TABLE OF CONTENTS

CHAPTER 2

DATA COORDINATING CENTER PROCEDURES

2.1 INTRODUCTION

The Data Coordinating Center (DCC) is organized and staffed in the Maryland Medical Research Institute to serve the needs of T3. The DCC staff fulfill key roles in the design and conduct of T3. The major responsibilities of the DCC, which serves as the central data repository for the information collected under the study protocols, are: (1) entry, inventory, and edit of all study data on a computer database, (2) generation of analyses to monitor for evidence of adverse and/or beneficial effects and for adherence to the study protocol, and (3) maintenance of files of all study forms and documents.

2.2 OBJECTIVES OF THE DATA COORDINATING CENTER

The general aims of the T3 DCC are to:

- Serve as a collaborating partner with the other investigators in the organization, design, conduct, and analysis of the trial.
- Provide biostatistical and epidemiologic expertise to the study in the area of design and operation of this multicenter trial.
- Provide expertise in the area of data processing and statistical analyses.
- Serve as the data and document repository for the trial.
- Develop and implement the required data processing procedures for handling all study forms and materials.
- Develop, implement and maintain quality control procedures to detect and correct deficiencies in data collection, processing or analyses.
- Provide facilities and staff to carry out appropriate analyses to monitor the study for adverse or beneficial treatment effects.
- Serve as the communication center for the study.
- Prepare progress reports and assist in preparation of publications.

2.3 PLANNING AND TRAINING

The members of the T3 DCC played a major role in the organization and conduct of investigator meetings, subcommittee meetings, and conference calls held during the planning phase of the study.

During patient recruitment and follow-up, it is anticipated that a number of aspects of the protocol will be clarified, certain procedures revised as a result of the Clinical Center experience, and specifications for other procedures developed. T3 DCC staff will periodically review current procedures and develop additional procedures as needed throughout the course of the study.

The T3 DCC staff provide training to T3 Clinical Center staff as necessary in the collection and preparation of data. In addition, the T3 DCC staff provide logistical support for orientation and training sessions.

2.4 DATA COLLECTION AND STORAGE

2.4.1 T3 Manual of Operations and Study Forms

The T3 Manual of Operations provides a description of study design, organization, methods, definitions, and procedures used in data collection. The professional staff of the DCC in conjunction with appropriate T3 committees coordinate the preparation of this document for approval by the Operations Committee and Steering Committee. Substantial staff time is required for drafting, assembling exhibits, and telephone discussions to resolve problems. There are numerous submissions of each chapter to the Operations Committee and appropriate T3 Committee Chairpersons for review, revision, proofreading, etc., before distribution to the Clinical Centers.

The T3 DCC staff prepare and supply all T3 study forms and other customized supplies to the T3 participants. Considerable staff time is required for drafting, skilled assembly, telephone discussions, and proofreading of the numerous interim versions of the forms which are submitted to the Operations Committee and appropriate T3 Committee Chairpersons for review and approval.

2.4.2 Coordination

Within the T3 DCC, the Coordination staff are responsible for the development and maintenance of storage systems for all study materials including study forms. These systems are briefly described in Section 2.4.3 through Section 2.4.5. The Coordination staff are responsible for clinic monitoring and communications including monitoring of the treatment allocation process described in Section 2.5.3.

2.4.3 Receipt, Inventory, and Storage of Study Forms

Information arriving by fax, courier services, or regular mail from the Clinical Centers is reviewed the same day it is received by the Coordination staff. Each form is stamped with the date of receipt. The Transmittal List accompanying the forms is compared with the forms. If there are no problems, the forms are then electronically registered using a video display terminal. This process is referred to as the pre-inventory. Each record contains the patient identification number, NAME CODE, date of examination, date received, and other information pertinent to the status of the particular material being pre-inventoried.

After a form has been pre-inventoried, the Coordination staff transfer the forms to the data entry staff. When the forms are returned from data entry, the Coordination staff file them. Knowledge of the location and status of all forms is a key responsibility of the Coordination staff.

2.4.4 Data from the Core Laboratories

The T3 DCC staff are responsible for the receipt and storage of data from the T3 Core Laboratories. A regular schedule for transmission of this information has been established.

The exact medium for this transmission may be electronic, floppy diskette or paper copies of information depending upon the Core Laboratory that is sending information. The Quantitative Core Laboratory, ECG Core Laboratory, Coagulation Core Laboratory, and Holter Core Laboratory transmit information by electronic means or diskette. The Thallium Core Laboratory and the Qualitative Core Laboratory report using paper forms. Data from the Core Laboratories include information

both on the overall quality of information being collected from the Clinical Centers and information to be used in evaluating primary and secondary end points.

2.4.5 Storage System for Study Reports, Minutes and Important Documents

A storage system for study reports, minutes of meetings, and important documents has been designed and implemented and is updated regularly.

2.4.6 Processing of Event Documentation

The Coordination staff have responsibility for handling the materials for event (death, fatal or non-fatal MI, and hemorrhages) documentation required by the Mortality and Morbidity Classification Committee and the Hemorrhagic Event Review Committee. This involves photocopying the forms and all accompanying materials, assigning reviewers, completing the initial portion of the classification form, monitoring the return of the forms, and reporting the results.

2.5 CLINIC MONITORING AND COMMUNICATIONS

T3 DCC staff are responsible for monitoring for protocol violations and for notifying all appropriate T3 personnel or appropriate committees of these violations when they occur. To minimize the number of protocol violations, T3 DCC staff have designed and distributed certain protocol adherence aids to the Clinical Centers. These include patient appointment schedules and monthly lists of patients due for one-year follow-up in the next 30 to 60 days.

The T3 DCC staff provide logistical support for meetings and training sessions. They have responsibility for preparing handouts and other materials for meeting participants as well as for preparing and distributing the minutes of these meetings.

T3 DCC staff are a resource for the numerous telephone inquiries and written inquiries concerning the study procedures from study investigators and Clinical Center personnel.

T3 DCC staff maintain and distribute a T3 address directory. This directory contains a listing of study personnel from each Clinical Center and Core Laboratory as well as personnel from the Program Office

at the National Heart,Lung, and Blood Institute. A list of the membership of all study committees is included. This directory is updated periodically and revised pages are distributed to all centers.

2.5.1 Certification

In cooperation with the Steering Committee, the T3 DCC staff have developed, implemented and monitored the T3 staff certification program. The following aspects of the certification program are the responsibility of the DCC:

a) Documentation of certification procedures.

b) Coordination of training schedules.

c) Participation at training sessions.

d) Conduct of training sessions for Research Coordinators.

e) Distribution of materials.

f) Receipt of certification materials.

g) Certification of Research Coordinators and their assistants.

h) Issuing of certification numbers and maintenance of an index of certified staff and assignment of certification numbers for each Clinical Center.

i) Monitoring of the use of certification numbers as recorded on study examination forms and material during the course of the study.

2.5.2 Additional Reports

Weekly reports on the status of recruitment are prepared by the DCC staff and circulated to the T3 Operations Committee, Core Laboratories, and the Drug Distribution Center. Reports on clinic performance and adherence to the protocol are prepared two times a year. Additional reports on clinic performance are prepared as needed in response to specific requests.

2.5.3 Treatment Allocations

Separate randomization schedules for each Clinical Center were computer generated at the DCC. Each schedule is designed to balance the number of patients assigned to the treatment groups at specified intervals.

The treatment allocation will be issued via either a sealed treatment allocation mailer to be opened at the completion of the screening process. The DCC has provided each Clinical Center with preprinted Treatment Allocation Mailers.

The DCC staff are responsible for monitoring the treatment allocation process through ascertainment of the completeness of each patient's forms and review of their contents.

2.6 DATA MANAGEMENT AND MAINTENANCE

The T3 DCC staff have designed a computer data storage system using the ORACLE relational data base management system. Using this system, DCC staff inventory and store all information from the Clinical Centers and Core Laboratories. DCC staff have also developed edit systems to monitor the completeness and quality of all data. The T3 data flow diagram is presented in Exhibit 2-1.

2.6.1 Data Entry

The entry of data from written responses on the T3 paper forms to a computer readable format occurs through the use of Data General Terminals with support programs written in scientific query language (SQL). Software packages have been developed which make it easy to generate "screen images" of each study form which reproduce the form items on the terminal screen. This facilitates the correct and rapid transcription of data on the study forms. These support programs provide a check of patient identification for each form with previously entered data from other forms and subject each field of transcribed data to a preliminary edit for valid code, out-of-range values and inconsistencies. Each form is keyed independently by two different operators and recorded files for the two operators for a batch of forms are compared electronically. Only those records for which every field of the form matches are committed to the data base. Discrepancies identified by the electronic match are reviewed and adjudicated by a third operator, usually the supervisor of the data preparation unit. If this adjudication agrees with one of the two data entries, the consensus value is entered in the data base. If all three readers disagree, the form is totally re-entered.

Data entry guidelines (Exhibit 2-2) provide written instructions for the DCC data entry staff. These guidelines help insure the accuracy of the data.

2.6.2 Inventory File

The pre-inventory, which is described in Section 2.4.3, is a record of all forms and materials received in the DCC. The pre-inventory updates an electronic inventory containing a record of each patient which describes the data processing status of each form received. This file is updated by the DCC coordination staff on a daily basis to record receipt of each form in the DCC. In addition to the pre-inventory information and information on the status of the edit, this file also contains the treatment assignment for each patient randomly assigned, and the time windows for each expected follow-up visit. This file is updated on a daily basis after data entry is completed.

2.6.3 Record Editing

A general edit program system has been designed with the goal of specifying the edit for any form through a series of parameters and tables in order to minimize the amount of programmer time required to develop the program for a specific form and to quickly respond to form revision. The components of this system are a list of edit parameters for each field specifying acceptable ranges for the response and a table consisting of groups of item numbers and their associated responses which are inconsistent. The specified goals can be met for some forms more easily than for other forms.

Corrections received in response to edit messages are entered through a data entry screen. The corrected data are then re-edited in the same manner as used in the original edit.

All data received from the Clinical Centers will be subjected to an extensive computer edit. The process of editing forms will begin with the record inventory and the data entry procedures. At the time of pre-inventory, an initial edit check will determine whether the form is properly labeled and consistently identified and whether the examination was performed within the permissible time limits. Preliminary editing

during data entry will check for inadmissible values, missing data, and responses inconsistent with the pre-inventory record.

Additional editing, including cross-editing among forms for the same patient and more sophisticated editing for consistency within a form, will take place at a later time. All study data will be edited for completeness, internal consistency, consistency with previous data from the same patient, numerical values outside specified limits, illegal codes, illegible responses and adherence to the treatment allocation protocol. All edit messages for a given form will be sent promptly to the Clinical Center where the form was completed.

The data management system will be designed so that new or revised information received in response to edit statements can be processed in much the same way as individual forms are processed. Forms which fail to pass edit are marked with flags to indicate potentially incorrect data. When the response to an edit statement is received from a Clinical Center, the data will be corrected and this form will be edited completely. By using this method, it should not be necessary to re-edit the main data file.

2.7 DATA ANALYSES

During T3, the findings for specific primary and secondary end points and other salient information concerning the effects of the treatment groups will be reviewed by the Data and Safety Monitoring Committee at specified intervals. The data reports prepared at the DCC will include data on the patients enrolled with emphasis on baseline comparability of the patients in the treatment groups, reports on end points and results during the course of the study for the different treatment groups, and reports on overall study and individual Clinical Center performance with regard to patient recruitment and follow-up.

Details of the data analysis plan are contained in Chapter 13, Study End Points and Chapter 15, Study Monitoring of Volume I of the T3 Manual of Operations.

2.8 DATA REPORTING

T3 DCC staff will assist, if requested, the participating Clinical Centers staff in the preparation of publications which have received

prior approval according to study procedures (see Chapter 6 of Volume I). Upon request of the National Institutes of Health (NIH) any and all of the above data will be made available to the NIH to access and utilize at any time after the completion of the T3 investigation. At that time any and all data requested by the NIH shall be transferred to the National Heart, Lung and Blood Institute (NHLBI).

2.9 PATIENT PRIVACY, CONFIDENTIALITY OF DATA, AND DATA SECURITY

Because of the importance of protecting study data at the DCC from theft or unauthorized perusal or alteration, access to the study records is restricted to study personnel. Access to computer files is also restricted through the use of passwords. Protection of the computer files from catastrophic loss is accomplished by a back-up system.

To maintain patient privacy, the study forms and records submitted to the DCC do not contain patient's name, address or other identifying information. Each patient record is identified by a unique number and NAME CODE. Names and addresses corresponding to the identifying codes are kept on file at the Clinical Centers on a special form (T3 Form 01, Patient Information Form).

All study forms will be microfilmed after the forms have been edited and there has been sufficient time for the Clinical Centers to respond to edit queries and the returned corrections for these forms processed and the forms re-edited.

A back-up system for the computer database has been designed to permit the recreation of the entire system with a minimum expenditure of time and money should the original study records or files be destroyed because of man-made or natural disaster. Once a week the magnetic disk files which contain the inventory and all data from the forms are copied onto magnetic tape. One copy of the tape is stored in an off site vault and the other at the DCC. Backup tapes containing all current computer programs used for updating, editing, and analysis of the data files are also kept both at the DCC and the off site vault. These tapes are generated monthly. In addition, on a daily basis the database is copied onto tape. There is a tape for each day of the week and each tape is recycled on the corresponding day of the next week. There is also a

program which copies all computer programs, including those being developed, onto tape once a week.

2.10 QUALITY CONTROL

2.10.1 Quality Control of Data Preparation

In developing the procedures for inventory and data entry of all study forms, DCC staff have included the steps required to monitor the timeliness and accuracy of processing study forms. Information arriving from the Clinical Centers is reviewed the same day it is received. Each form is stamped with the date of receipt and the form is pre-inventoried in the Coordination Office. Periodically the database is electronically examined to identify discrepancies. Examination of the database identifies the following types of problems:

(a) Materials which for one reason or another did not make it from the Coordination Office to the computer data file.

(b) Errors in identification of a given record.

(c) Errors in the dates of examination either in the Coordination Office inventory or database inventory.

All study forms are keyed independently by two operators and electronically compared. At the end of each comparison run, a list of all forms passing the comparison procedures (i.e., no discrepancies between keyings) is generated as well as a list of forms which failed this validation. The list of forms failing the comparison includes the identification of the particular item failing. The program also generates a summary table for each form type within each study. This information is utilized to review the items which most frequently fail the edit to determine if the form should be redesigned or additional instructions given to the Clinical Center staff or data entry staff as well as to evaluate the performance of individual data entry operators.

2.10.2 Quality Assurance of Information Stored in Computer Database

After keying, all forms are extensively edited and all corrections made at the Clinical Centers in response to edit messages are posted. To test edit programs, a mock set of study forms which contain errors and inconsistencies are prepared. The edit program is tested on these test forms. The edit program is then run on a few forms received from the

Clinical Centers and the edit output is carefully checked. If that test indicates no problems, the edit program becomes part of the usual maintenance procedures, but the edit output continues to be checked for a period of time before deciding the program has been adequately tested. The validity of information on the computer master file is ascertained by means of a forms audit. This is a structured procedure to compare (for a sample of each type of study form) the information on actual patient records with a printout of the record as entered on the computer master file. If master file problems are identified as a result of the audit, required corrective action is then taken. Any major discrepancies are discussed with the staff and appropriate changes made to resolve these problems.

Printouts listing baseline and follow-up values for important study variables for individual patients are generated. These printouts are prepared so that a site visitor to a Clinical Center may compare the printouts for selected patients against the original Clinical Center records. All discrepancies are noted and appropriate steps taken to resolve and rectify these problems.

2.10.3 Quality Assurance Procedures for Data Analysis

The checking of analysis programs is done primarily by preparing hand tabulations of the data for small subgroups of patients which have been selected either randomly or systematically. In some cases, the tabulations are prepared by referring to the original study forms and in other cases, by utilizing the computer data file for a sample of patients. Another preliminary step to data analysis which is utilized to identify any anomalies in the data is to obtain a point frequency distribution for every variable on the analysis file.

Various statistical methods are used to detect potential outlier observations. All observations identified as outliers are verified for correctness and if verified as correct, a decision is made as to whether the value should be included in the data analysis. The means, standard deviations, and frequency distributions as well as total number of observations for each variable included in a given report are routinely

checked with corresponding values given in a previous report. Within a report, the consistency of denominators is also checked.

To avoid possible errors in transcription of data from computer output to typewritten tables, either the computer output is printed in the format required for the report or the typed tables are proofread using the computer output as the source document before the report is submitted to the appropriate groups.

EXHIBIT 2-1

T3 DATA FLOW DIAGRAM

February 24, 1993

EXHIBIT 2-2

T3 DATA COORDINATING CENTER DATA ENTRY GUIDELINES

The underlying principle in processing information in the Data Coordinating Center (DCC) is to process the information as submitted without interpretation or second guessing what the recorder had intended. The providers of the data are requested to complete the forms as clearly and as legibly as possible, but also to follow certain conventions in reporting data to minimize the possibility of errors in processing the data collection forms. The procedures followed by the T3 DCC data entry staff are as outlined below.

I. Responses Answered by a Check Mark (/) or an "X"

If a response is to be answered by a check mark (/) or an "X", then only a check mark or an "X" within the parentheses is the acceptable response. This guideline has several implications.

A. The check mark (/) or the "x" must be in the parentheses for the response. A response outside the parentheses will be entered as a missing response (see example 1).

B. If there is no entry within the parentheses for the response and an identifier like "Yes" is circled, then the response will be entered as a missing response (see example 2).

C. A continuous line appearing through a series of responses when a check mark (/) or an "X" is required, will be entered as missing for each item (see example 3). Each item must be clearly marked.

II. Numeric Responses

When a numeric response is requested, the entire response space is to be completed. This guideline has the following implications.

A. If an item has a specified number of response spaces and the number of digits do not fill the number of spaces, the item will be entered as missing (see example 4).

B. If an item has a specified number of response spaces and the number of digits exceed the number of spaces, the item will be entered as missing (see example 5). (Do not enter fractions or add decimal points. If a decimal point is not provided on the form, round to nearest whole number).

C. If the response spaces do not contain punctuation marks or a symbol (e.g., a comma, decimal point, feet symbol, inches symbol) and a punctuation mark or symbol has been added, then the item will be entered as missing (see example 6).

D. If a response space is expected to be numeric and one or more alphabetic characters are entered in the response spaces, the item will be entered as missing (see example 7).

III. Legibility

If a response is to be.answered with something other than a check mark (/) or an "X", then the response is to be PRINTED clearly in the spaces provided. Abbreviations are not to be used by the Clinical Center staff unless absolutely necessary and then they are to use only widely recognized abbreviations. If any doubt exists as to the legibility of the response, then the item will be entered as missing (see example 8).

If items are completed improperly as outlined in the examples above, an edit message will be produced. An asterisk (*) will be used under the original code column to indicate a missing response. The correct response must then be entered under the correct column (see example 9).

IV. Overwritten Responses

A. If the response has been overwritten to carefully delineate the existing mark, the response is acceptable (see example 10). The tracing of the existing mark(s) should be done in

black ink. (All forms should be completed in black or blue ink. Never use pencil or red or other colored ink).

B. If the response has been overwritten to change the response, then the response will be considered illegible (see example 11) and will be keyed as missing data. The correct check mark or "X" must be clearly and neatly circled, initialed and dated by the individual correcting the response. An incorrect numeric or alphabetic response should be completely crossed out and the correct numeric or alphabetic response written clearly and neatly above or below the original response, circled, initialed and dated by the individual making the correction (see example 12).

V. Unsolicited Response

Unsolicited responses written within the items on the forms are not keyed and thus this information is not entered into the computer system (see example 13). Remarks should be recorded only in specified areas.

EXAMPLES

EXAMPLE 1 - INCORRECT RESPONSE SINCE OUTSIDE PARENTHESES

EXAMPLE 1 - CORRECT RESPONSE SINCE INSIDE PARENTHESES

EXAMPLE 2 - INCORRECT RESPONSE SINCE RESPONSE IDENTIFIER CIRCLED

EXAMPLE 2 - CORRECT RESPONSE SINCE RESPONSE IS CHECKED INSIDE PARENTHESES

EXAMPLE 3 - INCORRECT RESPONSE SINCE CONTINUOUS LINE THROUGH SERIES OF RESPONSES

EXAMPLE 3 - CORRECT RESPONSE SINCE EACH ITEM IS CHECKED

EXAMPLE 4 - INCORRECT RESPONSE SINCE NUMBER OF SPACES NOT COMPLETELY FILLED

EXAMPLE 4 - CORRECT RESPONSE AS PRECEDING ZERO IS FILLED IN

EXAMPLE 5 - INCORRECT RESPONSE SINCE TOO MANY DIGITS FOR NUMBER OF SPACES

EXAMPLE 5 - CORRECT RESPONSE SINCE NO EXTRA DIGITS ARE ENTERED

EXAMPLE 6 - INCORRECT RESPONSE SINCE COMMA OR DECIMAL POINT WAS ADDED TO ITEM

EXAMPLE 6 - CORRECT RESPONSE SINCE NO COMMA OR DECIMAL POINT ADDED

EXAMPLE 7 - INCORRECT RESPONSE SINCE ALPHABETIC CHARACTERS IN NUMERIC FIELDS

EXAMPLE 7 - CORRECT RESPONSE SINCE NUMBERS ARE FILLED IN

EXAMPLE 8 - ILLEGIBLE RESPONSES

EXAMPLE 8 - LEGIBLE RESPONSES

EXAMPLE 9 ????

EXAMPLE 10 - CORRECT RESPONSE SINCE OVERWRITTEN RESPONSE TO DELINEATE EXISTING MARK

EXAMPLE 11 - INCORRECT RESPONSE SINCE OVERWRITTEN RESPONSE TO CHANGE RESPONSE AND DESIRED RESPONSE IS NOT CLEARLY DESIGNATED, INITIALED AND DATED

EXAMPLE 12 - CORRECT RESPONSE SINCE OVERWRITTEN RESPONSE TO CHANGE CHECK MARK OR "X" AND NUMERIC RESPONSES ARE CLEARLY DESIGNATED BY CIRCLE, INITIALED AND DATED

EXAMPLE 13 - UNSOLICITED WRITE-IN RESPONSE