STATISTICAL ANALYSIS PLANS
PRINCIPLES AND PRACTICE
Workshop Number 8

Presented at the
Society for Clinical Trials
2007 Annual Meeting
Montreal, Canada
Sunday May 20, 2007

James R. Johnson, Ph.D.
David Fitts, Ph.D., MPH
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Presented By: James R. Johnson, PhD
David Fitts, PhD, MPH

Learning Objectives

• At the end of this session you should have a comprehensive understanding of the:
  – Why we Plan for Statistical Analysis?
  – Definition of the Statistical Analysis Plan (SAP).
  – Historical and Regulatory (FDA, EMEA, ICH) framework for the SAP.
  – Relationship of the SAP to Internal and External Documents/Publications.
  – SAP audience(s).
  – The SAP and Statistical Ethics.
  – Structure and Content of the SAP.
  – SAP Template(s).
    • Drug/Device Development Program Planning
    • Phase I PK/PD Safety Studies
    • Phase II Screening and Dose Finding Studies
    • Phase IIb/III Registration Studies
  – Communication and Writing Style.
Why do we Plan Statistical Analyses?

Why Plan?

1. **Study Design**
   - Sets the groundwork for establishing Good Statistical Practices

2. **Study Methods**
   - Implementing the Plan outlined in the Study Design. Concerned primarily with Data Collection Methods, and validation of the data collection methodology.

3. **Study Analysis**
   - Rational analysis of the planned study design, implemented with solid methodology; generally results in observations that are true to the experiment.

4. **Feedback Loop**
   - The Study Analysis serves to provide a check on the Original Study Design. Is an indicator of how well the design, data management, and statistical practices were established and implemented.
Statistical Planning in a Study

- Statistical Planning phases start at the beginning of a study with the primary research question.
- Key planning issues that “significantly influence” statistical analysis include:
  - Assessment of Study Objectives and Endpoints.
  - Methods for Data Collection
  - Key Variable Identifications, Data Dictionary Definitions
  - Methods for Key Variable Validation and Robustness
  - Methods for Subject Randomization (if applicable)
  - Relationships for Database Design

Study Design Phase

- At Study Design the concept of rational statistical practices must be started.
- Critical questions that must be addressed at the conception of a Research Protocol.
  - What is the “Clear” Objective of the study?
  - What is the Key Variable(s) to be assessed in the study?
  - How are the Key Variable(s) measured?
  - Can Key Variable measurements be reproduced and validated.
  - Are the Key Variables:
    - Objective Assessments by an Independent Assessor or Instrument?
    - Subject Assessments supplied by the Subject or Observation?
- STOP...If you cannot answer these Questions?
Why Plan? \(\Rightarrow\) Data Errors??

- A Data Error may be defined as any deviation from the true or expected value where the cause of the deviation may be know or unknown, due to random chance or systematic biases.

- Clearly, we plan to avoid and/or eliminate “systematic biases”.

Why Plan? \(\Rightarrow\) Data Errors?

- Where do “data errors” come from in a clinical trial?
  - During the design stage of the trial (Protocol, Case Record Forms, Poor Statistical Planning).
  - During the Training of Investigators and Study Coordinators on “How to assess each data item in the study”.
  - During Edit specifications and Medical Review.
  - During Coding of Adverse Events and/or Medications.
  - During the Analysis and Tabulation of Study Results.
  - During the writing and publication of Study Results.
SAP Definition

The Definition of what is an SAP comes primarily from professional organizations and regulatory authorities:

- ICH E9 (Statistical Principles for Clinical Trials)
- FDA (Federal Register Vol. 63, No. 179, Wednesday, September 16, 1998)
- National Institutes of Health (NIH)
- PSI (Statisticians in the Pharmaceutical Industry)
- GMDS (Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V.)
SAP Definition

• From the ICH E9 and FDA CFR:
  - A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and included detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. (ICH Guidelines: E9) (Federal Register Vol. 63, No. 179, Wednesday, September 16, 1998)

SAP Definition

• From the NIH:
  - A comprehensive and detailed description of the methods for, and presentation of, data analyses for a study protocol. The plan ensures that analyses are conducted in a scientifically valid manner and that decisions are documented. (National Institutes of Health: Glossary of Terms)
SAP Definition

- From PSI (Statisticians in the Pharmaceutical Industry):
  - The statistical analysis plan is intended to be a comprehensive and detailed description of the methods and presentation of data analyses proposed for a clinical trial, in order to avoid post hoc decisions which may affect the interpretation of the statistical analysis. (PSI: Guidelines for Standard Operating Procedures for Good Statistical Practice in Clinical Research and also in North PM. DIA Journal 1996;(32):665-682)

- From Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie e.V. (GMDS):
  - The statistical analysis plan is intended to be a comprehensive and detailed description of the methods and presentation of data analyses proposed for a project, in order to avoid post hoc decisions which may affect the interpretation of the statistical analysis. (GMDS e.V)

  - Furthermore the GMDS states: "The statistical analysis plan prevents medical professionals from drowning in technical terms and protects the biometrician from useless data torturing. (Mills JL. NEJM 1993; (329):1196-1199)"
SAP Definition

• Each definition is articulating the following principles:
  – Elaboration of study protocol hypotheses.
  – Comprehensive and detailed description of the *prospective statistical methods* to evaluate planned study hypotheses.
  – Procedures for executing the planned statistical analyses.
  – *A priori* methods to avoid post-hoc decisions which may affect the interpretation of the statistical analysis (and Regulatory Acceptance!)
  – Details on how results will be presented and reported.
  – Obligations for Good Statistical Practice and Statistical Ethics.

Historical Basis for the SAP
Historical Basis for the SAP

- There has been some historical precedent for the creation of a “Statistical Analysis Plan”…although called by many other names.
  - Originated in Europe (19th and 20th Century)
  - US in late 20th Century

Historical Basis for the SAP

- Florence Nightingale (1820-1910) is relevant to statistics today. She is often quoted with regard to “healthcare auditing” and “quality management” in presenting “medical observations”.
- She is regarded as a pioneer for documenting epidemiological methods for reporting public health statistics.
- Often spoke on the “far reaching application of statistics” and “how one needed to be aware of how data could be manipulated”.
- Elected in 1858 the first female member of the Royal Statistical Society; Named an honorary lifetime member of the American Statistical Association.
Historical Basis for the SAP

- British Statistician Sir Ronald Aylmer Fisher (1890-1960) is generally credited with being the first advocate to explain the use of randomization in experiments. [Fisher RA. The arrangement of field experiments. J. Ministry Agriculture in Great Briton 1926;(33):503-513]
- Documented the need to “explain in a written plan” to the Biologist the randomization and reduction of sampling bias.
- Original work was in Agriculture and Soil Science.

Sir R.A Fisher
1890-1962

Historical Basis for the SAP

- Article fully specified statistical methods and set the standard for the BMJ for publishing clinical trials, with a “full statistical plan”, and for the medical research councils to have a statistician work alongside a physician.

Sir Austin Bradford Hill
1897-1991
Historical Basis for the SAP

• CONSORT Statement:
  - To comprehend the results of a randomized controlled trial (RCT), readers must understand its design, conduct, analysis, and interpretation. (From Abstract)
  - 22-Item Check List: 11 of the items are related to Statistical Planning, Analysis, and Reporting for the RCT
Historical Basis for the SAP

- Statistical Science has historical roots at the FDA:
  - 1962: Division of New Drugs, Medical Evaluation Branch formed with responsibility for reviewing Safety and Efficacy Data. First evidence of applied statistical review to applications.
  - 1974: Office of Biometrics and Epidemiology formed to support “FDA Science”, provided statistical consulting to FDA Medical Evaluation Branch reviewers upon request.
  - 1984: Office of Biostatistics and Epidemiology (Gerald Faich, MD, MPH, Director) starts completing a statistical review of NDAs.
  - 2002: Office of Biostatistics formed (Robert T. O’Neil, Ph.D., Director) with expanded responsibilities across the spectrum of drug and biologics review.

[Abstracted From the FDA History Web Page: 2005]

Regulatory Roots for the SAP
Regulatory Roots for the SAP

- ICH Guidelines: E9
  - I. Introduction [Part A: Background and Purpose]
    This guidance is intended to give direction to sponsors in the design, conduct, analysis, and evaluation of clinical trials of an investigational product in the context of its overall clinical development.

Regulatory Roots for the SAP

- ICH Guidelines: E9
  - II. Considerations for Overall Clinical Development [Part A.1: Development Plan]
    A statistical summary, overview, or meta-analysis may be informative when medical questions are addressed in more than one trial. Where possible, this should be envisaged in the plan so than relevant trials are clearly identified and any necessary common features of their designs are specified in advance. Other major statistical issues (if any) that are expected to affect a number of trials in a common plan should be addressed in that plan.
Regulatory Roots for the SAP

- Roots for the ICH Guidelines: E9 originate from:

Regulatory Roots for the SAP

- The Impact of the ICH E9 Guidance on the pharmaceutical industry has been reviewed in an article in Statistics in Medicine.
Regulatory Roots for the SAP

• Recent FDA and EMEA Guidance each identify the SAP as an important component of the particular application and program:
  - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA Guidance: April 2005)
  - Analysis Plans for DMCs (FDA Draft Guidance: December 2005)
  - Points to Consider for Missing Data (EMEA Guidance November 2001)
  - Points to Consider on Clinical Investigation of Medicinal Products for the Treatment of Acute Stroke (EMEA Guidance September 2001)
  - Fast Track Drug Development Programs-Designation, Application, and Review (FDA Guidance: January 2006)

These guidance documents are rooted in ICH E3, E8, and E9.

Regulatory Roots for the SAP

• Trend in Regulatory Agency practices is to treat the SAP as a document that may be reviewed as part of the pre-approval process at:
  - End of Phase I and Phase II Meetings (Development Plan Reviews)
  - Special Protocol or Development Plan Reviews
  - Orphan or Fast Track Status Reviews
  - CTD Completion: Specifically Modules 2.5 & 2.7 (Clinical Overview & Clinical Summaries) and Module 5 (Clinical Study Reports)
  - Other special requests
SAP Document Relationships

- Supports both Internal and External documents prepared for clinical research.

![Diagram showing relationships between Clinical Development Plan, Investigator's Brochure, Registration of Clinical Studies, Clinical Protocol and CSR, Registration Dossiers, Public Disclosure of Clinical Study Results, Publication of Clinical Study Results, Product Labeling, and Statistical Analysis Plan Supports.](image_url)
SAP and Document Relationships

• Any SAP developed must be viewed for internal support and consistency among the:
  - Clinical Development Plan
  - Investigators Brochure
  - Clinical Protocol and CSR
  - Registration Dossier’s (NDA, PLA)

• Consistency in statistical methods between studies is identified in ICH E9 documents at the Development Plan level.
  - Allows for development of a common analysis theme across a program.

The SAP must support policies for Registration of Clinical Trials, and requirements outlined by the FDA for trial registration. (Specifically Phase II and III studies)
SAP and Document Relationships

- The SAP will support Clinical Trials Results Disclosure.

SAP Audiences
SAP Audiences

- The SAP Must be written assuming that a diverse group of individuals, with a diverse set of skills, with a diverse understanding of Biostatistics may read the SAP...and make decisions from information derived from the SAP.
SAP and Statistical Ethics

- Ethics associated with statistical practice are documented in:
  - Good Biometrical Practice in Medical Research (Mansmann, Jensen, and Dirschdel for Deutsche Gesellschaft für Medizinische Informatik, Biometrie und Epidemiologie)
  - The Royal Statistical Society Code of Conduct (Royal Statistical Society August 1993)
SAP and Statistical Ethics

• A common theme in all the statistical ethics guidelines is the appropriate documentation (communication) of statistical practice.
  – ASA Guidelines for Responsibilities in Publications addresses the need “to report sufficient information to give readers, including other practitioners,…, a clear understanding of the intent of the work, and any limitations on its validity”

SAP and Statistical Ethics

• Sufficient Information and Clear Understanding Means Providing Information:
  – To allow for the analysis to be repeated by reviewing authorities.
  – To document the reasoning for the choice of the model to be applied to the analysis.
  – To ensure that any limitations to the planned analysis are declared a priori, if they are known or expected.
  – To preserve the integrity of the data, while ensuring that the safety and confidentiality of human subjects is preserved.
**SAP: Structure and Content**

**Structure and Content: Development Plan: Statistical Planning**

- Statistical Planning starts when a development plan is initiated and before the first subject is treated. Plan for consistency across a development program for:
  - Endpoints and Definitions
  - Assessment Methods for Endpoints
  - Analysis Methods for Endpoints

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Objective</th>
<th>Endpoint</th>
<th>Definition of Endpoint</th>
<th>Assessment Method</th>
<th>Analysis Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study #1</td>
<td>To evaluate the efficacy of Drug X compared to Control in Adult Subjects with Disease A.</td>
<td>Time to elimination of Symptoms of Disease</td>
<td>Defined as the time of randomization to the time when all 5 symptoms are absent, and remain absent for 24 hour.</td>
<td>5 Symptoms (S1, S2, S3, S4, S5) are scored on a 0 to 10 scale TID. A score of 0 or 1 is considered absent.</td>
<td>Treatment differences will be assessed using a Cox Regression model with effects for gender and treatment group.</td>
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<tr>
<td>Study #2</td>
<td>...</td>
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Structure and Content of SAP

- The Statistical Analysis Plan **IS NOT** a regurgitation of the protocol!
  - Cross Reference to the following documents is very useful:
    - Clinical Research Protocol, and amendments.
    - Case report forms (CRFs) for Protocol.
    - Other Named Documentation.
    - ICH Guidance on Statistical Principles for Clinical Trials.
  - The SAP should not be viewed as a stand alone document and readers should be encouraged to also read the clinical protocols for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.
### Structure and Content of the SAP (Phase IIb-III Version)

**SAP SECTION** | **REFERENCES**
---|---
1.0 PREFACE | E3 (9.7.1); E8 (3.2.4)
2.0 PURPOSE OF SAP | E3 (9.0); E9 (5.1)
3.0 STUDY OBJECTIVES AND ENDPOINTS | E3 (9.0); E9 (2.1, 2.2.2)
3.1 STUDY OBJECTIVES | E3 (9.0)
3.1.1 PRIMARY STUDY OBJECTIVE | E9 (2.2.2)
3.1.2 SECONDARY OBJECTIVE(S) | E9 (9.5.2, Annex VIII)
3.2 STUDY ENDPOINTS | E9 (9.5.2, Annex VIII)
3.2.1 PRIMARY TARGET VARIABLE | E9 (9.5.2, Annex VIII)
3.2.2 SECONDARY TARGET VARIABLE(S) | E9 (9.5.2, Annex VIII)
3.2.2.1 APPROPRIATENESS OF SECONDARY TARGET VARIABLE | E9 (9.5.2, Annex VIII)

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| 4.0 STUDY METHODS | REFERENCES |
---|---|
4.1 OVERALL STUDY DESIGN AND PLAN | E3 (9.1); E9 (3.1) |
4.2 SELECTION OF STUDY POPULATION | E3 (9.3); E9 (2.2.1, 4.2) |
4.3 METHOD OF TREATMENT ASSIGNMENT AND RANDOMIZATION | E3 (9.4.3); E9 (2.3.2) |
4.4 TREATMENT MASKING (BLINDING) | E3 (9.4.6); E9 (2.3.1) |
5.0 SEQUENCE OF PLANNED ANALYSES | E9 (3.2.4) |
5.1 INTERIM ANALYSES | E3 (9.7.1, 11.4.2.3); E8 (3.2.4); E9 (4.1, 4.5) |
5.2 FINAL ANALYSES AND REPORTING | E9 (7.1) |
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(Phase IIb-III Version)

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<td>19.0 ATTACHMENTS</td>
<td>No E3 or E9 Reference</td>
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</table>

May be used to present additional information relevant to the planned analyses (e.g. VAS Scale, model validation, etc.)

SAP Template(s)
SAP Templates

- Developed in MS Word, as Document Templates
- Contains Hidden Text *(in Red Italic)* describing the function of the respective Section.
- 1st and 2nd level headers (Header1, Header2) structure should be maintained for consistency across programs.

Hidden Text in MS Word

- To Turn ON/Off Display of Hidden Text
  - On the Tool Bar
  - Tools, Options
  - Check Hidden Text to Turn On
  - Remove Check to Turn Off
SAP Template(s)

- Draft SAP Template for Phase I Studies
  (with Safety and PK/PK Components, No Efficacy)
- Draft SAP Template for Phase I-IIa / POC Studies
  (with an Exploratory Proof Of Concept or screening study Efficacy Component)
- Draft SAP Template for Phase IIb / III Studies
  (Confirmatory, Registration, Studies)

SAP Template(s): Required Figure for ALL Clinical Study Reports

- Patient Disposition
  (ICH E3)
  (CONSORT)
Table, Listing, Figure Template

• The production of Tables, Listings, and Figures (TLF) is separate from the completion of the SAP.

• TLF Production template is a guide for the form and function of each planned TLF, and serves as a programming guide.

• Draft TLF Production Template
  – (Note: TLF shells can be included that are study, program, or organization specific.)

SAP Communication & Writing Styles
(Some Tips for Effective Statistical Writing)
SAP: Effective Communication

• If the reader is to grasp what the writer means, the writer must understand what the reader needs.

• The fundamental purpose of scientific discourse is not the mere presentation of information and thought, but its communication. …. it matters only whether a large majority of the reading audience accurately perceives what the author had in mind.


SAP: Effective Communication

• Myth: Obscurity Equals Brilliance

  – Many people use jargon and obscure writing that makes their words inscrutable to everyone except the two colleagues who already know their work…..What obscurity really does, however, is conveniently mask ignorance and error; if no one understands your work, no one can evaluate it either. (Terra Ziporyn, Ph.D., Associate Editor for JAMA and Scientific Writing Professor)

  – Vagueness does not make for good science or good writing; clarity, precision, and specificity do!
SAP: Effective Communication

• Myth: Writing Well is Easy
  – Clear and concise writing takes time and effort.
  – Effective writing goes hand-in-hand with clear thinking and a well
developed self-critical sense to be able to judge your own writing
objectively, and honestly evaluate the work’s ability to communicate the
science. (Terra Ziporyn, Ph.D., Associate Editor for JAMA and
Scientific Writing Professor)

SAP: Effective Communication

• Statistics is NOT easy to Communicate
  – Recommended Reading:
    • Day RA. Scientific English: A Guide for Scientists and Other Professionals,
    • Mathews JR. Bowen JM, Mathews RW. Successful Scientific Writing: A
Step-by-Step Guide to the Biological and Medical Sciences. 2001.
    • Lang TA. How to Report Statistics in Medicine: Annotated Guidelines for
SAP: Effective Communication

10 Tips to Consider:

1. Plan your writing; Determine what you need to communicate before you write; Think in Terms of an Outline (Use the SAP Template).
2. Know your audience and plan writing accordingly.
3. Keep it Simple and Short (KISS); Avoid Redundancy.
4. Avoid Jargon and Obscure Words.
5. Get to the Point (Quickly).
6. Don’t Ramble; Precise, concise, language is much stronger.
7. Do Not confuse issue(s); Singular points are always clearer.
8. Use active voice (generally 3rd person); Avoid a passive voice.
9. Edit, Edit, and Edit again…...Then have a colleague edit for you.
10. Allow plenty of time to Write and Edit.

Conclusions

What have we learned?

- Definition and Origin of the SAP
- Regulatory Roots and framework for an SAP (ICH E3, E8, E9), with consideration for published medical literature. (CONSORT).
- Ethical Reporting and Statistical Practice: International in Scope (PSI, RSS, GMDS e.V, ASA)
- The relationship of the SAP to Internal and External Documents and reporting of trial results.
- Who are audiences for an SAP.
- Structure and Content of the SAP with reference to appropriate E3, E8, E9, and other documentation.
- SAP Template(s).
- Some general comment on Communication and Writing Style.
Download this Workshop

If you wish to download an electronic copy of this workshop go to:
Web Page: www.minimalsufficency.com
Or
Email david.fitts@minimalsufficancy.com

The presentation and templates are available for free as Microsoft Word (*.dot) files.

Questions
STATISTICAL ANALYSIS PLANS
PRINCIPLES AND PRACTICE

Society for Clinical Trials Workshop
May 20, 2007

Attachment
SAP Template for a Phase II/III Study
STATISTICAL ANALYSIS PLAN

Insert the full protocol title, final protocol date, SAP Author and versioning, and the name(s) of individuals who will approve the SAP.

Protocol Title: <full title of Protocol>
(Number): (protocol number)

Protocol Date:

SAP Author:

SAP Version:

SAP Date:

CONFIDENTIAL
**Approvals:**

Approved By:

Name: <Name>  
<Title>  

Date:

Name: <Name>  
<Title>  

Date:
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ABBREVIATIONS

Common abbreviations used in the SAP are already present in the list. Insert only those abbreviations relevant to the SAP and to the statistical nomenclature used in the SAP. It is not necessary to insert abbreviations that are related only to the clinical protocol, as they may be cross-referenced with the protocol.

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-To-Treat Population</td>
</tr>
<tr>
<td>PP</td>
<td>Per-Protocol Population</td>
</tr>
<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
</tr>
</tbody>
</table>
1. PREFACE

The PREFACE section is used to present an abbreviated introduction to why this statistical analysis plan is being developed, and for what protocol this SAP will support. Language is suggested to highlight protocol identification, the phase (II or III) of the program, and details that the structure and content are compatible with the CSR structure and content and ICH/FDA Guidance documents.

The preface also identifies documents that were reviewed to complete this SAP. Inserting this text for documents reviewed allows the writer to reference key components of the protocol without duplication.

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for <insert name of organization> protocol <number> (<full title>).

This phase <II  or III> study is being completed to assess the safety and efficacy of <name of drug> for the treatment of <name of primary target disease> in a <brief description of target population>.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association and the Royal Statistical Society, for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol <protocol number>, and amendments <if appropriate> issued <date>.
- Case report forms (CRFs) for Protocol <protocol number>.
- <Other named> Documentation.
- ICH Guidance on Statistical Principles for Clinical Trials.

The reader of this SAP is encouraged to also read the clinical protocols for details on the conduct of this study, and the operational aspects of clinical assessments and timing for completing a patient in this study.
2. PURPOSE OF SAP

This section is a very brief rationale why the SAP is being completed and where the results of this work may be used. Suggested language is provided to streamline this section.

A key element of the PURPOSE is to identify when and where the SAP may be amended. ICH E3 and E9 indicate that planned analyses may be documented in either the protocol or a statistical analysis plan. Post-hoc analyses are discouraged, yet often are necessary, so it is critical to detail how post-hoc or ad-hoc analyses may be documented in the final clinical study report, and that the SAP need not be amended to support these types of additional analyses.

The purpose of this SAP is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol <protocol number>. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.
3. STUDY OBJECTIVES AND ENDPOINTS

The study objectives (primary and secondary) are to be inserted in this section verbatim from the study protocol. Section 3.1 is for the Objective, 3.2 are for the Endpoints with corresponding Target Variables.

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective is …

3.1.2 Secondary Objectives

Secondary objectives are …

3.2 Study Endpoints (Target Variables)

Note that the Primary Variable is the variable from which the sample size should have been estimated for the study, and is the variable that is capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial.

3.2.1 Primary Target Variable

If either the primary or secondary target variables are COMPOSITE variables, that is a combination of multiple measurements; then it is very important to provide a brief explanation on the validity of the combined measurement and any information regarding the validation or acceptance of the combined measurement. (See section B3 in ICH E9). The same requirement for Multiple Primary Variables or Surrogate Variables is also applicable to this requirement for additional explanation and supporting documentation. Sections 3.2.1.1 and 3.2.2.1 may be used to explain the appropriateness of the target variables, including justification (with reference to publications, previous data, or previous guidance from regulatory authorities) for the target variable.

The primary target variable (endpoint) is …

3.2.1.1 Appropriateness of Primary Target Variable

3.2.2 Secondary Target Variable(s)

Secondary target variables (endpoints) are …
3.2.2.1 Appropriateness of Secondary Target Variable(s)

4. STUDY METHODS

The section of the SAP devoted to Study Methods is not meant to be a redundancy of the study methods and plan in the protocol. Cross-referencing the protocol is adequate for this purpose. It is, however, important to present sufficient information for the identification, timing, and collection of study assessments relevant to the target variables (primary and secondary).

4.1 Overall Study Design and Plan

A brief paragraph from the protocol with the key features and rationale for the study design is inserted in this section. Any design techniques used to prevent and avoid selection or analytical bias should also be included. It may be appropriate to insert a copy of the T&E schedule from the protocol.

4.2 Selection of Study Population

A brief description of the KEY Inclusion and Exclusion criteria used to select the study population. It is NOT recommended that a repeat of the full Inclusion and Exclusion criteria outlined in the protocol be used as a substitute for identifying key inclusion and exclusion criteria pertinent to the analysis of the primary target variable. You may want to consider highlighting key inclusion and exclusion criteria that, if violated or wavered, may become major protocol violations that affect the disposition of subjects.

4.3 Method of Treatment Assignment and Randomization

Randomization is recognized as one of the most important design techniques for avoiding bias in a clinical study. In randomized studies it is important to describe in sufficient detail how randomization was developed and released (e.g. envelopes, IVRS, Internet, etc.) to the study sites, how the randomization schedule was secured, and how the study statistician was to remain blinded to the randomization schedule until an appropriate time. In an open-label study describe how patients were assigned to a treatment in an unbiased manner. It may also be advisable to provide a diagram of the randomization schema, especially if stratification variables are used to assign treatment for the study.
4.4 Treatment Masking (Blinding)

Treatment Masking or Blinding is recognized as one of the most important design techniques for avoiding bias in a clinical study. Describe how treatments were to be masked or made blind, with sufficient information to demonstrate that controls (placebo or active controls) are not detectably different from the test agent.
5. SEQUENCE OF PLANNED ANALYSES

5.1 Interim Analyses

An Interim Analysis is ANY analysis intended to compare treatment arms with respect to efficacy or safety at any time prior to the formal completion of the trial. It is highly desirable to have all interim analyses fully documented in the study protocol. This section of the SAP must fully specify the following when an interim analysis is planned for the study:

- Accrual rate and point of patient accrual when the interim analysis will be completed.
- Rule set for interpreting the interim analysis results. (e.g. stopping rules).
- Execution procedures for the interim analysis. (blinded v. unblended interim analysis, independent unblinded statistician, data quality issues, etc.)
- Role of an Independent Data and Safety Monitoring Committee in completing the Interim Analysis. Note that SAP review comments received from regulatory authorities have in the past indicated that full specification of the analysis plan for the DSMB is desirable, and it is generally not acceptable to indicate that this analysis will be subject of another DSMB analysis plan. It is desirable to identify the DSMB charter sections that highlight to analysis planned.

If NO interim analyses are planned prospectively in the protocol then the following statement is suggested for this section.

There are no planned Interim Analyses for this study.

5.2 Final Analyses and Reporting

A statement regarding the time and methodology for completing the final study analyses prospectively described in this SAP. This section ensures that the integrity of the analyses are maintained until such time as final unblinded analyses may be completed.

All final, planned, analyses identified in the protocol and in this SAP will be performed only after the last patient has completed the … A blinded data review meeting will be held prior to database lock and completion of the final analyses. In addition, no database may be locked, random code unblinded, or analyses completed until this SAP has been approved.
Key statistics and study results will be made available to <name of team or management> following database lock and prior to completion of the final CSR.

Any, post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses will also be clearly identified in the text of the CSR.
6. SAMPLE SIZE DETERMINATION

The number of subjects in a clinical trial should always be sufficient to provide a reliable answer to the question(s) addressed in the objectives. The sample size is almost always determined based upon the primary objective AND primary Target Variable in the study. At a minimum the following must be provided for the prospective determination of the appropriate sample size:

- The primary target variable with a statement of the variability surrounding the primary target variable. Generally a clinically relevant detectable difference between treatments is identified, and supported by literature or previous identifiable studies.
- A null hypothesis and alternative (working) hypothesis, which indicates consideration for treatment differences to be detected in the target population.
- The test statistic to be used to test the hypothesis.
- Type I error [probability of erroneously rejecting the null hypothesis].
- Type II error [probability of erroneously failing to reject the null hypothesis].
- Methods for treatment withdrawals or major protocol violations (generally percentage of the estimate to be added to the planned study population).
- Any assumptions regarding the study population or in the case of clinical events extrapolation procedures from the number of events to the eventual sample size.
- Methodology from which the target sample size is computed, together with all quantities used for the calculations (variances, mean values, response or event rates, differences to be detected, confidence intervals), along with the basis for using these quantities.
- Optionally, a sensitivity analysis of the sample size estimate may be appropriate. If multiple quantities, or a range, for the target sample size have been considered (e.g. deltas between say 0.01 and 0.1, or SD between 11.0 and 15.0) then it may be useful to provide a table of sample size estimates, with appropriate language to justify the selected sample size.
4. In Phase IIb, III, and Phase IV studies assumptions and quantities for planning the sample size must come from published data or results of earlier trials, with appropriate references.

5. The Sample size section may also require a statement on any sample size reestimation methods to be employed from interim analyses identified in the protocol. This is especially pertinent if a sequential or adaptive design is utilized or if the study is driven by an estimate of the number of events (e.g., deaths at 2 years, or number of AMIs at 3 months).

7. ANALYSIS POPULATIONS

All subjects who sign an informed consent and participate in any aspect of the study are to be accounted for in one or more analysis populations. At a minimum demographic and baseline data for all subjects who agree to participate in a study are to be identified and reported, regardless of their randomization or treatment status in the trial (See Section V(B) in ICH E9, and ICH E3 on Disposition of Patients in Clinical Studies). The choice of the name “Full Analysis Set” is consistent with ICH E9 and E3 documentation. However, it may be preferable to have the Intent-to-Treat nomenclature for the primary efficacy and/or safety analysis.

This section may be an expansion of what is presented in the study protocol. It should not, however, be contradictory to the protocol. Also note that in ICH E3 the guidance calls for identifying ALL patients who are screened for participation in a study, regardless of the patients treatment participation or randomization status.

The following analysis populations are planned for the studies:

- **Screening Population (SCREEN):** The Screening Population includes all subjects who provide informed consent and provide demographic and/or baseline screening assessments, regardless of the subject’s randomization and treatment status in the trial. **[THIS POPULATION MAY NOT BE RELEVANT DEPENDING UPON THE STUDY DESIGN]**

- **Safety Population (SAFETY):** The Safety Population includes all patients who receive any amount of planned study medication.

- **Full Analysis Set (EFFICACY):** **[or Intent-to-Treat Efficacy]** The Efficacy Population includes all patients who are randomized, receive at least one dose of planned study medication and **<insert additional criteria to preserve eligibility for the full analysis set>**.

- **Per-Protocol Efficacy (PP-EFFICACY):** The PP-Efficacy includes all patients in the Efficacy Population who **<insert measures of treatment**
compliance, availability of measurements, absence of major protocol violations, or entry criteria that are appropriate.
8. GENERAL ISSUES FOR STATISTICAL ANALYSIS

This section is useful for providing specific information on how general techniques may be applied for the SAP. Current guidance indicates that a brief explanation of the analysis software and the software environment should be included, specifics on how patients who withdraw prior to completing the study and the impact of missing observations should be discussed.

8.1 Analysis Software

Current guidance indicates that a brief explanation of the analysis software and the software environment should be included in the SAP. [IT IS SUGGESTED THAT WE ADD APPROPRIATE STANDARD LANGUAGE THAT IDENTIFIES THE VALIDATED COMPUTING ENVIRONMENT FROM WHICH SAS SOFTWARE IS BEING EXECUTED].

All analysis will be performed using SAS® Software version 9.1 or later. [add any additional software packages that may be used for study analyses]

8.2 Methods for Withdrawals, Missing Data, and Outliers

Current guidance indicates that an explanation of how patients who withdraw prior to completing the study and the impact of missing observations, or outliers, should be discussed. Specific methods (e.g. LOCF, imputation strategies, sensitivity analyses) for handling and exploring the impact of missing values and outliers should be provided in this section.

8.3 Data Transformations

Data transformations are generally not considered a very good idea for primary analysis. Yet certain assessments and the respective responses are better suited to a specific transformation (e.g. log-normal transformation, or square root). Specific methods for identifying if a particular assessment may be transformed should be included in this section. Particular attention should be placed on examining the primary and key secondary endpoints for planned model assumptions and setting any necessary boundaries for determining if a transformation is necessary for the assessment.
8.4 Multicenter Studies

Almost all Phase IIb and Phase III studies are multicenter studies. This section should be used to provide information on how centers may be pooled or not pooled for the analysis, and methods for examining the effects of center (or site) in any planned model(s). Particular attention should be placed on grouping centers from distinct geographic regions where differences in clinical outcomes may be evident [i.e. the North America may be different than Europe (eastern or western), or Asia].

8.5 Multiple Comparisons and Multiplicity

Multiple comparisons and the issues surrounding multiplicity may necessitate an adjustment to the Type I error. Methods to avoid or reduce multiplicity are preferable in confirmatory trials: including multiple key primary variables (multiple variables), or the choice of a critical treatment contrast (multiple comparisons), or the use of summary responses from repeated measures (such as an AUC). It is critical to prospectively identify any adjustment procedure or an explanation of why adjustments may not be necessary in this section.

8.6 Planned Subgroups, Interactions, and Covariates

Primary endpoints or assessments are often systemically related to and influenced by factors other than treatment. If variables are used to stratify a design it is appropriate to account for those factors in an analysis. Treatments in the study may also vary with a subgroup or covariate. All of these issues that are known a priori should be set forth in this section. In general, ICH E9 guidance indicates that subgroup or interaction analyses are exploratory and should be clearly identified as such in the SAP. It is important to identify each category within a planned subgroup and the expected distribution of the subgroup, as this may affect power and conclusions from any planned analyses with subgroups.

Also of note is that any conclusions of treatment efficacy or safety interpreted solely on exploratory subgroup or interaction analyses are unlikely to be accepted for registration.

8.7 Derived and Computed Variables

The SAP offers an opportunity to fully document the methods applied for any
derived or computed variables used for analysis. This is especially useful for composite variables where multiple scoring systems are to be employed to arrive at a specific result for each patient. Additionally it is important to identify variables, and associated valid values or ranges, that are to be computed that are from repeated measures (e.g. AUC, slopes or other regression coefficients, etc.)

The following derived and computed variables have been initially identified. It is expected that additional variables will be required. The SAP will not be amended for additional variables that are not related to the primary target or key secondary target variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create analysis files.

<table>
<thead>
<tr>
<th>Variable Name</th>
<th>Description</th>
<th>Valid Values (Ranges)</th>
<th>Computation Methods, Notes, or Equation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>Subject Age (in Years)</td>
<td>18 to 90 (as appropriate)</td>
<td>[ \text{Integer} \left( \frac{\text{ICDate} - \text{DateofBirth}}{365.25} \right) ]</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index (kg/m^2)</td>
<td>15 to 55</td>
<td>[ \left\lfloor \frac{\text{lbs}}{\text{inches}^2} \right\rfloor \times 703 ] or [ \frac{\text{Kg}}{m^2} ]</td>
</tr>
<tr>
<td>BMICAT</td>
<td>Body Mass Index Category</td>
<td>A = Underweight</td>
<td>If BMI &lt; 18.5 then BMICAT = A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B = Normal Weight</td>
<td>If 18.5 &gt;= BMI &lt;=24.9 then BMICAT = B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C = Overweight</td>
<td>If 25.0 &gt;= BMI &lt;=29.9 then BMICAT = C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D = Obese</td>
<td>If 30.0 &gt;= BMI &lt;=34.9 then BMICAT = D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E = Severely Obese</td>
<td>If 35.0 &gt;= BMI &lt;=39.9 then BMICAT = E</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F = Morbidly Obese</td>
<td>If BMI &gt;= 40.0 then BMICAT = F</td>
</tr>
</tbody>
</table>
9. STUDY SUBJECTS

9.1 Disposition of Subjects and Withdrawals

ICH E3 indicates that all patients who participate in a clinical trial are to be accounted for in the study population. Further guidance indicates that this can be interpreted as all patients who provide informed consent and are screened for inclusion in the study, regardless of the patient’s randomization status or participation. The ICH approved template for CSRs indicates that the following must be presented.

- Total number of subjects screened (=subjects who gave informed consent)
- Number of subjects who completed the pre-phase (if any), but did not participate in the further course of the study.
- Number of randomized subjects or in the case of non-randomized studies the number of subjects who received study medication at least one time.
- Number of randomized subjects who completed the study in each treatment group or in the case of cross-over studies the number who finished each treatment phase.
- Number of subjects who did not complete the pre-phase (if any) grouped by the main reason.
- Number of subjects who discontinued after randomization, grouped by treatment and main reason.
- Number of enrolled/screened, randomized, and analysis populations for each center.
- Note that it may also be necessary to present methods for how ignorable and non-ignorable drop-outs will be handled, specifically in studies where the presence of a high number of drop-outs is expected. This may be useful for longitudinal studies.

The number and percent are to be presented for each frequency distribution. The following suggested language is presented.

All subjects (or patients) who provide informed consent will be accounted for in this study. The frequency and percent of subjects in each population, study withdrawls, subgroups, and major protocol violations will also be presented.

9.2 Protocol Violations and Deviations
Protocol deviations may be significant contributors to analysis bias. Provide a clear description of what the rule set is for determining a major protocol violation (a violation that may be likely to affect the efficacy of treatment), and how these violations are to be determined and classified. A clear description of the rule set for eliminating a major protocol violator from the Per-Protocol Population (if any) from the Full Analysis Set (ITT Population) must be specified. The CSR template requires that the following be listed for major protocol violations:

- Number of Subjects (overall and by Center) with each major violation

[Optional if relevant to the study] Number of subjects (overall and by Center) with any minor protocol violation/deviation.

The number and percent are to be presented for each frequency distribution. It may be appropriate to insert language regarding a blinded data review meeting to assess protocol violations and deviations.

9.3 Inclusion and Exclusion Criteria

The number and percent are to be presented for subjects meeting each Inclusion and Exclusion Criteria. Generally, it is expected that the overall percentage will be 100% for inclusion and exclusion criteria, except when waivers are granted or when data review indicates that inclusion or exclusion criteria have been violated. It may be necessary to include language on how waiver [# (%)] are to be presented. This is supportive for the study population to be analyzed. The may be completed overall and optionally by study center (if relevant).

10. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The analysis of demographic and baseline characteristics of the study population is critical to describing the homogeneity or heterogeneity of the study population between treatment groups. In general, summaries of the key demographics by analysed population are to be provided. If sub-groups exist then a summary of the demographics for the subgroup may be relevant to fully characterizing the study population.

The use of p-values and inferential analysis of the demographics and other baseline conditions by treatment in a study population may not be relevant to the overall presentation of study results. Completion of inferential analysis is discouraged unless a compelling reason for the analysis is required to support potential differences that are expected due to randomization.
10.1 Demographics

At a minimum this should include age, gender, ethnic origin / race. Optionally, depending upon the study other demographics such as height, weight, body mass index (number and or classification), body surface area, and others may need to be included.

Continuous variables should include at a minimum the mean, standard deviation, median, and range. Optionally summary statistics may include inter-quartile ranges, coefficient of variation, or measures of skewness or kurtosis.

Categorical variables should include at a minimum the frequency and percentage.

10.2 Prior and Concurrent Medications

The frequency and percent of prior and concurrent medications should be tabulated overall and by treatment group. Medications are to be coded using the WHODRUG dictionary. Summaries by drug class and individual coded medications are to be completed. It is often time useful to identify relevant medications or medication classes that may have (or are known to have) a drug-drug interaction with the study treatment(s). This section should be used to identify this potential and relevant summaries described.

10.3 Baseline and Screening Conditions

The analysis of baseline characteristics of the study population is critical to describing relevant illness (history) and concomitant illness (current findings from a PE) at the initiation of a subjects participation. Relevant co-morbidities should be highlighted and particular attention in describing the findings for these conditions should be the emphasis of this section.

10.3.1 Baseline Medical History

The number and percent of subjects presenting with a baseline medical history, either by body systems or relevant disease specific history (e.g. renal disease, diabetes, heart failure, asthma, etc.). Consider providing relevant disease specific
medical history summaries if associated with specific exclusion or inclusion criteria. At a minimum patient listings of the medical history with any indication of the stability of these pre-existing conditions may be useful.

10.3.2 Baseline Physical Exam

The number and percent of subjects presenting with a baseline concomitant illness (current findings from a physical exam), either by body systems or relevant disease specific history (e.g. renal disease, diabetes, heart failure, asthma, etc.). Consider providing relevant disease specific concomitant illness summaries if associated with specific exclusion or inclusion criteria. Note that a baseline physical exam is not limited to the traditional PE and may include such aspects as summaries of specific modalities used to assess current concomitant illness (e.g. X-ray, MRI, Cardiac SPECT Imaging, Endoscopy, etc.)

10.3.3 <Disease Specific> Baseline and Screening History

This section of the SAP is optional and may be used to provide additional disease specific baseline and screening history. The addition of disease specific baseline and screening history is associated with identifying very specific observations or clinical laboratory findings that at screening are indicative and support of underlying disease is a specific patient population. The number and percent of subjects presenting a specific disease specific history or finding, and optionally a continuous summary of actual results, may be appropriate. Examples might include a summary of HbA1c at baseline for patients with diabetes, or presence or absence of elevated cholesterol in cardiac studies, baseline assessments for specific antibodies for a target disease, etc.

10.4 Measurement of Treatment Compliance

Compliance with treatment regimes in a clinical trial is often times one of the significant factors affecting efficact results (especially if a large placebo effect is evident). A clear description of issues, and rule set, surrounding treatment compliance should be included in this section, especially if used for assessment of a major protocol deviation, or if treatment compliance is used as a model covariate or main affect term.

In general this section is not particularly relevant for single dose treatments (either oral or injectable), or in studies where patient treatment is controlled by the investigator in a hospital or controlled setting, and compliance is not an
issue.

At a minimum for studies where the subject is self-administering doses of study medication a summary of the total amount of medication taken per specified unit (e.g. total daily dose, number of tablets per day or week, total weight (+ units) of study medication applied per body surface area unit) should be provided overall by treatment and by treatment and study center. If time is an important factor in measuring treatment compliance then summaries of treatment compliance over specific time intervals may also be relevant.

Another area that may be included in this section is summary methods for the measurement of drug concentrations in body fluids for treatment compliance. This may also be important if steady state drug concentrations are required to receive optimal benefit from a study treatment.

11. EFFICACY ANALYSES

This section of the SAP is to specify the hypotheses to be tested and/or treatment effects that are to be estimated to satisfy the primary objectives of the study. A clear and concise presentation of the statistical methods to be used to accomplish these tasks must be described for the primary and key secondary efficacy variables. The underlying statistical model to be used must be clearly stated, along with any baseline data that are to be used for each subject to adjust estimates for potential baseline differences (e.g. analysis of covariance)

11.1 <Primary Efficacy Variable Analysis>

The analysis of the primary efficacy variable should include a description of the hypothesis to be tested with the alternative hypothesis, statistical model, any model adjustments or covariates, or transformations, and should reflect the current state of medical and statistical knowledge about the primary variable and the study design. This section should also be used to describe how the model assumptions and statistical distribution for the primary and secondary efficacy variables will be evaluated for parametric or nonparametric methods, if appropriate to the discussion.

In general it is almost always better to use simple rather than complex statistical models to support the analysis to provide simplicity in the explanation of treatment effect differences observed. Also, the more complex the statistical model, the less likely the results from the analysis are generalizable across a population of patients with the target disease. Simple is better!

It is critical that this section clarify one or two sided testing. Note that regulatory
authorities generally frown upon one-sided tests. If a one-sided test is to be employed then a prospective justification must be clear and support a clinical rationale for this decision.

Any estimates of treatment effects must be accompanied with confidence intervals, aligned with the Type I error rate (e.g. $\alpha=0.05$ then CI = 95%, $\alpha=0.10$ then CI = 90%).

A description of how the primary and secondary analysis variables will be summarized and reported, and how statistical significance will be interpreted should also be included.

The analysis of the <insert name of efficacy variable> will include the following test of hypothesis:

$$H_0:$$

The alternative hypothesis is:

$$H_1:$$

Acceptance of ____ , for the <insert population>, will be considered to be a successful demonstration of efficacy.

The model used to complete the primary analysis is an ....[insert model and any relevant information regarding construction of the model]

11.2 <Secondary Efficacy Variable Analysis>

The same principles outlined for section 11.1 also apply for section 11.2 (secondary efficacy variables).

11.3 <Other Efficacy Variable Analysis>

The same principles outlined for section 11.1 also apply for section 11.3 (other efficacy variables). If this section is not relevant to the study then it may be deleted from the SAP.
12. SAFETY AND TOLERABILITY ANALYSES

Safety and Tolerability is generally completed for the set of subjects who complete one or more doses of trial medication (this may also include screening medications).

The analysis of safety assessments in this study will include summaries of the following categories of safety and tolerability data collected for each subject:

- Drug Exposure(s)
- Adverse Events
  - AEs and SAEs
  - AEs leading to withdrawal
  - Any Deaths
- Pregnancies (if any reported)
- Clinical Laboratory Investigations
- Hemodynamics (vital signs)
- ECG Investigations
- <Disease Specific> Assessments

12.1 Drug Exposure

Methods should be presented on how the extent of exposure to study medications is to be characterized. Generally this includes the distribution of patients at each dose, or cumulative doses and the duration of exposure at each dose. Items to consider for this summary include:

- Summaries of the total daily dose (if multiple dosing regimens are being studied).
- Summaries by treatment cycle (in oncology studies) of total dose exposed.
- Total cumulative dose exposed, as it relates to dose limiting toxicities may be useful.
- Depending upon the study drug it may be useful to summarize drug exposure by age groups, gender, or racial subgroups, or any other pertinent subgroups (e.g. exposure to antihypertensive agents would correlate with a summary of drug exposure by racial groups of black and non-black subgroups).
• A discussion on how drug exposure may be related to changes in safety assessments, such as liver function or renal function tests may also be necessary.

12.2 Adverse Events

A clear description of how Adverse Events are to be coded and summarized is required by ICH E3 and ICH E9. The incidence of adverse events is usually expressed in the form of a proportion relating the number of subjects experiencing events to the number of subjects at risk. The number of subjects at risk is usually the number of subjects in each treatment group, and overall treatment groups.

However, other methods such as risk ratios for an adverse event, or survival analysis methods, or cumulative adverse event rates should be considered when long-term safety assessment is planned and a large proportion of the subjects will withdraw or die during the course of the study.

Suggested language for standard adverse event summaries is presented in section 12.1.1(All Adverse Events), 12.1.2 (Adverse Events Leading to Withdrawals), 12.1.3 (Serious Adverse Events), and 12.1.4 (Deaths) for consideration. This language should be modified to match the study protocol and the degree of adverse event assessment planned for the program.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, version x.x or greater.

12.2.1 All Adverse Events

The following is standard language for summaries of Adverse Events. This language may be modified to fit the particular needs of the study. Additional language will be required if inferential testing or model development is completed for adverse events. Another aspect that may need to be considered is the presence of rare events of interest (if relevant), in which case additional methods for analysis of his may be required. It may also be necessary to include language on any toxicity grading scales that will be used, along with a justification of the scale(s).

Summaries of incidence rates (frequencies and percentages), intensity, and relationship to study drug of individual AEs by System Organ Class and Preferred Term (MedDRA) will be prepared. Each patient will be counted only once within each preferred term per study period. If a patient experiences more than one AE
within a preferred term for the same recording period, only the AE with the strongest relationship or the greatest intensity, as appropriate, will be included in the summaries of relationship and intensity.

Summaries will be presented by treatment group for … Fisher’s exact test will be used to compare rates for System Organ Classes across treatment groups. A similar summary by treatment group will be presented for all patients in the Safety Population.

Counts of AEs by maximum intensity will be presented for patients in the Safety Population by treatment group, grouped by the treatment the patient had received most recently prior to the AE. Only AEs beginning at or after the beginning of study drug administration will be included. Similarly, counts of AEs by strongest relationship to study drug will be presented.

A data listing will also be presented showing all AEs which started prior to the administration of any study drug.

12.2.2  Adverse Events Leading to Withdrawal

ICH E3 and ICH E9 require that a clear summary and description of those patients in the study who withdrawn from participation due to an adverse event must be disclosed and summaries presented. Generally are counts and percents, and rarely would inferential analysis be required for this summary.

A summary of incidence rates (frequencies and percentages) of AEs leading to withdrawal, by treatment group, System Organ Class, and Preferred Term, will be prepared for the Safety Population. No statistical tests will be performed.

A data listing of AEs leading to withdrawal will also be provided, displaying details of the event(s) captured on the CRF.

12.2.3  Serious Adverse Events

ICH E3 and ICH E9 also require a summation of SAEs, along with the summary narratives produced by drug surveillance. This section of the SAP should be an agreement with clinical research and drug safety and surveillance departments.

Serious adverse event reconciliation will be performed by Data Management, Clinical Research, and [insert name of organization] Drug Safety and Pharmacovigilance via data listings.

A summary of incidence rates (frequencies and percentages) of SAEs by treatment group, System Organ Class, and Preferred Term will be prepared for the Safety Population. No statistical tests will be performed.
A data listing of SAEs will also be provided, displaying details of the event(s) captured on the CRF. Serious adverse event narratives will be provided for the CSR by the Drug Safety and Pharmacovigilance Department.

12.2.4 Deaths

ICH E3 and ICH E9 also require a summary of deaths, along with the summary death narratives produced by drug surveillance. However, if death is an efficacy endpoint (e.g. survival analysis) and the protocol indicates that death is expected and not considered an SAE (unless some indication that death is drug related) then this language will need to be modified to match the protocol.

If any patients die during the study, relevant information will be supplied in a data listing, and appropriate SAE narratives.

12.2.5 Other AE Assessments

This section should be used to define the methods for any study specific adverse event assessments of interest. Otherwise, indicate no other assessments or analysis are planned.

No additional Adverse Event Assessments were completed, and no additional analysis is planned.

12.3 Pregnancies

If a pregnancy registry is used than language indicating how pregnancies will be censored for any planned analysis and followed for the registry should be included.

Pregnancy data will be shown in a data listing. No special analysis will be performed on the pregnancy data. Patients are to be discontinued from the study if they become pregnant.

12.4 Clinical Laboratory Evaluations

Clinical laboratory investigations for safety may take on many different and unique features, depending upon the drug under study. At a minimum, if clinical laboratories are collected pre and post treatment then listings and shift tables should be completed, as well as any mean changes, by treatment.

If clinical laboratory studies are being completed over time, with sequential samples over time then analysis over time or visit may be necessary. ICH E3 guidance recommends the consideration of graphs and other visual displays to examine and present this type of data. Special consideration may be necessary of ranges other than the normal range (e.g. twice the upper normal limit, 5 times the upper limit, or other range selection).
Descriptive summaries (mean, SD, median, minimum, and maximum) of changes from baseline will be presented for clinical laboratory values by treatment for the Safety Population.

The number of patients with clinical laboratory values below, within, or above normal ranges, <or other specific ranges of interest> pre-procedure versus post-procedure will be tabulated for each test, for the Safety Population by treatment group. Pre- and post-procedure values will also be presented with an analysis of mean changes from baseline.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a data listing.

12.5 Hemodynamics (Vital Signs)

Hemodynamic data should be analysed and presented in ways similar to clinical laboratory investigations. Changes from baseline, sequential assessments, mean changes, etc. should all be considered. For particular importance is the relationship of hemodynamic changes related to dose or concentration data. A discussion on how this relationship will be examined and presented may be useful especially for drugs with a short duration of action or drugs where cumulative doses may be shown to affect changes in hemodynamics.

Descriptive summaries (mean, SD, median, minimum, and maximum) of actual values and changes from baseline will be calculated for SBP, DBP, and HR. These summaries will be presented by treatment for the Safety Population.

12.6 ECGs

Electrocardiogram (ECG) analysis should follow methods similar to that of hemodynamics and clinical laboratory investigations with respect to summaries and changes over time or from baseline. In addition, it may be necessary to provide summaries regarding QT prolongation and evidence for (or against) a drug related effect for QT prolongation. If QT data are collected in the Phase Ib or Phase III study then these summaries are required, along with the appropriate correction factors. Standard language for this computation is provided for consideration.

The number and percentage of patients with normal and abnormal ECG results will be summarized for the Safety Population by treatment group. Abnormal results will be grouped as …

[IF QT DATA ANALYSIS IS REQUIRED THEN CONSIDER THE FOLLOWING] A comparison of QT results will be presented. Summary statistics for baseline values at Screening, <other assessment times>, and Follow-up will be
displayed for QT and both QTc correction methods, side-by-side, by treatment
group. Both the Bazett’s and Fridericia’s corrections methods for QTc will be
applied as follows:
The Bazett’s Correction ($QTc_b$) and Fridericia’s Correction ($QTc_f$) will be derived
as follows:

$$QTc_b = \frac{QT_{msec}}{\sqrt{RR}}$$

$$QTc_f = \frac{QT_{msec}}{\sqrt[3]{RR}}$$

where: Relative Rate: $RR = 60 / HR$
HR = Heart Rate obtained from the ECG.

Change will be compared between treatments using a crossover ANOVA model,
including terms for ..., and treatment. Also, the number and percent of patients in
each treatment group who experienced a change >30 ms or a change >60 ms will
be presented.

Descriptive summaries (mean, SD, median, minimum, and maximum) will be
presented for ECG measures of PR interval, QRS interval, QT interval, QTc
interval (both correction methods), and HR. These summaries will be presented
by treatment.
13. OTHER PLANNED ANALYSES

The SAP for a Phase IIb or Phase III study may include many different analyses including Pharmacokinetic parameters (possibly population PK work), pharmacodynamic parameters (possibly population pharmacodynamics), QOL or pharmacoeconomics, Genetic analyses (genotyping or phenotypic markers), or Biomarker analysis. If so, then a description of these other planned analyses is necessary, or reference to the department of specialist who will complete these additional analyses should be provided.

13.1 Pharmacokinetic Analysis
The following pharmacokinetic parameters are to be computed for samples obtained ... [or]
No pharmacokinetic analyses are planned for this study. [or]
Pharmacokinetic analysis will be completed by the <name of department>, and a separate PK report will be completed and attached to the CSR.

13.2 Pharmacodynamic Analysis
The following pharmacodynamic parameters are to be computed for samples obtained ... [or]
No pharmacodynamic analyses are planned for this study. [or]
Pharmacokinetic analysis will be completed by the <name of department>, and a separate PK report will be completed and attached to the CSR.

13.3 Quality of Life Analysis
Quality of Life (QOL) was assessed using the <name of instrument> and the following analyses will be performed ... [or]
No Quality of Life analyses are planned for this study. [or]
Quality of Life analysis will be completed by the <name of department>, and a separate QOL report will be completed and attached to the CSR.

13.4 Heath Outcomes Analysis (Pharmacoeconomics)
Health Outcomes were assessed with <name of instrument> or <names of health information data sources> ... The following Health Outcomes related analyses are to be performed ... 
No Health Outcomes (Pharmacoeconomics) analyses are planned for this study. [or]
Health Outcomes (Pharmacoeconomics) analysis will be completed by the <name of department>, and a separate QOL report will be completed and attached to the CSR.

13.5 Genetic Analyses

<Insert name of genotype or phenotypic> analyses were completed were assessed with <name of instrument> or <names of Biomarkers or surrogates>…. The following <name analysis type> related analyses are to be performed …

No Genetic analyses) analyses are planned for this study. [or]

Genetic analyses will be completed by the <name of department>, and a separate report will be completed and attached to the CSR.
14. REPORTING CONVENTIONS

Standard text for reporting conventions should be adopted and utilized across ALL SAPs. Review and agreement is required. The following are only suggested to facilitate discussion. Reporting standards from statistical operations and from the standard TLF work previously completed should be incorporated.

The following reporting conventions will be adopted for the SAP. These conventions will enhance the review process and help to standardize presentation with common notations.

14.1 General Reporting Conventions

- All tables and data listings will be presented in Landscape Orientation, unless presented as part of the text in a CSR.

- Figures will be presented in Landscape Orientation, unless Portrait Orientation suggests that the information presented is easier to interpret.

- Legends will be used for all figures with more than one variable or item displayed.

- Figures will be in black and white (no color). Symbols on figures will not be filled. Lines should be wide enough to see the line after being copied.

- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.

- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).

- All titles will be centered on a page. The first title line will be the number of the table, figure, or data listing. The second (and if required, third) line will be the description of the table, figure, or data listing. The ICH numbering convention is to be used for all TLGs.

- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
• Missing values for both numeric and character variables will be presented as blanks in a table or data listing.

• All date values will be presented as DDMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.

• All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.

• Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

• All tables, figure, and data listings will have the name of the program and a date/time stamp on the bottom of each output.

• All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested). It is recommend that a 1:1 relationship between table and analysis program be used to facilitate this convention.

14.2 Population Summary Conventions

• Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.

• Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) Full Analysis or ITT, (b) All Patients, (c) PP or Per-Protocol, (d) Efficacy, and (e) Safety.

• Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.

• Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.

• Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
• All population summaries for categorical variables will include categories that the patients had a response in these categories. Percentages corresponding to null categories (cells) will be suppressed.

• All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g. median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.

• All percentages are rounded and reported to a single decimal point (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

• Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.
15. REFERENCES

Complete and comprehensive referencing of appropriate literature adds credibility to the SAP. Endnote formatting is suggested to facilitate automatic numbering in the text. Cross-referencing clinical literature, especially as it relates to sample size, efficacy or safety analyses is strongly suggested. It is generally not necessary to reference statistics text-books for standard procedures such as ANOVA, ANCOVA, or COX Proportional Hazards Models. It is, however, advisable to provide appropriate reference where significant changes to a standard model or procedure have been made or a new method is being introduced.


http://www.amstat.org/profession/ethicalstatistics.html

http://www.rss.org.uk/about/conduct.html
16. TABLES

Table numbering should follow ICH E3 to match the CSR.

16.1 Planned Table Descriptions

The following are planned summary tables for protocol <number>. Tables will numbered according to the nomenclature used to support the clinical study report.

<table>
<thead>
<tr>
<th>Table Number</th>
<th>Population</th>
<th>Table Title / Summary</th>
<th>Supporting Listing Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.1 DEMOGRAPHIC DATA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.1.1</td>
<td>All Patients</td>
<td>Disposition of All Subjects</td>
<td>16.2.1.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.2 EFFICACY DATA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.2.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.3 SAFETY DATA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.3.1</td>
<td>Safety</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14.3.1.1</td>
<td>Safety</td>
<td>Summary of All Adverse Events</td>
<td></td>
</tr>
<tr>
<td>14.3.1.2</td>
<td>Safety</td>
<td>Summary of Adverse Events Leading to Study Withdrawal</td>
<td></td>
</tr>
</tbody>
</table>
### 14.3.2 Safety

#### 14.3.2.1 Safety

| Listing of Deaths and Other Serious and Significant Adverse Events |

### 14.3.3 Narratives

### 14.3.4 Safety

#### 14.3.4.1 Safety

| Summary of <clinical laboratory> |

#### 14.3.4.2 Safety

| Listing of Clinically Significant Abnormalities. |

### 14.3.5

### 14.3.6
17. LISTINGS

*Data Listing numbering should follow ICH E3 to match the CSR.*

17.1 Planned Listing Descriptions

The following are planned data and patient listings for protocol <number>. Listings will numbered according to the nomenclature used to support the clinical study report.

<table>
<thead>
<tr>
<th>Listing Number</th>
<th>Population</th>
<th>Listing Title / Summary</th>
<th>Supports Table or Figure Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.2.1.1</td>
<td>All Patients</td>
<td>Listing of Study Population Status for each Patient</td>
<td>14.1.1</td>
</tr>
<tr>
<td>16.2.1.2</td>
<td>Randomized Patients</td>
<td>Listing of Discontinued Patients</td>
<td>14.1.1</td>
</tr>
<tr>
<td>16.2.2</td>
<td>Randomized Patients</td>
<td>Listing of Major Protocol Deviations</td>
<td>14.1.1</td>
</tr>
<tr>
<td>16.2.3</td>
<td>Randomized Patients</td>
<td>Listing of Patients Excluded from Primary and Secondary Efficacy Analyses</td>
<td>14.1.1</td>
</tr>
<tr>
<td>16.2.4</td>
<td>All Patients</td>
<td>Listing of Patient Demographics</td>
<td></td>
</tr>
</tbody>
</table>
18. FIGURES

*Figure numbering should follow ICH E3 to match the CSR.*

### 18.1 Planned Figure Descriptions

The following are planned summary figure for protocol `<number>`. Figures will numbered according to the nomenclature used to support the clinical study report.

<table>
<thead>
<tr>
<th>Figure Number</th>
<th>Population</th>
<th>Figure Title / Summary</th>
<th>Supporting Listing Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.x.x</td>
<td></td>
<td></td>
<td>16.2.x.x</td>
</tr>
</tbody>
</table>


19. ATTACHMENT

Identify and relevant attachments to the SAP. This may include, but is not limited, such items as information on composite scales used for efficacy, or rule sets for classification or grading of disease states, or special computations that do not necessarily fit into the derived and computed variables section. Addition of second level header information for each attachment is the best procedure for including an attachment.
STATISTICAL ANALYSIS PLANS
PRINCIPLES AND PRACTICE

Society for Clinical Trials Workshop
May 20, 2007

Attachment
Template for Developing Tables, Listings, Figures
that Support an SAP
TABLES, LISTINGS, AND FIGURES
DEVELOPMENT DOCUMENTATION

Insert the full protocol title, final protocol date, SAP Author and date. Insert the Statistical Programmer responsible for the TLF Development for the project. This TLF Programming Development Documentation Template is useful for prospectively defining the structure and form of planned TLFs for a particular study. By separating the TLF production from the SAP development the SAP can be finalized earlier in the process and the TLF development may evolve over the course of the development process.

Protocol Title
(Number):<full title of Protocol>(protocol number)

Protocol Date:

SAP Author:
SAP Date:

Statistical Programmer:

CONFIDENTIAL
# DOCUMENT HISTORY

<table>
<thead>
<tr>
<th>No.</th>
<th>Date</th>
<th>Author</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dd-mmm-yyyy</td>
<td>Original author name</td>
<td>Original Draft of Document</td>
</tr>
<tr>
<td>2</td>
<td></td>
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<td>3</td>
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<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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1. **INTRODUCTION**

This Tables, Listing, and Figures (TLF) development document provides the documentation and templates and for development, validation, and approval of the TLFs planned for <insert study protocol number>. May want to insert a paragraph regarding the SOP that supports Statistical Operations programming standards and other relevant SOP’s within BDS for support.

All program development will be completed with SAS Software, Version 9.x, on the <name of operating system or server>. The location of all programs, macros, data sets, and supporting documentation for <insert study protocol number> may be found in <insert the file location>.

This TLF Development Document evolves during the course of a study and is supported by the following documents:

- Protocol: <insert study protocol number>
- Annotated Case record Form for <insert study protocol number>
- Statistical Analysis Plan for <insert study protocol number>

Following completion of the TLF development attachments to this document include validation documentation, and copies of the approval documentation. Additional programming documentation (log files or output) are also attached to further document the production of the TLFs.
2. REPORTING CONVENTIONS

Standard text for reporting conventions should be adopted and utilized across ALL SAPs and TLF Development. Review and agreement is required. The following are only suggested to facilitate discussion. Reporting standards from statistical operations and from the standard TLF work previously completed should be incorporated.

The following reporting conventions will be adopted for the production of TLFs. These conventions will enhance the review process and help to standardize presentation with common notations.

2.1 General Reporting Conventions

- All tables and data listings will be presented in Landscape Orientation, unless presented as part of the text in a CSR.

- Figures will be presented in Landscape Orientation, unless Portrait Orientation suggests that the information presented is easier to interpret.

- Legends will be used for all figures with more than one variable or item displayed.

- Figures will be in black and white (no color). Symbols on figures will not be filled. Lines should be wide enough to see the line after being copied.

- Specialized text styles, such as bolding, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.

- Only standard keyboard characters should be used in tables and data listings. Special characters, such as non-printable control characters, printer specific, or font specific characters, will not be used on a table, figure, or data listing. Hexadecimal character representations are allowed (e.g., μ, α, β).

- All titles will be centered on a page. The first title line will be the number of the table, figure, or data listing. The second (and if required, third) line will be the description of the table, figure, or data listing. The ICH numbering convention is to be used for all TLGs.

- All footnotes will be left justified and the bottom of a page. Footnotes must be present on the page where they are first referenced. Footnotes should be used sparingly and must add value to the table, figure, or data listing. If more than four footnote lines are planned then a cover page may be used to display footnotes.
• Missing values for both numeric and character variables will be presented as blanks in a table or data listing.

• All date values will be presented as DDMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates.

• All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.

• Time durations will be reported in mixed HHhr MMm SSs notation (e.g., 5h 32m, or 27h 52m 31s). The use of decimal notation to present time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

• All tables, figure, and data listings will have the name of the program and a date/time stamp on the bottom of each output.

• All analysis programs developed for a table, figure, or data listing display will be self-contained to facilitate transfer of programs to multiple computing environments and transfer to a regulatory agency (if requested). It is recommend that a 1:1 relationship between table and analysis program be used to facilitate this convention.

2.2 Population Summary Conventions

• Population(s) represented on the tables or data listings will be clearly identified in the last title of the Table as “Population: <name of population>” and will be identical in name to that identified in the protocol or SAP.

• Consistent terminology will be used to define and identify a population. Common nomenclature may include (a) Full Analysis or ITT, (b) All Patients, (c) PP or Per-Protocol, (d) Efficacy, and (e) Safety.

• Sub-population(s) or special population(s) descriptions will provide sufficient detail to ensure comprehension of the population (e.g., ITT Females, Per-Protocol Males >60 years of age) used for analysis in a table or figure.

• Population sizes may be presented for each treatment or dosing category as totals in the column header as (N=xxxx), where appropriate.

• Population sizes shown with summary statistics are the samples sizes (n) of patients with non-missing values.
• All population summaries for categorical variables will include categories that the patients had a response in these categories. Percentages corresponding to null categories (cells) will be suppressed.

• All population summaries for continuous variables will include: N, mean, SD, minimum, and maximum. Other summaries (e.g. median, quartiles, 5%, 95% intervals, CV or %CV) may be used as appropriate.

• All percentages are rounded and reported to a single decimal point (xx.x%). If percentages are reported as integers, percentages greater than 0% but <1% will be reported as <1%, whereas percentages greater than 99% but <100% will be reported as >99%. A percentage of 100% will be reported as 100%. No value of 0% should be reported. Any computation of percent that results in 0% is to be reported as a blank.

• Population summaries that include p-values will report the p-value to three decimal places with a leading zero (0.001). All p-values reported on default output from statistical software (i.e., SAS® Software) may be reported at the default level of precision. P-values <0.001 should be reported as <0.001 not 0.000.

3. STUDY DATA SETS

The organization and contents of the data sets for this study are located in 〈insert directory name〉. Contents of the final study data sets are attached to this document.

〈may want to add more〉
4. TLF TEMPLATE ANNOTATIONS

Within each TLF template specified annotations are made to support the development of the particular output.

Legend Annotation:

- Red italicized text (Text) indicates table variables
- Blue italicized text in brackets [Text] indicates optional/possible fields to be displayed.
- Information following each TLF describes additional programming and repeat directives.
5. **TABLE SHELL TEMPLATES**

The following Tables are planned for this study. Each Shell Table contains a template, and programming notes for development and validation of the respective table. Final Numbering for the Tables will be completed after consultation with the medical writer and project statistician.

5.1 **List of Planned Tables**

Table 1. (14.1.1) Analysis Populations

| Table 1. | (14.1.1) Analysis Populations | 10 |
Table 1.  (14.1.1) Summary of Enrollment

<table>
<thead>
<tr>
<th></th>
<th>Trmt Grp A</th>
<th>Trmt Grp B</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subject Screened</td>
<td>xxxx</td>
<td></td>
<td>xxxx (xx%)</td>
</tr>
<tr>
<td>Number of Subjects Failing Screening</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx (xx%)</td>
</tr>
<tr>
<td>Number of Subjects Randomized</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx</td>
</tr>
<tr>
<td>Safety Population (SP)</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx (xx%)</td>
</tr>
<tr>
<td>Efficacy Full Analysis Set (ITT)</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx (xx%)</td>
</tr>
<tr>
<td>Efficacy Per Protocol Set (PP)</td>
<td>xxxx</td>
<td>xxxx</td>
<td>xxxx (xx%)</td>
</tr>
</tbody>
</table>

Table Programming Information and Directives:

- Overall total will be total by treatment arms and all treatment groups combined
- Additional footnotes to be study specific
- Population definitions/breakdown to be defined in SAP
6. LISTING SHELL TEMPLATES

The following Listings are planned for this study. Each shell Listing contains a template, and programming notes for development and validation of the respective Listing. Final numbering for the Listings will be completed after consultation with the medical writer and project statistician.

6.1 List of Planned Listings
7. FIGURE SHELL TEMPLATES

The following Figures are planned for this study. Each shell figure contains a template, and programming notes for development and validation of the respective figure. Final Numbering for the Figures will be completed after consultation with the medical writer and project statistician.

7.1 List of Planned Figures
8. ATTACHMENTS

Attachments to the TLF Development Document are Not numbered.

<Insert List of Attachments to be placed with this documentation>