DCP CHEMOPREVENTION PROTOCOLS:
Requirements and Instructions

Protocol Document Requirements during the Solicitation Period:

As stated in the Request for Proposal, a clinical protocol document shall be provided with the technical proposal. This "Protocol Document Template" presents the recommended format and required content for the clinical protocol document. During the competitive source selection those Offerors in the competitive range may be asked to respond to questions from the DCP Technical Evaluation Panel to improve and strengthen their proposal and to make the corresponding changes in the protocol document.

Post-Award DCP Protocol Review & Approval Process:

A. Following contract award, the Contractor will have **30 calender days** to submit the following documents to the DCP Protocol Information Office:
   1) Draft of the final protocol document including Protocol Submission Worksheet
   2) Informed consent form
   3) Study-specific Case Report Forms

B. Submission of protocol documents to DCP PIO
   1) Electronic submission of protocol documents is **required**.
   2) Documents may be sent as a pdf file or as an e-mail attachment in MS Word or WordPerfect.
   3) All document submissions shall be accompanied by the DCP PIO Protocol Submission Worksheet. The worksheet may be downloaded from: http://rcb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm For revised or amended protocols, only the applicable sections of the worksheet need be completed.
   4) Documents shall be e-mailed to Linda Parreco, RN, MS, Head, DCP Protocol Information Office at: **parrecol@mail.nih.gov**.
   5) Attachments which are difficult to incorporate electronically may be sent by Fed Ex to :

      Linda Parreco, RN, MS
      DCP Protocol Information Office
      6130 Executive Blvd., Room 2050
      Rockville, MD 20852

C. DCP protocol review process

1) Protocols arriving in the PIO will undergo an administrative check to ensure that all elements listed in the protocol template are included in the protocol document. Protocols lacking elements may be returned to the PI for completion before undergoing DCP review.
2) Protocols will be reviewed by the DCP Protocol and Safety Review Committee (PSRC).
3) Protocols are evaluated against the criteria in the DCP protocol template. Close adherence to these guidelines will decrease the number of protocol revisions required before final approval is granted.
4) The PI will receive a comprehensive report from the PSRC outlining recommended and required changes to the protocol document.
5) The PI must submit a revised protocol to the DCP PIO within 30 calender days.
6) The revised protocol submission shall include the following:
   a. Point by point response to the items listed in the PSRC review
   b. Highlighted version of the protocol indicating changes
   c. Clean version of the protocol with highlights removed
7) All changes made prior to protocol activation will be referred to as "VERSIONS". *All protocols submitted for review shall include a footer on each page of the protocol which includes NCI protocol number, date of submission to the NCI, and current version number of the protocol.*

D. DCP protocol approval process

1) Once the Project Officer and PIO approve the protocol, it will be submitted to the FDA under a DCP-sponsored IND, if applicable.
2) Protocol changes requested by the FDA will be addressed by the PI and submitted to DCP for final protocol approval.
3) The PI will be notified of final protocol approval
4) Note: final protocol approval is **one of several steps** required before the clinical trial can open for accrual.

E. Initiation of the clinical trial

1) **The clinical trial will be initiated at the direction of the NCI Project Officer only after Food and Drug Administration (FDA) approves the protocol, IRB approval has been documented, all required documentation has been submitted,**

and the drug is available and secured for the specific trial.

2) The following documents must be received by DCP prior to protocol initiation:
   a. IRB Approval(s) of protocol at each site
   b. IRB Approved Informed Consent Document for each site
   c. Form FDA 1572, signed and dated for each site
   d. Investigator's current curriculum vitae
   e. Subinvestigator's current curriculum vitae
   f. Medical license
   g. Lab certification (*e.g.*, CLIA, CAP)
   h. Lab normal reference ranges
   i. IRB Membership list/letter from IRB

F. Changes to the protocol following clinical trial activation
   1) Changes to protocols after activation are called amendments.
   2) Each change to a DCP-approved protocol must be documented and submitted to the DCP PIO as a protocol amendment.
   3) DCP must be notified of proposed protocol amendments to assess impact or trial safety and management of regulatory submission.
   4) A full copy of the amended protocol must be submitted to DCP PIO for review and approval prior to initiating the changes.
   5) The amended protocol document must be accompanied by a cover sheet detailing the protocol changes, rationale for change, impact on other areas of the protocol, and specific reference to the changed protocol sections.
   6) The protocol shall be clearly marked with the amendment number.
   7) All protocol amendments must be approved in writing by the DCP Project Officer prior to activation.

Using the DCP Protocol Template:

The DCP Protocol Template is designed to simplify and standardize the process of writing a chemoprevention protocol. The DCP Protocol Template can be downloaded at: http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm.
In addition to the protocol template, the above web location also includes templates for the Case Report Forms, Progress Reports, Final Reports, and the Biomarker Methods Validation Report.

Currently, the protocol template is available for viewing in pdf format, or for downloading in WordPerfect. The WordPerfect version can be copied as a file and used to develop new

chemoprevention protocols, thus reducing the time required for extensive formatting. In addition, examples of recommended language to be incorporated in the protocol are included. The reader is referred to several web addresses throughout the template. These addresses may provide a certain section of the protocol document (*i.e.* the Common Toxicity Criteria), may direct the reader to important policy descriptions (*i.e.* new NCI Data and Safety Monitoring Policy), or may provide helpful background information (ethics, tissue banking).

Questions regarding the use of the templates or submission of documents may be directed to the DCP Protocol Information Office at (301) 496-0265.

COVER SHEET TEMPLATE

Title of Protocol

Principal Investigator
Institution
Address, Phone Number, Fax, E-Mail

NCI Contract/Grant Number:

Name and location of study site(s) or institution(s):

Date of current protocol submission and version number:

Date of previous submission dates and version numbers:

Name(s) of study agent(s):

IND number/IND holder (if applicable):

SCHEMA TEMPLATE

Protocol Title

Name of Principal Investigator and Institution

Subject Population (*e.g.*, women with newly diagnosed CIN III)

9

Randomize to X mg drug A or placebo qd for 6 months (3-day holiday/month) (25/arm)

9

Summary of evaluations to be conducted and time points (*e.g.*, Repeat colposcopy at 3 months; colposcopy with biopsy at 6 months; pap smears at 3 and 6 months)

9

Summary of endpoints (histological response of CIN; modulation of intermediate biomarkers)

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1.0 OBJECTIVES

Study objectives are concise statements of the primary and secondary clinical and statistical questions that the study is designed to answer. Each objective should be stated as specifically and succinctly as possible. Both primary and secondary hypotheses must relate to the hypotheses presented in the rationale (section 6.0) and should be consistent with the objectives described in the statistical section (section 16.0). Clearly differentiate primary and secondary objectives. Number objectives in order of priority or importance, *e.g.*:

1.1 First objective/hypothesis
1.2 Second objective/hypothesis
1.3 Third objective/hypothesis

EXAMPLE: To evaluate the effects of a daily dose N of drug E in population X on parameters Y and Z by continuous or daily recording of results obtained in tests A and B during time period C, as compared with drug D at dose E, under the same experimental conditions.

Do not write that the objective is "to determine the mechanism of action of drug X"; this objective is too general, vague, and merely restates the overall goal of the study.

2.0 BACKGROUND AND RATIONALE

Provide sufficient background information to describe the rationale for the study. Present possible mechanisms and/or theoretical framework for conducting the study. Include relevant literature review and pertinent preclinical, pilot, and preliminary and/or unpublished data to support conduct of the proposed study. Clearly state hypotheses for the primary and secondary objectives (Section 5.0). Justify selection of the target population, chemopreventive agent(s), and study endpoints (*e.g.*, specific surrogate endpoint biomarkers), the choice of particular techniques for endpoint assessment and measurement of drugs, metabolites and drug effects.

3.0 SUMMARY OF STUDY PLAN

For the convenience of the reader, this section should provide a brief synopsis of the following points. It should be a brief narrative of the study schema in Section 3.0.

- Study design (*e.g.*, double-blind, placebo-controlled, multi- or single center, Phase I, II).
- Number of subjects to be enrolled (total number and number per arm).
- Brief description of the subject population.
- Treatment plan, including treatment groups, dose(s), and duration of exposure to study drug.
- Description of run-in period, if applicable
- The points at which subjects will be assessed.
- Description of measurements taken to meet study objectives.

- Description of clinical procedures, lab tests or other measurements taken to monitor effects of study drug on human safety and to minimize risk.
- Duration of follow-up.
- Duration of study.

4.0 SUBJECT SELECTION

4.1 Study Population:

Defines the composition of the study population, including:

- Health status as related to cancer (*e.g.*, healthy volunteers, persons at increased cancer risk, or subjects with prior cancer diagnosis).
- Anticipated demographic make-up (*e.g.*, age and gender) of subjects to be enrolled. Include estimated targets for gender and minority inclusion, as per NIH Guidelines (http://grants.nih.gov/grants/funding/women_min/women_min.htm.
- Where appropriate, address the inclusion or exclusion of children, as per NIH Guidelines. This section should demonstrate that the study population is appropriate (e.g., a chemopreventive drug can modulate tissue being evaluated, population is sufficiently homogeneous to allow meaningful analysis of endpoints, appropriate risk status or disease stage, etc.)

4.2 Participating Centers:

If multiple facilities (*e.g.*, centers, clinics or hospitals) are participating in the study, all should be identified specifically in this section.

4.3 Sources or methods of recruitment:

Describe source of study populations and methods for identifying and recruiting them (e.g. media, high-risk clinic rosters, cancer registry, physician referrals, etc.) Plans are specified for gender and minority recruitment, as per NIH Guidelines.

4.4 Method of subject numbering:
Describe method of assigning subject numbers.

NOTE: It is preferable for a site to identify and use one unique subject number throughout the study, regardless of the phase the subject is in.

4.5 Inclusion Criteria:
Inclusion criteria are comprehensive, unambiguous, and not unnecessarily restrictive. For each, provide methods for assessing inclusion criteria (e.g., risk assessment tools, clinical evaluations, pathology review criteria, etc.).
These criteria include the following:

- Specific health risk or disease requirements (*e.g.*, age, Eastern Cooperative Oncology Group (ECOG) performance status, life expectancy).
- Health status requirements
- Organ function parameters
- Other areas specifically relevant to the methodology of the study

NOTE: Provide histologic confirmation of diagnosis, time from diagnosis, and disease status at entry (stage or extent of disease) for cancer subjects or subjects with precancerous lesions.

EXAMPLE: Inclusion Criteria:
1. Is the subject over 18 years of age?
2. Does the subject have an ECOG Performance Status of 0-2?
3. Has the subject been properly informed of the study and signed the Informed Consent?

4.6 Exclusion Criteria:
Exclusion criteria are comprehensive, unambiguous, and not unnecessarily restrictive.
These criteria include:
- Contraindication to participation based on agent pharmacology and metabolism, toxicology, clinical and methodology considerations.

NOTE: Healthy volunteers may be required to demonstrate absence of chronic medical conditions or regular use of certain medications.

EXAMPLE:	Exclusion Criteria: 1. Use of any nonsteroidal anti-inflammatory agent within two weeks prior to enrollment. 2. Participation in another chemoprevention investigational study within one month prior to enrollment. 3. A history of smoking within one month prior to enrollment. 4. Active malignancy at any other site.

5.0 AGENT INFORMATION AND ADMINISTRATION

5.1 Name of Agent: If indicated, include IND number and Sponsor.

5.2 Dose Groups and Duration of Exposure

5.3 Dose Selection: Describe the method and data supporting the dose(s) to be administered.

5.4 Formulation

Include:

- Agent formulation to be used (*e.g.,* oral)
- If alternative formulations are available, justify why the chosen formulation will be used for the study.
- Description of the agent (*e.g.,* gelatin capsules, clear liquid)
- List of ingredients in the vehicle/excipient.

NOTE: This information may be provided by NCI.

5.5 Administration

Indicate who will administer the agent, how much should be administered, when it should be taken, and whether it should be taken with food and any other instructions for taking the agent.

EXAMPLE:	Subject will self-administer the drug, and will be instructed to take one capsule orally each day, immediately after breakfast.

5.6 Side Effects

Describe toxicity profile and related data for the agent at the selected does and schedule. Information available from the NCI DCP Clinical Development Plan, Investigational Drug Brochure (if applicable) or the package insert (if applicable) relevant to clinicians participating in this trial may be added to this section. If the amount of information is large, append the relevant information (see Section 16.4).

5.7 Contraindications

Indicate any limitations on medications, herbs, and vitamin and mineral supplements (other than study agents) while participating in the study. Include time periods, if applicable. Also, list restrictions that subjects should follow when using the agent (e.g. limit sun exposure).

5.8 Manufacturer and Supplier
Indicate who will provide the agent for the study. NOTE: It is sufficient to note NCI or NCI Repository Contractor as the distributor of the agent, when appropriate.

5.9 Packaging and Labels: Describe in detail how the agent will be packaged. This description should include container(s) (*e.g.*, box, bottle, blister), amount of agent per container (*e.g.*, two bottles per box with 30 capsules in each bottle), the information noted on the label of each container (*e.g.*, subject ID, study number, distributor) and if blinded, how the label will be constructed to maintain the blind (*e.g.*, three-part occluded label). In some cases, this information may be supplied by the NCI.

5.10 Storage: Provide instructions regarding proper storage of the agent at study site.

NOTE: These may be provided to the PI by NCI.

EXAMPLE: Study medication will be stored at room temperature (22.2°C), protected from environmental extremes and in a locked cabinet or room.

5.11 Distribution: Identify the party responsible for dispensing the agent to the subject, and the procedures for distribution.

EXAMPLE: All study personnel except the pharmacist will be blinded to the study drug treatment.

5.11.1 Run-in procedures:
If a placebo run-in period will occur before randomization to determine subject's compliance, describe procedures for the run-in period including administration of placebo, dose, length of period, and timing of assessment of compliance. Compliance should be clearly defined.

5.11.2 Randomization:
For randomized trials, describe the procedure for randomizing a subject to a group.

EXAMPLE: There will be 2 groups, each consisting of 10 subjects. Following determination of eligibility, each subject will be given a randomization code (if used, the subject will continue to be referred to by his/her unique subject number) and thereby be assigned to a dose group. Subjects will be randomized in a 50/50 ratio to receive agent X or placebo.

5.11.3 Blinding and unblinding methods:

For blinded studies, describe blinding and unblinding methods. Address the following points:

- Procedure for retaining the blind
- Person authorized to break the blind
- Circumstances for breaking the blind
- Procedure for breaking the blind

5.12 Dose Modification: Indicate when and how is it appropriate to reduce the dose of the agent during this study. If applicable, describe procedures for increasing dose after reduction of dose due to toxicity.

EXAMPLE: For grade 1 toxicity or less, no dose modification will be made. For grade 2 toxicity probably or possibly related to drug, dose of study drug will be reduced by 50%. Reduced dose will be maintained until the adverse event (AE) resolves; then drug reintroduced. If the AE recurs, maintain reduced dose for remainder of study. For grade 3 or 4 toxicity probably or possibly related to drug, therapy will be discontinued until toxicity resolves to grade 1 or less. At that time, use of study drug will be resumed at 50% of original dose.

5.13 Adherence/Compliance

5.13.1 Method: Describe the method(s) used to monitor each subject's drug compliance (*e.g.*, medication diaries, pill counts, drug/metabolite plasma levels, and/or drug effect biomarkers).

EXAMPLE: The research staff will evaluate drug compliance using the following means:

1. At each clinic visit, subjects will be given a calendar and instructed to initial it each time a dose is taken.
2. Each subject will be given a bottle containing 30 capsules of study drug at each clinic visit and instructed to return all unused capsules to the investigator. At end of treatment, the actual quantity of unused drug will be compared to the anticipated amount of unused drug and subject calendar.
3. At each clinic visit, the subject will provide a blood sample for evaluation of serum drug level.

5.13.2 Definition: Provide a definition of compliance that will be used to describe which subjects are considered evaluable (will be included in the statistical analysis as indicated in Section 13.0). (This definition may have implications for the off-study criteria as well, see Section 11.0).

EXAMPLE:	A subject is considered evaluable for determining the effect of study drug if $80% compliance is determined by quantity of unused drug returned to the site and pharmacokinetic analysis indicates a serum drug level of x or greater.

5.14 Drug Accountability: List in detail records that must be maintained regarding receipt, distribution, and disposition of study drug. Indicate who will be responsible for maintaining such records.

EXAMPLE:	The investigator is required to maintain adequate records of receipt, dispensing and final disposition of study drug. This responsibility has been delegated to the Pharmacy. Include on receipt record (*e.g.*, packing slip) from and to whom study drug was shipped, date, quantity, and batch or lot number. On dispensing record, note quantities and dates study drug was dispensed to and returned by each subject. At completion of investigation, return all unused study drug to NCI/DCP repository. The record documenting the return of unused drug should include quantity, date, batch or code, and name of the person or department to whom the drug was returned.

5.15 Drug destruction/disposal: indicate procedure for handling the unused drug including: method of disposal, documentation of disposal, and any other standard operating procedures relevant to the destruction of investigational agents.

6.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

Delineation of study endpoints and methods for measuring or evaluating them is described here. In chemoprevention studies, endpoints usually fall into the following categories:

Efficacy Endpoints: Depending on the study hypotheses and design, efficacy endpoints may include an incidence of invasive or preinvasive disease (*e.g.*, polyp incidence); clinical response (*e.g.*, change in number and severity of leukoplakia by physical examination); histologic or cytologic response (*e.g.*, change in severity of dysplasia in biopsy materials); and/or modulation of surrogate endpoint biomarkers (SEBs). Define endpoints clearly. Methods for assessment may be described briefly and referenced in this section.

Pharmacokinetics, Safety Studies and Drug Effect Biomarkers: As appropriate, other endpoints (serum/plasma/tissue drug/metabolite levels, other drug effect biomarkers) should be defined clearly. Methods for assessment may be described briefly and referenced in this section with detailed descriptions of

laboratory and computer modeling procedures provided in the Appendix (16.6) "Pharmacokinetic and Biomarker Method Development".

7.0 CLINICAL EVALUATIONS and PROCEDURES

7.1 Schedule of Events: A table that lists procedures and laboratory evaluations to be performed and when each is to be completed. The table should also indicate when each Case Report From (CRF) is to be completed. A template for the Schedule of Events is included on the following page.

7.2 Pre-intervention Procedures: Describe in detail all procedures that must be completed for a subject before the study intervention can be initiated. Include description of run-in procedures, if applicable.

7.3 Evaluations during the Study Intervention: Indicate what procedures will be completed, and at what stage of the study, while subject is receiving the study agent(s).

7.4 Evaluations at Completion of Study Intervention: Specify what evaluations must be performed when a subject discontinues use of study agent. These evaluations should be consistent with the endpoints described in the objectives and statistical analysis sections of the protocol.

7.5 Follow-up Evaluations: If applicable, specify what evaluations must be performed when a subject is on follow-up. Follow-up is a protocol-specific evaluation period that occurs after the subject stops taking the study agent. The section should carefully define and justify the follow-up period for the protocol. These evaluations should be consistent with the endpoints described in the objectives and statistical analysis sections of the protocol.

7.6 Methods for and Clinical Procedures (*e.g.*, Endoscopy, Biopsy): document any special processes, instructions, or methodologies for clinical procedures required by the protocol. Include relevant information related to the testing process, for example, instructions for taking study agents if the prep requires 'NPO' period; scheduling details for tests which may be available only at certain locations or times.

7.0 (continued) **SCHEDULE OF EVENTS TEMPLATE**

Evaluation/Procedures	Screening/ Baseline (Day 0)	Day 1	Week 1	Month 1	Month 3	Month 6/ Termination	Early Withdrawal
Informed Consent	X						
Randomization	X						
On-Study Form	X						
Medical History	X						
Physical Exam	X					X	X
Pregnancy Test	X						
Height/Weight	X	X					
Vital Signs		X	X	X	X	X	X
Serum Chemistry	X			X	X	X	X
Hematology	X			X	X	X	X
Urinalysis	X			X	X	X	X
PK Blood Samples (As applicable)		X				X	X
SEB Measurements (As applicable)	X				X	X	
Adverse Events			X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X
Dispense/Record Study Medication		X	X	X	X	X	X
Off-Study Form						X	X
Compliance Count/ Returned Drug				X	X	X	

8.0 LABORATORY EVALUATIONS and PROCEDURES

8.1 Laboratories: Identify the laboratory(ies) that will perform each analysis for each sample. Where appropriate, list individuals who will perform analysis and/or procedures for conducting consensus reviews of samples.

8.2 Collection and Handling Procedures: For each type of sample obtained (*e.g.*, biopsy, serum), describe the following:

- amount to be collected
- when sample should be obtained (*e.g.*, fasting, prior to A.M. dose)
- processing of sample (*e.g.*, details of tissue fixation, embedding, processing and sectioning)
- labeling of sample
- tracking of samples (*e.g.* logs or tracking sheets for subjects)
- temperature storage requirements (*e.g.*, frozen at –20EC).
- storage duration (*e.g.* minimum/maxim length of time)

8.3 Shipping Instructions:

Include this sub-section only if samples must be shipped to an off-site laboratory for analysis. For each sample, describe: packaging (*e.g.*, in a polystyrene container surrounded with dry ice), carrier requirements (*e.g.*, overnight carrier), when samples can be shipped (*e.g.*, Monday through Wednesday), and name, address and telephone number of the person to whom the samples are being sent.

8.4 Methods for Laboratory Procedures Including Necessary Preparations and Anticipated Risks:

If this information is lengthy, please place in the Appendix (16.5) instead of the body of the protocol document.

9.0 REPORTING ADVERSE EVENTS

(Note: Below are subsections to be included in this section of the protocol, along with **recommended language** for each.)

9.1 Definition: An adverse event (AE) is any condition which appears or worsens after the subject is enrolled in an investigational study. Note all adverse events on the Adverse Event Case Report Form (CRF), whether or not related to study drug.

9.2 The following information will be collected for all Adverse Events:

a. Start and stop dates
b. Severity (grade)
c. Relationship to study drugs (attribution)
d. Whether or not the subject dropped due to the AE

This data is reported on the Adverse Events Reporting Form which is included in the Case Report Forms set.

9.3 Severity: Adverse events will be graded by a numerical score according to NCI Common Toxicity Criteria (CTC), version 2.0 (http://ctep.info.nih.gov/CTC3/default.htm).

NOTE: Situations may arise where the Common Toxicity Criteria, Version 2.0 do not represent certain chemoprevention agent-specific effects, severity of these effects, and attribution of the effect. Examples of this situation include ocular and dermatologic effects associated with retenoids. Therefore, on these occasions the CTC criteria may be expanded or modified to include these situations. The additional criteria should be consistent with those used in earlier studies of the same or related agents. Score Adverse Events not included in the defined NCI CTC according to their impact on the subject's ability to perform daily activities as follows:

a. Mild (causing no limitation of usual activities)
b. Moderate (causing some limitation of usual activities)
c. Severe (causing inability to carry out usual activities)

The Adverse Events Case Report Form should include this alternate scale as well.

9.4 Follow-up: All AEs, including laboratory abnormalities that in the opinion of the Investigator are clinically significant, will be followed up according to good medical practices, and documented as such.

9.5 **Serious Adverse Events (SAE)**: A serious adverse event is defined (by ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997) as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is immediately life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect

In addition, events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

9.6 **Expedited Reporting of SAEs**: **In the interest of subject safety in this study and to fulfill regulatory requirements, all Serious Adverse Events, regardless of whether or not it is related to the study drug, will be reported to the Sponsor (NCI, DCP) by telephone or fax within 24 hours, and in writing within 48 hours, of the investigator learning of the event.** This written information shall be documented on the "NCI Division of Cancer Prevention Serious Adverse Event Form" which can be found in Section 17.6 of this document. In addition all SAEs must be entered in the Adverse Event Case Report Form as part of the cumulative report. Prompt follow-up reports of the clinical outcome will be sent to NCI.

The contact information for telephone calls and written reports is as follows:

Phone calls or fax within 24 hours of Serious Adverse Events:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Phone: (301) 496-8563
Fax: (301) 402-0553

Submission of DCP SAE form within 48 hours of Serious Adverse Event to:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 300
9000 Rockville Pike
Bethesda, MD 20892-7340

Alternate address for Express Mail by hand delivery:

Executive Plaza North, Suite 300
6130 Executive Blvd
Rockville, MD 20852

10.0 CONCOMITANT MEDICATIONS

10.1 Indicate any limitations on medications (other than study drug) while participating in the study. Include time periods, if applicable.

EXAMPLE: No ASA or products containing ASA within three weeks of study entry.

10.2 All medications (prescription and over-the-counter),vitamin and mineral supplements, and/or herbs taken by the subject during the study will be documented on a CRF with information including:

- Start and stop dates of drugs, herbs, or supplements
- Dose and route of administration
- Purpose for taking the medication, herbs, or supplements

11.0 OFF- STUDY" CRITERIA

11.1 Study Termination: Specify the criteria for removing a subject from chemoprevention intervention or from the study protocol. State that NCI, as Sponsor, has the right to discontinue the investigation at any time.

EXAMPLE:	The NCI as Sponsor can decide to terminate a subject's participation in the study. This decision could be based on factors such as unacceptable adverse events, lack of Surrogate Endpoint Biomarker modulation on preliminary analysis, *etc*.

11.2 Premature Removal of a Subject: This subsection should define criteria for premature removal of a subject from the intervention and from the study.

EXAMPLES:

1. Personal reason.
   Note: A subject may withdraw from the study at any time.
2. Non-compliance.
3. Lost to follow-up
   Note: Diligent attempts must be made by telephone and letter to determine the circumstances for loss to follow-up, since such loss may be related to the study drug.
4. Death.

12.0 DATA MANAGEMENT

12.1. Case Report Form Set:

NOTE: The Case Report Form (CRF), a set of forms for each subject, provides a record of data generated according to protocol. These forms are to be completed on an ongoing basis during the study. The medical chart is the source of verification of data. During the study, the CRF will be monitored for completeness, accuracy, legibility and attention to detail. The CRF will be retained for review.

In this section of the protocol, specify the document on which each of the following is to be recorded, where it is to be sent, and on what schedule. A set of forms may include:

- On-study form
- Eligibility checklist
- Medical history/surgical history
- Physical Examination
- Laboratory data
- Informed consent documents
- Flow sheets and other interim monitoring mechanisms
- Specialty forms for pathology, radiology, or surgery as required
- Symptom and other assessment forms
- Study drug administration/compliance
- Concomitant medications
- Drug calender records
- Adverse Events
- Agent-specific Adverse Events
- Social habits (and changes)
- Efficacy (including biomarker data)
- Physician's notes
- Other forms for interim safety and efficacy evaluations
- Off-study form
- Follow-up summary sheets

NOTE: Please see the DCP Internet Supplemental Information for instructions on developing and completing case report forms. Template forms on the web site may be downloaded and modified to meet the requirements for individual studies. A WordPerfect file of these forms is also available available from the DCP Protocol Information Office at (301) 496-0265. The Internet address for the Case Report Form templates is:
http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm

12.2 Data Entry, Data Management and Quality Control

Discuss the following information:

- Who will complete the CRF?
- Identify the facility responsible for managing data generated by the study.
- Describe the procedure for data entry (*i.e.*, how data from the CRF will be entered into the database).
- Describe quality control procedures (*e.g.*, double entry, edit or cross checks).
- Describe the format for submitting data to NCI.
- Provide validation documentation of data management system.
- Include standard operating procedures and/or guidelines, if possible.

NOTE: Be sure that appropriate identification is included on every form (*i.e*. no patient names, but always include patient and protocol ID numbers). Data capture and reporting is complete. CRFs are consistent with protocol and consent form. Data sheets include instructions for completing the CRF (schedule on which data sheet is to be completed).

12.3 Progress Reports: State the contract criteria for submission of progress reports. *NOTE: The required format and content for the Quarterly and Annual Progress Reports is found in the DCP Internet Supplemental Information at:*
http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm

12.4 Final Report: State the contract deliverables criteria for the submission of draft final and final reports. *NOTE: The required format and content for the Quarterly and Annual Progress Reports is found in the DCP Internet Supplemental Information at:*
http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm

12.5 Additional Reporting Requirements: In addition to the quarterly and annual progress reports, the following items are required to be sent to DCP at the appropriate times during the conduct of the clinical trial.

12.5.1 Protocol revisions and amendments:

- NCI DCP must be notified of proposed protocol amendments to assess impact on trial safety and management of regulatory submission.
- A full copy of the amended protocol must be submitted to DCP for review and approval prior to initiating the amended protocol.
- The revised or amended protocol document must be accompanied by a cover sheet detailing the protocol changes, rationale for change, impact on other areas of the protocol, and specific reference to the changed protocol sections.

- The protocol shall be clearly marked with the protocol version number or amendment number
- All protocol amendments must be approved by the Project Officer, Division of Cancer Prevention prior to activation.

12.5.2 Administrative Changes

- Change in Principal Investigator
- Addition of study institutions
- Changes in contact information

12.5.3 Lab Certifications

12.5.4 Assay Validation Reports (PK and SEBs)

13.0 STATISTICAL METHODS

This section should identify the party responsible for analyzing the study data. An adequate statistical section discusses study design in relation to study objectives, and the data evaluation plan, specifically:

13.1 Primary and all secondary hypotheses are clearly stated.

13.2 Sample Size Justification:
Total sample size (including gender and minority considerations) and sampling strategy are described and justified for testing the primary and secondary hypotheses. Power calculations for proposed sample size and endpoints are presented. For comparative studies, differences to be detected are clearly stated and justified with pilot or published data.

13.3 Methods for Randomization and Stratification:
Procedures for randomization and stratification are described and justified. Blocking and/or other techniques used to balance treatment assignment are described.

13.4 Outcome measures:
Appropriate outcome measures (response rate, time to progression, survival time, etc.) are selected and methods for measuring outcomes are described.

13.5 Statistical Analyses:
This section provides a data analysis plan that is logical and appropriate for endpoints selected. Plan does not introduce bias through exclusion of participants from analysis. Clinical relevance of the results as well as statistical significance are discussed. Methods of computing confidence intervals for outcome measures are described. Size of expected intervals are indicated.

13.6 Assumptions:

State any assumptions, underlying selection, what they are, are they testable, and method of testing.

13.7 Compliance and missing data:
Definition of compliance is clearly stated. Non-compliance is sufficiently addressed. Particular consideration is given to drop-outs, drop-ins and lost-to-follow up. Handling of missing data or data from non-compliers are described. Any methods used to impute missing data should be described.

13.8 Interim Analyses:
If relevant to the investigational agent(s) and study design, provides a plan for interim analysis and stopping rules. Include plans for monitoring the progress of the trial to implement early termination.

13.9 Ancillary Studies:
Address analysis of data from ancillary studies, if relevant.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

(Note: Below are subsections to be included in this section of the protocol, along with **recommended language** for each.)

14.1 Form FDA 1572: Prior to initiating this study, the Principal Investigator will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations.

14.2 Institutional Review Board (IRB) Approval: Prior to initiating the study and receiving drug, the PI must obtain written approval to conduct the study from the appropriate IRB and NCI.. Should changes to study protocol become necessary, protocol amendments will be submitted in writing by the PI to the Project Officer (via the DCP PIO) and, when approved, to the IRB for approval prior to implementation.

14.3 Informed Consent: All potential candidates for the study will be given a copy of the study Informed Consent to read. The investigator will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate decides to participate in the study, he/she will be asked to sign the Informed Consent Document. The study agent(s) will not be released to a subject who has not signed the Informed Consent Document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent document must be reviewed and approved by the NCI DCP and the IRB prior to study initiation. Any subsequent changes to the informed consent must be approved by the NCI DCP and then submitted to the IRB for approval prior to activation.

14.4 Data and Safety Monitoring:

NIH and NCI policy requires that grantees and contractors have in place procedures for the data and safety monitoring of clinical trials. The purpose of the data and safety monitoring plan is to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include:

a. Monitoring the progress of trials and the safety of participants
b. Plans for assuring compliance with requirements regarding the reporting of adverse events (AE)
c. Plans for assuring that any action resulting in a temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI program director responsible for the grant. (Applicable to investigator-initiated research where DCP is not the IND holder).
d. Plans for assuring data accuracy and protocol compliance.

Effective October 2000, investigators must submit a monitoring plan for Phase I and II clinical trials to DCP for approval before the trial begins. A general description of the Data and Safety Monitoring Plan is acceptable during the proposal phase of review. However, upon contract or grant award a detailed monitoring plan MUST be included as part of the protocol, must be reviewed and approved by DCP and must be submitted to the local IRB prior to study initiation.

Please refer to the following web addresses carefully:

NCI policy (4/24/01) http://cancertrials.nci.nih.gov/researchers/dsm/index.html

Further Guidance on Data & Safety Monitoring for Phase I and Phase II Trials:
Http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html

NIH Policy for Data and Safety Monitoring:
Http://grants.nih.gov/grants/guide/notice-files/not98-084.html

NCI Requirements for Data & Safety Monitoring Boards:
Http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm

Guidance on Reporting Adverse Events to Institutional Review Boards for NIH-supported Multi-center Clinical Trials:
Http://grants.nih.gov/grants/guide/notice-files/not99-107.html

14.5 Sponsor or FDA Monitoring: The FDA and NCI/DCP or their designees may monitor/audit various aspects of the study. These monitors will be given access to facilities, supplies and records to review and verify data pertinent to this study.

14.6 Record Retention: Clinical records for all subjects studied, including CRFs, history and physical findings, laboratory data, and results of consultations, will be maintained by the Investigator in a secure storage facility and stored until the NCI directs the material to be destroyed.

14.7 Certificate of Confidentiality: See Appendix VI of the DCP Supplemental Internet Information regarding the appropriate use of Certificates of Confidentiality
http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm

15.0 REFERENCES

16.0 APPENDICES

16.1 Informed Consent: Please insert the consent form for the protocol here.
Background and instructions for preparing the informed consent form: In recent years, the NCI recognized that informed consent documents for cancer clinical trials had become lengthy, complicated and difficult to understand, and were not adequately fulfilling the obligation to inform individuals about potential research participation. Therefore, the NCI along with the Office for Human Research Protections and the Food and Drug Administration, formed an Informed Consent Working Group to propose solutions to improve the quality of informed consent documents in cancer clinical trials. The Working Group included a diverse group of experts: physicians, nurses, patient advocates, Institutional Review Board (IRB) members, ethicists, legal experts, communication experts, and representatives of the pharmaceutical industry. The National Cancer Institute's Informed Consent Working Group published a set of recommendations and a template for informed consent for cancer treatment protocols. The Division of Cancer Prevention modified this template for use in chemoprevention protocols. The DCP template is attached at the end of this document (Attachment A). This template will help you develop a consent form document that meets both IRB and Federal requirements.

The NCI DCP Chemoprevention Informed Consent Template shall be used for all DCP Phase I and II chemoprevention trials. If this template is not used, justification must be provided for an alternate format. Please note that studies involving banking of human tissues require a separate signature area to allow participants the opportunity to opt out of allowing their tissues to be collected and stored for research that is not part of the protocol.

Some guidelines for customizing the consent template to a specific protocol:

- Explain the study as you would to an eighth-grade student
- Use short sentences
- Avoid polysyllabic words
- Define all acronyms and medical terms
- Delete all italicized and nonapplicable areas

The web sites listed below provide additional information about the consent template, the informed consent process, and issues related to consent for tissue banking.

NCI Recommendations and Consent Form Template:
http://cancertrials.nci.nih.gov/researchers/safeguards/consent/index.html

Tissue Banking Consent:
http://bioethics.gov/hbm.pdf
http://www-cdp.ims.nci.nih.gov/legal.html

16.2 Sample Case Report Form Set
In the protocol document, please insert the protocol-specific set of case report forms here. See the NCI DCP guidelines for completing and designing case report forms located at:
http://amb.nci.nih.gov/appl/rfp/DCPPhase2/DCP.htm

16.3 NCI Common Toxicity Criteria, version 2.0
In the protocol document please insert copy of CTC version 2.0 here. The CTC document may be referenced and downloaded from the following site:
Http://ctep.info.nih.gov/CTC3/ctc_ind_term.htm

16.4 Investigational Drug Brochures and Package Inserts (if applicable)

16.5 Methods for Laboratory Procedures:
Including Necessary Preparations and Anticipated Risks:
Specimen Collection, Handling, Transportation, Storage, and Processing;
Drug Metabolite Levels and/or Drug Effect Biomarkers;
Computer-Assisted Image Analysis and Algorithm Development;
Surrogate Endpoint Biomarkers

16.6 Pharmacokinetic and Biomarker Method Development

16.7 Serious Adverse Events: Please insert the following two forms into the protocol document:

16.71 NCI, DCP Adverse Event Reporting Policy for Phase I-III Chemoprevention Trials (provided in this template as 'Attachment B')

16.72 NCI, DCP Serious Adverse Event Form (provided in this template as 'Attachment C')

16.8 Data and Safety Monitoring Plan: Please insert the Data and Safety Monitoring Plan for the study.

Attachment 'A'

INFORMED CONSENT TEMPLATE FOR CHEMOPREVENTION STUDIES (BASED ON NCI TEMPLATE)

NOTE:

! Model text is in **bold**.

! Instructions are in *[italics]*.
! _____ Indicates that the investigator should fill in the appropriate information.

STUDY TITLE

This is a clinical trial (a type of research study). Clinical trials include only persons who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.
[Attach NCI booklet "Taking Part in Clinical Trials: Cancer Prevention Studies; What Participants Need to Know" *which can be obtained at*
http://cancertrials.nci.nih.gov/understanding/bookshelf/prevention/preintro1.html

You are being asked to take part in this study because you are at increased risk for ***TYPE OF*** **cancer.**
[Reference and attach information about the type of cancer (and eligibility requirements, if desired).]

WHY IS THIS STUDY BEING DONE?

[Suggestion for applicable text for Phase II studies:]
The purpose of this study is to find out what effects (good and bad) _DRUG/INTERVENTION **has on you and your** RISK (BIOMARKERS) FOR *TYPE OF* **cancer.**

This research is being done because_
[Explain in one or two sentences. Examples are: **"Currently, there is no effective way to prevent this type of cancer in people at increased risk,"** *or* **"We do not know which of these two commonly-used therapies is better."**]

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

[If appropriate:]
About _____ people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

[Provide simplified schema and/or calendar.]

[For randomized studies:]
You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in. You will have an *EQUAL/ONE IN THREE/ETC*. **chance of being placed in any group.**

[For nonrandomized and randomized studies:]

If you take part in this study, you will have the following tests and procedures:
[List procedures and their frequency under the categories below. For randomized studies, list the study groups and under each describe categories of procedures. Include whether a patient will be at home, in the hospital, or in an outpatient setting. If objectives include a comparison of interventions, list all procedures, even those considered standard.]

! **Procedures that are part of regular care** *FOR SOMEONE AT INCREASED RISK FOR TYPE OF CANCER* **and may be done even if you do not join the study.**
! **Standard procedures being done because you are in this study.**
! **Procedures that are being tested in this study.**

NOTE:

- *Specify how subjects will take the study agent (times/day, dosage, and route), if applicable.*
- *List all paperwork (i.e., diaries, questionnaires) that the subject will be asked to complete.*
- *List specimens to be collected, include frequency and amount.*
- *If specimens will be used for any purpose other than required by the protocol, the intended use must be disclosed and the participant should be given the opportunity to "opt out" of the collection, storage, and use of specimens for non-protocol related purposes.*

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for *MONTHS/WEEKS, UNTIL A CERTAIN EVENT* **.**
[Where appropriate, state that the study will involve long-term follow up.]

The researcher may decide to take you off this study if _____.
[List circumstances, such as in the participant's medical best interest, funding is stopped, drug supply is insufficient, patient's condition worsens, new information becomes available.]

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.
[Describe any serious consequences of sudden withdrawal from the study.]

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the *INTERVENTION/DRUGS* **are stopped, but in some cases side effects can be serious or long-lasting or permanent.**
[List by regimen the physical and nonphysical risks of participating in the study in categories of "very likely" and "less likely but serious." Nonphysical risks may include such things as the inability to work. Do not describe risks in a narrative fashion. Highlight or otherwise identify side effects that may be irreversible or long-term or life threatening.]

Risks and side effects related to the *PROCEDURES, DRUGS, OR DEVICES* **we are studying include:**
[List risks related to the investigational aspects of the trial. Specifically identify those that may not be reversible.]

[When appropriate]
Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.
[Include a statement about possible sterility when appropriate.]
[Attach additional information about contraception, etc.]

For more information about risks and side effects, ask the researcher or contact _____.
[Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit others at risk for *TYPE OF CANCER* **in the future.**

[When appropriate:]
The possible benefits of taking part in the study are the same as receiving *STANDARD DRUG/INTERVENTION* **without being in the study.**

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:
[List alternatives including commonly-used therapy and **"No therapy at this time with routine testing."***]*

[If appropriate (for noninvestigational treatments):]
You may get *STUDY TREATMENTS/DRUGS AT THIS CENTER AND OTHER CENTERS* **even if you do not take part in the study.**

Please talk to your regular doctor about these and other options.
[Reference and attach information about alternatives.]

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:
[List relevant agencies like the National Cancer Institute, Food and Drug Administration, study sponsor, etc.]

If results of the study are presented or published, your name will not be used.

PAYMENT FOR STUDY:

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

[If appropriate:]
If, during the study, the *STUDY DRUG* becomes commercially available, you may have to pay for the amount of drug needed to complete the study.

You will receive no payment for taking part in this study. *[or*] **You will receive no payment for the costs of procedures, tests or visits in connection with this research. Costs such as parking fees as a result of participating in this study may be incurred and these costs will not be covered directly. However, to help defray these costs, you will be reimbursed . . .** *[Specify exactly the amount to be given and how the funds will be distributed over the study period, if applicable.*]

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. If you decide not to take part in the study or if you leave the study after you agreed to take part, it will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* **at** *TELEPHONE NUMBER* .

For questions about your rights as a research participant, contact the researcher *NAME OF CENTER* **Institutional Review Board (which is a group of people who review the research to protect your rights) at** *TELEPHONE NUMBER* . *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's **Cancer Information Service** at
1–800–4–CANCER (1–800–422–6237) or **TTY: 1–800–332–8615**

Visit the NCI's Web sites…
cancerTrials: comprehensive clinical trials information **http://cancertrials.nci.nih.gov.**

CancerNet™: accurate cancer information including PDQ **http://cancernet.nci.nih.gov.**

You will get a copy of this form. You may also request a copy of the protocol (full study plan).
[Attach information materials and checklist of attachments. Signature page should be at the end of package.]

SIGNATURE

I agree to take part in this study.

Participant _____ Date _____

Attachment 'B'

National Cancer Institute, Division of Cancer Prevention (DCP)

Adverse Event Reporting Policy
Phase I-III Chemoprevention Trials

Reaction	*Reporting Obligation*
a. ALL SERIOUS ADVERSE EVENTS Any adverse event (AE) occurring at any dose that: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.	REPORT BY PHONE TO DCP WITHIN 24 HOURS.[1] (written report to follow within 48 hrs[2])
b. ALL ADVERSE EVENTS (SERIOUS, NON-SERIOUS)[3]	REPORTED in the AE CRF and Progress Reports.

[1] Telephone number available 24 hours daily: 301-496-8563 (Recorder after hours); FAX: 301-402-0553 or 301-594-2943.

[2] Report to:

Medical Monitor (as specified in the contract)
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 300
9000 Rockville Pike
Bethesda, MD 20892-7540
For Express (*e.g.*, Federal Express, DHL, Airborne) or Hand Delivery
Executive Plaza North, Suite 300
6130 Executive Blvd.
Rockville, MD 20852

[3] A list of all known toxicities can be found in the Investigator's Brochure, package insert, or other material provided by NCI.

NCI Contract/Grant No._____ Study Subject No._____
IRB Protocol No. _____
(9/99)

Attachment 'C'

NCI, DIVISION OF CANCER PREVENTION (DCP)
SERIOUS ADVERSE EVENT FORM

REQUIRED FIELDS ON ALL REPORTS

Today's Date:	**Sponsor: NCI, DCP**	**Study (Indication):**
Drug under Investigation:	**IND No.:**	

A. Study Subject Information

1. Patient Initials	**2. Date of Birth:** _____ **(Month/Day/Year)**	**3. Weight at Time of Event:** _____ **[ ] kg [ ] lbs [ ] not available**	**4. Height at Time of Event:** _____ **[ ] cm [ ] ft [ ] not available**

B. Event Information

[ ] Initial Event Report **[ ] Follow-up**	**Gender: (circle one) M F**	**Dose at Event:**
Event Onset Date: **(Month/Day/Year)**	**Primary Event (diagnosis):**	
Event Approx. Time: **(indicate A.M./P.M.)**		
Event Occurred at:		
Duration of Drug Exposure at Event:	**Primary Treatment Approx. Time (A.M./P.M.):** **Primary Treatment of Event:**	
Attending Physician (Name): **Phone/FAX No.:** **Hospital/Clinic:** **Address:**		
Describe Event (if applicable, include dates of hospitalization for event):		
Form Completed by: (Print Name) _____ Title_____ **Investigator Signature _____ Date _____ Phone No. _____** **(Month/Day/Year)**		

NCI Contract/Grant No._____ Study Subject No._____
IRB Protocol No. _____
(9/99)

ALL FIELDS APPEARING IN THE FOLLOWING PAGES (C–F) MUST BE COMPLETED FOR THE INITIAL REPORT; THEREAFTER, FILL IN ONLY SECTIONS THAT PROVIDE ADDITIONAL/ CORRECTIVE INFORMATION.

C. Site information

1. Investigator Name
2. Address

D. Suspect Medication(s)

1. Study Design: [ ] Blind [ ] Open/Unblind

Possible Dose (*e.g.*, 300 mg) _____ Frequency (*e.g.*, qd) _____ Route (*e.g.*, po)_____

2. Study Drug	**Formulation (*e.g.*, tablet, solution)**
	Lot No. (If known)

3. Start Date of Study Drug (Month/Day/Year):

4. Was blind broken due to event? [ ] No [ ] Yes [ ] NA

5. Was Study Drug stopped/interrupted/reduced in response to event? [ ] No [ ] Yes

>> If yes, complete a–e:

a. If stopped, specify date study drug last taken: _____ [ ] NA
(Month/Day/Year)

b. If reduced, specify: New dose _____ Date reduced _____ [ ] NA
(Month/Day/Year)

c. If interrupted, specify total number of days not given: _____ [ ] NA

d. Did event abate after study drug was stopped or dose reduced? [ ] NA [ ] Yes [ ] No

e. Did event reappear after study drug was reintroduced? [ ] NA [ ] Yes [ ] No

6. Was patient taking any other medications concomitantly at the time of the event? [ ] No [ ] Yes >> If yes, complete below.
(DO NOT LIST DRUGS USED TO TREAT EVENT)

Drug Name **Doses (units, frequency, route, indication for use)**	**Start Date**			**Stop Date** **or mark (X) if continuing**				
		Month	**Day**	**Year**	**Month**	**Day**	**Year**	**(X)**

(continue on a separate sheet if necessary)

E. Adverse Event

1. Relevant Laboratory/Diagnostic Tests [ ] No tests performed

Date			Test	Results	
				Actual Value	Normal Range
	Month	Day	Year		

(continue on a separate sheet if necessary)

2. Relevant Medical History, including preexisting conditions (*e.g.*, allergies, pregnancy, smoking & alcohol use, hepatic/renal dysfunction, medical/surgical history, *etc.*)

Date (if known)			Diseases/Surgeries/Treatment

(continue on a separate sheet if necessary)

3. NCI Toxicity GRADE of the Event (use NCI Common Toxicity Criteria): [ ] 0 [ ] 1 [ ] 2 [ ] 3 [ ] 4
If not gradable by NCI CTC, check one of the following: [ ] Mild (Causing no limitation of usual activities)
[ ] Moderate (Causing some limitation of usual activities) [ ] Severe (Causing inability to carry out usual activities)

4. Why Serious?
[ ] Results in death [ ] Is life-threatening [ ] Requires inpatient hospitalization or prolongation of existing hospitalization
[ ] Results in persistent or significant disability/incapacity [ ] Is a congenital anomaly/birth defect
[ ] Other, specify:_____

5. Outcome of Event (at time of report)

[ ] Resolved–date: _____ [ ] Improved [ ] Unchanged [ ] Worse [ ] Not available
(Month/Day/Year)
[ ] Fatal–date of death: _____ Autopsy performed? Y N
(Month/Day/Year) (circle one)
Cause of death: _____ (please attach death certificate and autopsy report, if applicable)

6. Investigator's opinion of the relationship between the event and the study drug (If more than one event is being reported,
list secondary events and corresponding relationship to study drug in the comments section below.) Check applicable box:

[ ] Not related [ ] Unlikely [ ] Possible [ ] Probable [ ] Definite

7. Was this event reported by the Investigator to (check all that apply): [ ] IRB [ ] Manufacturer/Distributor
[ ] Other Investigators participating in this study, if checked, please list names and institutions

_____
_____
_____
_____
_____

F. Comments/Clarifications:

FOR NCI USE ONLY

1. **Date NCI notified of event (Month/Day/Year):**

2. **Medical Monitor Review:**

Medical Assessment of Event (including drug relationship and expectancy):

Is this an FDA reportable (7 calendar days) event? [ ] Yes [ ] No

Is this an FDA reportable (15 calendar days) event? [ ] Yes [ ] No

>> If No, specify reason:_____

Is more information expected? [ ] Yes [ ] No

>> If Yes, specify:_____

Is this event to be communicated to other NCI contractors using this investigational drug? [ ] Yes [ ] No

>> If Yes, how? By telephone (attach a TC Form): [ ] Yes, attached TC Form [ ] No

Other (FAX, mail, e-mail, *etc.*): [ ] Yes, attached a copy of the correspondence [ ] No

Medical Monitor: Print name _____ Signature _____ Date _____