

VA NEW YORK HARBOR HEALTHCARE SYSTEM RESEARCH AND DEVELOPMENT

Projects involving humans as subjects of research require the review and approval of the Subcommittee for Human Studies, which is the VA equivalent of an Institutional Review Board (IRB). The research activity can only be initiated after the Research and Development (R&D) committee grants final approval.

The information requested is needed for the IRB determinations including evaluation of risk and potential benefits of this proposed research. Complete this questionnaire only if item A applies. Human Subject is defined as a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information (38 CFR 16.102(F)). For questions regarding this form please contact the IRB Manager at 212-686-7500 x 4455.

Veterans Administration		<h3 style="margin: 0;">HUMAN STUDIES QUESTIONNAIRE</h3>
NAME OF PRINCIPAL INVESTIGATOR AND DEGREES HELD: ,		E-MAIL ADDRESS & TELEPHONE NUMBER:
STUDY COORDINATOR/CONTACT PERSON: (Check box if you prefer that all Correspondence be sent to this person) <input checked="" type="checkbox"/>		E-MAIL ADDRESS & TELEPHONE NUMBER:
PROJECT NO.	DATE: 5/2007	OTHER CONTACT # /TEL/PAGER:
STUDY TITLE:		

A. Is this Activity Research Involving Human Subjects?

1. Check all that apply: Mark the box above if item A is No.

- The research involves obtaining information about **living** individuals.
- The research involves **intervention or interaction** with the individuals.
- The information obtained is individually **identifiable**¹.
- The information obtained is **private**².

2. Research activity includes:

- | | |
|---|---|
| <input checked="" type="checkbox"/> Data repository | <input type="checkbox"/> Event monitoring |
| <input type="checkbox"/> Instruction/Counseling | <input type="checkbox"/> Interview/Survey |
| <input type="checkbox"/> Retrospective Chart Review | <input checked="" type="checkbox"/> Tissue Repository |
| <input type="checkbox"/> Use of Focus Groups | <input type="checkbox"/> Video or Audio Taping |
| <input type="checkbox"/> Tele-health | <input type="checkbox"/> Other: Specify _____ |

¹ The identity of the subject is or may readily be ascertained by the investigator or associated with the information

² About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

4. If any deception (withholding of complete information) is required for the validity of this activity, explain why this is necessary and attach a debriefing statement.

No deception is required

5. **Tissue Repository:**³ Check all that apply:

- a) All human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations are maintained at **VA approved** tissue banks.
- b) The human biologic specimens obtained could be part of, or lead to the development of a commercially valuable product.
- c) The human biological specimens obtained are to be retained after the end of the study*
- d) The study involves genetic testing.*
- e) If using a **non-VA tissue bank**, a VA Central Office documentation of approval for tissue banking or applicable waiver is attached.

* c) and d) apply only to those patients signing consent for correlative studies

D. Consideration of Risks:

Mark this box if item D is NA.

1. **Describe** the risks that may result from the research based on the following classifications. Indicate if none by checking the box.
- A. Physical Harms (e.g. minor pain, discomfort, injury from invasive procedures, or harm from drug side effects). None
See attached pages 15-19
- B. Psychological Harms (e.g. depression, confusion, hallucination, stress, guilt, embarrassment, invasion of privacy). None
Patients name and other personal information will not be used so there is no psychological harm. Patients personal information may be given out if required by law.
- C. Social and Economic Harms (e.g. loss of employment, criminal prosecution, embarrassment within the subject's business or social group, stigma, added costs, breach of confidentiality). None

2. **List** steps taken to minimize risk(s) mentioned above:

The study is being conducted by the Eastern Cooperative Oncology Group (ECOG). ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS) to protect patient's privacy. Specimens will be identified by number only and reports will not be put into patient's records.

³ Refer to VHA Directive 2000-043, Banking of Human Research Subjects' Specimens.

Patients will be monitored frequently to assess any adverse effects of treatment.

- 3. What is the impact of study design on risk (sources and mitigator of risk)?
There is minimal risk of loss of confidentiality though every precaution will be taken to avoid this. No identifying information will be revealed. There may also be uncommon or previously unrecognized risks that might unforeseeably occur.
- 4. What are the provisions for safety monitoring?⁴
A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study.
- 5. In the absence of a formal DSMB or DMC, describe the provisions for monitoring the data and ensuring the safety of participants:
There is a DSMB.

E. Vulnerable Subjects:



Mark this box if item E is NA.

- 1. Indicate *vulnerable populations* that may become potential subjects in this research. These are populations who may be less capable of understanding the nature and risks of the research *or* who may be more subject to coercion.

(Check all that applies)

- | | |
|--|--|
| <input type="checkbox"/> VA employees | <input type="checkbox"/> Economically disadvantaged persons |
| <input type="checkbox"/> VA volunteer | <input type="checkbox"/> Educationally disadvantaged persons |
| <input type="checkbox"/> Pregnant women | <input type="checkbox"/> Terminally ill |
| <input type="checkbox"/> Mentally disabled | <input type="checkbox"/> Other: Specify _____ |

- 2. Please provide reasons for including vulnerable subjects:

- 3. List additional safeguards that were included to protect the rights and welfare of vulnerable subjects. List steps taken to avoid causing potential subjects to be or feel coerced into participating in the research.⁵

- 4. Check the statements below that apply to this research.

- No additional safeguards are needed.
- No vulnerable populations will be included in this research.
- All subjects are presumed to be legally competent.

⁴ All clinical trials require safety monitoring. Examples: Data Monitoring Committee/DMC, for FDA regulated studies or Data and Safety Monitoring Boards/DSMB.

⁵ If the investigator believes that no additional safeguards are needed to protect vulnerable subjects in this study, provide justification here.

F. Subject Selection:

Mark this box if item F is NA.

1. Indicate type of subject included in this research:

Specify ____ Age range: From 18 y.o. to ____ y.o.

(Check all that applies)

- Patients
- Healthy volunteers
- Non-veteran population
- Physicians/Healthcare Provider
- VA Employees
- Other: Specify ____

2. Number of subjects to be studied:

Total for the entire study, including all sites 2100 (for multi-center studies only)

Total for the local site for duration of study 5-10

Total during the **first** year of study: 1-3 (only from local site)

Indicate total # of subjects from each of the following facilities:

- Brooklyn Campus 5-10
- New York Campus _____
- St. Albans Campus _____
- BK Vet Center at Chapel St. _____
- NYU Hospital _____

3. Justification for number of subjects proposed. Explain statistical procedures used to arrive at the number of subjects proposed to test hypothesis. Indicate the page number(s) in the protocol that detail(s) the power analysis.

Pages 57-61 – Statistical Considerations

4. Sources of subjects: Describe clinic, in-patient or out-patient, or hospital service area where investigator intends to target recruitment.
Subjects will be recruited from the VA patient population who meet the eligibility criteria.

5. Justify **investigator access** to the population that would allow recruitment of the required number of subjects:
Patients with cancer diagnosis are seen by an oncologist in the oncology clinic on a regular basis as part of their standard care.

6. Criteria for subject selection:
See Page 15-20 – Selection of Patients

7. Criteria for subject exclusion:
See Page 15-20 – Selection of Patients

8. Check box if applicable and provide justification:

a) Groups of population *who might potentially benefit* from this research are **excluded** from participating?

b) Please provide scientific and ethical justification for any **exclusion of specific gender, age, and racial or ethnic** groups:

G. Methods of recruitment:

Mark this box if item G is NA.

1. What methods are used **to obtain information** about individuals who may be recruited to participate in the research study?

The study coordinator will discuss the eligibility criteria with the oncology fellows, nurse practitioners and physicians/surgeons that treat cancer patients.

Does it involve the use of personally identifiable records such as protected health information (PHI)? Yes No

2. Is there **authorization to use PHI**? NA Yes No

If the answer is YES in # 2 above and NO in #3, please complete a request for Waiver of Authorization to Access and Use PHI for Research (section O.3).

3. Describe all recruitment methods employed. Attach copy of advertisements and other recruitment materials.

Education materials about clinical trials will be made available to oncology patients. VA providers seeing these patients will be given information on available studies.

4. Describe procedures for participant enrollment and indicate who will approach potential subjects to solicit their participation.

The primary physician/surgeon who is treating the patient for cancer will initially approach patient. The principal investigator and/or study coordinator will speak with interested patients about the study and obtain their consent before screening.

5. Describe provisions to protect the privacy of participants.

Identifiable health information is protected as per the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Additionally, privacy of the patients will be protected as per all other applicable VA laws and statutes listed in the VHA Handbook 1605.1.

ECOG has a Certificate of Confidentiality obtained from the Dept. of Health and Human Services.

6. Justify the need to recruit subjects outside the VA population, if any.

None

H. Confidentiality:

Mark this box if item H is NA.

- Data⁶ **obtained** can be directly linked back to the subjects.
- Data **stored** can be directly linked back to the subjects.

1. Complete and attach a completed "Supplement to research protocols involving the use of Individually-identifiable Health Information (IIHI)" if any of the items above are checked.
2. List those individuals (co-investigators, fellows, research nurses, research coordinator), outside group (sponsor), agency (FDA), institution (NYU), organization who will require access to medical records and attach a completed Research Staff Credentialing Form. Note VA researchers may be provided VHA III as needed in the performance of his/her official VA duties under 5 USC 552a(b)(1).

Eastern Cooperative Oncology Group (ECOG)
 National Cancer Institute (NCI)
 Cancer Trials Support Unit (CTSU)
 North Central Cancer Treatment Group (NCCTG)
 National Surgical Adjuvant Breast and Bowel Project (NSABP)
 Food and Drug Administration (FDA), Office for Human Research Protection (OHRP)
 Government Accounting Office (GAO)
 Other regulatory agencies and/or their designated representatives
 Drug manufacturers: Genentech, Inc. & Sanofi-Aventis
 NCI Central Institutional Review Board (CIRB)
 Central laboratories and reviewers, tissue banks
 List of names of investigators and coordinators involved in the study.

3. How long does the Sponsor of this research project require that records be maintained in the R&D Service after the study is completed?
Records are to be retained two years after FDA approves or disapproves the marketing application. Two years after the FDA is notified by the sponsor of the discontinuation of trial and a marketing application will not be submitted.

I. Adequacy of Resources to Protect Participants: Mark this box if item I is NA.

Describe resources necessary for the conduct of this research:

1. **Investigator effort** (Indicate that investigator (including co-investigators) has sufficient time to conduct and complete the research). Complete table below.

List each investigator who is participating in this research	Total # of work hours per week	% time effort for this study	Total # of Active research being conducted	Adequate Check box if Yes
First name. last, MD	45-50	3-6%	9	<input checked="" type="checkbox"/>
First name. last., RN	45-50	3-6%	9	<input checked="" type="checkbox"/>
	10	1-2%	9	<input checked="" type="checkbox"/>
* First name. last., MD	45-50	< 5%	9	<input type="checkbox"/>
* First name. last., MD	45-50	< 5%	9	<input type="checkbox"/>
* First name. last, MD	45-50	< 5%	9	<input type="checkbox"/>

⁶ Includes records, samples, specimens, surveys and databases.

*Co-investigators are listed for the purpose of evaluating and treating study patients when principal investigator is not available.

- 2. **Staffing and Personnel** (Describe availability of qualified staff including number, expertise, and experience needed. Indicate any plans for hiring new employees or none where applicable.) Attach Research Staff Credentialing Form.
Research Coordinator: First name. last., RN
Research Assistant: First name. last., RN

- 3. **Medical or Psychological services** (Describe availability of psychological, social or medical services, including counseling or social support services that may be required as a consequence of research participation. If none are available, what provisions are made when necessary)
Patients that require psychological, social or medical services will be given the appropriate consults/referrals by VA providers.

- 4. **Facilities** (Describe psychological, social or medical monitoring, ancillary care, equipment needed to protect participants. Indicate none where applicable.)
NONE

- 5. **Other resources needed for the conduct of this research** (List other services that need to be involved and describe availability, e.g. participant communication needs language translation services.)
Oncology pharmacy, social work, laboratory and physicians will be available to qualified VA patients.

J. Consideration of Benefits:

Mark this box if item J is NA.

- 1. What is the importance of the knowledge that may be reasonably expected to result from the research?
This research may show what combination of drugs will improve survival/recurrence of rectal cancer patients that received pre-op chemo-radiation when the cancer has been surgically removed.

- 2. Describe the anticipated benefits of the research activity (to the individual):
There may or may not be any direct benefits to the patient. The patient can benefit if there is not recurrence of disease, longer survival and better quality of life.

- 3. Explain how the benefits outweigh the risks:
Patients are given same medications post-op (standard of care) without bevacizumab. Adding bevacizumab increases some risks, however, the benefit may include longer disease-free survival.
If the patient receives treatment and does not show any benefit, the physician will discuss alternative treatments.

4. Will subject be offered compensation for participating in the research?
 Yes No
5. If Yes, what is the nature of the compensation? (Indicate here amounts and schedule of payments as well as conditions for subject receiving compensation for participating in the research and the section on the consent form where this is stated, e.g. page and paragraph number)

6. If No, indicate the page where there is a statement in the consent form informing the subject:
Page 14

K. Investigational drugs/devices:

Mark this box if item K is NA.

1. List of investigational drugs⁷ used on human subjects and attach a completed VA form 10-9012 for each:
 Oxaliplatin, 5-Fluorouracil, Leucovorin, Bevacizumab
2. List of investigational devices⁸ used on human subjects and determine if the device has significant risk (SR) or non-significant risk (NSR): Attach a completed Supplement to Protocol Involving the Use of Investigational Device Form.
- | <u>Device</u> | <u>SR</u> | <u>NSR</u> |
|---------------|--------------------------|--------------------------|
| _____ | <input type="checkbox"/> | <input type="checkbox"/> |
- This is a FDA-regulated Study: Yes No

3. Provide IND/IDE No. and attach FDA documentation. If none is required, provide justification.
Bevacizumab (IND 7921) – The bevacizumab supplied for this protocol by PMB(NCI) is not the commercially available bevacizumab.
Oxaliplatin (NSC 266046) supplied by NCI.
5-FU and Leucovorin are commercially available

4. Name and address of IND/IDE Sponsor:
XXXXXXXXXXXXXXXXXXXX Branch
XXXXXXXXXXXXXXXXXXXX
XXXXXXXXXXXXXXXXXXXX

5. If the investigational drug is subject to the Controlled Substance Act, describe provisions for adequate storage and control of drug.

⁷ Any drug or biologic product used in a clinical investigation. It may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

⁸ A device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device. It may be an approved device that is being studied for an unapproved use or efficacy.

NA

6. Check all that apply:

- a) Investigator is aware of the specific reporting requirement imposed upon the sponsor by the FDA concerning drugs for which an approved IND was obtained.
- b) If the investigator assumes the sponsor function, the investigator is aware of the applicable FDA regulations and ensures that research is conducted according to the signed agreement and the approved protocol.
- c) Investigator has made appropriate arrangements with the Pharmacy Service. Attach Pharmacy approval form signed by the Chief of Pharmacy Service.

L. Research Setting:

Mark this box if item L is NA.

1. Describe the setting in which research procedures will be carried out.
(Include information on laboratory, clinic or in-patient service, and subject condition.)
Procedures and visits will take place in the oncology clinic on 8E.
Medication will be dispensed by the Oncology Pharmacy on 8E
and infused in Chemotherapy area on 8E.
2. Is this a multi-center study? Yes No
This investigator is the LEAD INVESTIGATOR Yes No
This facility is the LEAD SITE Yes No
3. If Yes to any item in #2, describe provisions for the management of information obtained from the different sites that might be relevant to the protection of participants.
Information is disseminated through e-mails. We will ensure that information is disseminated only if PKI is installed. Alternatively the sensitive information will be disseminated by tracked shipping such as FEDEX to ensure that it is signed and received by only the person it was sent to.
4. List below all other participating sites (Name of Institution, PI, and address). If documented in the protocol you may refer to the page number here listed on the Title Page

Institution	Principal Investigator	Address and Contact Information	Check for presence at each site:	
			IRB	Permission granted for research to be conducted at this site
1.				
2.				
3.				
4.				

5. Will VA patients be evaluated as in-patients or outpatients at any institution other than the VA NYHHS for this study? Yes No NA
 If so, provide details:

6. Will any procedures in this study take place at the NYU SOM located at the VA Manhattan Campus? Yes No NA

M. Assessment of risk and anticipated benefit of the research:

Mark this box if item M is NA.

1. Expected mortality in the natural course of the illness in the subjects being studied in the protocol (if applicable):
The expected 5 year survival for Stage II patients is 52% and for Stage III patients is 37%.
2. Follow up planned as part of the procedures:
Actual treatment period is approximately 6 months. Follow-up is 10 years from enrollment.
3. Plan for handling possible adverse effects and unanticipated events:
Pages 25-38
4. Your assessment of risk:

Check	Risk Level	Description
<input type="checkbox"/> A	No Risk	
<input type="checkbox"/> B	Minimal Risk	The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests
<input checked="" type="checkbox"/> C	Greater than minimal risk	Has potential direct benefit
<input type="checkbox"/> D	Greater than minimal risk	Has no direct benefit but has potential to yield generalizable knowledge about the subject's disorder or condition.

Mark this box below if item N is NA.

N. Informed Consent Plan:

Unless waived by the IRB, informed consent is necessary for all research involving human subjects and must be documented in some manner. The investigator may determine which method would best serve the interest of the subject population, but the IRB reserves the right to require alternative or more stringent means of securing consent.

For DHHS-supported multi-center clinical trials attach copies of DHHS-approved informed consent template and the complete DHHS-approved protocol if one exists.

Which of the following apply to this research:

- A. Informed consent will be obtained from all subjects and documented with a signed written consent form. Attach VA form 10-1086. Please refer to the Informed

Consent Checklist for “required basic elements” of an informed consent form and “required additional elements” when appropriate in accordance with VHA Handbook 1200.5.

1. Describe how the required information is being presented to subjects (consent form, orally, information sheet, etc.). Attach a copy of what is being presented to subjects.

Consent form (10-1086) is presented orally and a written copy is given to the patient.

2. Describe the circumstances under which consent will be obtained, including where the process will take place

Principal investigator will explain and review consent form with patient before he is registered and after eligibility is determined in the Oncology Research Clinic.

3. How will it be determined that the subjects or the subjects’ authorized representatives understand the information presented?

The consent will be explained and subject will be given the opportunity to ask questions.

4. If English is not the subjects’ (or authorized representative) native language, how will translation be provided?

Translation will be provided by clinic personnel, if they cannot translate, we will use the VA telephone translation service cyracom.com.

5. Does the sponsor require a witness to the consent process in addition to witnessing the subject’s signature? If so, could one person serve in both capacities? Yes No

6. Will any subjects be cognitively impaired so that they may not have the capacity to give consent? Yes No

If yes, provide a plan for evaluation and documentation of consent capacity.

7. List here all persons delegated for obtaining consent. The Investigator must ensure the individual(s) are adequately informed about the protocol, and either have previous experience in or trained in obtaining informed consent.

	Person Obtaining Informed Consent	Indications of experience in obtaining informed consent	Signature	Date of Training
1	xxxxxxxxxxxxx MD	Principal Investigator		12/2006
2	xxxxxxxxxxxxx, RN	Research Coordinator		12/2006
3	xxxxxxxxxxxxx RN	Research Nurse		12/2006
4				
5				

6			
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B. Informed consent will be obtained from subjects, but no signed consent form will be used. This includes oral consent and implied consent (e.g. completing a survey). A waiver of documentation of consent must be requested from the IRB. If this is checked, skip the questions below and proceed to section O. For oral presentation attach here a copy of the written summary of what is to be said to the subject.

8. How will the subjects' informed consent be documented? Please indicate all the ways in which consent is documented:

Informed consent is signed and then documented in progress notes. A study enrollment template is filled out in the computer. Consents are sent to research department for scanning into electronic records. A copy will be given to the subject.

9. If non-English speaking subjects will be included, describe how translation of consent forms will be provided. All translated consent forms must be submitted to the IRB along with back translations.

The VA has phone and document translational service CYRACOM available for situations in which the prospective subject does not understand English language. Information is available through their web site <http://www.cyacom.com>

10. If subjects cannot read the consent form, due to literacy or language problems, how will consent be documented? See the instructions on the "short form" for guidance, VHA Handbook 1200.5 Appendix C and attach copy of the short form of consent document.

The consent form may be read to the subject or the subject's legally-authorized representative. Alternatively, we will use "short form" procedure as per 1200.5 handbook. The investigator will ensure that the subject (or representative) is given adequate opportunity to read the form and ask questions before signing it.

O. Complete and attach Supplement IRB Request for Waiver:

P. Principal Investigator Assurance:

1. I certify that the information provided, regarding the proposed research project is complete and accurate.
2. The research project will be conducted in accordance with institution policies and state and federal regulations.
3. All individuals assisting with the research have completed mandatory research training and are adequately informed about the protocol and their research-related duties and functions. I will ensure ethical conduct in the recruitment of human subjects and provide appropriate supervision.
4. Any proposed modification(s) to this research project, which may affect the risk to research subject or the patient's participation in the research will be immediately

reported to the VA NYHHS IRB Manager Office and the appropriate IRB and R&D Committee approvals will be sought prior to implementation.

PI Signature over Printed Name – Andrea N. Leaf, MD

Date Signed

IRB USE ONLY			Check Attachments received
<ul style="list-style-type: none"> ____ 1. <u>Grant Application</u> ____ 2. <u>Budget Page</u> ____ 3. <u>Tissue Bank approval /Waiver</u> ____ 4. <u>Advertisement and/or other recruitment materials</u> ____ 5. <u>Supplement for protocols using IHI</u> ____ 6. <u>Research Staff Credentialing Form</u> ____ 7. <u>VAF 10-9012</u> ____ 8. <u>Supplement for protocols using Investigational Device Form</u> ____ 9. <u>IND/IDE documentation</u> ____ 10. <u>Pharmacy approval</u> ____ 11. <u>DHHS-approved sample consent form</u> ____ 12. <u>DHHS-approved protocol</u> ____ 13. <u>VAF 10-1086</u> ____ 14. <u>Written summary of oral consent</u> ____ 15. <u>Supplement Request for IRB Waivers</u> 			
Date Received	IRB Meeting Date	Received By:	
			Signature of IRB Manager

Section D – Consideration of Risks:

Oxaliplatin, Leucovorin and 5-Fluorouracil

Likely

- Lowered white blood cells (may make you more likely to get infections)
- Lowered platelets (may make you more likely to bruise or bleed)
- Lowered red blood cells (may make you feel tired or weak)
- Fatigue (feeling tired all the time)
- Nausea (feeling sick to your stomach) and vomiting (throwing up)
- Diarrhea (frequent bowel movements with loose, watery stools)
- Numbness or tingling in your hands and/or feet (may feel stronger if exposed to cold)
- Feeling of tightness or fullness in the throat, making it feel like it is difficult to breathe or swallow)
- Soreness or redness where the drug is injected.
- Temporary hair loss
- Pain and the risk of infection where the drugs are injected
- Mouth sores or sore throat, which may make swallowing difficult
- Sunlight sensitivity
- Nail changes, loss
- Constipation (having fewer and harder bowel movements)
- Dehydration (decreased fluid in the body because of diarrhea or inability to drink fluids)
- Appetite loss
- Skin darkening, hives, itchy dry skin
- Shortness of breath
- Rash
- Fever
- Pain that could be in the belly, chest, bones, muscles or joints, along the spine and legs.
- Trouble sleeping
- Hearing loss
- Damage to the liver and kidneys
- Headache

Less Likely:

- Flu-like symptoms such as fevers, chills and muscle aches
- Watery eyes, runny nose
- High blood pressure, change in your heart rate (rapid heart beat)
- Swelling in the arms and legs
- Changes in taste, dry mouth
- Upset stomach, heartburn, gas
- Temporary blockage or paralysis of the bowels, resulting in abdominal pain and cramping, which may prevent normal bowel movements.

- Changes in the salts in the bloodstream, such as phosphorous, calcium, magnesium, sodium and/or potassium
- Swelling of the lungs
- Blistering on the palms of the hands and soles of the feet
- Hot flashes or flushing, (redness of face and neck)
- Cough, hiccups
- Fluid collecting in the abdomen
- Vision changes (blurring) usually brief
- Allergic reaction (symptoms vary but difficulty breathing, upset stomach, nausea, vomiting, diarrhea, skin rash and/or itching are common)
- Temporary blindness

Rare

- Confusion, memory loss, depression, anxiety or other mental changes
- Lack of balance (feeling as if you might fall down), dizziness
- Chest pain or heart attack
- Blood clot in the brain
- Seizure or passing out
- Blood clot in the lungs, legs
- Abnormal liver function
- Infection
- Muscle spasms or loss of normal muscle function
- Changes in nerve function, lack of coordination
- Slurred speech
- Hoarseness, loss or alteration in voice, laryngitis
- Abnormal eye muscle movement, fluid in or around the eye
- Pain while peeing, inability to pee or frequent need to pee, blood in the urine

Rare, but Serious

- Hemolytic Uremic Syndrome – a breakdown of red blood cells, low platelets and kidney failure together.
- Pulmonary Fibrosis - lung problems such as cough, shortness of breath, trouble breathing, build-up of scar tissue in lungs; thickening and stiffening of lung tissue. Can be life threatening - tell your doctor right away if you experience any of these problems.
- Tumor Lysis Syndrome – complication can occur when cancer cells are destroyed by treatment. Cell destruction may damage kidneys and change calcium levels, which may lead to kidney dialysis, usually on a short-term basis.
- Disruption of blood proteins where bleeding and blood clots can occur at the same time, which could be life-threatening.
- Bleeding from any source including stomach (throwing up blood or black stools), lung (coughing up blood), bowels (blood in the stool) or brain; which could be life-threatening.
- Veno-occlusive disease – liver injury which leads to an enlarged liver, enlarged spleen, swelling in the abdomen and jaundice (yellowing of the skin); could be life-threatening.

- Although very rare, it is possible that treatment-related side effects could result in death.
- Visual changes (including temporary blindness, usually lasting less than 1 minute)

Bevacizumab

Likely:

- High blood pressure (including dangerously high blood pressure called hypertensive crisis)
- Shortness of breath
- Abnormal levels of protein in the urine (which may indicate kidney damage)
- Mild to moderate bleeding in the gastrointestinal tract
- Nose bleeds
- Sores in mouth and/or throat
- Changes in taste
- Skin changes (including itching, rash, discoloration, ulcers or peeling)

Less Likely:

- Clots in the arteries, including stroke or heart attack. When several studies were looked at together, problems due to clots in arteries were increased about two-fold (up to 4-5%) in patients receiving chemotherapy plus bevacizumab compared to chemotherapy alone (about 2%). Patients who were elderly and had a past history of clots in the arteries appeared to be at greater risk for these problems. Problems due to blood clots in the arteries were seen in about 2.9% of patients 65 or older receiving chemotherapy alone, and about 8.5% of patients 65 or older receiving bevacizumab with chemotherapy. Patients who were both 65 or older and reported a history of past problems with blood clots in their arteries appeared to be at even higher risk, although further study is required before an estimate of the risk can be provided. These conditions can be life threatening or fatal.
- Lowered white blood cell count (may make you more likely to get infections)
- Lowered platelet count that might interfere with clotting (may make you more likely to bruise or bleed)
- Lowered sodium and/or potassium levels that might make you feel weak or dizzy
- Changes in blood tests that indicate possible damage to the kidney
- Gastrointestinal upset (which may include gas, constipation, diarrhea, nausea, vomiting, loss of appetite, heartburn, or dry mouth)
- Cough
- Watery eyes
- Voice changes (hoarseness)
- Headache
- Pain
- Weight loss
- Confusion
- Poor coordination and balance

- Frequent urination (peeing)
- Tiredness/weakness
- Flu-like symptoms, such as fever, chills, stiffness and muscle aches

Rare but Serious

- Coughing up blood
- Worsening of any fluid within the tissues of the lung/lung problems
- Delay in wound healing or breakdown of a wound that had healed
- Heart problems (including irregular heartbeats, changes in blood pressure, fluid collections surrounding the heart, chest pain and possibly heart attack or heart failure)
- Bleeding in various parts of the body including the brain (stroke), the lungs (especially in lung cancer patients), the stomach, and the colon. This bleeding can lead to disability or death.
- Blood clots in the legs, lungs, or abdomen
- Serious stomach and/or bowel problems (such as the breakdown of tissue at the site where bowel is re-attached after removal of a tumor, formation of a hole in the stomach or bowel wall) which can lead to serious infection and require surgery to repair
- Bowel perforation - an opening occurs in the bowel wall, allowing bowel contents to spill into the abdomen
- Breakdown in the surgical connection between two pieces of bowel (bowel anastomotic dehiscence). These events can be life-threatening.
- Blockage of the intestines and breakdown of the tissue in the intestines
- Reversible changes in liver function tests that may indicate liver damage
- Damage to the kidney
- Allergic reaction
- Infection
- Death
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome: RPLS is a medical condition related to leakiness of blood vessels in the brain and can cause confusion, blindness or vision changes, seizure and other symptoms, as well as changes in brain scans. This condition is usually reversible, but in rare cases, it is potentially life-threatening and may have a long-term effect on brain function.

Reproductive risks: Patients in arm B will receive drugs that may affect the way a woman's ovaries work and her ability to get pregnant. The drugs in this study can affect an unborn baby. Therefore, women should not become pregnant and men should not father a baby while on this study.

(Men and women in Treatment Arm B should continue to take precautions for at least 3 months after their last dose of bevacizumab). Both male and female patients should ask about counseling and more information about preventing pregnancy. Female patients who think they might be pregnant, even though they practiced birth control, must notify the study doctor immediately. A pregnancy test may be performed. Male patients should also inform the study doctor immediately if their sexual partner(s) become

pregnant while the patient is receiving treatment. Women should not breastfeed a baby while on this study, and, if they are in Treatment Arm B, for at least 3 months after their last dose of bevacizumab.

Doctors do not know for sure how bevacizumab may affect unborn children or children nursed by mothers who received bevacizumab. We do not know how long after stopping bevacizumab that you safely can become pregnant, father a child or nurse a child. A period of at least 3 months is recommended, although we do not know if this is actually best. It is best to discuss your concerns with your doctor.

Risks/Side Effects of Intravenous Injection: Escape of the chemotherapy drug from the vein at the site of the injection may cause inflammation in this area.

Risks/Side Effects of Blood Testing and X-rays: Blood testing may cause some discomfort such as pain, bruising or soreness at the site of the needle puncture. There is minimal exposure to radiation, CAT scan or bone scan and any potential health risk is considered small.

Risks/Side Effects Insertion of a Central Catheter (Port): Risks from central venous catheters (used to give the chemotherapy) may happen. Intravenous catheters must be placed surgically. Therefore, surgical complications could occur and include: discomfort, infection, bleeding, breakage or leakage of the catheter, disconnection of the catheter with bleeding or air entering circulation, clotting of the catheter or vein, or malfunction of the pump. All care will be taken to lessen these side effects, but they are unpredictable in both nature and severity.



SUPPLEMENT: REQUEST FOR IRB WAIVERS

1. Request for waiver of **documentation of consent**.

a. Please select one of the following:

1. The research involves no more than minimal risk; and involves only procedures that do not require written consent outside of research. Please explain:

2. The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether or not they want documentation linking them to the research and their wishes will govern.

b. Please explain how, in the absence of signed written consent forms, consent will be documented, e.g. tape recordings, videos, chart notes, etc.

2. Request for **waiver of informed consent**.

a. In order to waive the requirement for informed consent, **ALL** of the following criteria must be met:

1. The research involves no more than minimal risk. Please explain:

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects. Please explain:

3. The research could not be carried out without the waiver or alteration. Please explain:

4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation. Please explain:

3. Request for **waiver of authorization to access and/or use PHI for research**.

1. The proposed study poses minimal risk to the privacy of the subjects because:

a. The identifiable information will be protected from improper use or disclosure (*detail how this will be accomplished including limitations of physical or electronic access to the information and other protections*)

- b. The identifiers will be destroyed at the earliest opportunity consistent with the research (*discuss the timeframe or the reasons the identifiers must be retained, including health or research justifications or any legal requirement to retain them*)

- c. The identifiable information will not be reused or disclosed to any other person or entity outside the VHA other than those listed below, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

2. Discuss reasons why it would not be possible to obtain authorization from individual subjects

3. Discuss reasons why it would not be possible to conduct the research without the identifiable information being requested

**SUPPLEMENT TO PROTOCOL INVOLVING THE USE OF
INVESTIGATIONAL DEVICE:**

PRINCIPAL INVESTIGATOR		MIRB ID:	
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DEVICE DESCRIPTION

1. Name of device:

2. Description of device:

3. Manufacturer of device:

4. Source of device:

5. Therapeutic classification/expected therapeutic effects of device:

6. List all designations of device:

7. Regulatory classification of the device being under study (submit investigators brochure/device information)
 - a. Is this device to be evaluated an investigational new device? Yes No
 - i. If yes, what is the IDE number?

 - b. Is this device being used under FDA pre-market notification (510K) status?
Yes No

 - c. Is this device being used for an FDA approved indication?
Yes No

 - d. Is an FDA comparator device being used? Yes No
 - i. If yes, what is the comparator device?

CONTROL OF THE DEVICE (Receipt, storage, security, dispensing/use and return)

If your research involves the use of an investigational medical device, describe your plans for receipt, storage, security, dispensing, and use of the investigational device. In particular, describe how the device will be controlled so that only authorized personnel will be able to use or dispense the device and so that the device will be used only in subjects who have consented to be in the research. Please use the Investigational Device Control Inventory Sheet to document the receipt, use, and/or dispensing of the device and the disposition of remaining devices at the conclusion of the investigation. Reference: HRPP SOP under “10.5.1.1 Responsibilities of Investigator”.

1. What are the manufacturer/supplier requirements for storage?

2. Where will the device be stored?

3. How will the device be stored?

4. How will the device be secured?

5. Who will have access to the device?

6. Who will be responsible/accountable for the device?

7. Who will be responsible for maintaining the records for the control (receipt, storage, security, dispensing/use, return/disposition) of this device?



**Supplement to Research Protocols involving the use of
Individually-Identifiable Health Information (IIHI)**

1. List, in detail, the health information that is **collected** for the research activity.

1. Physical exam including height, weight, B/P.
2. Laboratory results including pathology
3. Radiology exams
4. Medication history

2. Check which of the following identifiers will be associated with this information? (Note, this includes information about the subject, subject's relatives, employers or household members.)

- Names (includes initials only)
- All geographic subdivisions smaller than a state
- All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except when such ages and elements may be aggregated into a single category of age 90 or older.
- Telephone numbers
- Facsimile numbers
- Electronic mail address
- Social security numbers (includes scrambled last four digits only)
- Medical record numbers (or employees numbers)
- Health plan beneficiary numbers
- Account numbers
- Certificate/license numbers
- Vehicle identifiers and serial numbers, including license plate numbers
- Device identifiers and serial numbers
- Web universal resource locators (URLs)
- Internet protocol (IP) address numbers
- Biometric identifiers, including fingerprints and voiceprints
- Full-face photographic images and any comparable images
- Any other unique identifying number, characteristic or code, unless otherwise permitted by the privacy rule for re-identification.

5. List names of individuals who will have **access to** the individually-identified health information (IIHI) **within VA**?

1. Principal Investigator, research coordinator/nurse.

6. List provisions for controlling access to data.

Data is stored in locked office/locked file. Patients are given a study # when registered. All data sent to ECOG has patient's ID # and initials only.

4. Describe provisions employed to ensure confidentiality of data. Where/How will individually-identifiable health information (electronic and paper) be stored and secured? Indicate who will have copies and where.

Paper files are stored in a locked office/file and data sent to ECOG/CTSU is electronically transmitted to CTEP under NCI/FDA and HIPAA regulations.

5. Will individually-identifiable health information be **disclosed to anyone outside the VA**?

Yes No

If you answer “yes” to the above question, the protocol must be reviewed and approved by the VA NYHHS Privacy Officer. ([212] 686-7500 x3670)

List Below all entities **receiving** the information: Note all non-routine transfer of data to other VHA organizations for research purposes require an internal data use agreement with a time limited agreement for return or destruction of the data.

1. ECOG/CTSU (sponsoring group) submits data to CTEP (NCI) which has a Cooperative Research and Development Agreement (CRADA) – Appendix VIII

6. List below all **procedures for transmission** of IIHI outside the VA: Check here if N/A.

1. This study will be monitored by the Clinical Data Update System Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means.

7. List below the procedures for disposition of IIHI. Will it be **destroyed or returned** to NYHHS?

1. IIHI will be Destroyed

Signature of Principal Investigator over Printed Name
Andrea N. Leaf, MD

Date Signed

For Privacy Officer Use only:

- The protocol is in compliance with all privacy and security requirements.*
 The protocol is not in compliance with all privacy and security requirements. The following is required:

Signature of Privacy Officer

Date Signed