T3 MANUAL OF OPERATIONS, VOLUME II

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CHAPTER 3

TRAINING AND CERTIFICATION PROCEDURES

3.1 INTRODUCTION

In any multicenter clinical trial or research study it is important that procedures be standardized within and among Clinical Centers to assure that the data from all centers are comparable and, therefore, can be pooled. In the Thrombolysis in Myocardial Ischemia Clinical Trial (T3) provisions for standardization include:

A. Standard data collection forms to be used by all participating centers;

B. Documented procedures for clinical measurements and evaluation;

C. Standard procedures for administration of the assigned treatment;

D. Documented procedures for grading coronary angiograms, grading Thallium and ETT tests, and reading ECGs at the respective Core Laboratories;

E. Standard procedures for data processing and quality assurance at the Data Coordinating Center;

F. Training in study procedures for Clinical Center personnel;

G. Certification of Clinical Center personnel to perform required tasks;

H. Certification of Clinical Centers to recruit and treat patients;

I. Periodic site visits to all participating centers; and

J. Central monitoring of all participating centers.

Items A through E, I and J are discussed elsewhere in the T3 Manual of Operations. This chapter will deal specifically with Items F through H, i.e., with training, with procedures for certification of Clinical Centers and personnel, and with procedures for coordinating the certification program.

3.2 TRAINING

Before the start of the study, training sessions were organized for Clinical Center personnel. The protocol, Manual of Operations and organizational structure of the study were explained. The training sessions covered procedures for collecting patient data and for completing examination forms, and instructions in the mechanics of edit procedures.

Procedures for collecting and processing other study materials were reviewed by Core Laboratory personnel. The Quantitative/Qualitative Core Laboratories provided training and instruction in radiographic procedures. The Thallium Core Laboratory provided training and instruction in radionuclide procedures. The Holter Monitoring Core Laboratory and the ECG Core Laboratory provided training and instructions in obtaining Holters and ECGs.

As new Research Coordinators join the study in progress, a special training session can be scheduled at the Data Coordinating Center, in conjunction with a site visit to the Clinical Center, or with a certified Research Coordinator at the Clinical Center.

3.3 REQUIREMENTS FOR CERTIFICATION AND REGISTRATION OF CLINICAL CENTER STAFF

In order to recruit and treat T3 patients, each participating Clinical Center is required to have one or more individuals on the staff certified or registered in each of five categories. The personnel for whom certification/registration is required are as follows:

1. T3 Investigator.
2. Research Coordinator.
3. Holter Monitoring Technician.
4. PTCA Operator (T3B only).
5. ETT Technician (T3B only).

Training and/or experience is required for each individual to be certified/registered. All persons requesting certification or registra-

tion are expected to have read the T3 Protocol and appropriate sections of the T3 Manual of Operations. Individuals request certification by submitting the appropriate request to either the Data Coordinating Center or the Core Laboratory. Specific requirements must be met in each category in order to be eligible for certification. In general, practical experience in following T3 procedures and completing T3 data collection forms is necessary. These requirements are described below. Once the required materials are submitted for central review and assessed as satisfactory, certification or registration is provided in writing and a T3 Staff number is assigned. Periodically, an updated Staff Number List will be sent to each Clinical Center (See Exhibit 3-1, T3 Form 100).

3.3.1 T3 Investigator

Any Clinical Center physician responsible for evaluating patients for eligibility or completing the medical history or physical examination sections of data collection forms must be registered as a T3 investigator. Hospital home staff (interns, residents and fellows) are not to be registered. A list of T3 Investigators must be sent to the Data Coordinating Center with the Clinical Center Certification Form 121. Each registered physician will be assigned a T3 Staff number by the Data Coordinating Center prior to the beginning of patient recruitment and during the course of the study.

3.3.2 Research Coordinator

A description of the responsibilities for the Research Coordinator is presented elsewhere (see Volume I, Chapter 14). Requirements for certification focus on the Coordinator's primary role in assuring the quality and completeness of data reported to the Data Coordinating Center. The following requirements for certification must be met.

1. Attendance at T3 Research Coordinators Training Session or equivalent.

2. Provisional Certification, T3 Form 101 (Exhibit 3-2). Completion of a set of Screening, Admission and Hospital Discharge Forms (T3 Forms 03, 04 and 10) for three patients presenting with unstable angina, non-Q-wave infarction or from the T3 study and submission of these to the Data Coordinating Center for review. Research Coordinators who were certified during TIMI Phase II or UNSA are not required to submit these three sets of forms. Prior to the time of Clinical Center certification, all forms received at the Data Coordinating Center will be considered for certification purposes. Once randomization has begun in a Clinical Center, forms for patients who are T3 patients should be duplicated if used for Provisional Certification purposes. The original set of forms should be submitted in the usual manner with a Transmittal List. The duplicated set of forms should be submitted with Form 101 to be assessed for certification purposes.
3. Final certification is awarded upon satisfactory submission and review of complete sets of forms for T3 patients after the study has begun. No certification application is required for final certification. The Data Coordinating Center will monitor the process and notify the Clinical Centers when final certification is awarded.
4. Continued certification is contingent upon the timely submission of study forms and prompt and accurate responses to edit messages.

3.3.3 Holter Monitoring Technician

The Holter Monitoring Technician is certified by the Holter Monitoring Core Laboratory. The technician is responsible for supervising the administration of the Holter test at the Clinical Center. A 24-hour trial recording using the monitor to be used in T3 (using any person willing to wear the monitor) is to be submitted to the Holter

Core Laboratory. (See Appendix C. Use current T3 Address Directory to verify name of coordinator and mailing address.)

3.3.4 PTCA Operator (T3B Only)

Each physician (including the Principal Investigator) wishing to be certified as a T3 PTCA Operator must have:

1. Performed at least 250 procedures.
2. Achieved at least an 85% success rate in the last 100 cases performed.
3. Had no more than 5% of patients experience post-PTCA associated myocardial infarction.
4. Had no more than 2% PTCA associated mortality.
5. Had less than 5% post-PTCA coronary artery bypass graft surgery.
6. Performed PTCA either prior to or following thrombolytic therapy in at least 20 patients with acute myocardial infarction.
7. Achieved at least an 85% success rate in the 20 cases or more with acute myocardial infarction.

It is desirable for each site to have more than one PTCA operator certified to perform PTCA. In sites participating in T3B, only certified T3B PTCA operators may perform procedures for study patients. PTCA operators requesting certification should submit cine-angiograms for their last five successful PTCA cases for review in the T3B Qualitative Core Laboratory (Providence, Rhode Island). This is not required for PTCA Operators who were certified in TIMI II. (See Appendix D. Use current T3 Address Directory to verify name of coordinator and mailing address.)

3.3.5 ETT Technician

The ECG Core Laboratory will certify the ETT technicians, who will perform exercise treadmill testing. (See Appendix A. Use current T3 Address Directory to verify name of coordinator and mailing address.)

3.4 REQUIREMENTS FOR CERTIFICATION OF CLINICAL CENTERS

Before a T3 Clinical Center can begin to recruit and treat patients, the following requirements must be met (Exhibits 3-3, 3-4).

1. Approval by local Institutional Review Board (IRB) to conduct T3.
2. Submission of IND materials to the Data Coordinating Center. This includes evidence of IRB approval, a copy of the IRB approved informed consent form (either T3 model informed consent form or submission for review of a proposed informed consent form), a signed FDA Form 1572, curriculum vitae of key investigators, signed Conflict of Interest Guidelines and Confidentiality Agreement, and submission of report of local laboratory normal ranges.
3. Certification of at least one individual in each required category.
4. For T3A, certification of the Cardiac Catheterization Laboratory by the Quantitative Core Laboratory.
5. For T3B, certification of the Cardiac Catheterization Laboratory by the Qualitative Core Laboratory and the Radionuclide Laboratory by the Thallium Core Laboratory.
6. Submission of Request for Clinical Center Certification (T3 Form 121A or 121B). (Exhibits 3-5, 3-6)

3.5 ROLE OF THE DATA COORDINATING CENTER IN CERTIFICATION

The tasks related to the entire certification program for which Data Coordinating Center staff has responsibility are:

1. Documentation of certification procedures.
2. Coordination of training schedule.
3. Participation in training sessions.
4. Distribution of materials.
5. Receipt of certification materials.
6. Distribution of materials to reviewers.

7. Certification of Research Coordinators and Clinical Centers.
8. Reporting to the Operations Committee.
9. Monitoring use of T3 Staff numbers.

Although procedures for certification of Clinical Center staff to perform various tasks are developed by the T3 investigators who have special interests and expertise in each area, systemization of procedures and documentation of procedures are the responsibility of the Study Chairman's office, the Core Laboratories and the Data Coordinating Center staff.

3.5.1 Processing Requests for Certification of Clinical Center Staff

Staff at the Data Coordinating Center process all requests for certification. Upon receipt of a request for certification the Study Coordinator reviews the request and materials to assure that dates of training sessions attended have been supplied and that all required materials have been received.

3.5.2 Certification of Research Coordinators

Data Coordinating Center staff are responsible for review of certification materials submitted for Research Coordinators. Review is carried out by the Study Coordinator of the Data Coordinating Center staff. A certification log is maintained for each Clinical Center which is updated as each certification is issued.

3.5.3 Notification of Certification

Some individuals perform adequately in certain areas but may make mistakes or oversights in other areas. Therefore, certification is sometimes made conditional on submission of corrected forms or on repetitions of procedures which are again reviewed. In those instances in which certification is not recommended, the Operations Committee is notified. If certification is recommended, the Principal Investigator of the Clinical Center and the Research Coordinator are notified in writing by the Data Coordinating Center. A unique T3 staff number is assigned to each certified individual. If an individual is certified in several categories, the same T3 staff number is retained.

3.5.4 Processing Requests for Certification of Clinical Centers

Requests for Clinical Center Certification are also logged at the Data Coordinating Center and each is reviewed to assure that the required staff have been certified. The Data Coordinating Center notifies each Clinical Center when certification to begin patient recruitment has been granted (T3 Form 122 Notification of Clinical Center Certification - Exhibits 3-7 and 3-8). Along with notification,

each Clinical Center receives supplies of data collection forms and all other materials required to begin patient recruitment.

3.5.5 Liaison Activities

The Data Coordinating Center maintains regular telephone communications with staff in each Clinical Center to monitor and resolve any problems encountered in the certification process. Problems which are not resolved are referred to a designated member of the Operations Committee.

The Data Coordinating Center staff are also responsible for preparing reports on the progress of certification and patient recruitment which are distributed to the Operations Committee and to the Principal Investigators of all Clinical Centers.

3.6 RESCINDING CERTIFICATION

3.6.1 Research Coordinator

Ongoing review of Research Coordinator performance is undertaken by the Data Coordinating Center staff. The quality, completeness and timeliness of submission of the T3 forms and responses to edit messages and memoranda are the primary criteria used in evaluation. If efforts by the Data Coordinating Center staff to improve the unsatisfactory performance of a Research Coordinator have failed, the Data Coordinating Center staff will review the problem with a designated member of the Operations Committee and will ask the Study Chairman's office to contact the Principal Investigator of the Clinical Center. If there is no resolution within two months, the Data Coordinating Center staff will notify the appropriate individual in writing that his/her certification has been rescinded and send copies of this letter to the Principal Investigator of the Clinical Center. The de-certified staff member will be re-certified only when all of the following conditions have been met:

1. At least 30 forms or three months work have been reviewed and co-signed by the Principal Investigator and all are satisfactory.

2. Any outstanding edit messages and memoranda have been received and are satisfactory.
3. Current work is satisfactory and is submitted in a timely fashion.

In the extenuating circumstance that no certified Research Coordinator is available at the Clinical Center due to illness or other unexpected events or while new staff are being recruited and certified, T3 forms will be accepted by the Data Coordinating Center only if each form is reviewed and co-signed by the Principal Investigator.

3.6.2 Holter Monitoring Technician

Ongoing review of the performance of the Holter Monitoring Technician is the responsibility of the Holter Monitoring Core Laboratory. Quality of submitted Holter tests will be summarized at regular intervals. On the basis of review of test quality, recommendations for rescinding certification may be made to the Operations Committee.

3.6.3 PTCA Operator (T3B Only)

Only PTCA operators certified with expertise meeting the stringent T3 criteria will be permitted to perform PTCA in study patients. The results of angiography and PTCA will be reviewed by the Qualitative Core Laboratory. The Operations Committee will work with the Qualitative Core Laboratory in identifying and correcting any problems that may be identified in the quality of performance. Resolution of problems may involve site visits to the Clinical Centers to make specific recommendations regarding PTCA performance.

Ongoing review of performance is undertaken for PTCA operators through review of cineangiograms sent to the Qualitative Core Laboratory. On the basis of these reviews, recommendations for rescinding certification may be made to the Operations Committee.

Operators will be evaluated on the basis of their adherence to protocol, specifically in regard to the radiographic procedures that affect: 1) image quality; 2) the ability of the Qualitative Core

Laboratory to perform analysis; and 3) PTCA performance. Close attention will be paid to the reasons non-protocol PTCA's were performed.

Because the performance of PTCA is intimately related to successful completion of the study, close attention will be paid to the success rate of PTCA in each of the Clinical Centers.

3.6.4 ETT Technician

Ongoing evaluation of performance is undertaken through review of electrocardiograms sent to the ECG Core Laboratory. On the basis of these reviews, recommendations for rescinding certification may be made to the Operations Committee.

3.7 ONGOING REVIEW OF FORMS

During the course of the study, the Data Coordinating Center staff will periodically select forms for review and monitor the use of T3 Staff numbers. The timeliness and quality of data submission will also be scored and reported in a biennial evaluation of each Clinical Center.

EXHIBIT 3-3

SUMMARY OF PROCEDURES FOR CERTIFICATION TO BEGIN PATIENT RECRUITMENT FOR T3A

1. IRB approval of protocol dated 3/90

2. Submission of IND materials to Data Coordinating Center

   a. evidence of IRB approval
   b. copy of IRB approved informed consent form
   c. signed FDA Form 1572
   d. curriculum vitae of key investigators
   e. signed Conflict of Interest Guidelines
   f. signed Confidentiality Agreement
   g. report of local laboratory normal ranges

3. Provisional certification of Research Coordinator(s)

4. Submission to Data Coordinating Center:

   a. List of T3 Investigators responsible for evaluating patients and completing study forms.

   b. List of CABG surgeons

5. Holter Core Lab certification of Holter Monitoring Technician(s)

6. Quantitative Core Lab certification of Cardiac Catheterization Laboratory

7. Submission of Request for Clinical Center Certification T3 Form 121A

EXHIBIT 3-4

SUMMARY OF PROCEDURES FOR CERTIFICATION TO BEGIN PATIENT RECRUITMENT FOR T3B

1. IRB approval of protocol dated 3/90

2. Submission of IND materials to Data Coordinating Center

   a. evidence of IRB approval
   b. copy of IRB approved informed consent form
   c. signed FDA Form 1572
   d. curriculum vitae of key investigators
   e. signed Conflict of Interest Guidelines
   f. signed Confidentiality Agreement
   g. report of local laboratory normal ranges

3. Provisional certification of Research Coordinator(s)

4. Submission to Data Coordinating Center:

   a. List of T3 Investigators responsible for evaluating patients and completing study forms.

   b. List of CABG surgeons

5. Holter Core Lab certification of Holter Monitoring Technician(s)

6. Thallium Core Lab certification of Radionuclide Laboratory

7. Qualitative Core Lab certification of PTCA operator(s) and Cardiac Catheterization Laboratory

8. ECG Core Lab certification of ETT technician(s)

9. Submission of Request for Clinical Center Certification T3 Form 121B

CERTIFICATION FORM FOR STRESS LAB TECHNICIANS

Instructions:

1. Thorough review of enclosed ETT Manual of Operations by each Stress Lab Technician.

2. Place each exercise test in clearly labelled separate envelope. Each test should be marked with the Stress Technician name, date of ETT, and TIMI Clinic number.

3. Send completed packet to:

   Leslie Shaw, M.A.
   Suite 333
   4144 Lindell Blvd.
   St. Louis, MO 63108

   (314) 533-0040

QUANTITATIVE CARDIAC CATHETERIZATION
CERTIFICATION FORM

Instructions:

1. Carefully follow the attached instructions.

2. Label each cineangiogram with TIMI Clinical Unit # and a return address.

   Send to:

   B. Greg Brown, M.D.
   Cardiology, RG-22
   University of Washington
   Seattle, WA 98195

   (206) 543-3055

CERTIFICATION FORM FOR HOLTER MONITOR TECHNICIAN

Instructions:

1. Carefully follow the attached Manual of Operations when obtaining the test tape.

2. Label (patient namecode, Clinical Unit - hospital, date) and send this form with tapes to:

Gail MacCallum
T3 Holter Core Laboratory
454 Brookline Avenue, Suite 05
Boston, Massachusetts 02215

(617) 735-0685

MANUAL OF OPERATIONS

CINEANGIOGRAPHY QUALITY CONTROL CERTIFICATION

1. Cine Film and Angiographic Protocol Certification

The purpose of this component of the certification process is to ensure that each cardiac catheterization suite in which TIMI III patients are to be studied will provide coronary cineangiograms of acceptable quality. In addition, the ability of the primary catheterization physician and support staff to follow the TIMI III angiographic protocol will be assessed.

A cineangiogram including a left ventriculogram and selective coronary angiogram will be performed in each catheterization suite wherein TIMI III patients will undergo cardiac catheterization. Left ventriculograms will be obtained in the 35° RAO projection with a selective injection of contrast from 12-20 ml/sec with a total volume of contrast of 30-50 ml. Care should be taken in positioning the catheter to avoid premature ventricular contractions and catheter-induced mitral regurgitation.

Selective coronary cineangiography will be performed in the projections described in Table I. Since patterns of coronary anatomy and intra-thoracic cardiac position vary among patients, slight modifications in the recommended projections may be necessary to optimize visualization of coronary arterial segments. Each certifying angiogram should be accompanied by a written log which describes the specific angle for each projection as well as MAS, KVP values, and field size (see log form).

To appropriately evaluate the cine system in each laboratory, the certifying angiograms should be performed in patients weighing between 185-220 pounds. Each cineangiogram should be labeled to identify the clinic site as well as the specific laboratory and x-ray plane being assessed. Bi-plane rooms should submit cine films from each plane if both planes are to be employed for coronary cineangiography.

Cineangiograms and logs should be sent to the TIMI Quality Control Laboratory, care of Paula Ferreira, R.N., APC Building, Room 981, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02902. Procedural Log Sheet should be folded and included within each cine film can. The laboratory will review each cineangiogram for protocol compliance, the extent to which coronary anatomy is displayed in order to enable complete interpretation and cine film quality. Operator technique will also be assessed with particular attention toward the adequacy of contract injection, appropriateness of panning and collimation. An assessment form will be completed for each cineangiogram and forwarded to the Principal Investigator, the Data Coordinating Center and to the Clinical Unit.

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CHAPTER 3, APPENDIX A

ECG CORE LABORATORY
CERTIFICATION REQUIREMENTS
IIIB CENTERS

I. Personnel to be Certified

1. All Stress Lab Technicians performing ETT's on TIMI patients at each participating hospital.

II. Materials to be Submitted to Core Lab

For Each Technician:

1. Certification request form.

2. 5 consecutive exercise tests (ECG tracings) in their entirety (tests may be copies).

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CHAPTER 3, APPENDIX B

QUANTITATIVE CORE LAB
CERTIFICATION REQUIREMENTS
IIIA CENTERS

I. Requirements*

1. Cath Lab coronary calibration must be performed for <u>each</u> catheterization laboratory to be used in the trial.

2. Five consecutive cineangiograms from the same laboratory.

*NOTE:
1. Certification for this Core Lab is <u>only</u> for IIIA centers.

2. Catheterization Labs already certified and calibrated from TIMI II do <u>not</u> need to be re-certified, unless major interval modifications have occurred.

II. Materials to be Submitted to Core Lab

1. Grid film performed according to the procedures outlined in Manual of Operations.

2. Information sheet for each cath lab.

3. Five consecutive cineangiograms.

4. Certification form for each hospital.

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CHAPTER 3, APPENDIX C

HOLTER CORE LABORATORY
CERTIFICATION REQUIREMENTS
IIIA AND IIIB CENTERS

I. Personnel to be Certified

1. Person responsible for supervising the quality of the Holter application at each of the participating hospitals.

*NOTE: Clinical Units participating in the UNSA Trial do not require certification for Holters.

II. Materials to be Submitted to Core Lab

1. 1 - 24 hour test recording using the monitor to be used in TIMI III. The recording may be performed on any person willing to wear the monitor (does not need to be a patient).

2. Certification request form.

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CHAPTER 3, APPENDIX D

QUALITATIVE CORE LABORATORY CERTIFICATION REQUIREMENTS IIIB CENTERS

I. Personnel/Laboratory to be Certified

1. Physicians who will perform PTCA on TIMI III patients.

2. Each cardiac catheterization suite in which TIMI III patients will be studied.

II. Materials to be Submitted to Each Core Lab

1. A cineangiogram (left ventriculogram and selective coronary angiogram) performed according to the procedure outlined in the attached Manual of Operations for each cardiac catheterization suite at each participating hospital.

2. An accompanying angiography log form for each cineangiogram submitted.

3. A cardiac catheterization certification form for each hospital.

4. A PTCA certification form for each operator requesting certification for performing TIMI III PTCA.

5. 5 consecutive PTCA cineangiograms for each operator filing for certification.

T3 MANUAL OF OPERATIONS - VOLUME II:
CHAPTER 3, APPENDIX E

THALLIUM CORE LABORATORY
CERTIFICATION REQUIREMENTS
IIIB CENTERS ONLY

I. Personnel to be Certified

1. Chief Nuclear Technologist responsible for the imaging procedures performed at each participating hospital.

II. Materials to be Submitted to Core Lab

1. Completed personnel and equipment survey form separate for each hospital. (please return to Core Lab by July 1, 1989).

2. For each hospital:

   a. Certification form

   b. 3 consecutive thallium tests on floppy disks - 1 normal and 2 abnormal tests.