medical Systems, Inc, South Jordan, UT) until arterial blood flow to the tumor is substantially reduced (pruned tree appearance on post-embolization arteriography). Embolization with bland particles prior to administration of chemoembolic emulsion may be performed in cases of hepatic artery to portal venous shunting. Following TACE, the patient will be admitted overnight for intravenous hydration, prophylactic antibiotics, and pain control as routinely performed at HUP(41). As part of routine TACE procedure, patients will receive prophylactic antibiotics against gram negative and anaerobic organisms prior to the start of TACE and to be continued orally for 3 days following the procedure to minimize risk for hepatic abscess(41).

Two weeks after initial TACE (Week 6), patients will undergo repeat laboratory evaluation with CBC, CMP and PT/INR. The patient will be contacted the week after of receiving these laboratory results to assess for toxicity/AEs. Subsequently, patients will undergo TACE of the contra-lateral lobe at Week 8if LFTs are below the threshold of dose limiting toxicity.

Following TACE of the contra-lateral lobe, the patient will undergo repeat CBC, CMP and PT/INR at Week 10 to evaluate for dose limiting hepatoxicity and nephrotoxicity. At Week 12, the patient will be evaluated with a clinical office visit, and contrast enhanced MRI or CT to assess imaging response of combined therapy. Patients will then undergo follow-up with clinical office visit, laboratory studies and imaging at 3 months (+/- 1 week) and 6 months (+/- 1 week) as part of routine clinical practice following TACE(41). Post-treatment imaging of all enrolled patients will be reviewed by a radiologist from the Abramson Cancer Center Clinical Imaging Core blinded to dose of HCQ. Post-treatment imaging will be assessed for mRECIST and EASL response to therapy and percentage of residual viable tumor. Response to therapy and progression of disease will be categorized using previously published mRECIST and EASL criteria (see Imaging Assessment of Response under Section 3.3)(42,43). These imaging criteria take into account percent necrosis as estimated by absence of tumor enhancement in addition to size reduction, and have been shown to correlate well with histopathologic data(13,44).

Follow-up study period to examine for late toxicity will end 6 months after cessation of HCQ therapy.

Time Line: Phase I Unilobar Disease



Timeline Unilobar HCC
For patients with unilobar HCC, duration of HCQ therapy, frequency/timing of laboratory assessments, and definition of DLTs will be the same as with bilobar HCC. However, imaging, response assessment to initial TACE and phone call or clinical office visit following initial TACE will be performed at calendar Week 7 . Repeat chemo-embolization may be performed at calendar Week 8 on HCCs with less then PR by mRECIST (see Imaging Assessment of Response under Section 3.3) or new HCCs which have developed since the initial TACE so long as LFTs are below the threshold of dose limiting toxicity. Subsequent follow-up clinic visits and imaging will be the same as with bilobar HCC - 3 months (+/- 1 week) and 6 months (+/- 1 week) following the last clinic visit.

Phase I: Dose Escalation using "3+3" Cohort Expansion Design

After initiating HCQ, dose limiting toxicity will be defined as events occurring at any time from initiation of HCQ (Week 0) up to Week 12. All patients who receive at least one day of HCQ will be included in the toxicity analysis.

DLT definition:
Toxicities will be graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. A DLT will be defined as one or more of the following occurring any time during the defined DLT period from initiation of HCQ (i.e Day -42 to -28) to completion of HCQ therapy 4 weeks following second TACE (Day 56 to Day 63): (1) grade 3 or higher hepatobiliary complication, except hepatic pain; (2) grade 4 or higher hepatic pain; (3) grade 3 or higher abnormality of liver function tests including total bilirubin (i.e. >3x the upper limit of normal) and transaminases (i.e. >5x the upper limit of normal, the Hospital of the University of Pennsylvania defines normal transaminases as AST< 41 IU/L and ALT < 63 IU/L); (4) grade 3 or higher elevation of serum creatinine (i.e >3x baseline or >3x upper limit of normal); (5) grade 3 or higher increase in international normalized ratio (i.e. greater than 2.5x upper limit of normal or >2.5x baseline if anti-coagulated); or (6) any grade 3 or higher toxicity that is possibly or definitely related to treatment. Given the prevalence of baseline thrombocytopenia in patients with HCC, decreases in platelet count will not be evaluated as a DLT.

The initial dose of HCQ will be 400mg PO daily. If the initial dose of HCQ 400mg PO daily incurs DLT, the dose will be reduced to 200mg and an additional 3 patients will be enrolled at this level (see "3+3" Cohort Expansion chart below). If DLTs do not occur at HCQ 400mg PO daily, the dose will be escalated by 400mg increments to a maximally administered dose of HCQ 1200mg (administered as 600mg PO twice daily) with enrollment of each cohort dictated by the "3+3" design (see "3+3" Cohort Expansion and Dose Schema Charts below). The dose may be escalated to the next level once at least 3 patients at a particular HCQ dosage have been observed for 1 month after second TACE (i.e. day 56 to day 63).

"3+3" Cohort Expansion Design Decision Making Regarding Dose Escalation

"3+3" Cohort Expansion Design Decision Making Regarding Dose Escalation	
Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Escalate
≥2	Stop Dose Escalation • This dose exceeds the MTD • Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose
1 out of 3	Enter 3 more patients at this dose level • If 0 of these 3 additional patients experience DLT, proceed with dose

	escalation to the next level • If 1 or more of these 3 additional patients experience DLT, then dose escalation is stopped. This dose level exceeds the MTD • Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that level
≤1 out of 6 at the highest tolerable dose	This is considered the MTD. At least 6 patients must be enrolled at the MTD.

Table: Hydroxychloroquine Dose Escalation Schema

Dose level	HCQ
-1a	200 mg qday (9AM)
1	400 mg qday (9AM)
2	400 mg BID (9AM/9PM)
3	600 mg BID (9AM/9PM)

Phase II: Effect of Combined Therapy on Complete Imaging Response using Simon's Two Stage Design

Following determination of the MTD, a cohort of patients will be enrolled at the MTD to examine the benefit of combined HCQ and TACE therapy on complete response rate. In the reported literature, the rate of complete necrosis of HCC ranges from 29-43% even after repeated TACE(7,11,13-18). Georgiades, et al., studied the radiologic responses of 116 patients who underwent TACE(19). After a second TACE, the complete radiologic response rate increased from 14 to 38%. However, still over 25% of the patients did not respond at all to two TACE treatments, and 62% of patients did not have a complete response by imaging (see Imaging Assessment of Response under Section 3.3)(19).

This phase of the trial will use a Simon's optimal two-stage design. The null hypothesis that the complete response (CR) rate of TACE and HCQ will be similar to TACE alone (p_0 =40%) will be tested against a one-sided alternative, the complete response (CR) rate of combined TACE and HCQ will be 60% (p_1). In the first stage, 12 patients will be accrued, of which 6 will patients treated at the MTD from the Phase I trial. If there are 7 or fewer complete responses by mRECIST in these 16 patients, the study will be stopped. The probability of stopping the trial after the first stage of the Simon's optimal design is 72%. Otherwise, 30 additional patients will be accrued for a total of 46 patients. The null hypothesis will be rejected if 23 or more responses are observed in 46 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the complete response rate by mRECIST of combined TACE and HCQ is 60%.

3.2 Primary Study Endpoints

Phase I:
The primary end points of Phase I are dose limiting toxicity and maximum tolerated dose. DLT, graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0, will be defined as one or more of the following events occurring any time during the defined DLT period from initiation of HCQ (Week 0) to 1 month following second TACE (Week 12) excluding the day immediately following TACE: (1) grade 3 or higher hepatobiliary complication, except hepatic pain; (2) grade 4 or higher hepatic pain; (3) grade 3 or higher abnormality of liver function tests including total bilirubin (i.e. >3x the upper limit of normal) and transaminases (i.e. >5x the upper limit of normal, the Hospital of the University of Pennsylvania defines normal transaminases as AST< 41 IU/L and ALT < 63 IU/L); (4) grade 3 or higher elevation of serum creatinine (i.e >3x baseline or >3x upper limit of normal); (5) grade 3 or higher increase in international normalized ratio (i.e. greater than 2.5x upper limit of normal or >2.5x baseline if

anti-coagulated); or (6) any grade 3 or higher toxicity that is possibly or definitely related to treatment. Given the prevalence of baseline thrombocytopenia in patients with HCC, decreases in platelet count will not be evaluated as a DLT.

Prior investigations have demonstrated the safety of TACE for HCC with a reported rate of major complications related renal dysfunction, biliary injury, gastrointestinal tract ulcer, and treatment related mortality ranging between 2 and 3%(45). Rates of hepatic failure in multiple studies have averaged 7.5%(45).

Phase II:

The primary end point of Phase II will be rate of complete imaging response by mRECIST (see Imaging Assessment of Response under Section 3.3).

3.3 Secondary Study Endpoints

Phase I:

Additional secondary endpoints of phase I will include rate of development of any late grade 1 or higher toxicity at any point during combined therapy or during follow up.

Phase II:

The secondary endpoints of the phase II trial will include local tumor control as measured by local progression free survival (LPFS) using mRECIST imaging criteria and overall survival(42,46). For the purposes of the primary and secondary endpoints regarding CR and LPFS, mRECIST will be used. Additionally, during collection of data, imaging response according to EASL guidelines will also be collected. LPFS is defined as time from initiating HCQ therapy (Week 0) to the first diagnosis of local progression of disease, need for TACE of a tumor previously treated with TACE, or death due to any cause. Overall survival is defined as death due to any cause or last patient contact alive.

Table: mRECIST and EASL Imaging Response Assessment

Assessment	Abbreviated Assessment	EASL Definition	mRECIST Definition
Complete Response	CR	100% Decrease in Amount of Enhancing Tissue in Target Lesion	100% Decrease in maximum diameter of Enhancing Tissue in Target Lesion
Partial Response	PR	>50% Decrease in Amount of Enhancing Tissue in Target Lesion	>30% Decrease in maximum diameter of Enhancing Tissue in Target Lesion
Stable Disease	SD	<50% Decrease in Amount of Enhancing Tissue in Target Lesion	<30% Decrease or <20% Increase in maximum diameter of Enhancing Tissue in Target Lesion
Progression of Disease	PD	>25% Increase in Amount of Enhancing Tissue in Target Lesion OR New enhancement in previously	>20% Increase in maximum diameter of Enhancing Tissue in Target Lesion

		treated lesion warranting further treatment	

3.4 Dose Reduction Schema

Toxicities will be evaluated using the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0. Patients developing grade 3 or higher toxicity of any kind, which does not meet the definition of DLT, will call for holding HCQ therapy until the toxicity resolves to grade ≤1. Any adverse effect attributed as possibly, probably or definitely related solely to HCQ will result in the dose being held until the adverse effect has resolved to ≤ grade 1 or baseline. If the adverse effect resolves, reinstitution of treatment can occur but at a reduced dose as described below (HCQ Dose Reduction Schema). If the adverse effect recurs at the reduced dose, treatment will be held until the adverse effect has resolved to ≤ grade 1 and when resolved treatment can be reinstituted at the next lower dose level. No more than 2 dose reductions are allowed during the maintenance cycles.

Toxicities that may be attributable to HCQ include nausea, vomiting, diarrhea, rash, and visual field changes. If any of these adverse events occur at grade ≤ 2, HCQ may be continued and the adverse event managed with supportive care. With particular regard to visual field deficits patients should be cautioned to report any visual symptoms, particularly difficulty seeing entire words or faces, intolerance to glare, decreased night vision, or loss of peripheral vision. These symptoms of peripheral retinal toxicity should prompt drug discontinuation and ophthalmologic evaluation.

Table: Hydroxychloroquine Dose Escalation Schema

Dose level	HCQ
-1a	200 mg qday (9AM)
1	400 mg qday (9AM)
2	400 mg BID (9AM/9PM)
3	600 mg BID (9AM/9PM)

4 Subject Selection and Withdrawal

4.1 Inclusion Criteria

1. Patient capable giving informed consent
2. Patient diagnosed with hepatocellular carcinoma of the liver by one of the following methods
    a. Pathologically confirmed HCC by biopsy, OR
    b. HCC >2 cm with classic radiographic findings of arterial phase enhancement with venous phase washout and pseudocapsule formation on contrast enhanced MRI or CT, OR
    c. Lesion greater than 2 cm with probable imaging features of HCC and imaging findings of cirrhosis and/or portal hypertension or a serum alphafetoprotein (AFP) greater than 200 ng/mL.
3. Patient not candidate for orthotopic liver transplantation at the Hospital of the University of Pennsylvania based on review of patient imaging and history at multidisciplinary Hepatic Tumor Conference at the Hospital of the University of Pennsylvania
4. Age ≥ 18 years old
5. Albumin > 2.4 g/dL; Total bilirubin < 2 mg/dL; INR ≤1.5; Creatinine < 2.0 mg/dL; AST≤ 121 IU/L; ALT ≤ 189 IU/L
6. Child-Turcotte-Pugh Classification A or B
7. Eastern Clinical Oncology Group performance status 0 or 1

4.2 Exclusion Criteria

1. Prior TACE to the HCC(s) to undergo TACE during this protocol
2. Active GI hemorrhage within 2 weeks of study enrollment
3. Ascites refractory to medical therapy
4. Contraindication to receiving HCQ or TACE
5. Women who are pregnant or nursing
6. Participation in another concurrent treatment protocol

4.3 Subject Recruitment and Screening

This trial is designed to be the initial prospective phase I-II investigation of the safety and effectiveness of combined HCQ and TACE for unresectable HCC. No clinical trials regarding the safety or efficacy of combination of TACE and HCQ have been or are being conducted. Patients will be recruited from the Interventional Oncology Clinic and the multidisciplinary Hepatic Tumor clinic at the Hospital of the University of Pennsylvania. Historically, approximately 50-60 new patients undergo initial TACE at HUP each year as therapy for unresectable HCC. During the initial consultation with Interventional Radiology, patients will be screened and recruited for this trial. Patients who are interested in enrollment will have a full discussion of the risks/benefits of combined therapy and be allowed to address any concerns or questions regarding combined therapy. We expect approximately 5 years will be needed complete enrollment and follow up. The knowledge gained from this phase I-II clinical trial will establish the safety of combined therapy, assess the efficacy in terms of complete response by imaging, and will allow for accurate estimate of the number of patients needed to adequately power larger phase II and III clinical trials.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

• PI Decision: Subjects may be withdrawn at any time during the study if the PI believes it is in the subject's best interest. In this event, the reasons for withdrawal will be documented.
• Subject Participation: Refusal to continue treatment, follow-up, comply with the protocol or withdrawal of consent. In this event, the reasons for withdrawal will be documented.

Patients withdrawing from the study will be entitled to pursue all treatment options available for the treatment of HCC without prejudice from the providing physicians.

Once the subject has discontinued treatment, the primary reason for discontinuing treatment must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the experimental therapy. If a subject withdraws consent to participate in the study, attempts will be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. Methods that may be used to obtain survival data will include phone calls to the subject, phone calls to next-of-kin if possible, and certified letters to the subject or next-of-kin. If permission to collect or the specific survival data cannot be obtained after 4 phone calls and 4 letters to the subject and/or next-of-kin, the patient will be regarded as lost to follow up.

5 Study Drug

5.1 Description

Hydroxychloroquine (HCQ) Sulfate, known by the trade name Plaquenil, is a colorless crystalline solid with the chemical structure 2-[[4-[(7-Chloro-4-quinolyl)amino]pentyl]ethylamino] ethanol sulfate. HCQ sulfate tablets come in 200mg doses, equivalent to 155 mg of the free HCQ base, for oral administration.
Inactive Ingredients contained in HCQ Sulfate tablets include: Dibasic Calcium Phosphate, Hydroxypropyl Methylcellulose, Magnesium Stearate, Polyethylene glycol 400, Polysorbate 80, Corn Starch, Titanium Dioxide.

5.2 Treatment Regimen

Dose may range from 200-1200mg orally according to cohort, which the patient is assigned as dictated by "3+3" design. The initial dose will be HCQ 400mg PO daily. Therapy will begin prior to TACE for approximately 28 days. The patient will continue HCQ therapy for approximately 8 weeks following initial TACE. Thus, total duration of HCQ therapy will be approximately 12 weeks. Patient medication compliance with HCQ will be assessed and documented at each follow-up phone call and clinical visit (e.g. patients will be asked if they have missed any doses of HCQ and this information will be recorded).

Table: Hydroxychloroquine Dose Escalation Schema

Dose level	HCQ
-1a	200 mg qday (9AM)
1	400 mg qday (9AM)
2	400 mg BID (9AM/9PM)
3	600 mg BID (9AM/9PM)

5.3 Method for Assigning Subjects to Treatment Groups

Patients will be assigned to a dosage level of HCQ with enrollment according to "3+3" cohort design as described above starting with an initial dosage of HCQ 400mg PO daily. Unblinded dose escalation according to the "3+3" design is desired to allow for close monitoring of patient symptoms/toxicity prior to escalation to the next dose.

5.4 Preparation and Administration of Study Drug

Following enrollment, the subject will be prescribed an assigned dose of hydroxychloroquine. Patients will be unblinded to the dose of therapy. Since hydroxychloroquine is an FDA approved drug, the prescription may be filled at a pharmacy, which is most convenient to the patient to facilitate compliance with therapy.

5.5 Subject Compliance Monitoring

Prior to TACE and with each follow-up phone call and clinical visit, the patient will be asked about their compliance with taking HCQ (e.g. patients will be asked if they have missed any doses of HCQ and this information will be recorded). Any reported missed doses will be recorded. Patients who miss greater then 5 consecutive days of therapy will be deemed non-compliant and asked to withdraw from the study. Non-compliant patients will be replaced in the dose escalation phase of the trial.

5.6 Prior and Concomitant Therapy

No other concomitant locoregional therapies for HCC will be accepted. Patients who have received prior locoregional treatments for HCC may be enrolled if these tumors are no longer viable and patient is now being referred to IR for TACE to treat newly identified HCCs.

HCQ has known effects on P450 enzymes, patients requiring anti-convulsants may be treated with any of the non-enzyme inducing anti-convulsants which include: felbamate, valproic acid, gabapentin, lamotrigine, tiagibine, topiramate, zonisamide, or levetiracetam. For nausea, aprepitant should be avoided.

5.7 Blinding of Study Drug

This protocol does not utilize blinding. Subjects and investigators will know the treatment being administered.

5.8 Receiving, Storage, Dispensing and Return

5.8.1 Receipt of Drug Supplies

Since hydroxychloroquine is an FDA approved drug, the prescription may be filled at a pharmacy, which is most convenient to the patient. Thus, no special procedures for receipt of the study drug are needed.

5.8.2 Storage

Since hydroxychloroquine is an FDA approved drug, no special procedures for storage of the study drug are needed.

5.8.3 Dispensing of Study Drug

Since hydroxychloroquine is an FDA approved drug, no special procedures for distribution of the study drug are needed.

5.8.4 Return or Destruction of Study Drug

Since hydroxychloroquine is an FDA approved drug, no special procedures for return of the study drug are needed. Unused HCQ may be disposed by the patient as they would with non-study prescription medication (e.g. based on the regulations of the municipality in which they live)..

6 Study Procedures

Please Note - All visits will be by calendar week. All visits from Weeks 0 to 14 will have a grace period of 14 days/2 weeks to allow for scheduling of procedures, weekends, holidays as well as off service days for the interventionalist while not exceeding a total of 15 weeks total time taking HCQ. In addition, all study visits/events are sequential so that a patient cannot procced to a study visit without completing the prior visit (e.g. Week 2 visit events must be completed before the Week 3 visit, Weeks 3 visit events must be completed before Week 4 visit, etc.).

6.1 Week 0:

All patients will undergo a standard of care consult office visit with IR at which time they will be approached about study consent and screened for eligibility. As soon as possible after patients' complete the study informed consent process, patients will begin HCQ therapy.

6.2 Week 2:

All patients will have laboratory assessments (Complete Blood Count, PT/INR, Complete Metabolic Panel) to check for DLT.

6.3 Week 3:

All patients will be contacted by phone after receiving the laboratory results to verify compliance with HCQ therapy and discuss toxicity and AEs.

6.4 Week 4:

All patients will undergo initial TACE. A single session of TACE can be used to treat all lesions within one lobe of the liver.

6.5 Week 6:

All patients will have laboratory assessments (CBC, PT/INR, CMP) to check for DLT.

6.6 Week 7:

All patients will be contacted by phone after receiving the laboratory results to verify compliance with HCQ therapy and discuss toxicity and AEs.

6.7 Week 8:

Patients with **bilobar disease** will undergo TACE of the contra-lateral lobe to treat additional HCC. This second session of TACE will be performed only if the patient's clinical status and laboratory assessments have returned to baseline and the patient has not had any dose limiting toxicity.

Patients with **unilobar disease** will undergo an IR clinical office visit. At the clinical office visit - compliance with HCQ therapy, toxicity and AEs will be recorded. In order to determine if a second session of TACE is needed for subjects, a response assessment with imaging (contrast enhanced MRI or CT) will also be conducted at this visit.

6.8 Week 10:

Patients with **bilobar disease** and patients with **unilobar disease not undergoing a second session of TACE** will have laboratory assessments (CBC, PT/INR, CMP) to check for DLT.

Other patients with **unilobar disease** will undergo second session of TACE. This second session of TACE will be performed only if 1.) the HCC is less then PR by mRECIST or new HCC has developed since the initial TACE, 2.) the patient's clinical status and laboratory assessments have returned to baseline and 3.) the patient has not had any dose limiting toxicity.

6.9 Week 12:

Patients with **bilobar disease** will undergo a contrast enhanced MR or CT, IR clinical office visit and response assessment. At the clinical office visit - compliance with HCQ therapy, toxicity and AEs will be recorded.

Patients with **unilobar disease** that **did not** undergo a **second session of TACE** will have an IR clinical phone call where compliance with HCQ therapy, toxicity and AEs will be recorded.

Patients with **unilobar disease** that **did undergo** a **second session of TACE** will not have any required study procedures at this time point.

6.10 Week 14:

Patients with **unilobar disease** that **did undergo** a **second session of TACE** will undergo a contrast enhanced MR or CT, IR clinical office visit and response assessment. At the clinical office visit - compliance with HCQ therapy, toxicity and AEs will be recorded.

Patients with **bilobar disease** and patients with **unilobar disease that did not undergo a second session of TACE** will not have any required study procedures at this time point.

6.11 Follow-Up Q3 Months:

Study follow-up of patients will occur at 3 months (+/- 1 week) and 6 months (+/- 1 week) after cessation of HCQ therapy (Week 12 or Week 14). The 3 month and 6 month follow-up visits will include contrast enhanced MRI or CT, laboratory assessments (CBC, PT/INR, CMP) and IR clinical office visits by an interventional radiologist. The follow-up study period will end at 6 months (+/- 1 week) after cessation of HCQ therapy (Week 12) to examine for late toxicity. Patients will continue to be followed beyond the end of follow-up study period per normal Interventional Radiology standard of care and *only* patient data regarding tumor progression and survival will be recorded during this time period to better assess LPFS and overall survival.

7 Statistical Plan

7.1 Study Objectives, Sample Size Determination and Power Calculation

Objectives
This trial is designed to be the initial prospective phase I-II investigation of the safety and effectiveness of combined HCQ and TACE for unresectable HCC.

Primary Objective (Phase I): To determine the dose limiting toxicities and maximum tolerated dose (MTD) of the oral administration of hydroxychloroquine (HCQ) in conjunction with transarterial chemoembolization (TACE) in treating unresectable hepatocellular carcinoma (HCC). A “3+3” design will be used.

Primary Objective (Phase II): To evaluate the complete response rate in a cohort of patients treated at the MTD. A Simon’s Optimal Two Stage design will be used.

The knowledge gained from this phase I-II clinical trial will establish the safety of combined therapy and allow for accurate estimate of the number of patients needed to adequately power larger phase II and III clinical trials.

Sample Size Determination and Power Calculation

In the reported literature, the rate of complete necrosis of HCC ranges from 29-43% even after repeated TACE(9,13,15-20). Georgiades, et al., studied the radiologic responses of 116 patients who underwent TACE(21). After a second TACE, the complete radiologic response rate increased from 14 to 38%. However, still over 25% of the patients did not respond at all to two TACE treatments, and 62% of patients did not have a complete response by imaging (see Imaging Assessment of Response under Section 3.3)(21).

Using a Simon’s optimal two-stage model, the efficacy of combined therapy at increasing complete imaging response rate will be tested. The null hypothesis that the complete response rate of TACE and HCQ will be similar to TACE alone (p_0 =40%) will be tested against a one-sided alternative, the complete

response rate of combined TACE and HCQ will be 60% (p_1). In the first stage, 16 patients will be accrued, of which 6 will be patients treated at the MTD in the phase I trial. If there are 7 or fewer complete responses in these 16 patients, the study will be stopped. The probability of stopping the trial after the first stage of the Simon's optimal design is 72%. Otherwise, 30 additional patients will be accrued for a total of 46 patients. The null hypothesis will be rejected if 23 or more responses are observed in 46 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the complete response rate of combined TACE and HCQ is 60%.

Thus, the maximum number of patients needed to complete the trial will be approximately 58. If all 3 dose levels are investigated in the Phase I trial, 18 patients will be required. Forty patients will be needed to complete the Phase II component, of which 6 will be patients treated at the MTD in the Phase I trial.

7.2 Statistical Methods

Phase I: Frequency of reported side effects and DLTs will be graded according to the Common Terminology Criteria of Adverse Events (CTCAE) version 4.0 and tabled by dose level. Additionally, the timing of these events relative to the first or second TACE will also be tabled by dose level.

Phase II: At the MTD, complete response rate to therapy and 95% confidence intervals will be calculated. Local progression free survival and overall survival curves will be estimated by the Kaplan-Meier method.

7.3 Subject Population(s) for Analysis and Duration of Study

Analysis of both primary and secondary end points will be performed on an intention to treat basis. A maximum of 58 patients will be required if all 3 dose levels are investigated in the Phase I trial. If 1-2 patients are enrolled per month, then we expect up to approximately 5 years will be needed to complete enrollment.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

Adverse Event
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 6 months following the last dose of hydroxychloroquine (i.e. approximately 8 months following initial TACE).

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if one or more of the following conditions is met:

- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management or treatment; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document (i.e. PennChart) to a paper AE form which will include event grade, start/stop dates, outcome. PI attribution of relation to study, PI attribution of expectedness and PI signature. Information completed on paper AE forms will then be entered into PennCTMS and the study's eCRF database (REDCap), All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period (up to 6 months after last dose of HCQ) must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.3.1 Investigator reporting: notifying the medical monitor

Any study-related unanticipated problem posing risk of harm to subjects or others, and any type of serious adverse event, must be reported to the medical monitor (per Section 8.6) within 5 working days of the event. The investigator will keep a copy of this SAE report on file at the study site.

Significant new information on ongoing serious adverse events should be provided promptly to the medical monitor as follow-up reports.

8.3.2 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

Reporting Process
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Other Reportable events:
For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
  - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
  - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.

  - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

8.3.3 Investigator reporting: Adverse Event Reporting to ACC Data and Safety Monitoring Committee (DSMC)

Common Toxicity Criteria: Toxicity will be evaluated with the NCI Common Toxicity Criteria (CTCAE) v. 4.0.

Serious Adverse Events (SAEs): SAE is defined as any of the following:

- Fatal or life-threatening (real risk of dying) event

- Requires or prolong hospitalization

- Causes persistent or significant disability/incapacity

- Results in a birth defect or congenital anomaly

- Causes cancer

- All hospitalizations or prolongation of existing hospitalization for medical events regardless of phase of study, expected or unexpected attributions are SAE's.

Serious, unexpected drug-related adverse events will be reported to the University of Pennsylvania IRB, and the University of Pennsylvania Cancer Center Data and Safety Monitoring Committee (DSMC) using the expedited reporting guidelines as is required by each board. Grade 3 or higher adverse events must be reported to the DSMC within 10 days of knowledge of the event. All unexpected deaths must be reported within 24 hours of knowledge of this event. All other deaths must be reported within 30 days of knowledge of this event. Adverse events that meet the DSMC reporting requirements will be entered into Velos with an e- mail alert (if applicable) to the DSMC.

8.3.4 Notifying the study sponsor

Investigators must report serious adverse events (SAE) attributed to TACE or HCQ to the study sponsor within the timelines described below.

• Relevant follow-up information such as resolution and duration of the SAE attributed to TACE or HCQ should be submitted to the study sponsor as soon as it becomes available.

- Serious AE reports that are related to the TACE or HCQ and AEs of Special Interest (regardless of causality) will be transmitted to the study sponsor within 10 working days from the date investigators are made aware of the AE.
- Serious AE reports that are unrelated to the TACE or HCQ will be transmitted to the study sponsor within thirty (30) working days from the date investigators are made aware of the AE.
- AEs of Special interest are defined as AEs involving hepatoxicity or renal toxicity occurring any time during the study period after initial TACE has been performed. These events are of special interest because they occur after therapies (i.e. HCQ and TACE) are first combined.
- All Non-serious Adverse Events originating from the study will be forwarded in an annual report to the study sponsor.

8.3.5 Sponsor reporting: Notifying FDA

This study is IND exempt and reporting to the FDA is voluntary using the FDA's website for voluntary reporting.

8.4 Unblinding Procedures

N/A

8.5 Stopping Rules

The study will be terminated after completed follow up of the last patient enrolled (ie 6 months after this patient completes HCQ therapy). Alternatively, the protocol may be terminated prematurely for safety/toxicity issues as outlined in section 3.4 or for failure to demonstrate efficacy in stage one of the Phase II clinical design.

8.6 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events to occur within 1 month of the event. Escalation of the dosage of HCQ in the phase I portion of the trial cannot proceed prior to review of patient records for DLT by the medical monitor.

The monitor's findings will be reported independently to the ACC and DSMC. If findings from the monitor's review of AEs are considered unacceptable due to major deficiencies, representatives from the Department of Compliance and Monitoring will meet with the PI to discuss the findings of the visit and review corrective actions as mandated by the DSMC. If the deficiencies involve subject safety or serious regulatory violations, the ACC Director, DSMC Chair, and DSMC Director will meet to discuss necessary actions concerning study status.

The PI is given five business days to respond to these finding. An evaluation of the deficiencies will be re-evaluated upon receiving the PI's response. At this time, if the DSMC Chair and the Director do not find the response satisfactory, the IRB and OHR will be alerted of the actions taken by the ACC. The DSMC Director will update the IRB and OHR of the corrective actions being taken and progress being made.

Medical monitoring by an independent clinician Dr. David Kaplan, MD, Department of Medicine, Division of Hepatology will include a regular assessment of the number and type of serious adverse events on a periodic basis. Dr. Kaplan is a board certified gastroenterologist with a clinical and research focus in hepatocellular carcinoma. Dr. Kaplan practices at the Philadelphia VA Medical center and therefore will not be biased by prior clinical contact or relationship with potential study subjects. Dr. Kaplan will be reached at dakaplan@mail.med.upenn.edu or via telephone at 610-316-8039.

8.6.1 Auditing and Inspection

This protocol will be audited by the ACC Department of Compliance and Monitoring in accordance with the NCI approved Institutional Data and Safety Monitoring Plan.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. eCRFs will be created in the Velos and REDCap systems to capture the data that the investigator wishes to collect for the purposes of research and for safety monitoring. Data will be entered into this system in a timely manner. Forms used in the source document should reflect the information needed for the completion of the eCRFs in Velos and REDCap.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last follow up visit with the last enrolled patient.

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

This study will be monitored according to the ACC DSMC monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents

and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

11 Ethical Considerations

This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment B for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12 Study Finances

12.1 Funding Source

Department of Radiology, Protocol Development Funding

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the applicable University conflict of interest policies.

12.3 Subject Stipends or Payments

None

13 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed

on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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University of Pennsylvania Research Subject Combined Informed Consent and Health Insurance Portability and Accountability Act (HIPAA) Authorization Form

Protocol Title:	Phase I-II Clinical Trial of the Safety and Preliminary Efficacy of Hydroxychloroquine Combined with Transarterial Chemoembolization for Unresectable Hepatocellular Carcinoma (UPCC 22213)
Principal Investigators:	Gregory Nadolski, MD Department of Radiology, Interventional Radiology Hospital of the University of Pennsylvania 1 Silverstein, 3400 Spruce Street, Philadelphia, PA 19104 Daytime Phone Number: 267.251.9926 Terence Gade, MD, PhD Department of Radiology, Interventional Radiology Hospital of the University of Pennsylvania 1 Silverstein, 3400 Spruce Street, Philadelphia, PA 19104
24-Hour Emergency Contact	Interventional Radiology Fellow On Call 215.662.2222 (ask to be connected to Interventional Radiology Fellow on Call)

Why am I being asked to volunteer?

You are being invited to participate in a research study, because you have been diagnosed with primary cancer of the liver known as hepatocellular carcinoma, or simply HCC. Your participation is voluntary which means you can choose whether or not you want to be part of the study. If you choose to participate, you may be assigned to receive an additional treatment, which is being studied. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of participating in the study, and what you will be asked to do if you choose to participate. The research team is going to talk to you about the study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, other doctors, or who ever helps you make medical decisions. You may find some of the medical language difficult to understand. Please ask the research team and/or the study doctor any questions you have regarding this form or the research study. If you decide to participate, you will be asked to sign this consent form.

What is the purpose of this research study?

Hepatocellular carcinoma, or HCC, is a life-threatening form of liver cancer. For patients with limited size and number of cancers, liver transplantation can be curable. Liver transplantation is the process of surgically replacing one person's (recipient) liver with another person's (donor) liver, which typically comes from an

individual who is recently deceased. In other patients, the size of and number of cancers in the liver is more then can be effectively treated by liver transplant. In this situation, other therapies may be prescribed to treat the cancer.

One such therapy, which is performed by Interventional Radiologists, is called transarterial chemoembolization, or simply TACE. In this procedure, chemotherapy (medicines toxic to the hepatocellular carcinoma) is given from inside the blood vessels supplying the tumor with oxygen and nutrients followed by embolization (intentional blockage) of these blood vessels. TACE is effective at completely killing the entire cancer in some but not all patients. Prior laboratory studies by the Department of Interventional Radiology at the University of Pennsylvania suggests the addition of a medication, which is already used to treat other diseases besides cancer, called hydroxychloroquine may assist TACE in treating liver cancer.

This study has two purposes. First is to determine the maximum dose of hydroxychloroquine, which can be added to TACE safely. Second is to examine the effect of adding hydroxychloroquine to TACE. The information gained by conducting this study will allow future investigation of comparing the combined therapy to TACE alone.

How many people will be in this research study?

A total of about 58 patients will be recruited at the Hospital of the University of Pennsylvania to participate in this study.

What am I being asked to do?

Patients who participate in the study will be asked to take a dose of hydroxychloroquine once or twice per day for approximately 4 weeks prior to TACE then continuing taken the medication for approximately 8 weeks after TACE. Additionally, patients who participate will be contacted by Interventional Radiology approximately 2 weeks after starting hydroxychloroquine and approximately 2 weeks after TACE to discuss side effects of the therapy. Patient will also be asked to have blood samples taken approximately 2 weeks after starting hydroxychloroquineto evaluate overall health as well as kidney and liver function. All other clinical visits, laboratory studies, and imaging before and after the TACE procedure will be the same as if one had not participated.

What are the possible risks?

Hydroxychloroquine, known by the trade name Plaquenil, is a colorless crystalline solid, which comes in tablets of 200mg doses for oral administration. Hydroxychloroquine is approved by the Food and Drug Administration (FDA) to prevent and treat the infectious disease malaria and treat chronic inflammatory conditions such as systemic lupus erythematosus and rheumatoid arthritis. The precise mechanism of action in treating these diseases is not known.

The use of hydroxychloroquine is not allowed in patients with vision problems attributed to prior use of hydroxychloroquine or with allergies to hydroxychloroquine. Additionally, the medical conditions psoriasis, porphyria, and glucose-6-phosphate dehydrogenase deficiency can be exacerbated by the use of hydroxychloroquine and therefore should be used with caution in patients with these conditions. Please inform the research team if any of these situations applies to you.

In general, the use of hydroxychloroquine is well tolerated with limited side effects and can be used daily for years in treating rheumatoid arthritis or lupus. However, adverse reactions can occur.

The risks, warnings and precautions of hydroxychloroquine therapy as detailed by the manufacturers of the drug are listed below.

1. Damage to the retina (part of the eye responsible for vision) sas been described in patients taken long term, high dose therapy. In its early form, it appears reversible on discontinuation of hydroxychloroquine. If allowed to develop, there may be a risk of progression even after treatment withdrawal.

2. Psychiatric disorders: Nervousness, emotional lability, psychosis, suicidal behavior.

3. Nervous system disorders: Dizziness, headache, convulsions have been reported with this class of drugs.

4. Skin and subcutaneous tissue disorders: Bullous eruptions including very rare cases of Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and exfoliative dermatitis have been reported.

In the current study we are most concerned about kidney and liver function following the combined therapy with TACE. Therefore, only patients with normal liver and kidney function are being asked to participate. To detect these side effects of combined therapy, participants will be seen by a doctor and have laboratory studies to examine kidney and liver function sooner then typically done after TACE. Additionally, participants will be provided with instructions on signs and symptoms of kidney or liver dysfunction, so if symptoms develop they may contact the research team for evaluation and appropriate treatment.

What are the possible benefits?

Society will benefit from the better understanding of the safety of combining hydroxychloroquine with TACE. Prior experiments suggest the addition of hydroxychloroquine to TACE will cause more damage the cancer and result in better treatment outcomes. However, this is yet to be proven and subjects may not directly benefit from the study.

What other choices do I have if I do not participate?

You do not have to participate in this study. If you choose not to participate in this study, you will receive the standard TACE treatment for your HCC, as described and documented separately in the "Consent for Transarterial Chemoembolization."

Will I have to pay for anything if I participate?

You will incur no additional charges for participating in the study. The cost of hydroxychloroquine (e.g. insurance co-pay) will be reimbursed to you by departmental/grant funds for this study.

Will I be paid for being in this study?

No, there will be no financial compensation for participation in this study.

What happens if I am injured from being in this study?

We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in this consent form.

How long will I be in this research study if I participate? Can I leave the study before it ends?

Patients who participate in this study will be followed for 6 months after stopping hydroxychloroquine. Your participation in this study is completely voluntary and you may withdraw at any time without prejudicing your present or future care. Should your physician find it necessary and/or in your best interest, he/she may withdraw you from the study.

What information about me may be collected, used, or shared with others?

Your name, age, medical record numbers, and results from examinations, tests, procedures, and imaging related to your treatment for HCC.

Why is my information being collected?

Your information will be used by the investigators to perform the research, to oversee the research, and to contact you if necessary. Your personal information will not be used in reporting the outcomes of this study.

Who may use and share information about me?

The investigators for the study and the study team at UPHS may use or share your information for this research study.

How long may the School of Medicine use or disclose my personal health information?

Your authorization for use of your personal health information for this specific study does not expire. Your information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study, unless you have given written authorization, the University of Pennsylvania's Institutional Review Board grants permission, or as permitted by law.

Can I change my mind about giving permission for use of my information?

Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to participate in this research study.

Who can see or use my information? How will my personal information be protected?

Every attempt will be made by the investigators to maintain all information collected in the study strictly confidential, except as may be required by a court order or by law. If necessary, authorized representatives at the University of Pennsylvania's Institutional Review Board (IRB), a committee charged with protecting the rights and welfare of research subjects, or the FDA (Food and Drug Administration) may be provided access to our research records. If any publication or presentation results from this research, study participants' data will be reported only in aggregate form without any individually identifiable information.

What if new information becomes available about this study?

You will be provided with a copy of this document for your records. We do not anticipate acquiring any new information that may affect your decision to participate in this research study. If we do, you will be informed.

Electronic Medical Records and Research Results

What is an Electronic Medical Record?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper

medical record. If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, results of research-related procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS.

Once placed in your EMR, these results are accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc).

Who can I call with questions, complaints, or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling (215) 898-2614.

Conclusion:

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, you have been given the opportunity to ask questions, your questions have been answered to your satisfaction, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study. Upon signing below, you will receive a copy of this consent form.

_____	_____	
Name of Subject (Please Print)	Signature of Subject	Date\

_____	_____	
Name of Person Obtaining Consent (Please Print)	Signature	Date