Informed Client Consent Form for COTC021 and COTC022

This clinical trial led by the National Cancer Institute (NCI) and sponsored by the Morris Animal Foundation seeks to evaluate in dogs with osteosarcoma the safety and effectiveness of Standard of Care therapy, with or without adjuvant rapamycin administration. Standard of Care is defined as definitive surgery, being amputation of the affected limb, followed by 4 doses of intravenous carboplatin chemotherapy given on a q21 day schedule. Carboplatin has been safely and effectively used to treat appendicular osteosarcoma in dogs for > 20 years, but the potential for unforeseen potentially life-threatening side effects from surgery, chemotherapy, and/or progressive cancer does exist. ALL dogs enrolled onto study will receive Standard of Care therapy; however, through a randomization process, some dogs entered into study will also receive additional therapy with oral rapamycin.

Rapamycin is a drug currently approved for immunosuppression during preparatory and maintenance regimens for organ and bone marrow transplant in human patients. Early work with rapamycin suggests that this agent might also have anti-cancer properties by inhibiting (reducing the effects of) an important pathway in cancer progression known as mTOR. Preclinical studies of rapamycin in mice, as well as recent data using analogous drugs in human patients (rapalogs), suggest that mTOR blockade might be effective in the treatment of several cancers.

Studies in mice have shown rapamycin to be safe when used to treat experimental cancers. In a recently completed study of rapamycin in dogs with cancer, a dose and schedule for rapamycin administration have been defined which appears to be safe and tolerable by most dogs. These 2 studies (COTC021 and COTC022) will evaluate if orally administered rapamycin following Standard of Care improves long-term disease control. Interactions between rapamycin and other drugs are unknown, thus it is necessary to disclose any medications (and supplements) your dog is currently taking to your attending study veterinarian. It is strongly encouraged to eliminate all unnecessary medications, thereby minimizing the likelihood for untoward side effects.

In order to better understand your dog’s participation in this study, the potential clinical adverse events that may be associated with either progression of the tumor and/or the study drug are listed below.

**Cancer Progression**: inappetance, pain, lameness/reluctance to walk or exercise, lethargy, respiratory impairment, gastrointestinal upset (vomiting, diarrhea, inappetance), evidence of metastatic spread of cancer cells to other parts of the body and subsequent organ failure.

**Drug toxicities (Rapamycin)**: fever, lethargy, low platelet counts (blood clotting cells), low white blood cell counts, anemia (low red blood cells), gastrointestinal upset (vomiting, diarrhea, inappetance), worsening kidney function, high blood cholesterol/lipid levels, low phosphorous levels, increased blood glucose (sugar) levels, elevated liver enzymes, rash, sepsis, fatality.
It is hopeful that minimal adverse events will be experienced by your pet. However, this is an experimental clinical trial so all potential adverse events associated with study cannot be completely predicted. Any sign of illness in your dog should be reported to your oncologist immediately and may require return to the Veterinary Teaching Hospital for evaluation.

Within this study, we ask that you consent to the surgical amputation of your dog’s affected limb. Your dog will return to the Veterinary Teaching Hospital every 3 weeks for 15 weeks for evaluation. On weeks 3, 6, 9 and 12 your dog will receive a dose of carboplatin. Precautions should be taken against contact with your dog’s urine or feces for 48 hours after carboplatin treatment. Blood work will be done on your dog prior to carboplatin administration. After 15 weeks of Standard of Care, based upon initial study randomization, your dog will either receive oral rapamycin on a 4 day on/3 day off schedule for 4 months or will not be treated with any additional medications and simply be monitored every 8 weeks. Costs associated with this study will be provided as part of your participation, including a $1000 hospital credit towards your dog’s limb amputation. According to your institution’s discretion, additional funds may be made available for adverse event management.

After completion of Standard of Care, and depending upon initial study randomization, you might be required to administer oral rapamycin (PO) at home for 4 months. The schedule for drug administration will be daily on Monday-Thursday (4 days on), with a drug holiday on Friday, Saturday and Sunday (no dosing, 3 days off). This will allow us to determine if oral rapamycin can be safely administered chronically and will require serial collections of blood on scheduled reevaluations to allow for measurements of rapamycin within your dog’s blood. Your dog will have a total of five 24-hour serial blood draws completed over the course of 4 months. At the end of the each study cycle (Day 25), your dog must return to the Veterinary Teaching Hospital for reassessment and further blood collections. If your dog has been randomized to receive oral rapamycin, these visits are required for inclusion in the study. If your dog is in the Standard of Care arm only, you will be required to return to the Veterinary Teaching Hospital every 8 weeks for evaluation.

Future studies in dogs with cancer, as well as humans with cancer, will be in part based on this information. The benefit to your dog associated with this treatment is not known and toxicity is possible. Prior to entry into this study, your dog must have a confirmed diagnosis of osteosarcoma and staging tests to ensure his/her general health and to evaluate how advanced the disease is prior to treatment. If your dog has been randomized to receive treatment with rapamycin, you will be responsible for administering oral rapamycin, in the morning, to your pet at home. This will require 4 hours of pre-dose and 1-hour of post dose fasting. Each dose of rapamycin must be administered within the same 1-hour window. You will also be responsible for recording these administrations in a provided log. This includes the date, time and amount of drug dosed. If your dog has been randomized to receive oral rapamycin, in the event any complications arise during the study period while rapamycin is being administered (4 months), their management will be covered by study funds up to $2000.00/per dog. This would include any unanticipated hospitalizations. These costs are only provided for care at the COTC institution.
Precautions should be taken against human ingestion or direct contact with rapamycin especially in immunosuppressed individuals. If you think you have increased risks of immune suppression, you should contact your physician before enrolling your dog on this trial. Women who are pregnant or potentially pregnant should not handle rapamycin.

**Please read the following and sign below:**

- [ ] I have been informed that my pet is only deemed on study once carboplatin treatment is initiated and all other screening has been completed following surgical amputation.

- [ ] I have been informed of the financial responsibilities in the event my dog does not start carboplatin.

- [ ] I have been informed of the possible benefits and risks associated with this treatment. I understand that side effects of rapamycin are not fully understood.

- [ ] I have been informed of the possible risks associated with surgical removal (amputation) of my dog’s affected limb.

- [ ] I understand the risks of general anesthesia needed for surgery for my pet (including death).

- [ ] I will administer the prescribed dose of rapamycin to my dog orally on a 4 days on and 3 days off schedule unless altered by my veterinary oncologist (COTC site PI) if my dog is assigned to this study arm.

- [ ] I will administer rapamycin in the morning within the same 1 hour window.

- [ ] I acknowledge that $1000.00 will be provided for my dog’s surgical limb amputation along with additional screening financial support once my dog begins carboplatin treatment.

- [ ] I will fast (no food, water is okay) my dog 4 hours before rapamycin administration and 1 hour post administration if my dog is assigned to this study arm.

- [ ] I will record the time, date and amount of rapamycin given to my dog in the provided collection log if my dog is assigned to receive rapamycin, and return with this written information to all of my scheduled recheck evaluations. I understand that failure to do this may result in loss of financial support and my dog’s subsequent withdrawal from this study.

- [ ] I have been informed of the study costs provided through participation in this study.

- [ ] I understand the need to return for all appropriate follow up care at the Veterinary Teaching Hospital as scheduled including:
  - Week 1 evaluation
  - Week 3 evaluation
  - Week 6 evaluation
  - Week 9 evaluation
- Week 12 evaluation
- Week 15 evaluation
- Every 4 weeks for 4 months (rapamycin arm), then every 8 weeks
- Every 8 weeks (SOC arm)

☐ I will contact my COTC institution immediately if my dog experiences any (even one episode) of vomiting, diarrhea, decreased appetite or lethargy.

☐ I agree to return to my COTC institution for evaluation if directed by my veterinary oncologist if my dog experiences any illness.

☐ I acknowledge that in the event of acute medical complications associated with rapamycin administration study funds will cover their management (up to $2000.00/per dog). This accounts for the study period only (4 months while rapamycin is being administered).

☐ I have been informed of the possible risks associated with rapamycin exposure to immunosuppressed people and pregnant woman or those who plan on becoming pregnant in the near future.

☐ I understand that I retain the right to remove my dog from this study at anytime, however if I do prior to the study’s conclusion then I forego further financial support.

☐ I understand that information; case materials, photos and patient information gathered in this study may be used for scientific presentations and publications.

☐ I have disclosed all medications my dog is receiving and I will not administer any new (not prescribed) medications during the course of this study (including vitamins, supplements, pain medications, novel NSAIDS, aspirin, etc.).

☐ I understand that in the unexpected event of my pet’s death while on study a post-mortem examination will be required.

☐ By signing below I agree to permit my dog ______________________ (insert name) to participate in this clinical study and understand the information provided herein. I understand that a copy of this document will be provided to me.

________________________  ________________________________  
Pet’s name    COTC ID Number

___________________  ___________________  
Signature of Owner   Attending Clinician

_________________________  ________________________________  
Date     Date