T3 MANUAL OF OPERATIONS

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CHAPTER 9

RANDOMIZATION AND ENROLLMENT OF PATIENTS

9.1 INTRODUCTION

All of the patients admitted to the Emergency Room, Coronary Care Unit or other services of the hospital with a diagnosis of unstable angina or rule out myocardial infarction should be evaluated for entry into the Thrombolysis in Myocardial Ischemia Study. In addition, patients in hospital who develop a diagnosis of unstable angina or rule out myocardial infarction should be considered for entry into the study. The patient eligibility flow chart (Exhibit 9-1) outlines the steps from screening until study entry for T3A and T3B.

9.2 DEFINITIONS

9.2.1 Clinical Center Number

Each Clinical Center or hospital participating in the Thrombolysis in Myocardial Ischemia Trial has been assigned a unique three-digit Clinical Center number by the Data Coordinating Center. To facilitate identification of individual patients the first three digits of the patient identification number will be the same as the affiliated hospital number. For example, the Albert Einstein Clinical Center was assigned Clinical Center 01.1 and identification numbers for all patients recruited at this hospital will have these numbers as the first three numbers of the patient identification number described below.

9.2.2 Patient Identification Number

A permanent T3 identification number (ID Number) is assigned to each patient once they have satisfied the eligibility criteria for the T3 investigation and have given informed consent. Patient identification numbers are assigned in order from a T3 Patient Identification List (Exhibit 9-2) prepared and supplied by the Data Coordinating Center staff. The identification number consists of six numbers and one letter. The first three numbers designate the Clinical Center or

hospital in which the patient was first screened for eligibility. The second three numbers indicate the sequence in which the patient has entered the T3 investigation. The letter at the end of the patient identification indicates whether the patient is participating in T3A or T3B. Once the patient has satisfied all the inclusion and exclusion criteria and has given informed consent, an identification number should be obtained for that patient by looking on the Patient Identification List. For example, referring to Exhibit 9-2, the first patient to be examined and found eligible for entry in Clinical Center 50.1 into T3B and who has given consent to be in the study would be permanently assigned a number of 50-1001B as the patient identification number. As indicated in Exhibit 9-2, certain identification numbers are not available for assignment to patients; for example, number 50-1004B may not be used for patient assignment. These numbers have been reserved for quality assurance activities in T3. Once a number has been assigned to a particular patient, it remains associated with this patient whether or not he or she enters the study or if he or she later transfers to another Clinical Center. Only one number is assigned to each patient and only one patient is given each number. Patients will not be assigned a T3 identification number if they fail to satisfy all of the inclusion criteria for entry into T3A or T3B or if they have at least one exclusion criterion. These criteria are listed in Forms 3A and 3B (Volume II T3 Manual of Operations), respectively.

Assignment of a patient identification number does not necessarily imply that the patient will be randomized and receive T3 study treatment. This is especially true for T3A in which patient eligibility is determined during the first catheterization.

9.2.3 Patient Name Code

Once a patient has been found to be eligible for T3 and has given informed consent, another identifier in addition to the patient identification number will be assigned to the patient. The second

identifier is the patient Name Code which is a group of five alphabetic characters formed by taking the first three letters of the last name of the patient and the first two letters of the first name. For example, the Name Code corresponding to John Smith is SMIJO. The Name Code, once determined, is never changed; even if the patient changes his or her name during the course of the study. If a patient does not have enough letters to fill in the first three letters or the last two letters of the Name Code, these spaces should be filled in with X's.

The patient identification number and the Name Code are the only two identifiers communicated to the Data Coordinating Center. Together they enable the Data Coordinating Center staff to link all data records for a specific patient. Therefore, it is essential that these two important pieces of information are always recorded clearly, correctly and consistently on all study forms and materials.

9.3 ELIGIBILITY ASSESSMENT

The Screening Form (T3 Form 3A or 3B) is completed for all patients assigned an identification number. This form documents whether the patient meets at least one of the study inclusion criteria and none of the exclusion criteria. The Screening Form must be submitted to the Data Coordinating Center for each patient assigned an identification number. An Information Sheet (T3 Form 01) should be completed for all patients for whom a Screening Form is completed. Form 01 is not sent to the Data Coordinating Center, but is kept at the Clinical Center for use if it is necessary to contact the patient after the study is terminated, or to assist in locating the patient if he/she misses scheduled visits or cannot be contacted.

9.4 RANDOMIZATION AND TREATMENT ALLOCATION

Separate randomization schedules for each Clinical Center or hospital are computer-generated at the Data Coordinating Center. Each schedule is designed to balance, at specified intervals, the number of patients assigned to initial therapy (t-PA versus placebo) in T3A and

initial therapy (t-PA versus placebo) and follow-up management (invasive versus conservative strategy) in T3B. Treatment Allocation Mailers for each Clinical Center are generated at the Data Coordinating Center. The outside of the Treatment Allocation Mailer (Exhibit 9-3) includes the Clinical Center or hospital number and the sequence number which specifies the order in which the envelope should be assigned. The mailer with the lowest sequence number should be used first. Although some patient identification numbers on the Patient Identification List are not available for assignment, all mailer sequence numbers should be used in the proper order. The inside of the mailer includes the Clinical Center or specific hospital number, the sequence number, and the randomization assignments for initial therapy (T3A and T3B) and subsequent management (T3B only). The appropriate treatment kit to be used for the patient is recorded in the upper right hand corner of the mailer. It should be noted that sequence number and kit number are not necessarily the same; therefore, the treatment kit should not be requested until the randomization mailer is opened. Failure to open the lowest sequence number or use the correct treatment kit is an error in randomization and must be reported to the Data Coordinating Center.

For T3B patients, just below the kit number is the indication of the follow-up management strategy that should also be used for the patient. Spaces are provided on the mailer to record patient ID Number, Name Code and the date the mailer was used. The inside of the mailer should be kept in the patient's file and returned with the Admission and Treatment Assignment Form (T3 Form 04). At this time the separate unblinding envelope for the kit number used to treat the patient should also be returned to the Data Coordinating Center.

If it is not possible to treat the patient within 25 hours of the onset of ischemic pain, this patient is ineligible and treatment with study drug should not be initiated. The Treatment Allocation Mailer will not be opened in this situation. The appropriate item on the Screening Form should be completed indicating that the patient was not

eligible for T3 because he/she could not be treated within the specified time.

9.4.1 Thrombolysis in Myocardial Ischemia Study A (T3A)

Randomization in T3A will be double-blind. Thus when the Treatment Allocation Mailer (Exhibit 9-3) is opened there will not be an indication of whether the patient is being treated with t-PA or with placebo. In the upper right hand corner of the mailer there is a kit number identifying the kit that should be used to initiate the study drug infusion for the patient (Exhibit 9-3 Inside of Mailer). Should treatment identification prove necessary, this can be accomplished by using the unblinding envelope for the appropriate treatment kit number (Exhibit 9-4). Unblinding is expected to be a very rare occurrence.

9.4.2 Thrombolysis in Myocardial Ischemia Study B (T3B)

One set of Treatment Allocation Mailers will be generated for each Clinical Center participating in T3B. Within each mailer (Exhibit 9-3 Inside of Mailer) there will be an indication of the study drug treatment kit that should be used to treat the patient initially and the management strategy that should be used to manage the patient subsequently. Both of these designations can be found in the upper right hand corner of the mailer once it is opened. Should treatment identification prove necessary, this can be accomplished by using the unblinding envelope (Exhibit 9-4) for the appropriate treatment kit number. Unblinding is expected to be a very rare occurrence.

9.5 DOCUMENTATION OF TREATMENT ASSIGNMENT

The Research Coordinator at each Clinical Center or hospital will notify the Data Coordinating Center no later than 48 hours following the initiation of study drug infusion to report that a Treatment Allocation Mailer has been opened and to transmit selected information concerning adverse events within the first 24 hours. This information should be sent to the Data Coordinating Center by Fax transmission ((301) 323-8622

or (301) 323-7694) using Form 5D. The information on this form (Form 5D) will be reviewed at the Data Coordinating Center to insure that the Clinical Center is following the correct allocation procedures. The Research Coordinators should mail the original of the Admission and Treatment Assignment Form (Form 04) as soon as possible. The Form 04 and the Form 5D will be reviewed for consistency. Results will be adjudicated by telephone.

9.6 CONSEQUENCES TO TREATMENT ASSIGNMENT

Initiation of thrombolytic therapy establishes the patient's entry into the study. The time of initiation of treatment will be recorded on the Treatment Assignment Form. Every patient for whom a Treatment Allocation Mailer is opened is counted as a participant in the study and will be included in all analyses.

EXHIBIT 9-1

T3A PATIENT FLOW CHART TO RANDOMIZATION

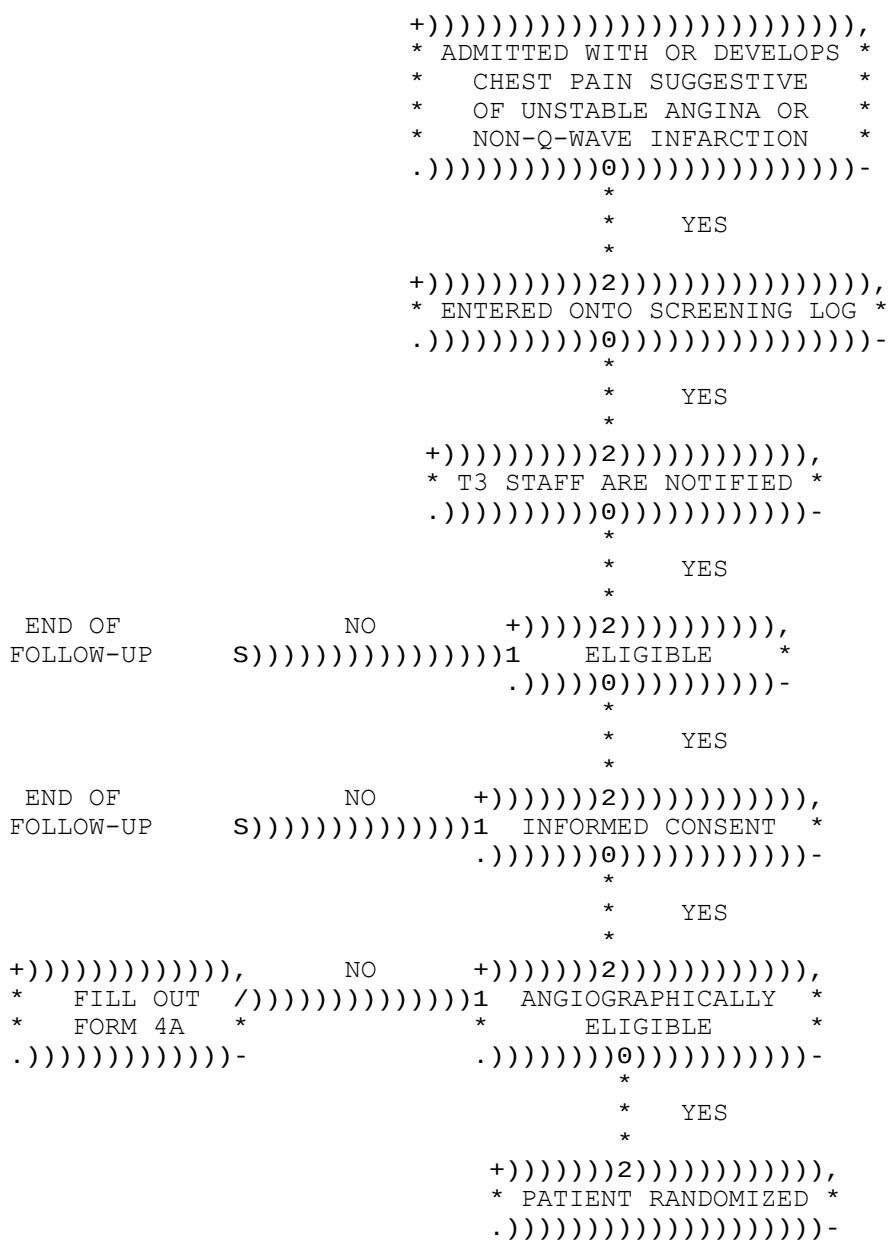

EXHIBIT 9-1 (Continued)

T3B PATIENT FLOW CHART TO RANDOMIZATION

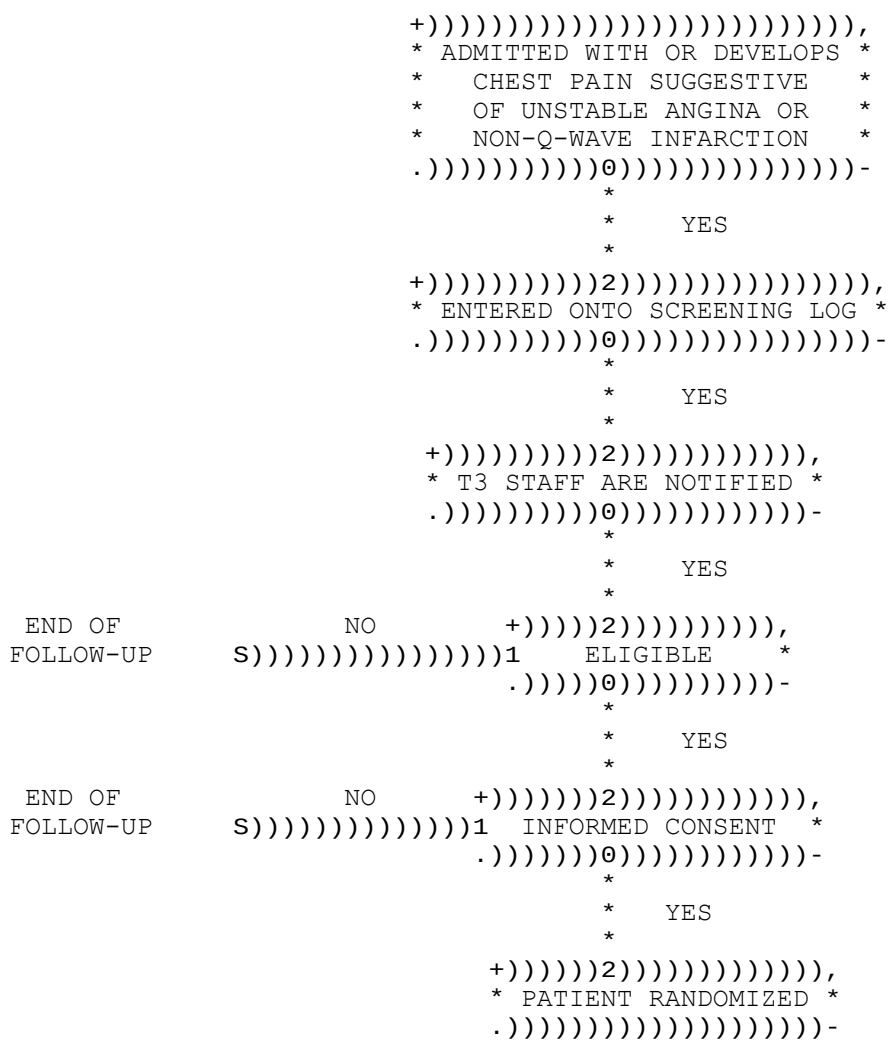

EXHIBIT 9-2

T3 PATIENT IDENTIFICATION LIST

CLINIC 50.1

PATIENT I.D. NUMBER	NAME CODE	DATE OF SCREENING FORM MONTH	DAY	YEAR	ELIGIBLE YES	ELIGIBLE NO	TREATMENT CONSENT YES	TREATMENT CONSENT NO	DATE OF ENTRY MONTH	DAY	YEAR	TREATED YES	TREATED NO
50-1001B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1002B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1003B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1004B	* * * * *	* NOT AVAILABLE FOR ASSIGNMENT *											
50-1005B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1006B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1007B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1008B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1009B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1010B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1011B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1012B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1013B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1014B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1015B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1016B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1017B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1018B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1019B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )
50-1020B	_ _ _ _ _	_ _	_ _	_ _	( )	( )	( )	( )	_ _	_ _	_ _	( )	( )

EXHIBIT 9-3

SAMPLE T3A RANDOMIZATION MAILER

OUTSIDE OF MAILER

TREATMENT ALLOCATION
FOR
T3A CLINIC 01-2
SEQUENCE NO. 001

TO

INSIDE OF MAILER

TREATMENT ALLOCATION
FOR
T3A CLINIC 01-2
SEQUENCE NO. 001

INITIAL THERAPY:

KIT NUMBER * 01-5-005A *

PATIENT I.D. NUMBER __ __ - __ * __ __ __ _A

NAME CODE __ __ __ __ __

DATE OPENED __ __ __ __ __ __

EXHIBIT 9-3 (Continued)

SAMPLE T3B RANDOMIZATION MAILER

OUTSIDE OF MAILER

FROM

TREATMENT ALLOCATION
FOR
T3B CLINIC 01-5
SEQUENCE NO. 001

TO

INSIDE OF MAILER

TREATMENT ALLOCATION
FOR
T3B CLINIC 01-5
SEQUENCE NO. 001

INITIAL THERAPY:

KIT NUMBER ********** * 01-5-0058 * **********

SUBSEQUENT THERAPY:
INVASIVE STRATEGY

PATIENT I.D. NUMBER __ __ - __ * __ __ __ __ -*

NAME CODE __ __ __ __ __

DATE OPENED __ __ __ __ __ __

EXHIBIT 9-4

UNOPENED UNBLINDING ENVELOPE

OPEN ONLY IN CLINICAL EMERGENCY

The only clinical circumstance for which unblinding is forseen is

suspected myocardial infarction.

Documentation of reason for unblinding is required.

After randomization, attach envelope (opened or unopened) to TJ Form 04 and return to TJ Data Coordinating Center

EXHIBIT 9-4 (Continued)

SAMPLE T3B RANDOMIZATION MAILER

OUTSIDE OF UNBLINDING ENVELOPE

T3 CENTER: 30-1
KIT NUMBER: 30-1-1018

RANS-O-GRAM

TURN ENVELOPE OVER FOR OPENING INSTRUCTIONS

TO:

After randomization, attach envelope (opened or unopened) to T3 Form 04 and return to T3 Data Coordinating Center

INSIDE OF UNBLINDING ENVELOPE

T3 CENTER: 30-1
KIT NUMBER: 30-1-1018

TRANS-O-GRAM

T3 STUDY DRUG = t-eA

After randomization, attach envelope (opened or unopened) to T3 Form 04 and return to T3 Data Coordinating Center