National Cancer Institute
Division of Cancer Prevention

Requirements for FINAL REPORTS: Phase I & II Clinical Trials of Chemoprevention Agents

Instructions and Templates

INTRODUCTION

The National Cancer Institute (NCI), Division of Cancer Prevention (DCP) requires a final report that summarizes all work performed and results obtained for the entire contract period of performance. This document presents the format and content required for the Final Report. A draft of the final report shall be submitted to the DCP Project Officer no less than 60 calender days before the end of the contract period. The Project Officer will return comments within 30 calender days. The Final Report is due to the Project Officer is due on the final day of the contract period. Use a running header or footer on each page indicating the NCI contract number (N01-CN-XXXXX) and the date of report submission to DCP. A list of the required sections and order of the Final Report format follows:

1.0 Title Page (template provided)
2.0 Synopsis Page (template provided)
3.0 Table of Contents
4.0 List of Abbreviations and Definition of Terms
5.0 Ethics
6.0 Investigators/Administrative Structure
7.0 Introduction
8.0 Study Objectives
9.0 Investigational Plan
10.0 Study Subjects
11.0 Efficacy Evaluation
12.0 Intermediate Biomarker Evaluation
13.0 Safety Evaluation
14.0 Discussion and Overall Conclusions
15.0 Tables, Figures and Graphs referred to but not included in text
16.0 Reference List
17.0 Appendices

The Final Report template begins on the following page.

Section 1.0
FINAL REPORT
TITLE PAGE

Study title and contract/grant number

Name of the investigational agent

Indication studied

Description of study: design, comparison, duration, dose and patient population

Name of sponsor

Protocol number

Phase of development (Phase I, IIa, IIb)

Study initiation date (first patient enrolled)

Study completion date (last patient complete, early study termination)

Name and affiliation of Principal or Coordinating Investigator(s)

Contact person for questions arising concerning the report

NCI DCP Project Officer

NCI DCP Medical Monitor

Statement indicting whether study performed in compliance with GLP

Date of Report

Section 2.0

FINAL REPORT OF CLINICAL STUDY
SYNOPSIS

Contract No._____ Protocol No. _____

Name of Sponsor/Company:	Name of Drug Product:	Name of Active Ingredient:
Title of Study:		
Investigators:		
Study Center(s):		
Study period (years): (date of first enrollment) (date of last completed)	Phase of development:	
Objectives:		
Methodology:		
Number of subjects (planned and analyzed)		
Diagnosis and main criteria for inclusion:		
Test product, dose and mode of administration, batch number:		

Name of Sponsor/Company:	Name of Drug Product:	Name of Active Ingredient:
Duration of treatment:		
Reference therapy, dose and model of administration, batch number:		

2.0 Synopsis (continued)

Name of Sponsor/Company:	Name of Drug Product:	Name of Active Ingredient:
Statistical methods:		

SUMMARY - CONCLUSIONS

EFFICACY RESULTS:

INTERMEDIATE BIOMARKER RESULTS:

SAFETY RESULTS:

CONCLUSION:

Date of the Report

Section 3.0 TABLE OF CONTENTS

Section 4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Provide a list of abbreviations, definitions of specialized or unusual terms, and

measurement units used in the report. At first appearance in the text, abbreviated terms should be spelled out; the abbreviation itself must be indicated in parentheses.

Section 5.0 ETHICS

5.1 Institutional Review Board (IRB): Confirm that the study and any amendments were reviewed by the IRB. Provide a list of all IRBs consulted in Appendix 17.1.3 and, if required by the regulatory authority, also provide the name of the committee Chair.

5.2 Ethical Conduct of the Study: Confirm that the study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

5.3 Patient Information and Consent: Describe how and when informed consent was obtained in relation to patient enrollment. Provide a sample of the patient consent form in Appendix 17.1.3, as well as copies of any other written information provided to the patient.

Section 6.0 INVESTIGATORS/ADMINISTRATIVE STRUCTURE

Briefly describe the administrative structure of the study (*e.g*., Principal Investigator, Coordinating Investigator, Steering Committee, Institutions, central laboratory facilities, contract research organization) in the body of the report. In Appendix 17.1.4, provide the following list of persons whose participation materially affected the conduct of the study, along with affiliations, role in the study, and *curricula vitae*:

6.1 Investigators.

6.2 Any other person carrying out observations of primary or other major efficacy variables, such as a nurse, physician's assistant, clinical psychologist, clinical pharmacist, or house staff physician.

6.3 Author(s) of the report, including the responsible biostatistician(s).

6.4 Persons responsible for receiving study samples (*e.g*., pharmacokinetic, pathology) at locations other than the study site.

Section 7.0 INTRODUCTION

The introduction should contain a brief statement (one page maximum) placing the study in context of development of the test drug/investigational product, relating critical

features of the study to that development. Describe or identify any guidelines that were followed in protocol development, or any other agreements/meetings between the sponsor, contractor and regulatory authorities, that are relevant to the particular study.

Section 8.0 STUDY OBJECTIVES

Provide a statement describing the overall purpose(s) of the study.

Section 9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan: Briefly describe the overall study plan and study design, using charts and diagrams as needed. Include actual protocol and any changes (including IND amendments submitted to FDA, if known, changes approved by the governing IRB(s), and changes initiated without IRB approval) as Appendix 17.1.1, and a sample case report form as Appendix 17.1.2. If information in this section comes from sources (*e.g*., clinical chemistry reports, pathology evaluations, pharmacokinetic data, *etc*.) other than the protocol, identify them and provide a copy of that part of the applicable report including:

- Treatments studied (specific drugs, doses, and procedures).
- Patient population studied and the number of patients to be included.
- Level and method of blinding/masking.
- Kind of control(s).
- Method of assignment to treatment (randomization, stratification).
- Sequence and duration of all study periods (including randomization). It is usually helpful to display the design graphically with a flow chart.
- Any safety, data monitoring, or special steering/evaluation committees.
- Any interim analyses.

9.2 Discussion of Study Design, Including Choice of Control Groups: Discuss the specific control chosen (*e.g*., concurrent placebo, concurrent dose comparison, historical) and the study design (*e.g.*, cross-over, randomized) used, as well as known or potential problems associated with the study design or control group chosen. Other specific features of the design may also deserve discussion, including presence or absence of washout periods, and rationale for dose and duration of treatment, especially for a chronic illness.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria: Describe patient population and selection criteria used to enter the patients into the study, and suitability of the population for purposes of the study discussed. Present specific diagnostic criteria used, as well as specific

disease requirements. Describe screening criteria and any additional criteria for randomization/entry into the test drug/investigational product treatment part of the trial. If there is reason to believe that there were additional entry criteria, not defined in the protocol, the implications of these should be discussed.

9.3.2 Exclusion Criteria: Specify criteria for exclusion from the study, and provide the rationale and impact.

9.3.3 Removal of Subjects From Therapy or Assessment: Describe predetermined reasons for removing subjects from therapy or assessment observation, and the nature and duration of any planned follow-up observations.

9.4 Treatments

9.4.1 Treatments Administered: Describe precise treatments or diagnostic agents to be administered in each arm of the study, and for each period of the study, including route and mode of administration, dose, and dosage schedule.

9.4.2 Identity of Investigational Product(s): Give a brief description of the test drug(s)/investigational product(s) [formulation, strength, batch number(s)] in the text of the report. If more than one batch of test drug/investigational product was used, identify subjects receiving each batch in Appendix 17.1.6. Describe any repackaging of the study drug from the sponsor. Note any use of test materials past their expiry date, and identify subjects receiving them. Describe any specific storage requirements.

9.4.3 Method of Assigning Subjects to Treatment Groups: Describe specific methods used to assign subjects to treatment groups, including centralized *vs*. site allocation, or stratification. Explain any unusual features. Give a detailed description of the randomization method, including how it was executed, in Appendix 17.1.7, with references cited if necessary. Present a table exhibiting the randomization codes, patient identifier, and treatment assigned in the Appendix.

9.4.4 Selection of Doses in the Study: Give doses/dose ranges used in the study for all treatments and describe the basis for choosing them.

9.4.5 Selection and Timing of Dose for Each Patient: Describe procedures for selecting each patient's dose of test drug/investigational product and active control/comparator. Describe timing (time of day, interval) of dosing and relation of dosing to meals, and note if timing was not specified.

9.4.6 Blinding: Provide a description of the specific procedures used to carry out blinding, including circumstances in which the blind would be broken for an individual or for all subjects, procedures used to do this, and a list of who had access to patient codes. If the study allowed for some investigators to remain unblinded, explain the means of shielding other investigators. If blinding was considered unnecessary to reduce bias for some or all of the observations, explain. If blinding was considered desirable but not feasible, discuss reasons and implications.

9.4.7 Prior and Concomitant Therapy: Describe which drugs or procedures were allowed before and during the study, whether and how their use was recorded, and any other specific rules and procedures related to, permitted, or prohibited regarding concomitant therapy. Discuss how the allowed concomitant therapy might affect outcome and how independent effects of concomitant and study therapies could be ascertained .

9.4.8 Treatment Compliance: Describe measures taken to ensure and document treatment compliance.

9.5 Efficacy, Intermediate Endpoint and Safety Variables: At present, efficacy in cancer chemoprevention trials is defined as measurements of histological lesions (malignant tumors, generally accepted premalignant tumors), including size, incidence, multiplicity and latency. For example, decreased size of existing colon adenomatous polyps or time to occurrence of a second primary cancer in the contralateral breast would be considered efficacy endpoints. Intermediate biomarkers other than accepted premalignant tumors are considered separately, since these have not been validated as surrogate trial endpoints (or surrogate endpoint biomarkers, SEBs) for cancer. Examples include proliferation biomarkers (PCNA, ODC synthesis), differentiation biomarkers (cytokeratins), genetic biomarkers (p53 mutations), biochemical biomarkers (PSA), and histological biomarkers (colonic aberrant crypts).

9.5.1 Efficacy, Intermediate Biomarker, and Safety Measurements Assessed and Flow Chart: Describe specific efficacy, intermediate biomarker, and safety variables that were assessed and laboratory tests that were conducted (including a list of normal ranges), their schedule, the methods for measuring them, and the persons responsible for the measurements. Report any changes in personnel carrying out critical measurements. It is usually helpful to display graphically the frequency and timing of efficacy, intermediate biomarker and safety measurements.

Explain in full any definitions used to characterize outcome. Describe any techniques used to standardize or compare results of laboratory tests or other clinical measurements. Identify anyone other than the investigator who was responsible for evaluating clinical outcomes. Fully describe procedures used, including means of maintaining blindness and centralizing readings and measurements.

Describe the means of obtaining adverse event data, and any rating of adverse events (*e.g*., grade, relationship to drug) by the investigator, sponsor, or external group. Five the criteria for such ratings, if any, and clearly identify the parties responsible for the ratings. If efficacy or safety was assessed in terms of categorical ratings or numerical scores, provide the criteria used for point assignment (*e.g*., NCI Common Toxicity Criteria grading for safety assessment; pathologic grading of tumors for efficacy assessment).

9.5.2 Appropriateness of Measurements: If the efficacy, intermediate biomarker or safety assessments were not standard, *i.e*., widely used and generally recognized as reliable, accurate and relevant, document their reliability, accuracy, and relevance. Part of the intermediate biomarker assay validation report could be used. Justify any assessment of an intermediate biomarker as a potential surrogate efficacy endpoint.

9.5.3 Primary Efficacy and Intermediate Endpoint Variable(s): Clearly specify primary measurements and endpoints used to determine efficacy. If the protocol did not identify primary variables, the study report should explain how these critical variables were selected and when they were identified. Describe any efficacy threshold defined in the protocol.

Clearly specify measurements and endpoints considered as intermediate biomarkers. If the protocol did not identify the primary variables, explain how these critical variables were selected and when they were identified.

9.5.4 Drug Concentration Measurements: Describe drug concentrations measured and sample collection times and periods in relation to timing of drug administration. Address any relation of drug administration and sampling to ingestion of food, posture, and possible effects of concomitant medication/alcohol/ caffeine/nicotine. Describe how the biological sample is measured, handling of samples, and method of measurement used, referring to published and/or internal assay validation documentation for methodological details. Where other factors are believed important in assessing pharmacokinetics, specify timing and plans which were used to measure these

factors.

9.6 Data Quality Assurance: Briefly describe implemented quality assurance and quality control systems; state if none were used. Document inter-laboratory standardization methods and quality assurance procedures, if used, under Appendix 17.1.10. Describe steps taken at the investigation site or centrally to ensure use of standard terminology and collection of accurate, consistent, complete and reliable data. Note whether investigator meetings or other steps were taken to prepare investigators and standardize performance. If the sponsor used an independent internal or external auditing procedure, mention here and describe in Appendix 17.1.8; provide audit certificates, if available, in the same appendix.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical Analytical Plans: Describe statistical analyses planned in the protocol and any changes made before outcome results were available. Emphasis should be on which analyses, comparisons, and statistical tests were planned, not on which were actually used. Describe any planned reasons for excluding from analysis subjects for whom data are available. Identify any subgroups whose results were to be examined separately. Clearly define categorical responses used in analyzing responses. Described planned monitoring of study results.

9.7.2 Determination of Sample Size: Provide planned sample size and the basis for it. Give methods for sample size calculation, together with their derivations or source reference. Give estimates used in the calculations, and explain how they were obtained.

9.8 Changes in the Conduct of the Study or Planned Analyses: Describe any change in conduct of the study or planned analyses instituted after the start of the study. Briefly discuss possible implications of change(s) for interpretations of the study in this section, and more fully in other appropriate sections of the report.

Section 10.0 STUDY SUBJECTS

10.1 Subject Disposition: Provide a clear accounting of all subjects who entered the study, using figures or tables, in the text of the report. Provide the numbers of subjects who were randomized and who entered and completed each phase of the study (or each week/month of the study), as well as reasons for all post-randomization discontinuations, grouped by treatment and by major reason. Make clear if subjects are followed for the duration of the study, even if drug is discontinued. In Appendix 17.2.1,

list all subjects discontinued from the study after enrollment, broken down by center and treatment group, giving a patient identifier, the specific reason for discontinuation, the treatment (drug and dose), cumulative dose (where appropriate), and the duration of treatment before discontinuation. Note whether or not the blind for the patient was broken at the time of discontinuation.

10.2 Protocol Deviations: Describe important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient managements or patient assessment. In the body of the text, appropriately summarize protocol deviations by center, grouped into different categories.

Section 11.0 EFFICACY EVALUATION

11.1 Data Set Analyzed: Define exactly which subjects were included in each efficacy analysis. It should be clear, if not defined in the study protocol, when and how inclusion/exclusion criteria for the data sets analyzed were developed. Provide a tabular listing of all subjects, visits, and observations excluded from the efficacy analysis provided in Appendix 17.2.3. Analyze reasons for exclusions for the whole treatment group over time.

11.2 Demographic and Other Baseline Characteristics: Present group data for the critical demographic and baseline characteristics of the subjects, as well as other factors arising during the study that could affect response, in this section. Provide a diagram showing the relationship between the entire sample and any other analysis groups. Critical variables, depending on the specific nature of the disease and on the protocol, will usually include:

11.2.1 Demographic variables of age, sex and race.

11.2.2 Disease factors:

- Specific entry criteria (if not uniform), duration, stage and severity of disease, and other clinical classifications and subgroupings in common usage or of known prognostic significance.
- Baseline values for critical clinical measurements carried out during the study or identified as important indicators of prognosis or response to therapy.
- Concomitant illness at trial initiation.
- Relevant previous illness.
- Relevant previous treatment for illness treated in the study.
- Concomitant treatment maintained, even if the dose was changed during the study; treatments stopped at entry into the study period (or changed

at study initiation).

11.2.3 Other factors that might affect response to therapy.

11.2.4 Other possibly relevant variables (*e.g*., smoking, alcohol intake, special diets, menstrual status).

In addition to tables and graphs giving group data for these baseline variables, present relevant individual patient demographic and baseline data, including laboratory values, and all concomitant medication for all individual subjects randomized (broken down by treatment and by center for multicenter studies) in by-patient tabular listings in Appendix 17.2.4.

11.3 Measurements of Treatment Compliance: Summarize measurements of compliance of individual subjects with the treatment regimen under study and drug concentrations in body fluids, analyze by treatment group and time interval, and tabulate in Appendix 17.2.5.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of Efficacy: Compare treatment groups for all critical measures of efficacy, as well as benefit/risk assessment(s), in each patient where these are used. The analysis should show the size (point estimate) of the difference between treatments, the associated confidence interval, and, where used, the results of hypothesis testing. If critical measurements or assessments of efficacy or safety outcomes were made by more than one part, show overall differences between the ratings and identify each patient having disparate assessments.

11.4.2 Statistical/Analytical Issues: In the text of the report, describe the statistical analysis used; present detailed documentation of statistical methods in Appendix 17.1.9. Discuss important features of the analysis, including particular methods used, adjustments made for demographic or baseline measurements or concomitant therapy, handling of dropouts and missing data, adjustments for multiple comparisons, special analyses of multicenter studies, and adjustments of interim analyses. Identify changes in analysis made after blind-breaking. In addition to the general discussion, address the following specific issues (unless not applicable):

11.4.2.1 Adjustments for Covariates: Explain selection of and adjustments for demographic or baseline measurements, concomitant therapy, or any other covariates or prognostic factors in the report, and include

methods of adjustment, results of analyses, and supportive information in the detailed documentation of statistical methods.

11.4.2.2 Handling Dropouts or Missing Data: Factors that may affect dropout rates include duration of study, nature of disease, efficacy and toxicity of drug under study, and other factors that are not therapy-related.

11.4.2.3 Interim Analyses and Data Monitoring: Describe interim analyses in full, as well as operating instructions or procedures used for such analyses. Describe data monitoring without code-breaking.

11.4.2.4 Multicenter Studies: Present individual center results; note and discuss extreme or opposite results among centers.

11.4.2.5 Multiple Comparisons/Multiplicity: For more than one primary endpoint or more than one analysis of a particular endpoint, or multiple treatment groups or subsets of the patient population being examined, the statistical analysis should reflect awareness of this and explain.

11.4.2.6 Use of an "Efficacy Subset" of Subjects: Substantial differences resulting from the choice of patient population for analysis should be the subject of explicit discussion.

11.4.2.7 Active-control Studies Intended to Show Equivalence: The analysis of active-control studies should show the confidence interval for comparison between two agents for critical endpoints and relate that interval to the prespecified degree of inferiority considered unacceptable.

11.4.2.8 Examination of Subgroups: A prior hypothesis of a differential effect in a particular subgroup and its assessment, where applicable, should be part of the planned statistical analysis.

11.4.3 Tabulation of Individual Response Data: Present individual response data and other relevant study information in tables. The study report should indicate what material is included as an Appendix, what is in the more extensive archival case report tabulations, and what is available on request.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response: When the dose for each patient can vary, the actual doses received should be shown and individual patient's doses should be tabulated. Also tabulate drug concentration information, if available (Appendix 17.2.5), and analyze it in pharmacokinetic terms related to pharmacodynamic or adverse effect response. Provide individual patient, patient ranges, and patient mean values for standard applicable pharmacokinetic parameters such as C_{max} and C_{min} for steady state determinations, peak concentration (C_{max}), time to reach peak concentration (t_{max}), area under the curve (AUC) , elimination rate constant (k_{el}), plasma half-life ($t_{1/2}$), volume of distribution (V_d), and plasma and renal clearance (Cl_p and Cl_r).

11.4.5 Drug-Drug and Drug-Disease Interactions: Describe any apparent relationship between response and concomitant therapy, and between response and past/concurrent illness.

11.4.6 By-Patient Displays: Individual patient data can be displayed in tabular listing as well as other formats.

11.4.7 Efficacy Conclusions: Important conclusions concerning efficacy should be concisely described.

Section 12.0 INTERMEDIATE BIOMARKER EVALUATION

Intermediate biomarkers are measurable parameters (histological, genetic, differentiation, proliferation or biochemical) which precede the formation of a malignant tumor. Biomarkers may be evaluated in clinical trials in three stages. The purpose of the first stage is to identify and evaluate biomarkers as predictors of increased cancer risk, *i.e.*, to establish the role of the biomarker in the etiology of the neoplasia under study. This involves determining if the biomarker is expressed differently in normal and high-risk tissue, is on or closely linked to the causal pathways for the cancer, can be measured quantitatively, reliably and accurately, and has a short latency compared to cancer. The next stage is to determine if the biomarker can be modulated by potential chemopreventive agents. Modulation by the study drug *vs*. placebo would then be evaluated as described above for efficacy. The final stage, validation of the biomarker as a surrogate endpoint for cancer in future trials, establishes that modulation of the biomarker correlates with decreased cancer incidence or increased latency. Only the sections below which apply to the stage of biomarker evaluation in a specific trial need to be included.

12.1 Applicability of Intermediate Biomarkers as Indicators of Increased Cancer Risk in Clinical Trials: If not presented previously, address sections (12.1.1–12.1.2) as discussed under efficacy evaluation (11.1–11.2). If both efficacy and

intermediate biomarkers were evaluated, the data sets may be different; for example, enough tissue may not be available for measurement of all biomarkers in each patient.

12.1.1 Data Set Analyzed.

12.1.2 Demographic and Other Baseline Characteristics.

12.1.3 Analysis of Intermediate Biomarkers: The following questions should be addressed in this section.

12.1.3.1 How easily can the biomarker be measured? Biomarkers that can be measured in tissues obtained by noninvasive techniques (sputum, urine, blood, mucosal brushings) and in small tissue specimens will be easier to obtain and are thus superior for use in chemoprevention studies. This may prove to be an important consideration for monitoring healthy individuals.

12.1.3.2 At what stage of carcinogenesis does the biomarker appear? The earlier a reliable biomarker (short latency) appears in the carcinogenic process, the greater the chance for successful intervention with resultant decreased cancer risk. Premalignant lesions are well-established precursors of cancer development; however, it is desirable to identify biomarkers that are manifest at earlier stages to maximize the probability of reversing the process.

12.1.3.3 Is the role of the biomarker in the etiology of neoplasia established? Can the progression of the biomarker from normal tissue to premalignant lesion to cancer be shown in a temporal fashion? Ideally, the biomarker should be differentially expressed in normal and high-risk tissue. In some cases, it will be absent in normal tissue and present in high-risk tissue (*e.g*., premalignant lesions); the biomarker may be present at even higher levels in malignant tissue, but not necessarily. In some cases, a different form may be present in precancerous tissue (*e.g*., colonic ODC), or lower or absent expression of the same form may occur (*e.g*., tumor suppressors).

12.1.3.4 How quantitative is the correlation between biomarker levels and cancer risk? Does the risk of cancer correlate with marker expression; does biomarker expression or the pattern of expression correlate directly with increased risk?

12.1.3.5 How reproducible are the experiments demonstrating the relationship between the biomarker and carcinogenesis?

12.1.3.6 How sensitive is the biomarker for predicting cancer risk? The sensitivity of the biomarker refers to that proportion of the population who exhibit the biomarker or have increased levels of the biomarker and later develop cancer or progression of premalignant lesions. The higher the rate at which the marker appears in a population or in premalignant lesions, the higher its estimated sensitivity and predictive value.

12.1.3.7 How specific is the biomarker for predicting cancer risk? A biomarker that is uniquely associated with a specific target tissue or tumor type may be considered to have more utility or predictive values for the purposes of intervention studies than one with wider occurrence. Also, expression of some biomarkers (*e.g*., growth factors and receptors) may increase during normal growth; they are thus nonspecific for cancer.

12.1.4 Statistical/Analytical Issues: Address this entire section if it was not discussed under efficacy or if statistical issues differ from the efficacy evaluation (see 11.4.2).

12.1.5 Tabulation of Individual Response Data: See Section 11.4.3.

12.1.6 By-Patient Displays: See section 11.4.6.

12.1.7 Conclusions: Concisely describe important conclusions concerning prediction of increased cancer risk by intermediate biomarkers.

12.2 Modulation of Intermediate Biomarkers by the Study Drug

12.2.1 Data Set Analyzed: See Section 11.1.

12.2.2 Demographic and Other Baseline Characteristics: See Section 11.2.

12.2.3 Measurements of Treatment Compliance: See Section 11.3.

12.3 Intermediate Biomarker Modulation Analysis and Tabulations of Individual Patient Data

12.3.1 Analysis of Intermediate Biomarker Modulation: Compare treatment groups for all intermediate biomarkers measured in each patient where these are used. The

analysis should show the size (point estimate) of the difference between the treatments, the associated confidence interval, and, where used, the results of hypothesis testing.

12.3.2 Statistical/Analytical Issues: See Section 11.4.2.

12.3.3 Tabulation of Individual Response Data: See Section 11.4.3.

12.3.4 Drug Dose, Drug Concentration, and Relationships to Response: See Section 11.4.4.

12.3.5 Drug-Drug and Drug-Disease Interactions: Describe any apparent relationship between intermediate biomarker response and concomitant therapy, and between response and past/concurrent illness.

12.3.6 By-Patient Displays: Individual patient data can be displayed in tabular listing as well as other formats.

12.3.7 Conclusions: Concisely describe important conclusions concerning modulation of intermediate biomarkers.

12.4 Validation of the Intermediate Biomarker as a Predictor of Cancer Risk

12.4.1 Data Set Analyzed: See Section 11.1.

12.4.2 Analysis of Intermediate Biomarker Validation: Does modulation of each intermediate biomarker result in decreased cancer risk (*e.g.*, decreased incidence, recurrence, multiplicity or increased latency)? For example, a high frequency of micronuclei (chromosome or chromatid fragments produced in proliferating cells as a result of clastogenesis) correlates with cancer risk in humans. However, suppression of micronucleus formation by chemopreventive agents did not result in a significant reduction in premalignant esophageal lesions in one study. Thus, use of this biomarker was not validated as a surrogate endpoint for increased cancer risk.

12.4.3 Statistical/Analytical Issues: See Section 11.4.2.

12.4.4 Tabulation of Individual Response Data: See Section 11.4.3.

12.4.5 Drug Dose, Drug Concentration, and Relationships to Response: See Section 11.4.4.

12.4.6 Drug-Drug and Drug-Disease Interactions: Describe any apparent relationship

between efficacy/biomarker response and concomitant therapy, and between response and past/concurrent illness.

12.4.7 By-Patient Displays: Individual patient data can be displayed in tabular listing as well as other formats.

12.4.8 Conclusions: Concisely describe important conclusions concerning correlation of efficacy result with modulation of intermediate biomarkers.

Section 13.0 SAFETY EVALUATION

In the following sections, three kinds of analysis and display are called for:

- Summarized data, often using tables and graphical presentations in the main body of the report;
- Listings of individual patient data; and
- Narrative statements of events of particular interest.

In all tabulations and analyses, display events associated with both test drug and control treatment.

13.1 Extent of Exposure: Characterize extent of exposure to test drugs/investigational products according to number of subjects exposed, duration of exposure, and dose to which they were exposed. It is assumed that all subjects entered into treatment who received at least one dose of the treatment are included in the safety analysis; if not, provide an explanation.

13.2 Adverse Events (AEs)

13.2.1 Brief Summary of Adverse Events: Describe the study's overall adverse event experience in a brief narrative, followed by supporting detailed tabulations and analyses. Provide copies of reports of serious adverse events and deaths, and related follow-up reports expeditiously submitted by the Sponsor to FDA via telephone or in writing, in Appendix 17.2.7.

13.2.2 Display of Adverse Events: Display adverse events occurring after initiation of study treatments in summary tables. Tables should include changes in vital signs and any laboratory changes considered serious adverse events under NCI and FDA criteria (fatal, all life-threatening events, any serious adverse event that results in hospitalization, a congenital anomaly, or a permanently disabling event) or other significant adverse events (marked hematological or other laboratory abnormalities, events that required intervention). The tables should list each adverse event, the number of subjects in each treatment group in

whom the event occurred, and the rate of occurrence. Subsequent analyses of the study or of the overall safety database may help to distinguish between adverse events that are, or are not, considered drug related.

Provide an additional summary table comparing treatment and control groups, without the patient identifying numbers and limited to relatively common adverse events, in the body of the report.

13.2.3 Analysis of Adverse Events: Use the basic display of adverse event rates described in section 13.2.2 of the report to compare rates in treatment and control groups. A variety of analyses may be suggested by study results or by pharmacology of test drug/investigational product.

13.2.4 Listing of Adverse Events by Patient: List all adverse events for each patient, including the same event on several occasions, in Appendix 17.2.7, giving both preferred COSTART term and the original term used by the investigator.

13.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

13.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events: Provide listings that contain the same information as called for in section 13.2.4, for the following events.

13.3.1.1 Deaths: List all deaths during the study by patient in section 15.0.

13.3.1.2 Other Serious Adverse Events: List all serious adverse events in section 15.0.

13.3.1.3 Other Significant Adverse Events: List marked hematological and other laboratory abnormalities, and any events that led to an intervention, other than those reported as serious adverse events, in section 15.0.

13.3.2 Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events: Provide a brief narrative describing each death, other serious adverse events, and other significant adverse events judged of special interest due to clinical importance.

13.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events: Assess the significance of deaths, other serious adverse events, and other significant adverse events leading to withdrawal, dose reduction, or institution of concomitant therapy, with respect to safety of test drug/investigational product.

13.4 Clinical Laboratory Evaluation

13.4.1 Listing of Individual Laboratory Measurements by Patient (Appendix 17.2.8) and Each Abnormal Laboratory Value (section 15.0): Provide a by-patient listing of all laboratory values outside of normal range for the facility in section 15.0.

13.4.2 Evaluation of Each Laboratory Parameter: Provide the following analyses. For each analysis, compare treatment and control groups, as appropriate and compatible with study size, and normal laboratory ranges.

13.4.2.1 Laboratory Values Over Time: For each parameter at each time over the course of the study, describe group mean/median values, range of values, and number of subjects with abnormal values.

13.4.2.2 Individual Patient Changes: Give an analysis of individual patient changes by treatment group. A variety of approaches may be used, including tables or graphs.

13.4.2.3 Individual Clinically Significant Abnormalities: Discuss clinically significant changes, and assess the significance of the changes and likely relation to treatment.

13.5 Vital Signs, Physical Findings, and Other Observations Related to Safety: Analyze vital signs, other physical findings, and other observations related to safety, and present similarly to laboratory variables. Pay particular attention to changes not evaluated as efficacy variables and to those considered to be adverse events.

13.6 Safety Conclusions: Review overall safety evaluation of test drug(s)/ investigational product(s). Identify subjects or patient groups at increased risk. Describe implications of safety evaluation for possible uses of the drug.

Section 14.0 DISCUSSION & OVERALL CONCLUSIONS

Briefly summarize and discuss efficacy, intermediate biomarker, and safety results of the study and relationship of risks and benefits, referring to tables, figures, and sections above as needed. Do not simply repeat the description of results nor introduce new results. Discussion and conclusions should clearly identify any new or unexpected findings, comment on their significance, and discuss any potential problems.

Section 15.0 TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN TEXT

Present important demographic, efficacy, and safety data in summary figures or tables in the text of the report. However, if these become obtrusive because of size or number, present them here, cross-referenced to the text, along with supportive or additional figures, tables or listings (*e.g*., Narratives of Deaths and Other Serious or Significant Adverse Events, Abnormal Laboratory Values by Patient).

Section 16.0 REFERENCE LIST

Provide a list of articles from the literature pertinent to the study evaluation.

Section 17.0 APPENDICES

Preface this section by a full list of Appendices available for the study report, clearly indicating those Appendices that are submitted with the report.

17.1 Study Information

17.1.1 Protocol and protocol amendments.

17.1.2 Sample case report form (unique pages only).

17.1.3 List of IRBs and representative written information for patient and sample consent forms.

17.1.4 List and description of investigators and other important participants in the study.

17.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer.

17.1.6 Listing of subjects receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.

17.1.7 Randomization scheme and codes.

17.1.8 Audit certificates.

17.1.9 Documentation of statistical methods.

17.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures.

17.1.11 Publications based on the study.

17.1.12 Important publications referenced in the report.

17.2 Patient Data Listings

17.2.1 Discontinued subjects.

17.2.2 Protocol deviations.

17.2.3 Subjects excluded from the efficacy analysis.

17.2.4 Demographic data.

17.2.5 Compliance and/or drug concentration data.

17.2.6 Individual efficacy response data.

17.2.7 Adverse event listings (each patient).

17.2.8 Listing of individual laboratory measurements by patient.

17.3 Representative Set of Case Report Forms (CRFs)

17.4 Individual Patient Data Listings