CHAPTER 3

T3A PROTOCOL

EVALUATION OF THE EFFECT OF T-PA ON ANGIOGRAPHIC FINDINGS IN PATIENTS WITH UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION

3.1 INTRODUCTION

The specific aim of this protocol is to evaluate the effect of t-PA on coronary angiographic findings (i.e., signs of thrombosis, degree of stenosis and coronary blood flow) in patients with unstable angina and non-Q-wave myocardial infarction (MI). Coronary arteriography will be carried out both before and after study-drug therapy.

3.2 PATIENT POPULATION

A log will be maintained of all patients with a diagnosis of unstable angina or rule out myocardial infarction admitted to the Coronary Care Unit(s), telemetry units, or other specialized care units of the participating institution. The inclusion and exclusion criteria will be noted.

3.3 ELIGIBILITY CRITERIA

Since prospective classification of patients with non-Q-wave MI as distinct from those with unstable angina is often impossible, the eligibility criteria (inclusion criteria plus exclusion criteria) will be the same for the two conditions.

3.3.1 Inclusion Criteria

All patients who have experienced an episode of rest pain, presumed to be ischemic in origin and lasting five or more minutes (but no longer than six hours) which was present within the prior 12 hours prior to the time of enrollment, will be evaluated for enrollment in the study. Patients may be eligible if pain is present within the 12 hours prior to enrollment. Pain need not start within the 12-hour period.

In addition, the patient must have evidence of coronary artery disease. Such evidence may consist of either a or b as follows:

a. New or presumably new ECG evidence of myocardial ischemia in a standard 12-lead ECG obtained during any attack of pain within 12 hours before enrollment. This may consist of transient or persistent ST-segment depression of at least 0.10 mV (0.80 seconds after the J-point) in two or more contiguous leads, OR transient or persistent T-wave inversion in two or more contiguous leads, OR transient (< 30 minutes in duration) ST-segment elevation of at least 0.10 mV in two or more contiguous leads. "New" ST-segment or T-wave changes are defined as those not present on an ECG recorded during the year prior to the qualifying episode of pain. (If a previous ECG is not available, ST-segment or T-wave changes noted on recordings obtained prior to randomization that can be ascribed to no other cause [e.g., digitalis, electrolyte disturbance] will be considered "presumably new.") ECG changes persisting after the termination of ischemic pain may be used as "new" changes.

b. Documented coronary artery disease manifest as either a documented prior myocardial infarction or at least 70% luminal diameter narrowing of a major coronary artery on a prior coronary angiogram. This angiogram may be a previous angiogram or an angiogram obtained during or shortly following the qualifying episode of rest pain.

3.3.2 Exclusion Criteria

Patients who fulfill the above inclusion criteria but who manifest any of the following exclusion criteria at the time of randomization will not be eligible for the study.

1. Pain radiating to the back or having other characteristics suggestive of aortic dissection.

2. Constant ischemic pain of more than six hours duration.

3. Age $\geq$ 76 years or < 21 years.

4. Left bundle branch block.

5. New or presumably new ST-segment elevation of at least 0.10 mV in two or more contiguous leads not reverting to < 0.10 mV within 30 minutes of administration of therapy (e.g., nitroglycerin).

6. A treatable cause for angina pectoris--e.g., arrhythmia, severe anemia, hypotension, or hyperthyroidism.

7. Acute pulmonary edema (rales heard over more than two-thirds of the lung fields that do not clear with cough).

8. Other major illness--e.g., a major infection; active cancer within the past five years; active severe hepatic disease; hemodynamically significant valvular, myocardial, or congenital heart disease; or renal failure with serum creatinine > 3 mg/ml.

9. A documented MI (CK-MB greater than normal, if available or total CK greater than two times the upper limit of normal; MB takes precedence over total CK) within the past 21 days (excluding suspected infarction within 12 hours of enrollment).

10. Systolic arterial blood pressure less than 90 mm Hg on at least two recordings obtained 15 minutes apart.

11. Inability to cooperate with the protocol.

12. A female of childbearing potential.

13. PTCA within the previous six months.

14. Prior coronary artery bypass surgery.

15. Oral anticoagulation therapy at the time of initial enrollment.

16. Heparin allergy or intolerance.

17. Thrombolytic therapy within prior 72 hours.

18. Contraindications to thrombolytic therapy:

a. Past or present bleeding disorder or active bleeding.

b. Any confirmed recording of systolic pressure exceeding 180 mm Hg, diastolic pressure exceeding 110 mm Hg on two measurements during the presenting illness prior to randomization, or uncontrolled hypertension at any time prior to entry (diastolic blood pressure > 110 mm Hg on several measurements).

c. Any history of cerebrovascular disease, including any form of stroke and/or transient ischemic attack.

d. Prolonged cardiopulmonary resuscitation with one minute or more of external cardiac massage within the last two weeks.

e. Severe trauma within the prior six months.

f. History of parenteral or other drug abuse.

g. Significant surgical procedure within the last two months.

h. Active peptic ulcer disease within the past six months.

i. Invasive procedure (or lithotripsy) within the preceding 14 days that would significantly increase the risk of hemorrhage, such as biopsy, cardiac catheterization, or unsuccessful central venous puncture.

j. Probable pericarditis.

3.3.2.1 Angiographic Exclusion Criteria

Patients should be excluded from T3A if any one of the following angiographic exclusion criteria apply:

1. < 60% stenosis in a major coronary segment.

2. ≥ 50% stenosis of LMCA.

3. Presence of extensive coronary disease such that emergency coronary artery bypass grafting of the culprit vessel(s) is necessary to prevent hemodynamic collapse.

   This criterion will allow those patients with active ischemia and critical obstructions supplying viable myocardium considered to be vital to prevent hemodynamic collapse, to receive emergent (within 24 hours) coronary bypass surgery.

4. Patients should be excluded from T3A, who are found to have only a single old total occlusion supplying non-viable myocardium. An "old total occlusion" is defined as a total occlusion that is presumed to have occurred at a time remote from the qualifying episode, such as a prior MI > 3 weeks prior to enrollment, or a total occlusion viewed angiographically to have characteristics consistent with an old age, such as vasa vasorum, bridging collaterals and absence of a stump beyond proximal side branches (Stone et al, JACC 1990).

5. Presence of a true posterior MI documented at angiography with the following: (1) a "new" or "presumably new" total occlusion in the artery supplying the posterior wall of the heart, (2) no collateral blood flow to the posterior wall of the heart, and (3) a qualifying episode of ischemic pain occurring

within six hours of angiography. (A time frame of six hours has been added to this exclusion criterion to define that group of patients in whom open label thrombolytic therapy is medically indicated.)

3.3.3 Consent

Patients will be enrolled in the study when found to be clinically eligible and randomized when found to be angiographically eligible. Prior to enrollment, informed consent will be sought from the patient and the attending physician. A draft copy of a standardized consent form will be provided to all Clinical Centers. This, form, or a modification based on the local Institutional Review Board recommendations, will be completed for all enrolled patients.

3.3.4 Conventional Therapy

3.3.4.1 General Measures

All patients enrolled in the study will receive standard CCU care, including bed rest and oxygen.

3.3.4.2 Heparin

The goal is to administer intravenous heparin therapy to maintain the APTT 1.5 to 2 times the normal APTT recorded when the patient was not receiving heparin. If the patient is already receiving heparin at the time of enrollment, the prior dosage should be continued, the APTT determined and the dosage adjusted according to the guidelines presented below. If heparin therapy has not been started prior to enrollment, it should be started at the time of enrollment in a bolus of 5,000 IU intravenously. The continuous infusion should be started within one hour following the bolus. The start of heparin therapy may be deferred if angiography (and arterial puncture) is planned within four hours subsequent to enrollment. Start of the infusion should be followed by an infusion at the rate of 1,000 IU per hour to be adjusted by APTT values (determined eight hours after the initial heparin bolus; determined three hours after a change in heparin dosages; and every 12 hours on maintenance therapy) to a level 1.5 to 2 times normal. Changes in dosage should be managed as follows:

APTT	Adjustment
> 3x control	Decrease infusion rate by 50%
2-3x control	Decrease by 25%
1.5-2x control	No change
< 1.5x control	Increase rate of infusion by 25% to a maximum rate of 2,500 units/hour

Four hours prior to the first angiogram, for which an arterial puncture must be performed, the heparin dosage should be reduced to 50% of the maintenance level. After the arterial sheath has been placed, a 5,000 IU dose of heparin should be administered intravenously and the full maintenance dose resumed one hour after the bolus. The sheath should be left in place until completion of the follow-up angiogram. Measurements of platelets, hemoglobin and hematocrit should be obtained every 24 hours while a patient is on maintenance heparin therapy.

3.3.4.3 Anti-ischemic Therapy

At the time of enrollment, therapy with a beta-adrenergic blocking agent, a calcium channel blocker and a nitrate preparation should be initiated, if not already being given. If the patient was receiving and tolerating an agent from these classes of drugs prior to enrollment, the same agent and dosage should be continued. If the patient was not receiving an agent from each of these classes, and the clinical situation permits, the following agents should be given. (Starting doses are indicated.) Dosage should be adjusted as deemed necessary according to the patient's tolerance.

Beta-adrenergic blockade -	Metoprolol 50 mg po q 12 h
Calcium Channel blockade -	Diltiazem 30 mg po q 6 h. Diltiazem should not be given if evidence of left ventricular dysfunction is present.
Nitrate therapy -	Isosorbide dinitrate 10 mg po q 8 h. Sublingual TNG prn.

(NOTE: Diltiazem has been selected as the calcium antagonist for conventional therapy because it is the only agent in this class reported to reduce the incidence of reinfarction. Metoprolol has been selected based on evidence that it is beneficial for the therapy of acute MI.)

If ischemic symptoms occur after enrollment, the dose of the above agents should be increased as clinically indicated. Intravenous nitroglycerin is not to be used as routine initial therapy for unstable angina or non-Q-wave infarction. It may be continued if required prior to enrollment, and initiated if clinical indications develop after enrollment. Intra-aortic balloon counterpulsation should not be utilized unless patients develop symptoms refractory to the above-mentioned therapy.

3.3.4.4 Aspirin

Aspirin will not be given routinely during the T3A protocol since all patients will be receiving heparin, and aspirin may increase the risk of hemorrhage during t-PA therapy.

If PTCA is likely to be performed immediately after the follow-up angiogram is obtained, aspirin (325 mg) may be given orally four hours prior to the PTCA. After completion of the follow-up angiogram, aspirin may be initiated if clinically indicated.

3.4 ENROLLMENT AND RANDOMIZATION

Initial cardiac catheterization, coronary arteriography, and contrast left ventriculography will be carried out as soon as possible, but not more than 12 hours after enrollment. Thus, angiography must be carried out within 24 hours of the termination of rest pain. The start of treatment with t-PA or placebo must be initiated within one hour after angiography, i.e., within 25 hours of the qualifying episode of ischemic pain. Details of the catheterization laboratory procedures are contained in T3A Catheterization Laboratory Sequences (Exhibit 3-1).

3.5 BASELINE ANGIOGRAM

All patients will be fully heparinized prior to angiography as described above. Patients with angiographic evidence of at least 50%

luminal obstruction of the left main coronary artery, left main equivalent stenosis, or with less than 60% obstruction of any major coronary artery will be excluded. Percent stenosis will be determined visually in each Clinical Center and later verified by quantitative angiography in the Core Laboratory. Patients found not to meet these criteria by the Core Laboratory will be analyzed separately in the final analysis. To minimize the number of such discrepancies, the Core Laboratory will provide direct feedback to the Clinical Centers as soon as such a discrepancy is noted.

The ventriculogram may aid in identifying the culprit vessel by localizing the area of akinesis and will provide a baseline measure of ejection fraction (to be determined visually).

3.6 RANDOMIZATION AND EXPERIMENTAL THERAPY

Randomization by sealed envelope to placebo or t-PA therapy will be performed immediately after the angiogram documents that the patient is eligible for the study. Eligible patients will receive t-PA or placebo in a double-blinded manner. The total dose of study agent will be 0.8 mg/kg (not to exceed a total dose of 80 mg). One-third of the total dose will be given initially as an intravenous push bolus (not to exceed 20 mg). The remaining two-thirds of the total dose will be given intravenously over 90 minutes. The t-PA or placebo infusion may be initiated in the Catheterization Laboratory or in the Coronary Care Unit. Not more than one hour should elapse between randomization and initiation of experimental therapy.

In addition to t-PA or placebo therapy, all patients will receive maintenance heparin therapy intravenously by constant infusion as described above. After the follow-up angiogram has been obtained, the study interventions will be completed and subsequent therapy will be directed by the treating physician.

3.7 DISCONTINUATION OF EXPERIMENTAL THERAPY AND UNBLINDING

If at any time during the study the physician responsible for the clinical care of the patient decides that t-PA therapy is contraindicated, administration of the experimental agent will be stopped. The study will remain blinded, unless continued blinding is also considered to be detrimental to optimal clinical care. For instance, if the patient develops fixed ST-segment elevation, it may be clinically important to know if the patient had received t-PA in the preceding hours. Unblinding will be accomplished by opening the unblinding envelope matching the treatment kit number for the patient. (Documentation of reasons for discontinuing the experimental agent and for unblinding will be required.) The determination that an MI was in progress at the time of enrollment, which is expected in many of the patients, will not by itself be an indication for alteration of the protocol. Routine determination of fibrinogen and FDP levels in an attempt to determine whether the patient received t-PA should not be performed. It is expected that unblinding will be a rare occurrence. It should be avoided if possible, since it complicates analysis of study results.

3.8 FOLLOW-UP MEASUREMENTS

Following angiography, patients will be transferred from the Catheterization Laboratory to the Coronary Care Unit (CCU) or telemetry area for observation prior to follow-up angiography, which will be performed 18 to 48 hours after the initial angiogram. During the observation period, patients will receive standard therapy for unstable angina or non-Q-wave infarction, as previously described. They will be observed for recurrent ischemic pain and monitored by means of one continuous 24-hour Holter recording to document and quantitate the

occurrence of painful or painless myocardial ischemia. The Holter may begin during infusion of the study drug. The time of infusion should be noted on the Holter diary. The Holter should be terminated at 18 hours if the repeat angiogram is done at that time. The time of the angiogram should be noted on the diary. Blood samples for CK-MB determination will be obtained at the following times: enrollment; four hours post-enrollment; immediately prior to treatment initiation; four hours after treatment initiation; 12 hours after treatment initiation; and immediately prior to the follow-up angiogram.

Twelve-lead ECGs will be obtained immediately prior to the initial and follow-up angiograms. A 12-lead ECG obtained within three days before hospital discharge will be sent to the ECG Core Laboratory. ECGs should be sent to the Core Lab to document ischemic changes after completion of the study drug infusion and before the second angiogram. If the combination of clinical deterioration and angiographic findings mandates emergency percutaneous transluminal coronary angioplasty (PTCA) before 18 hours have elapsed, the emergency (non-protocol) angiogram obtained immediately prior to PTCA will be utilized as the follow-up study.

Blood samples to be analyzed by the Coagulation Core Laboratory will be drawn at the following times: immediately prior to treatment initiation (Time 0), at 50 minutes, 12 hours, 24 hours, 48 hours and 96 hours following treatment initiation. The Core Laboratory will analyze the samples for fibrinogen, FDP's, d-Dimer, and heparin activity. The total volume of blood drawn will be 125 cc (25 cc per drawing).

3.9 POST-ANGIOGRAPHY CARE

After the follow-up angiogram has been obtained, patients will receive physician-directed therapy. Records will be kept of significant events that occur up to the time of hospital discharge (i.e., death, MI, and the need for PTCA or CABG). At six weeks post-randomization a follow-up telephone call will be made to determine the patient's health status.

3.10 ANALYSIS OF DATA

Analysis will be conducted on an "intention-to-treat" basis on all randomized patients as well as within the three prospectively identified subgroups discussed below.

The primary end point will be the successful result of therapy, defined as either an improvement in TIMI perfusion by two grades (from 0 to 2 or 3, or from 1 to 3) or a 10% reduction in the severity of stenosis. The reduction will be based on a comparison between the initial angiogram and the follow-up angiogram obtained 18 to 48 hours later with regard to the severity of the presumed culprit lesion.

Patients in whom culprit lesions cannot be identified on the basis of the initial ECG and angiographic findings will be analyzed separately for changes in any vessel from the first to the second angiogram.

Additional end points will include: (1) the need for emergency revascularization in the period between the baseline and follow-up angiograms; (2) recurrent ischemia as determined by Holter monitoring and the presence of symptoms (determined by the clinicians caring for the patients); (3) and the incidence of MI as determined by ECG and cardiac enzymes. Additional angiographic features will include average percent stenosis and the noting of disappearance of intracoronary filling defects considered to represent thrombi. An estimate will be made of the percent change in obstruction due to thrombus as opposed to the percent change of obstruction caused by thrombus and plaque combined. Lesions will be measured by quantitative arteriography performed

by the Quantitative Angiography Core Laboratory. Death and MI occurring between the time of randomization and hospital discharge will also be noted. The incidence of adverse effects, particularly hemorrhagic manifestations, will be recorded. Although the primary analysis will be by intention-to-treat, the relationship between each of the additional end points and the coronary angiographic findings will also be determined. "Outcome-outcome" relationships, such as the control of ischemia (clinical and Holter electrocardiographic) in patients with angiographic clearing of thrombus compared with the results in those without such clearing, will be evaluated. A subgroup analysis will be performed in those with angiographic evidence of thrombus on the initial angiogram.

3.10.1 Retrospective Differentiation of Patients with Transient Ischemia from Patients with Ongoing MI at Treatment

The study will be conducted in patients who have experienced an episode of pain at rest, presumed to be ischemic in origin, within the 12 hours prior to enrollment. This population will include patients with unstable angina (transient ischemia) and patients with ongoing non-Q-wave infarction. The final decision as to whether MI was present prior to treatment will be made by the Data Coordinating Center on the basis of CK-MB isoenzyme activity in serum samples obtained at treatment and 4 hours after treatment. These cardiac enzyme results will reflect the presence or absence of ongoing myocardial necrosis at the time of treatment. The upper limit of normal values for each laboratory will be recorded on standardized study forms.

3.10.2 Subgroups for Analysis

For analysis, patients will be divided into three groups based on the time of occurrence of their pain and results of CK-MB measurements:

GROUP I: No pain within the four hours prior to treatment initiation (i.e, the qualifying pain occurred four to 12 hours prior to treatment initiation)

AND

No CK-MB elevation in blood samples obtained at treatment initiation and four hours after treatment initiation;

GROUP II: Pain within the four hours prior to treatment initiation

AND

No CK-MB elevation in blood samples obtained at treatment initiation and four hours after treatment initiation;

GROUP III: Pain at any time within the 12 hours prior to treatment initiation

AND

CK-MB elevation in at least one of the two samples.

Patients in Groups I and II will presumably be free of ongoing myocardial infarction at the time of treatment initiation. Exclusion of pre-treatment infarction will be most certain in Group I (i.e., no pain in the four hours prior to treatment initiation). In this group, lack of CK-MB at the time of treatment initiation will reliably identify

patients without infarction prior to treatment, since over four hours would have elapsed since the last episode of pain, and the biologic time delay for CK-MB to enter the blood stream would have elapsed prior to treatment initiation. In Group II (i.e., pain during the four hours prior to treatment initiation), CK-MB values may be somewhat less reliable as indicators of treatment infarct status because therapy would be initiated after the occurrence of myocardial necrosis but before the appearance of CK-MB in the peripheral circulation. Analysis in this group must therefore take into account the possibility that treatment might affect the CK-MB as a marker of myocardial necrosis. This will be determined by comparison of the CK-MB results among the various treatment groups. Group III patients, all of whom will have documented CK-MB elevation, will have primarily non-Q-wave infarction, since patients with new Q-waves and persistent ST-segment elevation are excluded from the study. The various end points will be analyzed in these three groups of patients.

Other subgroups for analysis will include: (1) patients whose acute ischemic syndrome occurred despite prior aspirin therapy versus those whose disorder began without prior aspirin therapy; (2) the older half versus the younger half of the population; (3) those with symptom onset within one week versus those with symptom onset more than one week prior to enrollment; (4) males versus females; (5) those with versus those without a history of prior MI; (6) those with ST-segment elevation versus those without ST-segment depression; (7) those with only T-wave changes versus those with only ST-segment changes; (8) those with continued rest pain on maximal medical therapy prior to enrollment versus those without rest pain on maximal therapy; (9) those whose last episode of pain was within four hours of enrollment versus those with pain from four to 12 hours prior to enrollment; (10) those with versus those without an angiographically visualized thrombus; and (11) patients who failed heparin therapy prior to admission.

3.11 Sample Size Considerations

It is expected that 300 patients will be enrolled in the study, thus providing adequate power to detect significant differences between the use of t-PA versus placebo on angiographically determined coronary artery blood flow and stenosis. Details of sample size issues can be found in Chapter 2 Volume I of the T3 Manual of Operations.

3.12 Timetable

The total duration of the study will be 24 months. Randomization of patients began on September 30, 1989. Patient recruitment ended on October 24, 1990. During a final 12-month period, the data will be analyzed and the results prepared for publication.

EXHIBIT 3-1

T-3A: CATHETERIZATION LABORATORY SEQUENCES

* OBTAIN 12-LEAD ECG (ON CALL TO CATH LAB OR IN CATH LAB)

* PATIENT ARRIVES IN CATH LAB, CONSENT SIGNED
  - -- Initiate ECG monitoring
  - -- Prepare for catheterization (A, V access)
  - -- Optional Swan-Ganz and pacing catheters, only if needed
  - -- Heparin (initiate at 5000 U, and/or maintain at approximately 1000 U/hr)

* CORONARY ARTERIOGRAPHY:
  - -- #7 or #8 French catheter for angiography
  - -- NTG 0.03 mg or 0.4 mg s.l. (or 0.2 mg, if BP < 100 systolic)
  - -- "Non-ischemic" artery first. Look for late collateral fill (6-7°" mag)
  - -- "Ischemic" artery second, repeat NTG if > 15 min elapsed since first NTG (6-7" mag); adequate contrast to opacify ischemic vessel
  - -- Sufficient cine time to visualize washout of ischemic vessel
  - -- Projection angles: (Stay within ± 5 degrees of recommended views)

LCA	10° RAO	RCA:	45°
	90° LAO		45° LAO/10° Cranial
Pairs:	10° RAO/40° Cranial		
	35° RAO/15° Caudal	Additional views may be added to	
	45° LAO/30° Cranial	optimize information.	

* SELECT "BEST VIEW" BY REVIEW OF VIDEO
  - -- Exclude ineligible patients (< 60% lesion; ≥ 50% left main; other exclusions)

* CINE "BEST VIEW" AND ITS PERPENDICULAR PAIR AT 4-5" MAG

* LEFT HEART CATHETERIZATION:
  - -- Ao and LV pressures
  - -- LV angiogram 30° RAO ± 60° LAO biplane) (35-55 ml contrast at 12-15 ml/sec); filming rate at least 30 frames/sec; ionic or non-ionic contrast
  - -- Patient may leave cath lab when left heart catheterization completed

* FILM LV GRID

* OBTAIN BLOOD SAMPLE FOR CK, CK-MB AND COAGULATION CORE LAB AND RANDOMIZE

* INITIATE RANDOMLY ASSIGNED STUDY DRUG TREATMENT (Less than 1 hour after randomization. Study drug may be started in cath lab, CCU, or monitored area.)

* CARE OF PATIENTS IN CCU/TELEMETRY AREA
  - -- Continue heparin drip to maintain PTT (check 8 hrs post initial heparin bolus and q 12 hours) at 1.5-2.0 times normal--leave sheath in place
  - -- 325 mg ASA to be given 4 hours before final angiogram only if PTCA planned

EXHIBIT 3-1 (Continued)

T-3A: CATHETERIZATION LABORATORY SEQUENCES

* REVIEW DATA ENTRY FORMS FOR COMPLETENESS (FORM 7A)

* REPEAT LV AND CORONARY ANGIOGRAPHY AT 18-48 HOURS
  -- Repeat "best view" of culprit artery and perpendicular paired view (6-7" mag)
  -- Give sublingual NTG, repeat best view and its pair (4-5" mag)
  -- Repeat LV angio 30° RAO (± 60° LAO biplane) and pressure measurements
  -- RECORD DATA ON FORMS (7C; 06 if PTCA done)
  -- Film LV Grid

* MAIL FILMS TO Quantitative Angiography Core Laboratory
  -- Identify film with label provided by DCC
  -- Mail first film within 2-30 days after second film obtained
  -- Mail second and other films after first is returned
  -- Send to: Greg Brown, M.D., Ph.D.
     Cardiology, RG-22
     University of Washington
     Seattle, WA 98195

It is the Clinical Center's responsibility to mail the first film by 2-day courier 2 to 30 days after the second film has been obtained. A film should not be mailed unless another is available to remain in the Clinical Center for patient care considerations. The DCC will provide the Core Laboratory with a sequence reading list and will notify each Clinical Center if there are any films which are 1 month delinquent. The Core Laboratory will notify the DCC of any discrepancies in receipt of films based on review of the sequence list. When the first film is returned, the Clinical Center should mail the second film to the Core Laboratory.