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TIMI PHASE II PROTOCOL

THROMBOLYSIS IN MYOCARDIAL INFARCTION

NOTICE

THE CONTENTS OF THIS PROTOCOL ARE CONFIDENTIAL AND ARE NOT TO BE DISCUSSED OR QUOTED TO PERSONS OTHER THAN THOSE TO WHOM THIS PROTOCOL HAS BEEN CIRCULATED.

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CHAPTER 1

BACKGROUND AND STUDY CHRONOLOGY

1.1 INTRODUCTION

Recognizing that thrombolytic therapy was a promising, but unproven, addition to management of patients with acute myocardial infarction, the National Heart, Lung and Blood Institute (NHLBI) established the Thrombolysis in Myocardial Infarction (TIMI) Study Group in 1983. Thirteen Clinical Centers, a Radiographic Core Laboratory, a Radionuclide Core Laboratory, and a Coordinating Center were selected to participate in a multicenter collaborative trial to evaluate the effects of thrombolytic therapy in patients with acute myocardial infarction. The NHLBI charge to the TIMI investigators was to design a trial to test the hypothesis that intravenous administration of a thrombolytic agent to patients in the early hours of acute myocardial infarction will reduce subsequent morbidity and mortality.

During the Planning Phase, July 1983 to March 1984, it became apparent that in addition to streptokinase (SK) and urokinase, new thrombolytic agents would soon be available. Given the promise and availability of one of these new agents, tissue plasminogen activator (rt-PA), the TIMI investigators developed a two-stage approach to evaluating thrombolytic therapy. The first phase (Phase I) was designed to compare coronary recanalization rates in patients randomly assigned to intravenous rt-PA with those in patients assigned to intravenous SK. The initial plan for the second phase (Phase II) was to conduct a large-scale trial to assess the agent selected for further study based on Phase I results.

The TIMI Phase I Protocol received NHLBI approval in May 1984. Before recruitment for Phase I started, an Open Label Phase was conducted to develop familiarity with the Phase I Protocol and to pre-test data collection methods. During this Open Label Phase which began in June 1984, patients were managed according to the same Protocol developed for Phase I except that patients entered during the first several weeks were given known rt-PA; those entered in the next several weeks were given known SK. Patient recruitment for the Phase I randomized trial started in August 1984. In January 1985, the TIMI Policy and Data Monitoring Board recommended early termination of the study because there was a statistically significant difference between the effects of intravenous SK and intravenous rt-PA with respect to coronary recanalization rates in patients who had closed coronary arteries before treatment. Intravenous SK opened one-third of closed coronary arteries compared to intravenous rt-PA which opened about two-thirds. A further description of Phase I results is given in Section 1.3.

Thrombolytic therapy and its effect on limiting infarct size, and thus reducing myocardial damage, have been under intensive investigation since the TIMI Research Group was established. Reports of several recent studies suggest that thrombolytic therapy reduces subsequent short-term mortality; however, high grade residual stenosis is apparent in many reperfused arteries and these lesions tend to reocclude. Successful thrombolysis restores the vessel to the condition existing prior to the occlusive event. It is possible that elective

dilation of high grade lesions may substantially improve late outcome following successful reperfusion with a thrombolytic agent. Given angioplasty is capable of reducing the residual arterial obstruction in patients during the early post-MI state, it is logical to ask whether this procedure can reduce the incidence of post-thrombolytic reocclusion. The results of several studies are encouraging in that regard. TIMI Phase II has been developed based on the results of Phase I and current understanding of coronary thrombolysis. It is designed to answer the question of whether thrombolytic therapy should be followed by percutaneous transluminal coronary angioplasty (PTCA).

1.2 BACKGROUND

Coronary heart disease is the leading cause of death in the United States, resulting in the demise of approximately 550,000 individuals each year. It is estimated that between five and six million people have chronic, symptomatic coronary artery disease, and many more have asymptomatic coronary atherosclerosis. Each year over 600,000 individuals are discharged from U.S. hospitals with a diagnosis of myocardial infarction.

The medical management of myocardial infarction has changed over the past 30 years from a strategy of permitting the heart to heal by putting the patient and his heart at bed rest, to increasingly more active electrocardiographic and hemodynamic monitoring with aggressive treatment of identified abnormalities. With these new methods of managing myocardial infarction, it is unusual for a patient with myocardial infarction in a modern coronary care unit to die of primary rhythm disorders in the acute phase of infarction. Research efforts are now directed to finding interventions which will limit the size of myocardial infarction since loss of more than 40% of the left ventricular myocardium almost always results in death. Compromised left ventricular function resulting from large infarctions is also a major determinant of survival after hospital discharge. Thus, risk of mortality, both early and late, decreases with decreasing infarct size.

The size of myocardial infarction is probably not fixed when a patient develops clinical features of myocardial infarction but is dependent upon the disparity between myocardial oxygen demand and delivery in ischemic tissue over the initial four to six hours. It is likely that maneuvers that broaden the disparity increase infarct size, whereas those that decrease the disparity reduce infarct size. Various therapeutic interventions, such as propranolol, nitroglycerin, hyaluronidase, steroids and other anti-inflammatory agents, as well as intra-aortic balloon counterpulsation designed to reduce this disparity, have been tested over the past ten years. Although many studies have revealed trends in favor of treatment, conclusive findings documenting reduction of infarct size in man are reported only sporadically and not consistently for these interventions.[1] Furthermore, the effect of reduction of infarct size on subsequent morbidity and mortality is unknown.

The role of coronary thrombosis in the pathogenesis of myocardial infarction has been debated vigorously, since Herrick's description in 1912.[2] Recently investigators have approached this problem by submitting patients in the early hours of myocardial infarction to coronary arteriography. Coronary arteriography in 322 patients admitted to the hospital within 24 hours of the

onset of acute myocardial infarction revealed that the detection of total occlusion in the infarct-related artery was dependent upon the time interval between the onset of chest pain and time of coronary arteriography.[3] Nearly 90% of patients evaluated within four hours of the onset of symptoms had a total occlusion of the infarct-related artery, while in the group investigated between 12 and 24 hours after the onset of pain, 65% had total occlusion of the infarct-related artery. Approximately 80% of patients studied by means of coronary arteriography in the early hours of transmural myocardial infarction demonstrated complete occlusion of the infarct-related artery in three separate studies.[4-6] Most case series included only patients with prolonged ischemic chest pain and associated ST segment elevation. Complete occlusions rarely open with nitroglycerin; but antegrade coronary flow has been reestablished in as much as 60% to 80% of patients by means of intracoronary administration of thrombolytic agents, usually streptokinase or urokinase. In those in whom antegrade coronary flow is reestablished, a high grade coronary stenosis is often noted at the point of previous total occlusion. These findings suggest that the proximate cause of acute transmural myocardial infarction in two-thirds or more of patients presenting with chest pain and ST segment elevation is recent intraluminal coronary thrombosis superimposed on a long-standing high grade atherosclerotic lesion.

Studies in dogs demonstrate that timely reperfusion of an occluded artery reduces infarct size; with increasing duration of occlusion, myocyte death propagates from the subendocardium to the subepicardium.[7,8] Reperfusion carried out 40 minutes after coronary ligation in dogs salvaged 60 to 70 percent of the area at risk, whereas reperfusion carried out three hours after coronary ligation reduced infarct size by only 10 to 20 percent. After six hours of occlusion, reperfusion salvaged little if any of the myocardium at risk.

In man, the relationship of duration of occlusion and myocardial necrosis is less well defined. Unlike the canine model, the human coronary circulation may have well developed collaterals to the infarct zone which may provide some perfusion of the myocardium at risk despite acute coronary occlusion. In addition, subtotal occlusion is observed in about one-fifth of patients with acute myocardial infarction. Thus in man, salvage of myocardium by reperfusion may be possible as long as six hours beyond the onset of symptoms or perhaps longer, but substantial myocardial salvage is more likely to occur with reperfusion within four hours.

A major intermediate goal of therapies designed to limit infarct size is to preserve ventricular function. Ventricular function is an important predictor of subsequent morbidity and mortality in patients with infarction. Given myocardial salvage the rate of recovery of contractile function after reperfusion is inversely related to the duration of the occlusion. For example, in dogs a 15-minute occlusion, which is not long enough to cause irreversible myocellular injury, can cause a surprisingly lengthy period of systolic dysfunction after reperfusion is established. When reperfusion is carried out after two hours of coronary ligation, two weeks are required for recovery of systolic function of the ischemic nonnecrotic zone. Thus direct assessment of ventricular function must be carefully timed in recanalized infarction patients.

Several case series and small clinical trials of intracoronary SK have documented the efficacy of thrombolytic therapy in opening a closed coronary when given directly into the artery. Anderson reported improved left ventricular ejection fraction in patients treated with intracoronary SK over study controls.[9] Khaja reported no improvement in left ventricular ejection fraction in patients treated with intracoronary SK over study controls.[10] In Khaja's study, the mean time from onset of chest pain to infusion of study treatment was 5.4 hours for SK treated patients and 4.6 hours for controls. Leiboff reported no improvement in left ventricular ejection fraction in patients treated with intracoronary SK over study controls.[11] In Leiboff's study, infarct-related artery reocclusion occurred frequently between the time of therapy and ejection fraction measurement. Raizner reported no improvement in left ventricular ejection fraction in patients treated with SK over study controls.[12] In Raizner's study, the mean time from onset of chest pain to treatment with SK was 5.6 hours. A trend to greater improvement in regional function in the infarct distribution was seen in SK treated patients but did not achieve statistical significance over controls. Kennedy reported statistically significant reduction in mortality in patients treated with intracoronary SK over study controls.[13] However, given late recanalization and no parallel improvement in ventricular function in Kennedy's study, the mechanism for improved survival is unclear and may not be due to limitation of infarct size.

Intracoronary administration of a thrombolytic agent has many undesirable features. Delay in treatment in order to perform cardiac catheterization may compromise a beneficial effect since myocardial salvage is time dependent; substantial necrosis occurs within three hours. Cardiac catheterization requires specialized equipment and skilled personnel that are not available at many community hospitals. In addition, cardiac catheterization laboratories are rarely available around the clock. On the other hand intravenous thrombolytic treatment has the advantage of rapid delivery of therapy and is widely applicable. The incremental cost of intravenous thrombolytic therapy over standard medical care for acute myocardial infarction is small. Finally, intravenous therapy avoids the risk, discomfort, and the substantial cost associated with coronary arteriography.

Recognition of the rapid time course of myocardial necrosis has led to the use of very high dose intravenous SK administered over 30 to 60 minutes.[14,15] Pooled data from five studies in which intravenous infusion of high dose short-term SK was preceded by baseline angiographic studies showed a reperfusion rate of 45%, about 30 percentage points less than the reperfusion rate achieved by intracoronary administration.[16] Several trials did not have pretreatment angiography, and these trials have usually reported higher reperfusion rates after treatment than those studies which have based the results on only those patients who were totally occluded as determined by pretreatment angiography.

Reocclusion rates in studies of intracoronary SK have ranged from 0 to 45%. Thus, although intravenous thrombolytic therapy can be administered more rapidly than intracoronary therapy, and logistics favor intravenous administration, there are disadvantages, such as lower recanalization rates and much greater disruption of the clotting system.

Treatment with intravenous SK and its effect on mortality have been studied in many randomized, controlled trials. These trials vary widely in design features and span a lengthy period during which conventional therapy for patients with myocardial infarction changed considerably, including, for example, the development of the coronary care units and discontinuation of the requirement of prolonged bed rest. In addition to secular trends in diagnosis, treatment and fatality rates, design variations make cross trial comparisons difficult. Yusuf et al[17] analyzed the results of 24 randomized controlled trials of intravenous and intracoronary thrombolytic therapy in the first hours of an evolving myocardial infarction. Streptokinase was used in the majority of these trials, but a few investigators studied urokinase. In 16 of the trials, early mortality was lower in the thrombolytic agent-treated group than in the control group. The observed differences in five of the trials were considered statistically significant and all five had lower mortality in the group treated with thrombolytic therapy.

Several trials which were not included in the Yusuf review were reported in 1985. A total of 1,741 patients entered within six hours of the onset of chest pain were studied in the High Dose Intravenous Short-Time Streptokinase Infusion in Acute Myocardial Infarction (ISAM) Trial.[18] Twenty-one day mortality for placebo-treated patients was relatively low, 7.1% in the control group; the mortality in the SK group was 6.3% or a 16% reduction in mortality. This difference was not statistically significant, but was of the same order of magnitude as the reduction observed in the Italian study (GISSI) in which 11,712 patients were randomized to treatment within 12 hours of the onset of symptoms.[19] In the GISSI trial, in-hospital mortality was 13.0% in the control group and 10.7% in the SK group or a reduction of 18% in the treated group. In both of these SK trials patients treated within three hours experienced a greater reduction in mortality than those treated between three and six hours. The results of the Interuniversity Cardiology Institute of the Netherlands trial[20] involved 533 patients with acute myocardial infarction randomly assigned by the Zelen method to conventional care or thrombolytic therapy. Thrombolytic therapy consisted of either intracoronary SK or intravenous SK followed by intracoronary SK. Mortality at 28 days and at one year was significantly lower in the SK-treated group compared to the conventional care group.

The most commonly available thrombolytic agents, SK and urokinase, have relatively low specific affinity for fibrin and, therefore, activate circulating and fibrin-bound plasminogen relatively indiscriminately. Plasmin formed in circulation is neutralized very rapidly by α_2-antiplasmin and lost for thrombolysis. Once plasmin inhibitor becomes exhausted, excess plasmin will degrade several plasma proteins (fibrinogen, Factor V and Factor VIII) and result in a systemic lytic state. Streptokinase and urokinase are potent thrombolytic agents, and large systemic doses carry the risk of serious bleeding.

Alternatively, fibrin-selective thrombolysis might be expected if the activation of plasminogen can be localized and confined to the fibrin surface. This requires an activator which, like the physiological activator, absorbs to the fibrin surface and becomes active locally. Such plasminogen activators have been isolated from tissues (human uterus, pig ovaries and pig heart); but until recently the yield of such procedures was low. Collen and colleagues

isolated and characterized plasminogen activator from a human melanoma cell line.[21] This m-tPA was indistinguishable from human uterus derived plasminogen activator. In vitro studies demonstrated activity, potency, and specificity similar to the physiologic activator. Tissue-type plasminogen activator produced by recombinant techniques became available for human investigation in early 1984.

Clinical testing of new thrombolytic agents such as recombinant tissue type plasminogen activator (rt-PA), acylated streptokinase-plasminogen complexes and pro-urokinase has begun. A critical theoretical advantage of these substances is their avidity for fibrin which may promote coronary thrombolysis with less derangement of coagulation.

1.3 TIMI PHASE I

From August 20, 1984 through February 5, 1985, 316 patients were entered into TIMI Phase I; 157 were assigned to rt-PA and 159 to streptokinase.[22] Twenty-six patients did not receive treatment leaving 143 rt-PA assigned patients and 147 SK assigned patients. Those excluded from treatment included eight patients who had either normal or minimally involved coronary arteries, nine patients who became sufficiently unstable to preclude completion of the protocol before drug therapy was given, six patients in whom technical difficulties precluded completion of the protocol, and three patients who were found to be ineligible after randomization, but prior to administration of the drug. There were no adequate angiographic views of the infarct-related artery in one SK-treated patient due to faulty identification of the infarct-related artery. The two patient groups were quite similar with respect to entry clinical and angiographic findings. The interval between the onset of pain and the initiation of intravenous thrombolytic infusion averaged 287 minutes in the rt-PA group and 286 minutes in the SK group. The TIMI Phase I primary end point was the proportion of patients with total occlusion of the infarct-related artery prior to treatment who at 90 minutes had an opened coronary artery with either slow or normal antegrade flow. There were 113 rt-PA patients and 119 SK patients judged by central reading at the Radiographic Core Laboratory to have totally occluded infarct-related arteries prior to treatment. At 90 minutes, 62% of the rt-PA patients and 31% of the SK patients had reperfusion.[23] The incidence of both hemorrhagic and recurrent ischemic episodes was similar in both groups.[23] The Open Label studies[24,25] conducted prior to Phase I, had results very similar to the results of the randomized series.

1.4 TIMI OPEN LABEL PHASE 1985 - 86 STUDIES

During the course of Phase I, the manufacturer of rt-PA adopted a new and larger batch processing method for producing rt-PA. The rt-PA (G11021 or roller bottle rt-PA) used in Phase I was produced on a small scale in a liquid excipient and consisted predominantly of double-chain molecules. The new form of rt-PA (G11035, G11044 or suspension-culture rt-PA) was produced in lyophilized form and consists of predominantly single-chain molecules. The results of preliminary in vitro and animal studies demonstrated that the thrombolytic activity and specificity of the rt-PA produced by the new method was similar to the previous rt-PA investigated in TIMI Phase I. However, the

TIMI investigators thought it important to document that the suspension-culture rt-PA would yield results comparable to roller bottle rt-PA before initiating a large-scale trial.

The primary objective of TIMI Open Label Phase 1985 was to determine whether suspension-culture rt-PA, delivered intravenously, would be effective with respect to achieving lysis of coronary thrombosis within 90 minutes of initiation of treatment in patients who had angiographically proven total occlusion of the infarct-related coronary artery. Secondary objectives of TIMI Open Label Phase 1985 included the determination of the proportion of reperfused infarct-related arteries which remained patent at 18 to 48 hours and to determine the effect of coronary angioplasty in relieving stenosis and sustaining patency of the infarct-related artery.

In the first Open Label Phase 1985 (subsequently referred to as Open Label Phase A), patients were given 80 mg of suspension-culture rt-PA over a three-hour period (40 mg in the first hour and 20 mg in each of two subsequent hours). Review of the results for the first few patients indicated a recanalization rate of less than 50% and the coagulation studies indicated little or no change in fibrinogen, plasminogen, and fibrin-fibrinogen degradation products.[26] As a result, the Open Label Phase A was concluded after 48 patients had been treated and patient recruitment was started for Open Label Phase B in which patients were treated with 100 mg of suspension-culture rt-PA given over a three-hour period (60 mg in the first hour, with a 6 mg bolus given in the first minute, and 20 mg in each of two subsequent hours).

The results for patients treated with 100 mg of suspension-culture rt-PA were reviewed in November and December 1985; these findings indicated that the proportion of patients with reperfusion at 90 minutes was higher with 100 mg than with 80 mg of suspension-culture rt-PA and approximately the same as that which had been observed with 80 mg of the rt-PA used in Phase I.[26] However, the proportion of patients with clinical symptoms of reocclusion within the first 24 hours was higher in the group of patients treated with 100 mg than had been observed with 80 mg of suspension-culture rt-PA. The changes in fibrinogen, plasminogen, and fibrin-fibrinogen degradation products were not very different between 80 mg and 100 mg of suspension-culture rt-PA and substantially less than that which had been observed with roller bottle rt-PA.[26] On the basis of these findings, the TIMI Executive Committee determined that it would be safe to evaluate a higher dose and a longer period of infusion of suspension-culture rt-PA. After consultation with the manufacturer, it was agreed that at least 50 patients should be treated with 150 mg of suspension-culture rt-PA given over a six-hour period (90 mg in the first hour, with a 9 mg bolus given during the first minute of infusion, followed by 20 mg in the second hour and 10 mg in each of the next four consecutive hours).

A total of 65 patients with total occlusion were treated with the 150 mg dose. The proportion of patients with Grade 2 or 3 reperfusion at 90 minutes was approximately the same as with 100 mg.[26] However, the proportion with reperfusion at 30 minutes and 60 minutes was higher with the 150 mg dose than with 100 mg. Also the proportion of patients with clinical symptoms of reocclusion within the first 24 hours was substantially lower with 150 mg than with 100 mg of suspension-culture rt-PA. The changes in fibrinogen and plas-

minogen as well as fibrin-fibrinogen degradation products was about the same as had been observed in Phase I with 80 mg of roller bottle rt-PA.[26] After review of these findings, the Executive Committee recommended that 150 mg of suspension-culture rt-PA given over a six-hour period be used in Phase II.

1.5 TIMI CHRONOLOGY

In August 1982, the National Heart, Lung and Blood Institute (NHLBI) issued requests for proposals for centers to participate in a multicenter collaborative trial to determine whether the administration of thrombolytic therapy in patients with acute myocardial infarction would have a beneficial effect on infarct size, thus reducing subsequent morbidity and mortality. Contracts for this effort designated as "Thrombolysis in Myocardial Infarction" (TIMI) were awarded in June and July 1983. A summary of TIMI chronology is given in Table 1-1 and reviewed below.

The Principal Investigators of the participating centers (13 Clinical Centers, a Radiographic Core Laboratory, a Radionuclide Core Laboratory, a Coordinating Center, NHLBI Program Office) were organized as the Planning Committee to develop the detailed Protocol. A list of participating centers is given in Table 1-2. The following Technical Committees were established: Acute Catheterization, Concomitant Therapy, Entrance Criteria, Intervention and Nonfatal End Points. Each Subcommittee was charged with responsibility for developing specific aspects of the TIMI A and TIMI B Protocols, that is, the studies outlined in the original RFP. At a later time, a Mortality Subcommittee was established, this group was initially assigned responsibility for ascertaining the required study size. In November 1983, an Executive Committee was established. The Executive Committee was asked to guide the activities of the Planning Committee. The Study Chairman was selected in December 1983. In March and April 1984, a Drug Distribution Center and Core Laboratories to evaluate coagulation, electrocardiographic and pathologic studies were established.

As indicated previously, the TIMI investigators developed a two-stage approach - Phase I and Phase II. TIMI Phase I received NHLBI approval in May 1984 and began recruitment with an Open Label test period in June 1984, followed by the Randomized Trial which began in August 1984. A NHLBI Standing Committee was asked to serve as the Policy and Data Monitoring Board for TIMI Phase I and met in May 1984 and approved the Protocol for Phase I. In January 1985 this group reviewed the results for the first 214 patients treated in Phase I. On the basis of that review, they determined that recruitment for Phase I should terminate because a statistically significant difference between intravenous rt-PA and SK had been obtained for the primary end point.

Phase I, now completed, was designed to assess the relative thrombolytic activity and side effects of intravenous rt-PA versus intravenous SK in patients with acute myocardial infarction and angiographic documentation of totally occluded infarct-related coronary arteries. The preliminary results of Phase I reported in the April 4, 1985 issue of the New England Journal of Medicine, demonstrated that under the conditions specified prompt opening of the infarct-related coronary artery occurred in about two-thirds of patients treated with intravenous rt-PA; prompt opening of the infarct-related coronary artery occurred in about one-third of patients treated with intravenous SK.[22] The results of a European trial[27] comparing intravenous administration of SK and

rt-PA which was reported in the April 13, 1985 issue of Lancet were similar to TIMI results.

Open Label 1985/1986 Studies A, B, C and D were conducted to evaluate dosage regimens with suspension-culture rt-PA, produced by a different process than the rt-PA evaluated in Phase I, and the Phase II Protocol was developed during the 12-month period beginning March 1985.

In December 1985, the Director of NHLBI appointed a new Safety and Data Monitoring Committee for TIMI Phase II. This group reviewed the draft Protocol for Phase II in February 1986 and recommended to the Director of the NHLBI that this study proceed.

Request for proposals (RFP) for additional Clinical Centers to participate in Phase II were issued in mid-1985. Contracts were awarded to 12 clinical sites in March 1986 (see Table 1-2). Training sessions were held in March 1986 and all Clinical Centers began submitting the materials required to be certified to begin Phase II including recruitment of patients for Open Label E, pilot study for Phase II. Patient recruitment for Phase II started in April 1986. Twenty-four Clinical Centers were recruiting patients for Phase II in one or more participating hospitals by the end of June 1986. One Clinical Center withdrew prior to starting patient recruitment for Phase II.

Investigators at the University of Vermont submitted an application for funding to establish a Coagulation Core Laboratory for TIMI Phase II and were awarded funding in October 1986.

The Safety and Data Monitoring Committee met twice in October 1986. At the second meeting the TIMI Operations Committee recommended a reduction in rt-PA dose from 150 mg to 100 mg for Phase II and for Open Label E. The Safety and Data Monitoring Committee concurred and all investigators were notified immediately. A letter announcing this change was submitted for publication.[28] The Safety and Data Monitoring Committee met in December, 1986 and after review of all available data recommended that Phase II continue without additional Protocol changes.

Recruitment for Open Label E ended in January 1987 after 50 participating hospitals were certified to recruit patients for Phase II. In March 1987 a PTCA Quality Control Laboratory was established. The Safety and Data Monitoring Committee reviewed study progress and performance and all available data in June 1987 and again recommended Phase II continue without change.

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TABLE 1-1

TIMI CHRONOLOGY

November 1981 -	National Heart, Lung and Blood Institute (NHLBI), Division of Heart and Vascular Diseases with the Food and Drug Administration, Bureau of Biologics, sponsored a Workshop to review and summarize data available concerning the efficacy of thrombolytic agents with respect to limitation of infarct size
April 1982 -	NHLBI Cardiology Advisory Committee reviewed the Workshop recommendations and endorsed the concept of a collaborative clinical trial to evaluate thrombolytic therapy
May 1982 -	NHLBI Advisory Council endorsed the initiative for a collaborative clinical trial of thrombolytic therapy
August 1982 -	NHLBI issued Request for Proposals for centers to participate in a multicenter collaborative trial of thrombolytic therapy
June-July 1983 -	Contracts for "Thrombolysis in Myocardial Infarction" awarded to 13 Clinical Centers, a Radiographic Core Laboratory, a Radionuclide Core Laboratory, and a Coordinating Center
July 1983 -	First meeting of TIMI Principal Investigators
November 1983 -	TIMI Executive Committee established
December 1983 -	Study Chairman selected
March-April 1984 -	Drug Distribution Center and Coagulation Core Laboratory established
May 1984 -	Policy and Data Monitoring Board approved Phase I Protocol
June-July 1984 -	Open Label studies conducted
August 1984 -	Patient recruitment for Phase I started

TABLE 1-1 (Continued)

TIMI CHRONOLOGY

January 1985	-	TIMI Policy and Data Monitoring Board recommended early termination of Phase I
February 1985	-	Patient recruitment for Phase I terminated
April 1985	-	Preliminary results of Phase I reported in the New England Journal of Medicine
July 1985	-	Open Label Phase 1985 A started
September 1985	-	Open Label Phase 1985 B started
December 1985	-	NHLBI Director appointed Safety and Data Monitoring Committee for TIMI Phase II
December 1985	-	Open Label Phase 1985 C started
February 1986	-	Safety and Data Monitoring Committee approved Phase II Protocol
February 1986	-	Open Label Phase 1986 D started
March 1986	-	Twelve additional Clinical Centers funded for participation in Phase II
	-	Clinical Centers began submission of materials required to be certified to begin Phase II and recruitment for Open Label E begins
April 1986	-	Phase II patient recruitment started in Clinical Centers which had completed certification procedures
July 1986	-	Twenty-four Clinical Centers have one or more hospitals recruiting patients for Phase II. One Clinical Center ends participation in TIMI

TABLE 1-1 (Continued)

TIMI CHRONOLOGY

October 1986 - Coagulation Core Laboratory established at University of Vermont

- Two meetings of Safety and Data Monitoring Committee

- Protocol change in rt-PA dose for Phase II and Open Label E

December 1986 - Safety and Data Monitoring Committee met and recommended Phase II continue without additional Protocol changes

January 1987 - Patient recruitment for Open Label E ended after 50 hospitals were certified to recruit patients for Phase II

March 1987 - PTCA Quality Control Laboratory established at Brown University

June 1987 - Safety and Data Monitoring Committee met and recommended Phase II continue without additional Protocol changes

TABLE 1-2

PARTICIPATING UNITS IN TIMI

A. Clinical Centers Selected in 1983

Albert Einstein College of Medicine - New York, New York
Baylor College of Medicine - Houston, Texas
Boston University - Boston, Massachusetts
Brown University - Providence, Rhode Island
Columbia University - New York, New York
Cornell Medical Center - New York, New York

George Washington University - Washington, D.C.
Harvard University - Boston, Massachusetts
Mayo Foundation - Rochester, Minnesota
University of Massachusetts - Worcester, Massachusetts
University of Texas Health Science Center - Dallas, Texas
Washington University - St. Louis, Missouri
Yale University - New Haven, Connecticut

B. Additional Clinical Centers Selected in 1986*

Baystate Medical Center - Springfield, Massachusetts
Bridgeport Hospital - Bridgeport, Connecticut
Maine Medical Center - Portland, Maine
New York Medical College - Valhalla, New York
New York University - New York, New York
North Shore University - Manhasset, New York

Northwestern University - Chicago, Illinois
St. Louis University - St. Louis, Missouri
University of Alabama at Birmingham - Birmingham, Alabama
University of Minnesota - Minneapolis, Minnesota
William Beaumont Hospital - Royal Oak, Michigan

C. Central Units

Chairman's Office

Brigham & Women's and Beth Israel Hospitals, Boston, Massachusetts

Coagulation Core Laboratory

Temple University Health Science Center, Philadelphia, Pennsylvania
(Phase I and Open Label Studies 1985-86 A, B and C)

University of Vermont, Burlington, Vermont
(Open Label E and Phase II)

Coordinating Center

Maryland Medical Research Institute, Baltimore, Maryland

Drug Distribution Center

Veterans Administration Medical Center (151-I), Albuquerque, New Mexico

ECG Reading Center

George Washington University, Washington, D.C.

NHLBI Program Office

Division of Heart and Vascular Diseases, Bethesda, Maryland

Pathology Core Laboratory

Pathology Branch, NHLBI, National Institutes of Health, Bethesda, Maryland

PTCA Quality Control Laboratory (Phase II)

Brown University, Providence, Rhode Island

Radiographic Core Laboratory

University of Washington, Seattle, Washington

Radionuclide Core Laboratory

Yale University School of Medicine, New Haven, Connecticut

*One additional clinic funded but participation ended prior to starting patient recruitment for Phase II.

CHAPTER 2

OBJECTIVES AND DESIGN OF THE TRIAL

2.1 INTRODUCTION

The Thrombolysis in Myocardial Infarction (TIMI) Phase II study is designed to determine whether intravenous thrombolytic therapy given in the early hours of acute myocardial infarction should be followed by percutaneous transluminal coronary angioplasty (PTCA). All patients are treated with recombinant tissue plasminogen activator (rt-PA) within four hours of the onset of symptoms of acute myocardial infarction. In one group of TIMI Clinical Centers, patients are randomized to rt-PA alone or to one of two groups with PTCA to be performed either at two hours or at 18 to 48 hours after the start of the rt-PA infusion. In all other TIMI Clinical Centers, patients are randomized to rt-PA alone or rt-PA plus 18 to 48-hour PTCA. In addition, in these latter Clinical Centers all patients who are eligible for the initiation of beta-blocker therapy are randomized to either immediate or deferred beta-blocker therapy.

2.2 OBJECTIVES

The primary objective of TIMI Phase II is to determine the effects of thrombolytic therapy alone versus thrombolytic therapy followed by angioplasty within 18 to 48 hours (see Exhibit 2-1). The results for patients in all Clinical Centers randomly assigned to rt-PA alone compared to the results for all patients randomly assigned to rt-PA followed by 18 to 48-hour PTCA will be used for this assessment. The principal end point for this comparison is the combined end point total mortality and documented nonfatal myocardial infarction (MI) at six weeks after thrombolytic therapy. Secondary objectives of TIMI Phase II include assessment of: (1) effects of rt-PA versus rt-PA plus 18 to 48-hour PTCA on total mortality and nonfatal MI at ten days and one year; (2) treatment effects on total mortality alone at three time points: ten days, six weeks, and one year; and (3) treatment effects on the combined end point, total mortality and nonfatal MI, and total mortality alone in the subgroups defined by: (a) site of infarct; (b) time from onset of pain; and (c) risk group. High risk patients will be those with one or more of the following risk factors: (1) history of previous myocardial infarction; (2) ST segment elevation in anterior ECG leads; (3) rales extending upwards to cover more than one-third of the lung fields; (4) hypotension (systolic blood pressure less than 100 mm Hg) and sinus tachycardia (atrial rate greater than 100 beats per minute); (5) atrial fibrillation or flutter; and (6) age greater than or equal to 70 years. Low risk patients will be those with none of these findings. Cause-specific mortality, coronary events, and non-coronary events will be monitored for all patients in both treatment groups.

Each of the TIMI Clinical Center hospitals participates in only one of two subsidiary studies of TIMI Phase II; one being the study of the timing of PTCA which will be referred to as TIMI II A (see Exhibit 2-2) and the second the study of immediate versus deferred beta-blocker therapy which will be referred to as TIMI II B (see Exhibit 2-3). In the Clinical Center hospitals participating in TIMI II A, patients are randomized to one of three groups, rt-PA

alone or rt-PA followed by angioplasty at two hours after the start of the infusion of rt-PA or rt-PA followed by angioplasty within 18 to 48 hours of the start of the infusion of rt-PA. In the Clinical Center hospitals participating in TIMI II B, patients are randomized to either rt-PA alone or rt-PA plus 18 to 48-hour PTCA and patients eligible for beta-blocker therapy treatment are also randomized to immediate or deferred beta-blocker therapy.

In TIMI II A, the effects of thrombolytic therapy alone and thrombolytic therapy followed by two-hour PTCA or 18 to 48-hour PTCA will be assessed primarily on the basis of global left ventricular function measured by contrast radiography prior to hospital discharge. The effects of the timing of PTCA will also be compared by considering the complication rates, the proportion of patients judged to be eligible for angioplasty, the proportion judged to have had successful angioplasty, the proportion requiring emergency surgery following unsuccessful PTCA, the proportion of patients found to have reperfusion at time of catheterization prior to hospital discharge in each of the two PTCA groups, and assessment of regional wall motion by contrast ventriculography and assessment of global and regional ventricular function by rest and exercise radionuclide studies.

In the group of Clinical Center hospitals participating in TIMI II B, the study of immediate versus deferred beta-blocker therapy, all patients are randomized to rt-PA alone or to rt-PA followed by angioplasty within 18 to 48 hours of the initiation of rt-PA infusion (rt-PA plus 18 to 48-hour PTCA). In addition, those patients who are found to be eligible for the initiation of beta-blocker therapy are randomized to either immediate treatment with metoprolol or deferred treatment with metoprolol. Those patients assigned to immediate treatment receive intravenous metoprolol during the period of rt-PA infusion and then are started on oral metoprolol. Patients assigned to deferred therapy are started on oral metoprolol at six days after the start of the infusion of rt-PA. The effects of immediate initiation of beta-blocker therapy will be assessed primarily by comparing global ventricular function measured by rest radionuclide studies in the group randomly assigned to immediate beta-blocker treatment compared to those randomly assigned to deferred beta-blocker treatment for all patients, that is, pooling patients assigned to rt-PA alone and those assigned to rt-PA followed by 18 to 48-hour PTCA in each beta-blocker treatment group. Ventricular function measured by exercise radionuclide studies will also be evaluated. Ventricular function measured by rest and exercise radionuclide studies in the two beta-blocker groups will be compared within each of the two main treatment groups, the rt-PA alone group and the rt-PA plus 18 to 48-hour PTCA group. Ventricular function measured by contrast radiography at 18 to 48 hours will be available for patients assigned to rt-PA plus 18 to 48-hour PTCA and these measurements for this subgroup will be used to compare the effects of immediate versus deferred beta-blocker treatment. The occurrence of the combined end point, total mortality and nonfatal MI, at ten days, six weeks, and one year and total mortality alone at the same three time points will be compared in all patients randomly assigned to either immediate or deferred beta-blocker treatment.

In addition, various non-invasive methods to assess risk in patients prior to hospital discharge will be evaluated in subgroups of patients in a rigorous prospective manner. These evaluations will take the form of data bank or

ancillary studies in which patients from a particular Clinical Center or subset of centers will be involved. The non-invasive procedures which are being considered are (1) modified treadmill exercise testing (ETT) and (2) quantitative 201 thallium myocardial imaging. The objective of these studies will be to determine how non-invasive tests can be employed most appropriately in developing a strategy for treatment of patients following thrombolytic therapy.

2.3 STUDY RATIONALE

After TIMI participating units were funded in 1983, it became apparent that recombinant tissue-type plasminogen activator (rt-PA) would be available for evaluation and that this material had the potential for having the same lytic effects as streptokinase with less risk. Therefore, TIMI Phase I was designed to determine which of two thrombolytic agents (streptokinase or rt-PA) delivered intravenously was more effective with respect to achieving lysis of coronary thrombosis within 90 minutes of administration of treatment in patients who had angiographically proven infarct-related total occlusion. The Phase I study, as well as the Open Label rt-PA and SK studies which were performed in preparation for Phase I, revealed that the prompt opening of the infarct-related artery occurred in approximately two-thirds of patients treated with intravenous rt-PA compared to only one-third of patients treated with intravenous streptokinase.[1-4] On the basis of these results, rt-PA was selected for further study.

During the course of TIMI Phase I, the manufacturer of rt-PA changed methods for producing the agent. Although the preliminary in vitro and animal studies demonstrated that the thrombolytic activity and fibrin specificity of suspension-culture rt-PA (G11035 and G11044) produced by a new method were similar to the roller bottle rt-PA (G11021) studied in TIMI Phase I, the TIMI investigators decided that it would be necessary to assess the efficacy of suspension-culture rt-PA prior to initiation of the Phase II trial. The TIMI Open Label 1985 Protocol was implemented to determine the effectiveness of suspension-culture rt-PA in achieving reperfusion within 90 minutes of the start of treatment in patients with acute MI and angiographically proven total occlusion of the infarct-related coronary artery. The results of Open Label 1985 indicated that with three hours of infusion, 100 mg of suspension-culture rt-PA was at least as efficacious with respect to reperfusion as 80 mg of roller bottle rt-PA and appeared to be associated with less systemic fibrinolysis.[5] The infusion of 150 mg of suspension-culture rt-PA given over six hours was also evaluated and found to yield at least an equal or higher reperfusion rate at 30, 60 and 90 minutes with a low reocclusion rate and no significant increase in systemic fibrinolysis or hemorrhagic complications.[5] Thus, 150 mg of suspension-culture rt-PA given over six hours was selected for TIMI Open Label E, the prerandomization pilot study performed by all centers to become familiar with the Phase II Protocol, and for TIMI Phase II during the first few months of recruitment.

In Open Label E, 326 patients received the dosage regimen of 150 mg suspension-culture rt-PA including the initial bolus of 9 mg within four hours after clinical onset of infarction.[6] Intracerebral hemorrhage occurred in five of the 326 patients (1.5%), in contrast to only one of 386 patients, treated with rt-PA in prior TIMI Protocols.[7] For this reason, the 150 mg dose was

reduced to 100 mg in the on-going TIMI Phase II study and for 53 patients recruited subsequently for Open Label E.[6]

None of the TIMI studies demonstrated that intravenous thrombolytic therapy substantially increased ventricular function to an extent which would affect subsequent survival and/or clinical disability; perhaps because the patients treated in TIMI prior to Phase II were treated on the average of four and three-quarter hours after the onset of symptoms.[8] There was also a relatively high incidence of late reocclusion.[2] For these reasons it was decided that consideration should be given to performing percutaneous transluminal coronary angioplasty (PTCA), given appropriate coronary anatomy, within 18 to 48 hours of thrombolytic therapy. Open Label Phase 1985 allowed assessment of the feasibility of this approach. It was determined that at least 50% of infarct-related arteries would be good candidates for PTCA and would be patent at 18 to 48 hours.[9] These findings led the TIMI investigators to design a three-treatment group study with eligible patients assigned to placebo, rt-PA alone, or rt-PA followed by elective PTCA.

In late 1985, a large-scale, multicenter, randomized study conducted in Italy reported a biologically meaningful and statistically significant difference with respect to in-hospital mortality for patients treated with intravenous streptokinase given within 12 hours of the onset of the acute event compared to patients given conventional care.[10] The patients randomized to streptokinase experienced an 18% reduction in in-hospital mortality. The results for mortality after hospital discharge, which were reported in March 1987, indicated the difference persisted during one year of follow-up.[11] A smaller reduction (16%) in 21-day mortality was observed in the SK group compared to the placebo group in the Short-Time Streptokinase Infusion in Acute Myocardial Infarction (ISAM) Trial.[12] ISAM was a much smaller trial than the Italian study and the mortality difference was not statistically significant. Investigators from the Inter-university Cardiology Institute in the Netherlands randomly assigned, by the Zelen method, 533 patients to conventional therapy or streptokinase (administered directly into the coronary artery or first intravenously and then into the coronary artery).[13] These investigators observed a reduction of in-hospital mortality and one-year mortality in streptokinase-treated patients, but nonfatal reinfarction was more frequent in the streptokinase-treated patients. In addition, a review by Yusuf et al[14] indicated that although taken singly most of the randomized trials of intravenous streptokinase and urokinase did not yield statistically significant differences in mortality, pooling of results indicated that there was a statistically significant reduction of 22% in early mortality. The results of the large-scale Italian study which were supported by the results of pooling of several smaller studies precluded the incorporation of a placebo group in TIMI Phase II. As noted previously, the reperfusion results for patients in the TIMI Open Label and Phase I studies for all patients treated within seven hours of the onset of ischemic symptoms showed a statistically significant difference between the two thrombolytic therapies, rt-PA and streptokinase. These results suggested that rt-PA may lower mortality even more than streptokinase.

The findings of the published studies with respect to mortality and morbidity in the first year after hospital discharge were not as clear cut as the results for early mortality. In the TIMI Open Label and Phase I studies, the patients who were treated within four hours of onset of symptoms

had small improvements in ventricular function. The observed reocclusion rates in TIMI also supported the conclusion that additional intervention may be required in order to maintain patency of arteries which are unstable or likely to reocclude. For that reason, the TIMI Phase II study was designed to determine whether intravenous thrombolytic therapy given in the early hours of acute myocardial infarction should be followed by angioplasty.

Untoward events in the first or second day following thrombolytic therapy may interfere with the benefits of PTCA or prevent the performance of PTCA. For that reason, in some TIMI Clinical Center hospitals, eligible patients are randomized to PTCA to be performed two hours after start of rt-PA infusion or to PTCA to be performed 18 to 48 hours after start of rt-PA infusion or to no PTCA. Patients in these Clinical Center hospitals are not randomized to immediate or deferred treatment with a beta-blocker.

Initiation of beta-blocker treatment shortly after the onset of symptoms of myocardial infarction was shown to reduce in-hospital mortality in patients not treated with thrombolytic therapy in one large-scale study[15] and other studies[16-17] have shown similar trends. Preservation of jeopardized myocardium by restoration of blood supply is the presumed basis for the efficacy of thrombolytic therapy in acute myocardial infarction. Myocardial cell death proceeds promptly to completion within a few hours of blood supply deprivation. The speed with which myocardial cells die may be slowed by treatments to reduce myocardial cell metabolism and thus the magnitude of the gap between oxygen supply and oxygen demand. Beta-adrenergic antagonists reduce heart rate, contractility, and systolic blood pressure, major determinants of myocardial oxygen demand. If beta-blocking agents slow myocardial cell death, this benefit should translate into preservation of myocardial muscle mass and better preservation of left ventricular function with thrombolysis and/or PTCA.

In all Clinical Center hospitals except those evaluating the timing of PTCA (TIMI II A), patients in whom the initiation of beta-blocker treatment is not contraindicated are randomized to immediate or deferred beta-blocker treatment. Patients assigned to immediate beta-blocker treatment receive intravenous metoprolol during the rt-PA infusion followed by oral metoprolol. Patients assigned to deferred beta-blocker treatment are started on oral metoprolol on day six after enrollment. All patients in these Clinical Center hospitals are randomized to PTCA to be performed at 18 to 48 hours or to no PTCA following rt-PA infusion.

The objectives and major design features of Phase II are outlined in this chapter. The procedures and methods for TIMI Phase II are outlined in the remaining chapters of this protocol.

2.4 DESIGN FEATURES

Men and women less than 76 years of age who are admitted to hospital with clinical and electrocardiographic evidence of myocardial infarction are assessed for eligibility. Patients are eligible only if this assessment can be completed and treatment with rt-PA started within four hours of the onset of ischemic symptoms, that is, the time from the onset of chest pain precipitating hospital admission, not the onset of premonitory symptoms. If the time of onset of pain cannot be determined, the patient is not eligible.

Eligible patients are screened for randomization to the study of beta-blocker therapy in those Clinical Center hospitals participating in the assessment of immediate versus deferred beta-blocker therapy (TIMI II B).

Those patients meeting all of the eligibility criteria are asked to give informed consent. Treatment with rt-PA is initiated as soon as possible after obtaining informed consent, and, in all cases, within four hours of the onset of symptoms. Start of rt-PA infusion constitutes enrollment in the study. The dosage of rt-PA is given IV over six hours. The infusion is started in an environment where patients can be monitored closely, generally the hospital emergency room. Efforts are made to limit vascular trauma to minimize the likelihood of bleeding complications. After obtaining informed consent, the enrolling physician obtains the appropriate treatment allocation. This may be after the initiation of rt-PA therapy. In the Clinical Center hospitals participating in TIMI II A, the allocation indicates whether the patient is assigned to rt-PA only or two-hour PTCA or 18 to 48-hour PTCA (Exhibit 2-2). In the other Clinical Center hospitals participating in TIMI II B, the enrolling physician must select the appropriate treatment allocation based on the assessment of the patient's eligibility for the study of immediate beta-blocker therapy. For the beta-blocker study eligible patients, the allocation indicates whether the patient is assigned to immediate beta-blocker treatment or not and whether the patient is assigned to 18 to 48-hour PTCA or not. For the beta-blocker study ineligible patients, the allocation indicates only whether the patient is assigned to 18 to 48-hour PTCA or not (Exhibit 2-3).

In patients assigned to immediate beta-blocker treatment, intravenous administration of metoprolol is started as soon as possible after starting the rt-PA infusion. Three intravenous injections are administered at two minute intervals as tolerated (see Chapter 6). Each injection consists of 5 mg metoprolol. Patients who tolerate the full intravenous dose are given 50 mg metoprolol orally every 12 hours during the first 24 hours and beginning the next day receive 100 mg p.o. twice daily indefinitely.

Following the initiation of assigned therapy, patients are transported to the Coronary Care Unit. The guidelines for standard clinical care including the use of nitrates, calcium antagonists, heparin, and aspirin are presented in Chapter 7.

Patients assigned to thrombolytic therapy followed by two-hour PTCA have coronary angiography and ventriculography started within 120 minutes of the start of rt-PA infusion. If the coronary anatomy is suitable, PTCA is performed whether the infarct-related artery is open or closed. Patients assigned to thrombolytic therapy followed by 18 to 48-hour PTCA are scheduled for coronary angiography and ventriculography within 18 to 48 hours of the initiation of thrombolytic therapy. In this group PTCA is performed if coronary anatomy is suitable and the infarct-related artery is open. In TIMI patients, coronary artery bypass graft (CABG) surgery is to be limited to those with pressing clinical indications and those with specific coronary artery anatomy unsuitable for PTCA, well suited to CABG and of such a nature that closure of the infarct-related artery at the site of stenosis would result in severe hemodynamic collapse (see Chapter 5, Section 5.11). A more detailed description of catheterization procedures and the guidelines for performing angioplasty are given in Chapter 5.

Patients assigned to deferred beta-blocker therapy in the TIMI II B Clinical Center hospitals are started on day six on 50 mg twice daily for the first day and 100 mg of metoprolol twice a day indefinitely. Patients who are ineligible for randomization to immediate or deferred beta-blocker treatment in the hospitals participating in TIMI II B are assessed for initiation of oral beta-blocker therapy at day six after initiation of rt-PA treatment. Unless beta-blocker treatment is contraindicated, the patient is started on 50 mg of oral metoprolol twice a day for the first day and 100 mg twice a day, thereafter. After the predischarge catheterization, those patients in TIMI II A hospitals in whom beta-blockade is not contraindicated, are started on 50 mg of metoprolol twice a day for the first day and 100 mg twice a day, thereafter.

Rest and exercise radionuclide ventriculograms (RVG) with ECG recording are performed on day eight to ten following the initiation of thrombolytic therapy in all patients in all Clinical Centers. The patients in all three groups in TIMI II A centers have predischarge coronary angiography and ventriculography on day eight to ten but after the RVG studies. As noted above, after these procedures patients in TIMI II A are evaluated, and if appropriate, started on beta-blocker treatment.

Patients assigned to thrombolytic therapy only who develop an unstable clinical course, i.e., recurrent episodes of typical ischemic pain or objective signs of ischemia despite progressive stepwise medical therapy including nitrates, beta-blockers, and calcium antagonists (as outlined in Chapter 7) are considered for catheterization and PTCA or coronary artery bypass surgery depending on the anatomic findings (see Chapter 5).

A cardiovascular examination is conducted on all randomized patients just prior to hospital discharge and at six weeks and one year after entry. At six weeks all patients have rest and exercise radionuclide ventriculography with ECG recording. At three and six months after entry, patients are contacted by telephone to obtain information on vital status and information on any hospitalizations. After the one-year visit, the patient's vital status is ascertained at six-month intervals by telephone contact.

The overall recruitment goal for TIMI Phase II is 4000 patients. It is expected that it will take two years to achieve this recruitment goal. Each patient treated in the study will be followed for mortality for at least one year.

During Phase II, the specific primary and secondary end points as well as other information concerning the effects of thrombolytic therapy and thrombolytic therapy followed by PTCA will be reviewed by the Safety and Data Monitoring Committee. This committee will meet to review interim analyses every six months. This review will determine whether the accumulated data indicate protocol changes are warranted because of evidence of either adverse effects or beneficial effects in one or more treatment groups.

Individual cases of serious adverse effects possibly related to the study drugs and/or angioplasty will be reported immediately by the study physician by submitting Drug Experience Reports to the Coordinating Center and the NHLBI Program Office. The Program Office staff will forward these reports to the Food and Drug Administration.

2.5 RESPONSE VARIABLES TO BE MONITORED

The main objective of the study is the assessment of efficacy of thrombolytic therapy versus thrombolytic therapy followed by angioplasty performed, if appropriate, 18 to 48 hours after the start of thrombolytic therapy. For that purpose, the primary response variable will be the combined end point total mortality plus documented definite nonfatal myocardial infarction after six weeks of follow-up. The other response variables which will be examined are the combined end point at ten days and one year; total mortality at ten days, six weeks, and one year; cause-specific mortality; nonfatal coronary events other than myocardial infarction; resting and exercise ventricular function estimated by RVG tests, and non-coronary events such as hemorrhagic complications.

An independent Mortality and Morbidity Classification Committee will have responsibility for reviewing and classifying all fatal and nonfatal coronary events. Each event will be classified using predetermined definitions and without knowledge of TIMI treatment assignments. A detailed definition of documented definite nonfatal myocardial infarction is given in Chapter 9.

In TIMI II A, the effects of two-hour versus 18 to 48-hour PTCA will be evaluated primarily on the basis of global ventricular function measured by contrast radiography prior to hospital discharge. The proportion of patients eligible for PTCA, the proportion with successful PTCA, the proportion with open infarct-related arteries at the end of the procedure and prior to hospital discharge, the proportion requiring emergency surgery after unsuccessful PTCA, the occurrence of symptoms of reocclusion prior to hospital discharge, complications related to angioplasty, and hemorrhagic complications in the two PTCA groups will be compared. Global and regional ventricular function by cardiac catheterization prior to hospital discharge will be evaluated in all three treatment groups (rt-PA alone, two-hour PTCA, 18 to 48-hour PTCA). In-hospital mortality, occurrence of the combined end point, total mortality and documented definite nonfatal MI, and cause-specific mortality will be regarded as secondary response variables for the comparison of the rt-PA alone group and each of the two PTCA groups.

In TIMI II B, the primary response variable for assessing beta-blocker effects will be global ventricular function measured by resting radionuclide studies in all patients assigned to immediate beta-blocker treatment compared with all those assigned to deferred beta-blocker treatment. Resting and exercise ventricular function in the four groups, rt-PA alone with and without immediate beta-blocker treatment and rt-PA plus 18 to 48-hour PTCA with and without immediate beta-blocker treatment, will also be compared. A secondary response variable for assessing beta-blocker effects will be the comparison of ventricular function measured by contrast radiography at 18 to 48 hours for patients assigned to immediate beta-blocker versus those assigned to deferred beta-blocker treatment in the subgroup of patients assigned to rt-PA plus 18 to 48-hour PTCA. The combined end point, total mortality and documented definite nonfatal MI, and total mortality alone will be evaluated for the two beta-blocker groups and the four groups at ten-days, six weeks, and one year.

2.6 STUDY SIZE CONSIDERATIONS

The proposed number of patients to be enrolled in TIMI Phase II is 4,000 with 600 patients expected in the Clinical Centers participating in the study of PTCA timing (TIMI II A) and 3,400 patients in the Clinical Centers participating in the study of immediate versus deferred beta-blocker therapy (TIMI II B). This design will result in a total of 3,800 patients randomly assigned to rt-PA or rt-PA plus 18 to 48-hour PTCA pooling over all of the Clinical Centers. The remaining 200 patients will be assigned to rt-PA plus two-hour PTCA. It is expected that approximately 40% of the 3,400 patients in the TIMI II B Clinical Centers will be eligible for beta-blocker therapy. Assuming 40% of patients are eligible for immediate beta-blocker therapy, a total of 1,360 patients of the expected 3,400 patients in TIMI II B Clinical Centers will be randomized to either immediate beta-blocker therapy or deferred beta-blocker therapy with about half of each beta-blocker group (or approximately 680 patients) assigned to each of the two groups, rt-PA alone or rt-PA plus 18 to 48-hour PTCA.

2.6.1 Assessment of 18 to 48-hour PTCA

The assessment of the efficacy of angioplasty following thrombolytic therapy will be based on the results for patients in all Clinical Centers assigned to rt-PA alone versus the results for patients in all Clinical Centers assigned to rt-PA followed by PTCA performed within 18 to 48 hours of the initiation of rt-PA. As stated previously, the primary end point for assessing treatment differences will be the sum of total mortality and documented definite nonfatal myocardial infarction at six weeks after entry into the study. The differences for the combined end point total mortality and definite nonfatal MI will also be evaluated at ten days and one year after entry. Total mortality for these two treatment groups will also be examined at each of the three time points, ten days, six weeks, and one year after entry.

The event rates for total mortality plus definite nonfatal MI as well as for total mortality have been estimated for each of the two treatment groups. The estimated event rates were first calculated assuming no patients assigned to rt-PA alone will have PTCA during the course of follow-up. Comparable event rates were then calculated assuming 20% of the patients in the rt-PA alone group will have PTCA during the first six weeks. In all the models, the following assumptions were used: 1) 25% of patients have open arteries before treatment with rt-PA, 2) 70% of patients will have reperfusion as a result of thrombolytic therapy, 3) 67% of patients with an open infarct-related artery assigned to the rt-PA plus 18 to 48-hour PTCA will have angioplasty performed, 4) the expected mortality rate associated with PTCA is 1%, 5) 3% of patients will either die or have a nonfatal myocardial infarction as an immediate complication of angioplasty, and 6) the main effect of PTCA is to prevent reocclusion. The expected event rates for two end points at each of three time points using these assumptions are given in Table 1-1, Part A, for the model with no PTCA in the group assigned to rt-PA alone. Comparable rates with 20% of patients in the rt-PA alone group having PTCA are given in Table 1-1, Part B.

Estimates of power to detect differences between the two groups have been calculated based on the estimated rates and 1,900 patients in each of the two treatment groups, rt-PA alone and rt-PA plus 18 to 48-hour PTCA. These power estimates for the three models (no PTCA, 20% PTCA in the first six weeks and 20% PTCA in the first six weeks and an additional 10% with PTCA after six weeks in the group assigned to rt-PA alone) are given in Table 1-1, Parts A, B and C.

Review of Parts A and B of Table 1-1 indicates that there is at least 91% power to detect the postulated differences between the rt-PA and rt-PA plus 18 to 48-hour PTCA group for the combined end point total mortality and definite nonfatal MI at six weeks even if 20% of patients assigned to rt-PA alone have PTCA before six weeks. Much larger differences in total mortality alone than projected in these models would be required in order to have a reasonable chance of detecting the expected treatment differences with the projected number of patients in each of the treatment groups.

Patients who are judged to be ineligible for randomization to immediate beta-blocker therapy are expected to have a high mortality rate. A total of 2,040 patients are expected in this group with 1,020 patients in the rt-PA only group and 1,020 patients in the rt-PA plus 18 to 48-hour PTCA. The expected event rates for this group of patients and corresponding estimates of power to detect differences between the two groups for the three models (with no PTCA, with 20% PTCA and 30% PTCA in the group assigned to rt-PA alone) are given in Parts A, B and C of Table 1-2. If none of the patients in the group assigned to rt-PA alone have PTCA performed, there is an estimated 92% chance of detecting treatment differences between rt-PA and rt-PA plus 18 to 48-hour PTCA in the combined end point, total mortality and definite nonfatal MI, at six weeks. If as many as 20% of the rt-PA alone group have PTCA, there is a 71% chance of detecting differences between rt-PA and rt-PA plus 18 to 48-hour PTCA for the same end point.

The comparable event rates and power calculations for the rt-PA only group versus the rt-PA plus 18 to 48-hour PTCA group are given for the patients eligible to be randomly assigned to immediate beta-blocker therapy (see Table 1-3, Parts A, B and C). The total number of patients projected to be eligible for random assignment to immediate or deferred beta-blocker treatment is 1,360 with 680 patients assigned to immediate and 680 assigned to deferred beta-blocker treatment. This will result in 340 in each of two treatment groups, rt-PA only and rt-PA plus 18 to 48-hour PTCA within each of the two beta-blocker groups. The rt-PA versus rt-PA plus 18 to 48-hour PTCA differences will also be evaluated separately for patients assigned to immediate beta-blocker treatment and for patients assigned to deferred beta-blocker treatment. Expected event rates for rt-PA alone and rt-PA plus 18 to 48-hour PTCA have been estimated assuming no difference between immediate and deferred beta-blocker treatment and are given in Parts A, B and C of Table 1-4 for 340 patients in each group. There is an estimated 48% chance of detecting differences between rt-PA and rt-PA plus 18 to 48-hour PTCA for the combined end point, total mortality and definite nonfatal MI, at six weeks if there is no crossover in the rt-PA alone group and only a 29% chance if up to 20% of patients in the rt-PA alone group have PTCA performed.

2.6.2 TIMI II A - PTCA Timing Study

In TIMI II A, global left ventricular function measured by contrast radiography prior to hospital discharge will be used to assess the effects of thrombolytic therapy alone versus thrombolytic therapy followed by either two-hour PTCA or 18 to 48-hour PTCA. Power to detect specified differences in mean ventricular function values are given in Table 2. With 200 patients in each group there will be 85% power to detect differences of three units in left ventricular function and 98% power to detect differences of four units in left ventricular function.

2.6.3 TIMI II B - Assessment of Immediate Intravenous Beta-blocker Therapy

The effects of immediate initiation of beta-blocker treatment will be assessed in TIMI II B by comparing global ventricular function as measured by resting radionuclide ventriculography prior to hospital discharge. The effects of immediate beta-blocker therapy will be assessed within the rt-PA alone group and within the rt-PA plus 18 to 48-hour PTCA group as well as for the two latter groups combined. Power to detect specific differences in mean ejection fraction was calculated with 340 patients in each group and with 680 patients in each group and are given in Table 3. There is a reasonable chance of detecting treatment differences in mean ejection fraction of three units even if the effects of immediate versus deferred beta-blocker treatment are different in the rt-PA alone group compared to the rt-PA plus 18 to 48-hour PTCA group.

Power to detect specified interactions between the effects of 18 to 48-hour PTCA and of immediate beta-blocker therapy on mean ejection fraction as measured by radionuclide ventriculography is given in Table 4. An interaction, in this context, is defined as the difference in mean ejection fraction between immediate and deferred beta-blocker therapy in patients having PTCA minus this difference in patients not having PTCA. With 340 patients assigned to each of the four treatment comparisons, there will be 81% power to detect a difference of the differences in mean ejection fraction of four units.

REFERENCES

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EXHIBIT 2-1

TIMI PHASE II DESIGN

EXPECTED RECRUITMENT = 3800 PATIENTS

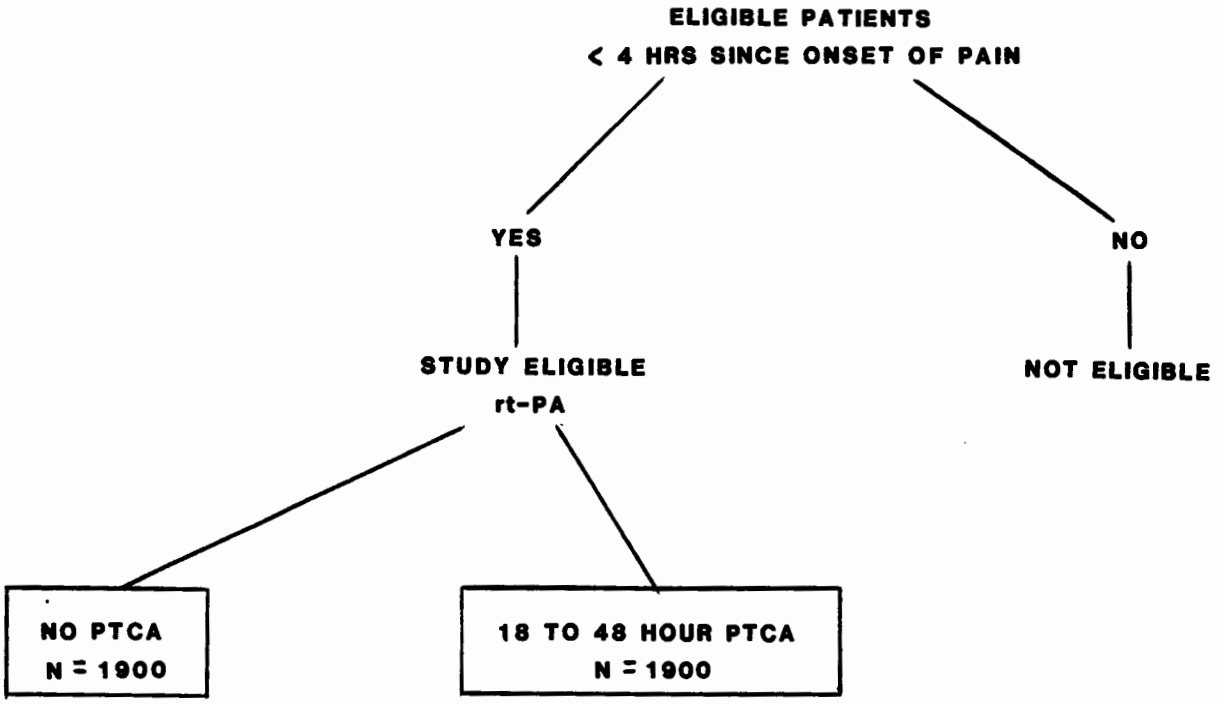
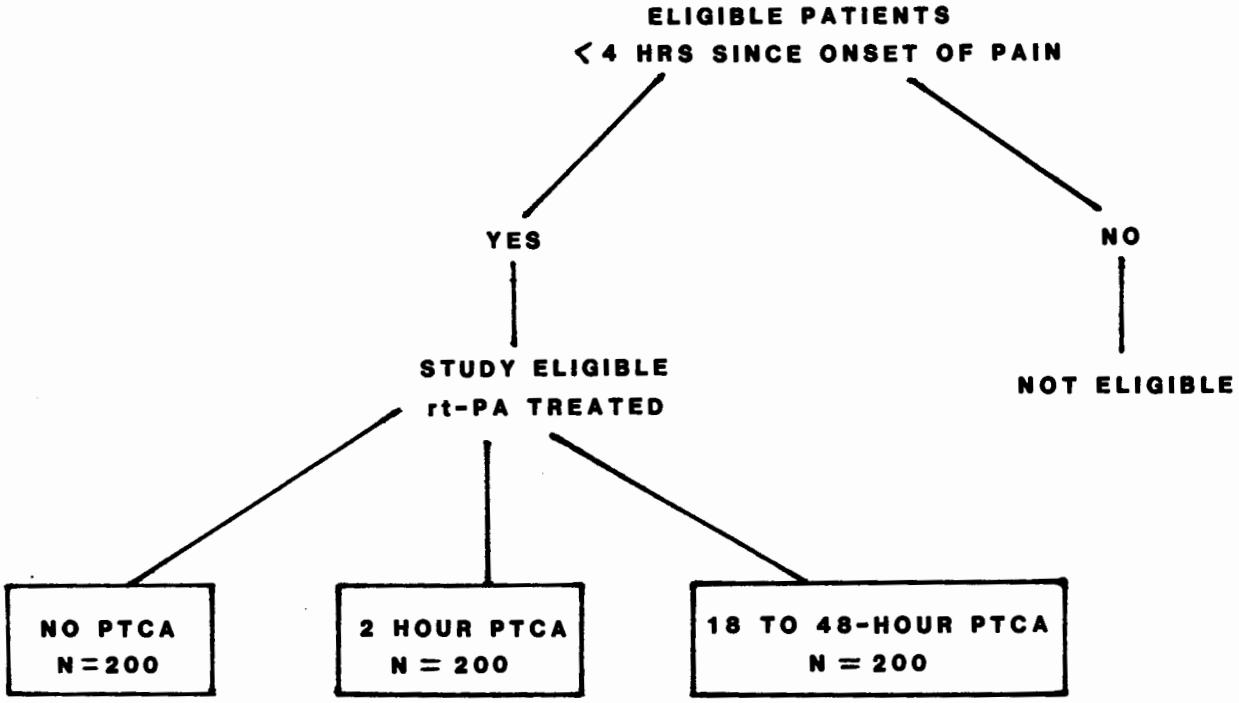


EXHIBIT 2-2

TIMI II A DESIGN

CLINICAL CENTERS ASSESSING TIMING OF PTCA

EXPECTED RECRUITMENT 600 PATIENTS



PROCEDURES FOR ALL GROUPS:

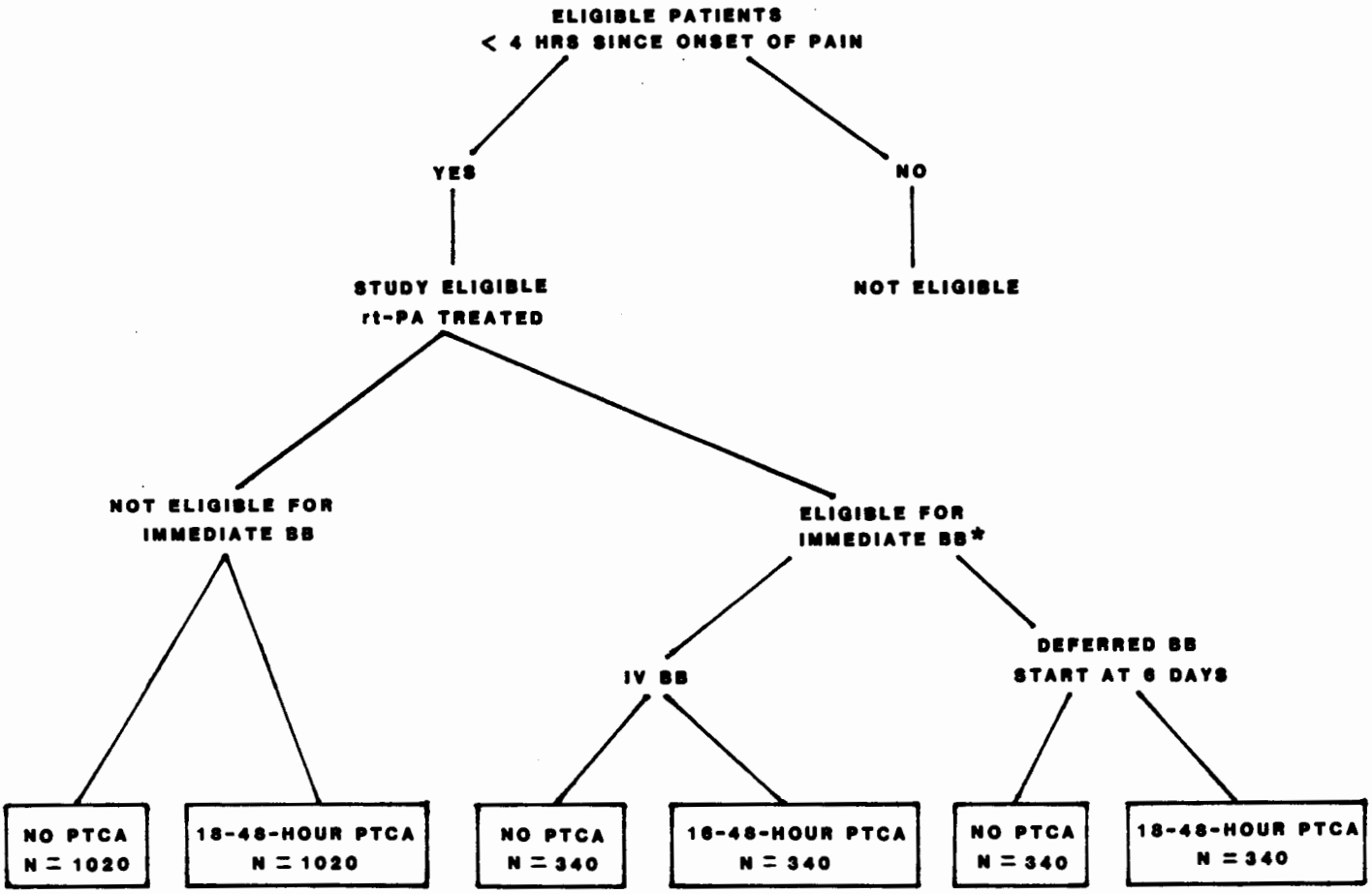
- 8-10 DAY REST AND EXERCISE RVG
- 8-10 DAY CATHETERIZATION WITH CORONARY ANGIOGRAPHY AND VENTRICULOGRAPHY (ALL GROUPS)
- BETA-BLOCKER ELIGIBLE START BETA-BLOCKERS AFTER PREDISCHARGE CATHETERIZATION
- FOLLOW-UP EXAMINATION AT SIX WEEKS AND ONE YEAR
- TELEPHONE CONTACT AT THREE MONTHS AND SIX MONTHS
- MORTALITY FOLLOW-UP AT SIX-MONTH INTERVALS BY TELEPHONE CONTACT TO STUDY END

EXHIBIT 2-3

TIMI II B DESIGN

CLINICAL CENTERS ASSESSING IMMEDIATE BETA-BLOCKER TREATMENT

EXPECTED RECRUITMENT = 3,400 PATIENTS



PROCEDURES FOR ALL GROUPS:

NO CATHETERIZATION EXCEPT FOR SYMPTOMS

8 - 10 DAY REST AND EXERCISE RVG (ALL GROUPS)

FOLLOW-UP EXAMINATION AT SIX WEEKS AND ONE YEAR

TELEPHONE CONTACT AT THREE MONTHS AND SIX MONTHS

MORTALITY FOLLOW-UP AT SIX-MONTH INTERVALS BY TELEPHONE CONTACT TO STUDY END

*ASSUME 40% ELIGIBLE FOR RANDOMIZATION.

TABLE 1-1

EXPECTED (%) EVENT RATES BY TREATMENT GROUP AND POWER TO DETECT THE DIFFERENCE

N = 1900 PER GROUP

	EXPECTED EVENT RATES		
	rt-PA	rt-PA + 18-48 HR PTCA	POWER
Part A: No PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week*	.25	.19	0.99
10 day	.19	.15	0.94
1 year	.38	.28	1.00
Mortality			
6 week	.07	.06	0.19
10 day	.05	.05	0.10
1 year	.11	.09	0.37
Part B: 20% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week*	.23	.19	0.91
10 day	.18	.15	0.73
1 year	.36	.28	0.99
Mortality			
6 week	.07	.06	0.09
10 day	.05	.05	0.06
1 year	.10	.09	0.18
Part C: 30% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.22	.19	0.78
10 day	.17	.15	0.55
1 year	.34	.28	0.98
Mortality			
6 week	.07	.06	0.07
10 day	.05	.05	0.05
1 year	.10	.09	0.11

*Primary end point for Phase II.

TABLE 1-2

EXPECTED (%) EVENT RATES BY TREATMENT GROUP AND POWER TO DETECT THE DIFFERENCE

N = 1020 PER GROUP

BETA-BLOCKER INELIGIBLES

	EXPECTED EVENT RATES		
	rt-PA	rt-PA + 18-48 HR PTCA	POWER
Part A: No PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.27	.21	0.92
10 day	.19	.15	0.73
1 year	.44	.33	0.99
Mortality			
6 week	.09	.08	0.16
10 day	.05	.05	0.07
1 year	.16	.14	0.38
Part B: 20% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.25	.21	0.71
10 day	.18	.15	0.47
1 year	.41	.33	0.67
Mortality			
6 week	.09	.08	0.09
10 day	.05	.05	0.05
1 year	.15	.14	0.19
Part C: 30% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.24	.21	0.54
10 day	.17	.15	0.33
1 year	.39	.33	0.87
Mortality			
6 week	.08	.08	0.06
10 day	.05	.05	0.04
1 year	.15	.14	0.12

TABLE 1-3

EXPECTED (%) EVENT RATES BY TREATMENT GROUP AND POWER TO DETECT THE DIFFERENCE

N = 680 PER GROUP

POOLED GROUPS ASSIGNED TO EITHER IMMEDIATE OR DEFERRED BETA-BLOCKERS

	EXPECTED EVENT RATES		
	rt-PA	rt-PA + 18-48 HR PTCA	POWER
Part A: No PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.25	.19	0.77
10 day	.19	.15	0.56
1 year	.38	.28	0.97
Mortality			
6 week	.07	.06	0.09
10 day	.05	.05	0.06
1 year	.11	.09	0.16
Part B: 20% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.23	.19	0.51
10 day	.18	.15	0.34
1 year	.36	.28	0.83
Mortality			
6 week	.07	.06	0.05
10 day	.05	.05	0.04
1 year	.10	.09	0.09
Part C: 30% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.22	.19	0.37
10 day	.17	.15	0.24
1 year	.34	.28	0.68
Mortality			
6 week	.07	.06	0.05
10 day	.05	.05	0.03
1 year	.10	.09	0.06

TABLE 1-4

EXPECTED (%) EVENT RATES BY TREATMENT GROUP AND POWER TO DETECT THE DIFFERENCE

N = 340 PER GROUP

WITHIN GROUPS ASSIGNED TO EITHER IMMEDIATE OR DEFERRED BETA-BLOCKERS

	EXPECTED EVENT RATES		
	rt-PA	rt-PA + 18-48 HR PTCA	POWER
Part A: No PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.25	.19	.48
10 day	.19	.15	.32
1 year	.38	.28	.80
Mortality			
6 week	.07	.06	.06
10 day	.05	.05	.04
1 year	.11	.09	.10
Part B: 20% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.23	.19	.29
10 day	.18	.15	.19
1 year	.36	.28	.54
Mortality			
6 week	.07	.06	.04
10 day	.05	.05	.03
1 year	.10	.09	.06
Part C: 30% PTCA Crossover in rt-PA Group			
Mortality + NFMI			
6 week	.22	.19	0.21
10 day	.17	.15	0.14
1 year	.34	.28	0.40
Mortality			
6 week	.07	.06	0.04
10 day	.05	.05	0.03
1 year	.10	.09	0.05

TABLE 2

POWER TO DETECT A DIFFERENCE IN MEAN EJECTION FRACTION (EF) MEASURED BY CONTRAST RADIOGRAPHY*

N = 200 PER GROUP

EF DIFFERENCE	POWER
1 unit	0.17
2 units	0.52
3 units	0.85
4 units	0.98

*Primary end point for TIMI II A.

TABLE 3

POWER TO DETECT A DIFFERENCE IN MEAN EJECTION FRACTION (EF) MEASURED BY RADIONUCLIDE STUDY*

EF DIFFERENCE	N = 340	N = 680
1 unit	0.17	0.29
2 units	0.52	0.81
3 units	0.85	0.98
4 units	0.98	0.99

*Primary end point for TIMI II B.

TABLE 4

POWER TO DETECT INTERACTION FOR MEAN EJECTION FRACTION (EF) MEASURED BY RADIONUCLIDE STUDY

N = 340

DIFFERENCE OF EF DIFFERENCES	POWER
2 units	0.29
3 units	0.57
4 units	0.81
5 units	0.94

CHAPTER 3

PATIENT ELIGIBILITY AND PATIENT ORIENTATION

3.1 INTRODUCTION

To be eligible for enrollment into TIMI Phase II, each patient must satisfy all inclusion criteria and none of the exclusion criteria.

3.2 INCLUSION CRITERIA

All of the following conditions must be satisfied for a patient to be eligible for randomization to TIMI Phase II.

1. As of the day of admission to the hospital, the patient's age at last birthday must be less than 76 years.

2. The patient must report severe chest pain of at least 30 minutes duration, clinically considered to possibly originate from ischemic myocardium. (Location of pain need not be limited to the chest.)

3. An electrocardiogram must reveal new or presumably new ST segment elevation of at least 0.1 mV. ST segment elevation is measured 0.08 sec after J point. The electrocardiographic findings must be present in at least one of the three locations:

   a. in at least two of the three inferior leads (II, III, aVF); or

   b. in at least two contiguous leads of the six precordial leads (V1-V6); or

   c. in leads I and aVL.

   Q waves are not a contraindication to eligibility.

4. Onset of chest pain must have occurred no more than four hours from initiation of rt-PA treatment. Onset of chest pain will be taken as the beginning of pain which caused the patient to come to the hospital; chest pain duration will thus not include premonitory symptoms. If the patient was in the hospital at the time of onset of chest pain, it is the beginning of pain which caused the hospital staff to evaluate the patient for enrollment in TIMI. If the time of onset of such pain cannot be determined by the patient, the patient will be considered not eligible for the study.

3.3 EXCLUSION CRITERIA

3.3.1 Exclusion for Administration of rt-PA

Patients will be excluded if any one of the following conditions are satisfied:

1. Agitation or lethargy such that informed consent cannot be obtained;

2. Childbearing potential;

3. Past or present bleeding disorder or significant gastrointestinal bleeding;

4. Any recording of systolic pressure exceeding 180 mm Hg or diastolic pressure exceeding 110 mm Hg during the presenting illness prior to randomization or uncontrolled hypertension prior to entry (diastolic blood pressure > 110 mm Hg by several measurements);

5. Any history at any time of cerebrovascular disease, including any form of stroke and/or transient ischemic attack;

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

7. Severe trauma within the last six months;

8. Oral anticoagulation therapy;

9. Left bundle branch block;

10. Prosthetic heart valve;

11. Dilated cardiomyopathy;

12. Other serious advanced illnesses such as cancer, renal or hepatic disorder;

13. Psychological or physical inability to participate; any history of parenteral or other drug abuse including alcoholism should render a prospective patient ineligible;

14. Previous coronary artery bypass graft;

15. Significant surgical procedure within the last two weeks;

16. PTCA within the last six months;

17. Previously participated in TIMI Phase II; or

18. Infusion of any thrombolytic agent for myocardial infarction within the last two weeks.

3.3.2 Exclusions for the Administration of Immediate Intravenous Metoprolol

Contraindications for randomization to immediate beta-blocker therapy include the following:

1. Current treatment with a beta-blocker (within 48 hours), verapamil (within 24 hours), or diltiazem (within 24 hours);

2. Ventricular rate at rest consistently < 55 beats per minute;

3. Systolic BP consistently < 100 mm Hg;

4. Moist rales that do not clear with coughing, involving 1/3 or more of the lung fields and interpreted as signs of congestive heart failure, or pulmonary edema with consistent chest x-ray findings;

5. Presence of significant first-degree AV block (PR > 0.24 sec) or second- or third-degree block;

6. Implanted pacemaker;

7. Asthma by history, wheezing by physical examination, or chronic obstructive pulmonary disease requiring chronic therapy with corticosteroids or $beta_2$ stimulants.

3.4 PATIENT ORIENTATION

The majority of patients who potentially will enter the study will be admitted through the emergency room with a diagnosis of suspected or proven acute myocardial infarction. Some patients will already be in the hospital. They will have been admitted previously with unstable angina or other medical problems and will suddenly develop symptoms of acute myocardial infarction. A triage officer, a nurse or a houseofficer in the emergency room or coronary care unit will call a member of the TIMI team. The member of the team will be either the Principal Investigator or his/her designate. That individual may be a cardiac fellow or the special TIMI Research Nurse/Coordinator. An initial decision concerning the candidacy of the patient will be made by the TIMI team member.

Once deemed appropriate the patient will then be approached by the Principal Investigator or his/her delegate. If possible, the physician of record will be involved in this phase of recruitment. If the family of the patient is available, the family will also be consulted.

The benefits and risks of the proposed procedure and study will be explained to the patient and the family; consent will be requested from the patient.

Patients who potentially might be entered into the protocol will have to be seen and evaluated early enough after onset of symptoms so that infusion of rt-PA is initiated $\leq$ 4 hours after clinical onset of infarction. Intravenous administration of metoprolol will begin subsequent to the bolus administration of rt-PA and after observation of the patient for five to ten minutes.

3.4.1 Informed Consent

After it has been determined that a patient meets all of the inclusion criteria and none of the exclusion criteria for administration of rt-PA, and after the study has been explained to the patient, he/she will be asked to sign a consent form. Failure to give informed consent renders the patient ineligible for the study. Copies of the required consent form will be made available to each participating Clinical Center. The Principal Investigator has the option to use a consent form prepared for local use incorporating the required consent form; the local form may not omit items from the required study consent form. Draft consent forms are given in Exhibits 3-1 and 3-2 for Clinical Centers participating in the TIMI II A - PTCA timing study and the TIMI II B - assessment of immediate beta-blocker therapy, respectively.

After the patient has stabilized the study physician will review the study goals and the key aspects of points covered in the consent form. In most cases this follow-up conference will be held approximately 24 hours after study entry when the study physician is evaluating the patient's condition.

EXHIBIT 3-1

INFORMED CONSENT TO PARTICIPATE IN CLINICAL INVESTIGATION

TIMI II A

You are being asked to participate in a research project as described in this form below. All such research projects carried out in this hospital are covered by the rules of both the Federal Government and this hospital. Under these rules, if you wish to participate in this study, this hospital's research staff will document that you have been fully informed about the study and agree to it by obtaining your signed consent.

The doctor will explain to you in detail the purpose of the project, the procedures to be used, and the potential benefits and possible risks of participation. You may ask him any questions you may have to help you understand the project. A basic explanation of the project is written below. Please read this explanation and discuss with the doctor any questions you might have.

If you decide to participate in the project, please sign this form on the line indicated below in the presence of a witness and the person who explained the project to you. You should be given a copy of this form to keep.

1. Nature and Purpose of the Study

You may be having a heart attack. The purpose of this study is to evaluate new treatments which may reduce your heart damage.

2. Explanation of Procedures

If you choose to participate in this study, TPA a new, clot dissolving drug will be given into a vein for six hours. You will receive a blood thinning medication, heparin, to prevent any new clot from forming in the heart artery. You will be assigned to either cardiac catheterization to evaluate your heart's arteries for angioplasty, a procedure which uses a balloon catheter to further open the artery, within the next two hours (33% chance) within the next two days (33% chance) or to treatment without coronary angioplasty (33% chance) unless your condition warrants it.

Cardiac catheterization is a commonly performed procedure which assesses heart function and detects blockages in heart arteries. Following local anesthesia, a small plastic tube (catheter) is inserted into a groin artery and advanced to the heart. Pictures of the heart pumping chamber and its arteries are obtained by injecting x-ray dye through the catheter. Coronary angioplasty, performed during cardiac catheterization involves advancing a special balloon tipped catheter into a blocked heart artery. Once the balloon straddles the blockage, it is briefly inflated to widen the opening of the artery and increase blood flow to the heart.

EXHIBIT 3-1 (Continued)

Your study doctors plan to analyze about eight tablespoonsful (4 ozs) of your blood during your first day in the hospital and a total of 16 tablespoonsful (8 ozs) over the course of your hospital stay. Also, your study doctors will use a small intravenous injection of radioactive particles and a special camera to see how well your heart muscle pumps while you rest and engage in light exercise. You will probably be asked to have a cardiac catheterization before leaving the hospital to check on your blocked artery and heart function. You will be asked to return for a check-up six weeks and again one year from now. We also will telephone you twice a year to ask how well you are. The study doctors may contact you some time in the future after these treatments to ask about long-term effects.

3. Discomfort and Risks

TPA is a new investigational drug. The doctors in this study have, none-the-less, already used it to treat over 1000 patients. Bleeding may occur and may be severe enough to require transfusion. Rarely there is bleeding into the brain where it may cause permanent damage. Other complications have been very rare.

If you have been assigned to be evaluated for angioplasty, your study doctors will start with a cardiac catheter study of your heart. Placing the catheter through the skin into an artery may cause minor pain. When pictures of the heart are taken, you may also notice a brief, warm feeling lasting a few seconds. Bleeding, blockage of a blood vessel and allergic reactions may occur. Any cardiac catheterization carries a small risk of death or stroke (one in a thousand).

In trying to open the blocked artery by angioplasty, there is a small possibility that the artery may be damaged. If this occurs, your doctor may decide that bypass surgery is necessary to help protect you from having further heart damage. The entire procedure will be directed and conducted by a cardiologist well experienced in its performance and the management of any potential complications.

Participation in this study may extend your hospital stay. There will be no charge to you for the blood clot dissolving medications or extra tests required for this study.

4. Benefits

The potential benefits from participating in this study include reducing the amount of heart damage and chance for a second heart attack and increasing your chances for survival. Preliminary analyses of patients treated in this way have shown a very low mortality rate.

EXHIBIT 3-1 (Continued)

5. Alternatives

Your alternative to taking part in this study is to receive your doctor's standard treatment for heart attack in the Coronary Care Unit. Standard treatment does not use TPA to dissolve clot in the coronary arteries, and does not use angioplasty to open narrowed arteries without special clinical reasons.

6. Confidentiality

In this study your doctors will make note of your initials, age, sex, weight, height and other facts about you. These details will be stored in a private Coordinating Center on a computer. The facts on the computer may be seen by staff at the National Heart, Lung and Blood Institute, the drug companies which provide the study drugs and the Food and Drug Administration. You will not be identified personally in any reports from this study. Every effort will be made to keep your own personal medical data confidential.

7. Refusal and Withdrawal

You may refuse to take part in or you may withdraw from this study at any time without harming your present or future care at this hospital.

8. Rights

Your study doctors do not expect any unusual risks as a direct result of this project. However, should an unforeseen physical injury occur, appropriate medical care as determined by the hospital will be provided and charged to (routine local billing sources), but no financial compensation will be given. Should you have any questions about your rights in the study you may call either (name and phone number) or the office of Research Administration at (phone number). You will be given a copy of this form to keep if you agree to take part in this study.

EXHIBIT 3-1 (Continued)

****

I have discussed the explanation of this study with the study doctor. I have had enough time with the study doctor to discuss all of my questions and concerns. I willingly consent to be part in this study.

I agree to release of medical information by study doctors to my referring doctor.

Signature of Patient	Date
Signature of Witness	Date

I confirm that I have explained to this patient the nature and purpose, the possible benefits, and possible risks of the study procedures and drugs.

Signature of Physician

Date and Time

EXHIBIT 3-2

INFORMED CONSENT TO PARTICIPATE IN CLINICAL INVESTIGATION

TIMI II B

You are being asked to participate in a research project as described in this form below. All such research projects carried out in this hospital are covered by the rules of both the Federal Government and this hospital. Under these rules, if you wish to participate in this study, this hospital's research staff will document that you have been fully informed about the study and agree to it by obtaining your signed consent.

The doctor will explain to you in detail the purpose of the project, the procedures to be used, and the potential benefits and possible risks of participation. You may ask him any questions you may have to help you understand the project. A basic explanation of the project is written below. Please read this explanation and discuss with the doctor any questions you might have.

If you decide to participate in the project, please sign this form on the line indicated below in the presence of a witness and the person who explained the project to you. You should be given a copy of this form to keep.

1. Nature and Purpose of the Study

You may be having a heart attack. The purpose of this study is to evaluate new treatments which may reduce your heart damage.

2. Explanation of Procedures

If you choose to participate in this study, TPA a new, clot dissolving drug will be given into a vein for six hours. You will receive a blood thinning medication, heparin, to prevent any new clot from forming in the heart artery. You will be assigned to either cardiac catheterization to evaluate your heart's arteries for angioplasty, a procedure which uses a balloon catheter to further open the artery, within the next two days (50% chance) or to treatment without coronary angioplasty (50% chance) unless your condition warrants it.

Cardiac catheterization is a commonly performed procedure which assesses heart function and detects blockages in heart arteries. Following local anesthesia, a small plastic tube (catheter) is inserted into a groin artery and advanced to the heart. Pictures of the heart pumping chamber and its arteries are obtained by injecting x-ray dye through the catheter. Coronary angioplasty, performed during cardiac catheterization involves advancing a special balloon tipped catheter into a blocked heart artery. Once the balloon straddles the blockage, it is briefly inflated to widen the opening of the artery and increase blood flow to the heart.

EXHIBIT 3-2 (Continued)

This study will also test the use of a drug, metoprolol, which slows the pulse and lowers blood pressure. Not every patient is suitable for treatment with metoprolol. If your condition is suitable for treatment with metoprolol you will be assigned to received metoprolol by three intravenous injections now followed by pill orally (50% chance) or to start the pills in a week (50% chance).

Your study doctors plan to analyze about eight tablespoonsful (4 ozs) of your blood during your first day in the hospital and a total of 16 tablespoonsful (8 ozs) over the course of your hospital stay. Also, your study doctors will use a small intravenous injection of radioactive particles and a special camera to see how well your heart muscle pumps while you rest and engage in light exercise. You will be asked to return for a check-up six weeks and again one year from now. We also will telephone you twice a year to ask how well you are. The study doctors may contact you some time in the future after these treatments to ask about long-term effects.

3. Discomfort and Risks

TPA is a new investigational drug. The doctors in this study have, none-the-less, already used it to treat over 1000 patients. Bleeding may occur and may be severe enough to require transfusion. Rarely there is bleeding into the brain where it may cause permanent damage. Other complications have been very rare.

If you have been assigned to be evaluated for angioplasty, your study doctors will start with a cardiac catheter study of your heart. Placing the catheter through the skin into an artery may cause minor pain. When pictures of the heart are taken, you may also notice a brief, warm feeling lasting a few seconds. Bleeding, blockage of a blood vessel and allergic reactions may occur. Any cardiac catheterization carries a small risk of death or stroke (one in a thousand).

In trying to open the blocked artery by angioplasty, there is a small possibility that the artery may be damaged. If this occurs, your doctor may decide that bypass surgery is necessary to help protect you from having further heart damage. The entire procedure will be directed and conducted by a cardiologist well experienced in its performance and the management of any potential complications.

Metoprolol is one of a well known class of drugs called beta-blockers. The doctors in this study have used oral beta-blocker treatments in many patients with heart attacks and in a few hundred patients by intravenous injection. This drug can cause trouble breathing in patients with asthma or weak heart muscles; slow pulse or abnormal electrocardiograms in patients with a weak heart beat; and low blood pressure in patients with weak heart muscles. Rarely patients taking this drug orally have had upset stomach, skin problems or difficulty concentrating and remembering.

EXHIBIT 3-2 (Continued)

Participation in this study may extend your hospital stay. There will be no charge to you for the blood clot dissolving medications or extra tests required for this study.

4. Benefits

The potential benefits from participating in this study include reducing the amount of heart damage and chance for a second heart attack and increasing your chances for survival. Preliminary analyses of patients treated in this way have shown a very low mortality rate.

5. Alternatives

Your alternative to taking part in this study is to receive your doctor's standard treatment for heart attack in the Coronary Care Unit. Standard treatment does not use TPA to dissolve clot in the coronary arteries, does not use intravenous metoprolol to slow the pulse early in the course of a heart attack, and does not use angioplasty to open narrowed arteries without special clinical reasons.

6. Confidentiality

In this study your doctors will make note of your initials, age, sex, weight, height and other facts about you. These details will be stored in a private Coordinating Center on a computer. The facts on the computer may be seen by staff at the National Heart, Lung and Blood Institute, the drug companies which provide the study drugs and the Food and Drug Administration. You will not be identified personally in any reports from this study. Every effort will be made to keep your own personal medical data confidential.

7. Refusal and Withdrawal

You may refuse to take part in or you may withdraw from this study at any time without harming your present or future care at this hospital.

8. Rights

Your study doctors do not expect any unusual risks as a direct result of this project. However, should an unforeseen physical injury occur, appropriate medical care as determined by the hospital will be provided and charged to (routine local billing sources), but no financial compensation will be given. Should you have any questions about your rights in the study you may call either (name and phone number) or the office of Research Administration at (phone number). You will be given a copy of this form to keep if you agree to take part in this study.

EXHIBIT 3-2 (Continued)

****

I have discussed the explanation of this study with the study doctor. I have had enough time with the study doctor to discuss all of my questions and concerns. I willingly consent to be part in this study.

I agree to release of medical information by study doctors to my referring doctor.

Signature of Patient	Date
Signature of Witness	Date

I confirm that I have explained to this patient the nature and purpose, the possible benefits, and possible risks of the study procedures and drugs.

Signature of Physician

Date and Time

CHAPTER 4

RANDOMIZATION AND ENROLLMENT OF PATIENTS

4.1 ELIGIBILITY ASSESSMENT

All patients with definite or suspect myocardial infarction (MI) appearing at the hospital emergency room or developing symptoms of acute MI while hospitalized will be evaluated for entry into the study. Those patients who appear to be eligible will be further screened and, if eligible, asked to give informed consent for treatment (see Section 3.4.1).

Those patients who give informed consent for treatment will be assigned to treatment as indicated by the next available treatment allocation (see Section 4.2), provided only that treatment can be initiated within four hours of the onset of symptoms of the myocardial infarction which qualifies the patient for enrollment in TIMI. This condition is one of the entrance criteria and is considered when assessing the patient's eligibility before asking for informed consent.

4.2 RANDOMIZATION AND TREATMENT ALLOCATION

4.2.1 Treatment Allocation

Treatment Allocation Mailers are computer-generated sequentially according to each randomization schedule. The outside of each mailer includes the Clinical Center hospital site number and a sequence number. The inside of the mailer includes the Clinical Center hospital number, sequence number, indication whether PTCA is to be performed, whether treatment with beta-blockers is to be immediate or deferred, if applicable, and spaces to record patient ID number, name code, and date opened. The sequentially numbered Treatment Allocation Mailers are sent to each Clinical Center by the Coordinating Center as needed.

When a patient has been judged eligible for the main study, and given informed consent, the lowest numbered Treatment Allocation Mailer from the appropriate set is opened. The first section of the Treatment Assignment Form is completed with the required information. Since all study patients will be treated with rt-PA, treatment may be begun before the mailer is open.

The Treatment Allocation Mailer system was replaced by a procedure for obtaining a treatment allocation using IBM PC computers at each Clinical Center hospital. The program designed for this purpose requires entry of patient ID number and name code and in TIMI II B sites whether the patient is eligible for randomization to immediate beta-blocker therapy and identifies the appropriate randomization schedule for each patient. The envelopes were returned to the Coordinating Center when the computer system was installed for each participating hospital.

4.2.2 TIMI II A - PTCA Timing Study

One randomization schedule was generated at the Coordinating Center for each Clinical Center participating in TIMI II A (PTCA timing study); a unique one for each hospital. Each schedule will assign equal numbers of patients to no PTCA, two-hour PTCA, or 18 to 48-hour PTCA. There are corresponding sets of Treatment Allocation Mailers or the schedule is stored on the Clinical Center's TIMI PC. These are similar to those used in the other centers, except treatment assignment will be to no PTCA, two-hour PTCA, or 18 to 48-hour PTCA. No patients in these Clinical Centers will be treated with immediate intravenous beta-blockers.

4.2.3 TIMI II B - Assessment of Immediate Intravenous Beta-Blocker Therapy

For each Clinical Center hospital participating in TIMI II B - assessment of immediate intravenous beta-blocker therapy, two randomization schedules were computer-generated at the Coordinating Center and these schedules are unique for each center. One set of randomization schedules is for patients not eligible for treatment with immediate beta-blocker. Each schedule is designed to allocate equal numbers of patients to no PTCA or to PTCA at 18 to 48 hours after a specified number of patients are enrolled. The second set of randomization schedules is for beta-blocker eligible patients. These schedules provide assignments for patients to immediate or deferred beta-blocker therapy as well as to 18 to 48-hour PTCA or no PTCA, with equal numbers of patients in each of the resulting four groups after a specified number are assigned.

4.3 DOCUMENTATION OF TREATMENT ASSIGNMENT

The Research Nurse/Coordinator at the Clinical Center will telephone the Coordinating Center as close as possible to 24 hours after treatment with rt-PA (no later than the morning of the next working day) to report that a Treatment Allocation Mailer has been opened and to transmit the selected information from the Treatment Assignment Form. This telephone call will be taped and reviewed immediately at the Coordinating Center to ensure that the Clinical Center is following the correct allocation procedures. The Research Nurse/Coordinator will mail a hard copy of the Treatment Assignment Form to the Coordinating Center as soon as possible. These forms will be reviewed to confirm their consistency with the information given via the telephone. The tape of the telephone call will be used to adjudicate any discrepancies between the information recorded at the time of the telephone call and that on the Treatment Assignment Form.

The IBM PC is also used to enter certain preliminary data for each patient and telephone calls to the Coordinating Center to report these data are not required. That is, that staff at Clinical Centers who are randomizing patients by IBM PC enter the preliminary data on the PC. Data transmission from Clinical Centers to the Coordinating Center is performed once a week.

The Research Nurse/Coordinator forwards the qualifying ECG which confirms the patient's eligibility to the Coordinating Center. These ECG's are reviewed centrally to verify the patient's eligibility in order to monitor the Clinical Center's adherence to this aspect of the study protocol.

4.4 CONSEQUENCES OF TREATMENT ASSIGNMENT

The initiation of thrombolytic therapy establishes the patient's entry into the study. Treatment with rt-PA may begin before obtaining the treatment allocation and the time of initiation of treatment will be recorded on the Treatment Assignment Form. Every patient started on rt-PA is counted as a participant in the study and will be included in all analyses.

CHAPTER 5

CARDIAC CATHETERIZATION AND CORONARY ANGIOPLASTY

5.1 INTRODUCTION

All patients entering Phase II of the TIMI trial will be recruited for the main study comparing the treatment effects of rt-PA to those of rt-PA plus percutaneous transluminal coronary angioplasty (PTCA). Each TIMI II Clinical Center will participate in one of two subsidiary studies: TIMI II A - PTCA timing study; or, TIMI II B - assessment of immediate intravenous beta-blocker therapy. At Clinical Centers performing the study of immediate intravenous beta-blocker therapy, patients will be randomized to intravenous (IV) rt-PA or to IV rt-PA plus cardiac catheterization with PTCA of the infarct-related artery 18 to 48 hours after the start of rt-PA infusion. Additional cardiac catheterization procedures will not be performed in TIMI II B patients unless clinically warranted for the management of recurrent ischemic events.

At Clinical Centers performing TIMI II A (PTCA timing study), all patients will be treated with IV rt-PA and randomized in equal numbers to one of three groups, rt-PA only, PTCA within two hours of the start of the rt-PA infusion, or PTCA performed 18 to 48 hours after the start of the rt-PA infusion. In the two-hour PTCA group, cardiac catheterization is started within two hours of the start of rt-PA infusion and in the 18 to 48-hour PTCA group, cardiac catheterization is scheduled no earlier than 18 hours. To compare the late patency rates of the infarct-related artery as well as global and regional left ventricular function among the three treatment groups, each patient in TIMI II A will undergo a cardiac catheterization prior to hospital discharge.

5.2 PRELIMINARY CONSIDERATIONS

During this phase of the TIMI trial, PTCA will be performed: (1) in patients within the acute phase of myocardial infarction; (2) in the absence of previous angiographic data; and (3) at different clinical sites.

The capabilities of laboratories participating in this trial must exceed those required for routine diagnostic cardiac catheterizations. First, since on-line judgement as to the suitability of the infarct-related artery for PTCA is required, each laboratory must have a fluoroscope and video chain capable of providing high quality images which enable accurate characterization of coronary artery anatomy. Alternatively, the laboratory may wish to process the cine films first (if this can be done expeditiously) and then make a decision regarding PTCA after review of the films. This latter alternative requires the availability of a rapid cine processor (at least forty feet per minute) and also prolongs the catheterization procedure for the patient.

Second, the laboratory must be able to perform PTCA with acceptable proficiency. Since the outcome of PTCA depends upon multiple factors, some of which include patient selection, skill and knowledge of the operator and

of the corrected flood should be done before patient data is acquired. If the correction device is malfunctioning, the camera should be serviced before its use in this study.

8.2.2.2 Pulse Height Analysis

Peaking of the camera should be performed "on the patient": Automatic pulse height analysis (PHA) tracking (140 keV, 20% symmetric window) is the preferred option. Manual pulse height analysis is acceptable as long as continual monitoring of the analyzer performance is done throughout data acquisition and proper adjustments are made for photopeak drift.

8.2.2.3 ECG Synchronization

Data acquisition depends upon adequate electrocardiographic gating. Using a standard 3-lead system, one electrode should be securely fastened on: (1) right shoulder (subclavicular area), (2) left shoulder (subclavicular area), and (3) subxiphoid area. Skin preparation is important for assuring good electrode contact. Wipe each area with alcohol prep and dry with gauze. Applying a small amount of tincture of benzoin is extremely helpful. Connect the patient lead wires (RA, LA, LL) to each appropriate electrode making sure each connection is secure.

Occasionally, the lead wires may be exchanged with each other to create a larger R-wave progression, or in the case of premature ventricular contractions (PVCs) to change the polarity of the ectopic beats. R-R intervals should not be windowed in the presence of arrhythmias. (All beats should be collected).

A 30 second ECG rhythm strip should be included with the submitted data.

8.2.2.4 Data Acquisition and Termination -- Resting Study

LEAP (low energy all purpose) collimation should be used for all studies. Data are acquired in 64x64 word images (to avoid pixel overflow) at 16 frames per RR interval. Depending upon the instrument, one of the following parameters is employed for ending acquisition: 200 counts/cm^2 in center of LV, 250,000 counts/frame, 5 million count total acquisition. Data should not be count normalized, temporally or spatially filtered.

8.2.2.5 Patient Positioning and Sequence of Imaging -- Resting Study

For the resting study the patient is imaged, while on the imaging table, with left lateral and left posterior oblique (LPO) views. Then the patient is placed on the exercise table where anterior and left anterior oblique (LAO) images are obtained. The heart is positioned in the center of the field of view. The spleen is excluded.

1. Left lateral view. This view is performed in the right side down lateral decubitis position with both arms extended over the head and both legs flexed toward the abdomen. The shoulder line is perpendicular to the floor. The camera head is positioned as closely as possible to the chest. Due to body curvature this sometimes may result in a slight cephaloid angulation.

2. Left posterior oblique (LPO) view. Identical position of patient as left lateral view. Conventional camera angulation is 30° toward the front surface of patient.

3. Anterior view. Camera angle of this view = angle of LAO view - 45°. For example, if the best LAO was obtained at 60°, the anterior view should be performed at 15° LAO. Again, if the best LAO was obtained at 25°, the anterior view is performed at 20° RAO.

4. Left anterior oblique (LAO) providing optimal separation of left and right ventricle ("best septal" LAO). Patient supine and camera angled between 20 and 70° in order to best separate the right ventricle and left ventricle. This is usually achieved when the septum is oriented vertically and the distance between the septum and lateral wall is minimized. The exact angulation for this view should be permanently recorded. The camera should be positioned as close to the patient as possible to minimize loss of resolution.

8.2.3 Exercise Study

For electrocardiographic monitoring during the exercise test, radiolucent electrodes are used for chest leads. A 12-lead electrocardiogram is recorded before exercise, at peak exercise, and immediately after the discontinuation of exercise. A three-lead (II, aVF, V_5) electrocardiogram is monitored throughout exercise and for ten minutes after completion of exercise. Blood pressure, measured with a sphygmomanometer, and heart rate are monitored before, during, and after exercise.

The exercise radionuclide ventriculographic study is obtained with the patient flat supine or semisupine (45°) and the feet in the stirrups of the bicycle. The camera's position is in the LAO angulation which provides best separation of right and left ventricle. Two additional baseline LAO studies are acquired, this time each for two minutes. The supine exercise is then started at a load of 200 kilopond meters (kpm) per minute and is increased by 200 kpm per minute after each three-minute exercise stage. During the last two minutes of each stage equilibrium radionuclide ventriculography is performed. Data acquisition for the second baseline and third LAO studies and the exercise studies is at 16 frames/RR cycle or about 25 msec/frame. The patient is exercised for three minutes at incremental workloads until one of the following end points is reached: (1) a heart rate of 120 bpm or 400 kpm/minute, (2) complex ventricular arrhythmias, (3) onset of angina pectoris, (4) decrease in blood pressure (greater than 20 mm Hg), (5) exhaustion or

marked dyspnea, (6) ST segment depression $\geq$ 2 mm (0.08 seconds after J-point) compared with the resting electrocardiogram. Immediately after discontinuation of exercise a two-minute recovery study with LAO angulation is acquired.

The follow-up study at six weeks will start identically to the predischarge study. However, the six week study will not conclude until a limiting symptom appears or a maximal heart rate is achieved.

8.2.4 Data Transfer to Core Laboratory

The data will be transferred on magnetic tape as for TIMI Phase I, or preferably on 8 inch floppy disk. Magnetic tapes should adhere to the following standards: 9-track magnetic tape, 800 bpi, NRZ (i.e., not phase encoded), and less than or equal to 4096 words per record. Data should be stored with quality control images (bar phantom and field flood in 128/128 word mode) first followed by patient studies (in 64/64 word mode). The order of each patient's studies should be as follows: Resting left lateral, LPO, anterior, and LAO projections followed by LAO studies at baseline 2 and 3, each exercise stage, and the post-exercise recovery period. A Rest/Exercise RVG Shipping Form (TIMI Form 8A) should accompany each tape. The disk or tape should be sent in the appropriate mailer via UPS to the Radionuclide Core Laboratory. The exercise electrocardiographic tracing should be sent to the Coordinating Center.

8.2.5 Data Processing

Data processing will be identical as for Phase I. The magnetic tapes containing the image data are read using the Star 80 megabyte disk drive. Translation routines coded in FORTRAN interpret these data and put them in proper format for analysis. On the resting multi-view studies the following parameters of cardiac function will be assessed: (1) global left ventricular ejection fraction, (2) regional left ventricular ejection fraction, (3) quantitative regional wall motion analysis based on the centerline method in both the LAO and long axis view (left lateral or LPO). The determination of global and regional ejection fraction is based on changes in count densities during the cardiac cycle whereas quantitative regional wall motion analysis is based on geometric analysis of chord shortening. This part of analysis is identical to those performed for the TIMI Phase I study. The exercise studies will be analyzed for changes in global and regional left ventricular ejection fraction, as well as changes in relative count-based diastolic and systolic left ventricular volume. Rather than using absolute volumes it is elected to employ relative volumes. This should be no disadvantage since serial measurements will be made during the exercise test. This appears to be preferable since standardization and quality control of absolute determinations are too complex and susceptible to error when multiple laboratories are involved.

8.2.6 Interpretation of Exercise Function Test

If the predischarge rest-exercise RVG is positive for ischemia, cardiac catheterization and coronary arteriography should be performed on approximately the tenth day after infarction. Patients who exercise to a level of 120 beats/minute or 400 kpm/minute (whichever should come first), who experience angina pectoris, a 2 mm ST segment depression, a 20 mm Hg fall in systolic blood pressure, a 5 unit fall in left ventricular ejection fraction, or complex ventricular arrhythmias are a high risk group who should have predischarge angiography. If none of these symptoms or signs occur, performance of the predischarge cardiac catheterization is to be discouraged.

If a patient develops any of the above symptoms or signs before reaching the specified workload (i.e., heart rate 120 bpm or 400 kpm/minute) then the study is considered positive; if a patient reaches this workload without developing any of the above symptoms, then the study is considered negative; if a patient is unable to reach a workload of 400 kpm/minute or a heart rate of 120 bpm and is asymptomatic then the study is considered inconclusive.

8.3 TREADMILL EXERCISE TEST

This procedure will be carried out at the one year follow-up visit.

8.3.1 Standard Operating Procedures

Stages of Exercise Test in TIMI

Stage (3 min each)	Speed (miles/hr)	Grade (%)
0	1.7	0
1/2	1.7	5
I	1.7	10
II	2.5	12
III	3.4	14
IV	4.2	16
V	5.0	18
VI	5.5	20
VII	6.0	22

The above table lists the stages of the Bruce Protocol with two three minute warmups at 1.7 mph and 0% grade (Bruce Stage 0) and 1.7 mph and 5% grade (Bruce Stage 1/2). Patients should rest their fingers on hand rails but should be discouraged from gripping rails. The one year exercise test starts at Bruce Stage 1 (1.7 mph at 10% grade) unless the patient has severe cardiac, orthopedic, or neurologic limitations. Under these cir-

cumstances, the test should be started either at Bruce Stage 0 or Bruce Stage 1/2. The stages at which exercise is started and stopped are noted as is the duration of the test in seconds. The one year study is a maximum symptom limited test. Some patients may undergo exercise testing at non-participating institutions which do not use the Bruce Protocol; these data will not be used for TIMI analyses.

If the patient experiences chest pain in the course of the exercise test, the pain should be graded and recorded on study forms according to the following four point scale: Grade I corresponds to initial onset of angina; Grade II corresponds to moderate angina which would commonly cause the patient to stop exercising; Grade III corresponds to moderate to severe angina greater than the patient usually tolerates prior to stopping activity; Grade IV corresponds to the worst chest pain the patient has ever experienced.

Grounds for discontinuing the test include the following: progressive chest pain (Grade II out of IV), classified as definite angina, or atypical chest pain; unsteady gait; hypotension (a 20 mm drop in systolic blood pressure on two successive measurements during exercise); complex ventriculr arrhythmia, including ventricular tachycardia (three or more ventricular extrasystoles in succession, or frequent ventricular couplets or frequent multifocal ventricular premature contractions) rapid supraventricular arrhythmias; and symptoms such as dizziness, dyspnea, lower extremity claudication, exhaustion, and poor motivation). Any new complications that occur within two hours of the exercise treadmill test are recorded although a formal post-test two hour observation is not required.

8.3.2 ECG Monitoring

ECG monitoring during exercise testing should be recorded using a 12 lead electrocardiogram (modified for exercise). The right and left arm electrodes should be placed in the subclavicular fossa as far laterally as possible without precluding high quality exercise tracings. The right and left leg electrodes should be placed above the anterior iliac crest just proximal to the anterior axillary line. The electrocardiogram should be recorded at rest before the test with the patient in a sitting position, in the standing position, 30 seconds prior to each change in exercise workload, at maximal exercise, and one, three and five minutes after the test with the patient in the sitting position. The baseline electrocardiogram is the one recorded at rest in a sitting position. All ECGs should be stored securely in the TIMI Clinical Center performing the study. Plans for central ECG analysis for these studies may still be made.

The maximum degree of ST segment abnormalities seen during exercise and in the recovery phase are classified relative to baseline. A normal resting ST segment is defined as J point depression < 0.05 mV and a horizontal or upsloping ST segment. Horizontal or downsloping ST segment depression ≥ 0.1 mV or a slow upsloping ST segment depressed ≥ 0.2 mV compared to baseline is considered an ischemic electrocardiographic response. When this response is seen during exercise or in the post exercise phase, the maximum depth of ischemic ST segment depression as well as the slope of the ST segment shift should be recorded.

In patients who have an ischemic ST segment response, the maximum depth of ST segment depression 80 msec after the J point should be recorded compared to baseline. For example, a patient may have 0.8 mm horizontal ST segment depression at rest in the sitting position. During exercise, the patient may have 2.8 mm of horizontal ST segment depression. 2.0 mm should be recorded as the maximum depth of ischemic ST segment depression seen during exercise. In many patients with a transmural myocardial infarction, ST segment elevation in Q wave leads is noted. The maximum height of ST segment elevation 80 msec after the J point in Q ($\geq$ 0.03 sec) wave or non-Q wave leads should be recorded in their respective category. The degree of ST segment elevation over baseline is the maximum amount of ST segment elevation that should be recorded.

Isolated premature ventricular beats are defined as less than 10 beats per minutes and absence of ventricular couplets, or ventricular tachycardia. Frequent premature ventricular beats are recorded when the premature ventricular contractions are $\geq$ 10 beats per minute or nonsustained or sustained ventricular tachycardia is noted. The heart rate and blood pressure should be recorded at rest in the sitting position, and in the standing position 30 seconds prior to each change in exercise load, at peak exercise, and in the post exercise sitting position within the first three minutes of the recovery phase. The percent of age predicted heart rate is calculated from the peak exercise heart rate achieved divided by 220 minus the patient's age. This simple prediction for heart rate will serve TIMI analytic needs. If an exercise thallium scan is recorded, the appropriate box should be checked.

8.3.3 Borg Perceived Exertion Scale

The Borg Perceived Exertion Scale is a 20 point grading system with 20 being the most severe level of exertion that the patient has ever performed. This scale can be placed in front of the treadmill and the patient requested to rate the level of exertion at the time the exercise test is stopped.

CHAPTER 9

STUDY END POINTS

9.1 INTRODUCTION

The objectives of TIMI Phase II are to determine the effects of percutaneous transluminal coronary angioplasty (PTCA), when carried out after intravenous rt-PA, on mortality, morbidity and left ventricular (LV) function during the hospitalization period, six weeks after infarction and one year later. The principal study will compare the outcome in patients treated with rt-PA, who receive PTCA only if they demonstrate recurrent ischemia, with that in patients treated with rt-PA plus PTCA (if feasible) 18 to 48 hours after the start of rt-PA infusion.

TIMI Phase II includes two subsidiary studies. TIMI II B will evaluate the effects of immediate intravenous beta-blocker therapy compared to deferred oral beta-blocker therapy. TIMI II A will evaluate the effects of the timing of PTCA as well as of PTCA itself by assigning one portion of PTCA patients to cardiac catheterization for PTCA within two hours of the start of rt-PA infusion and the remaining PTCA patients to cardiac catheterization for PTCA 18 to 48 hours after the start of rt-PA infusion; the third group of patients will be considered for PTCA only if they demonstrate recurrent ischemia.

9.2 PRIMARY END POINTS

The principal end point in the entire study (TIMI II A and II B) is the sum of total mortality and documented definite nonfatal myocardial infarction six weeks after study entry. Study criteria for documented definite nonfatal myocardial infarction are presented in Exhibit 9-1. Total mortality, cardiac-specific mortality and documented nonfatal myocardial infarction will all be assessed for final classification by an independent Mortality and Morbidity Classification Committee.

The principal end point in TIMI II A - PTCA timing study is global left ventricular function, measured by contrast radiography prior to hospital discharge; regional left ventricular function measured by contrast radiography will also be examined.

The principal end point in TIMI II B - assessment of immediate intravenous beta-blocker therapy is global left ventricular function measured by rest radionuclide studies (RVG) on day eight to ten following study entry.

9.3 SECONDARY END POINTS

As follows, various other clinical and physiological results will be of interest in comparing the effects of TIMI Phase II study treatments:

1. Mortality (total and cardiac-specific) at hospital discharge, and at six weeks and one year after entry;

2. Incidence of nonfatal myocardial infarction at hospital discharge, at six weeks and one year after entry;

3. The sum of mortality (both total and cardiac-specific) and confirmed nonfatal myocardial infarction at hospital discharge and one year after entry;

4. Global and regional left ventricular function at rest and during exercise measured by RVG at hospital discharge and at six weeks after entry;

5. Incidence of angina and the need for mechanical revascularization prior to hospital discharge, and at six weeks and one year after entry;

6. Left ventricular functions, global and regional, measured on the 18 to 48-hour pre-PTCA angiogram in patients in TIMI II B who are eligible for beta-blockade, will be compared among those assigned to immediate beta-blocker therapy and those assigned to deferred beta-blocker therapy;

7. Success of PTCA in two PTCA groups in TIMI II A.

The primary end points and the secondary end points will be analyzed for the TIMI Phase II population as a whole and for several defined subgroup comparisons of TIMI Phase II patients:

(a) patients receiving early treatment with rt-PA (within the first two hours of the onset of symptoms) as opposed to those receiving treatment two to four hours from the onset of symptoms;

(b) patients with anterior as opposed to those with inferior/posterior myocardial infarction;

(c) high risk patients, defined as those with one or more of the following risk factors:

(1) history of previous myocardial infarction;

(2) ST segment elevation in anterior ECG leads;

(3) rales extending upwards to cover more than one-third of the lung fields;

(4) hypotension (systolic blood pressure less than 100 mm Hg) and sinus tachycardia (atrial rate greater than 100 beats per minute);

(5) atrial fibrillation or flutter; and

(6) age greater than or equal to 70 years -- as opposed to low risk patients who have none of the high risk characteristics.

(d) TIMI II B patients eligible for the study of immediate intravenous beta-blocker therapy (metoprolol treated versus untreated, across both the rt-PA alone and the rt-PA plus PTCA groups) as opposed to TIMI II B patients ineligible for randomization to beta-blocker therapy; and

(e) all patients in TIMI II A.

Further end points of interest include:

1. Incidence of hemorrhagic complications (major and minor) prior to hospital discharge and their correlation with coagulation parameters;

2. Proportion of patients judged to be eligible for angioplasty;

3. The severity of stenosis of the infarct-related artery before and immediately following PTCA in all groups;

4. Incidence of complications secondary to PTCA prior to hospital discharge and within one year;

5. Incidence of post-PTCA restenosis;

6. Severity of stenosis and perfusion grade of the infarct-related artery at discharge catheterization in TIMI II A patients; and

7. Total mortality and total mortality plus confirmed nonfatal myocardial infarction at three and six months.

TIMI Phase II analyses will also investigate the relationship of clinical events and physiologic measurements (i.e., total and cardiac-specific mortality, global and regional left ventricular function at rest and during exercise, reocclusion, reinfarction, angina, and the need for second PTCA or CABG at hospital discharge, at six weeks and at one year after study entry) to arteriographic findings (including the degree of perfusion, and degree of arterial narrowing as determined at cardiac catheterization both before and after PTCA) in the patients assigned to rt-PA plus 18 to 48-hour PTCA. Similar analyses will be carried out in all other patients in whom cardiac catheterization and coronary arteriography is carried out prior to hospital discharge.

In all patients in TIMI II A and II B in whom early (< 48 hours) angiography is performed a comparison will be made of the outcome in those with univessel and multivessel disease (i.e., more than 70% stenosis in a non-infarct-related coronary artery). Evaluation of clinical outcome (mortality, nonfatal infarction, LV global function, inducible myocardial ischemia and ischemic symptoms) will be made. These assessments will be made on the pre-discharge radiocontrast angiogram (TIMI II A) and on the rest and exercise RVG in patients in TIMI II A and B.

The need for subsequent revascularization in patients who undergo PTCA and who develop restenosis will be compared to the need for late revascularization in patients treated with rt-PA alone.

The incidence of abrupt reclosure or later restenosis of the infarct-related artery will be compared in patients with and without angiographic presence of residual thrombi immediately prior to dilatation.

9.4 RISK ASSESSMENT

In addition, various non-invasive methods to assess risk in patients prior to hospital discharge will be evaluated in a rigorous prospective manner in subgroups of patients. These evaluations will take the form of data bank or ancillary studies in which patients from a particular Clinical Center or subset of Clinical Centers will be involved. The non-invasive procedures which are being considered are (1) modified treadmill exercise testing (ETT) and (2) quantitative 201 thallium myocardial imaging.

EXHIBIT 9-1

TIMI II Mortality and Morbidity Classification Committee

Criteria for Nonfatal Myocardial Infarction (NFMI)

I. Events which occur 18 hours or more after study entry

A. Enzyme Changes

Creatine kinase (CK) is collected routinely over the first ten days (Q4H x 6, Q6H x 4, QD x 8) of TIMI II enrollment, but only on indication (usually pain) thereafter.

1) If CK MB or CK are greater than two times the upper limit of normal, and 25% increase over the previous value. Qualitative CK MB must be positive when available, and CK MB takes precedence over CK.

2) If CK MB or CK are less than two times the upper limt of normal, and 50% increase over the previous value, and must exceed the upper limit of normal by at least 50%. Qualitative CK MB must be positive when available, and CK MB takes precedence over CK.

or

B. ECG

1) Major, new Q-waves in at least two or more leads.

2) New left bundle branch block in the absence of any previous left branch conduction defect.

or

C. Committee Vote

1) Failing independent classification by two MMCC members according to Enzyme or ECG Criteria, a simple majority vote of MMCC members (chairman casts tie breaking votes) at a meeting of the MMCC as a whole.

All classified cases will have a written note declaring the reasons for classification or rejection of classifications as NFMI.

EXHIBIT 9-1 (Continued)

II. Events which occur less than 18 hours after study entry

A. Pain

Greater than 20 minutes of new or markedly worse chest pain.

B. ECG

1) New ST segment depression or elevation $\geq$ 2 mm (0.2 mV) in at least two contiguous leads.

or

2) Elevation of ST segment $\geq$ 2 mm (0.2 mV) above ST segments prior to the onset of pain (last ECG).

C. Enzyme Changes

1) Appropriately timed increase of at least 33% following a 25% decrease (peak to valley) for values greater than two times the upper limit of normal.

or

2) Appropriately timed increase of at least 100% following a 50% decrease for values less than two times the upper limit of normal.

Events which occur less than 18 hours after study entry will be classified as indicated below:

Criteria	Pain	ECG	CK
Classes			
No recurrent event	+	-	-
Recurrent ischemic event	+	+	-
Nonfatal myocardial infarction	+	±	+

CHAPTER 10

FOLLOW-UP PROCEDURES

10.1 INTRODUCTION

Each patient enrolled in TIMI Phase II will be expected to return to a TIMI Clinical Center for a follow-up visit at six weeks and at one year after treatment. In addition, the TIMI Clinical Center staff will contact enrolled patients by telephone at three months and six months after treatment and every six months after their one year visit until the end of the study. Investigators will have to report all nonfatal events which may occur to patients in the intervals between contacts. While ascertainment of such events will in large part be made during the visit, the patient should be asked to notify the study physicians concerning interim hospitalizations and illnesses.

10.2 SCHEDULE OF FOLLOW-UP CONTACTS

At the time of discharge from the hospital, the Hospital Discharge Form will be completed by the physician who requested the treatment allocation. The patient will receive an appointment for a six-week follow-up visit, a letter to his/her general practitioner and/or cardiologist, and a study identification card.

Each patient will be expected to return to the Clinical Center for a follow-up visit at six weeks and at one year after entry. Unscheduled visits are permitted but will not be reported separately. Any noteworthy finding detected at an unscheduled visit will be recorded on the next Follow-up Visit Form.

Though it would be ideal for each patient to come to the Clinical Center exactly six weeks after entry, this may not always be possible. Therefore, a time window for this follow-up visit is defined as six weeks to 12 weeks after entry. The time window for the one year visit will be 12 months to 18 months.

Each scheduled follow-up visit will include an interim medical history, physical examination, resting electrocardiogram and laboratory studies. History will include special attention to side effects with inquiry into cardiovascular symptoms, neurologic status, hemostasis, dermatologic complaints, gastrointestinal complaints, genitourinary function, general state of well-being, and current health practices such as use of medications. Physical examination will be complete except for rectal and/or pelvic examination which will be included only if indicated. In addition, the six-week follow-up visit will include an ECG and evaluation of left ventricular function by means of rest and exercise RVGs. Evaluation of exercise capacity and myocardial ischemia will be made by means of a standardized maximal treadmill exercise test at the one year visit.

Telephone contacts will obtain information regarding any hospitalization or serious illness without hospitalization. Records documenting the hospitalization will be requested.

Any patient who does not complete the follow-up visit within the defined time window will be considered as having missed that visit. A Missed Visit Form should be completed for a missed follow-up visit. The patient remains in the trial. Every effort must be made to reestablish contact at the next opportunity, and to obtain as much information about a missing patient's medical status as possible. For all patients lost to follow-up, special procedures will be followed to use available resources to ascertain the vital status of the patient.

10.3 FOLLOW-UP OF FATAL AND NONFATAL EVENTS

It will be important to the conduct of the study for all fatal and nonfatal events to be detected, documented and validated. Ascertainment of death of study patients will be carried out by Clinical Center staff. A special form will be completed for each death, and every effort must be made to obtain detailed information about the death (i.e., prodromal illness, acute signs and symptoms, circumstances and chronology of the death event, hospital and/or physician summaries, death certificates, autopsy reports including both gross and microscopic findings, etc.). All documents and reports must be sent to the Coordinating Center.

For each reported myocardial infarction event, hemorrhagic event or rehospitalization, special event forms will be required from the investigator in addition to the coding of related items on the Follow-up Visit Form. These forms, together with any supporting documents, are to be sent to the Coordinating Center as soon as possible. For a list of study forms, see Appendix I.

Reports of all deaths, unusual health events, and hospitalizations will be periodically presented to a special committee (Mortality and Morbidity Classification Committee) for assessment. Reports of all nonfatal hemorrhagic events will be presented to a special committee (Hemorrhagic Event Review Committee) for assessment of severity and site. Results of these assessments will be added to the patient's file, both at the Clinical Center and at the Coordinating Center.

The Mortality and Morbidity Classification Committee will devise criteria to classify each case of nonfatal myocardial infarction reported at the clinic. The classification will be based on the amount of evidence which supported the diagnosis of myocardial infarction.

Individual cases of serious adverse effects, possibly related to study treatment, will be immediately and directly reported by the study physician to the Coordinating Center and the Program Office by telephone.

10.4 DEBRIEFING CONTACT

Debriefing contact is used to designate that contact with the patient and/or the patient's personal physician at the end of Phase II to disseminate study results. Patients may be contacted after the debriefing session to determine whether there have been any late sequelae to treatment.

CHAPTER 11

ORGANIZATIONAL STRUCTURE

11.1 INTRODUCTION

The participating investigators and centers in the TIMI Study collaborate through a study organization which is designed to maintain continuity of operations in the study and to facilitate effective communications and cooperation among the various functional units. Exhibit 11-1 summarizes the study administration.

11.2 PARTICIPATING UNITS

11.2.1 Clinical Centers

Twenty-four Clinical Centers with one or more hospitals participate in TIMI Phase II. Most are located at a major university hospital in the United States. Clinical Centers are responsible for screening and recruitment of eligible patients, administration of study medications, performance of percutaneous transluminal coronary angioplasty (PTCA), if appropriate, coordination of patient care and follow-up, and collection of all clinical information and test data required by the TIMI protocol. Some Clinical Centers have recruited other hospital facilities to participate as "satellite" hospitals. These latter facilities will screen and recruit patients for TIMI II B and if the patient is randomly assigned to rt-PA alone will provide patient care for the entire hospital stay. Patients randomized to rt-PA plus 18 to 48-hour PTCA will be transferred to the main TIMI Clinical Center for catheterization and assessment of suitability for PTCA. The list of Clinical Centers and affiliated hospitals is given in Exhibit 11-2.

11.2.2 Coordinating Center

The Coordinating Center (CC) at the Maryland Medical Research Institute (MMRI) in Baltimore, Maryland, has primary responsibility for the study's statistical design, data collection and management, and analysis of TIMI results. The CC staff will develop the operations manuals and pretest all TIMI data forms, conduct study size calculations and design and implement the randomization procedure during Phase II. The CC staff also are responsible for preparing and distributing regular TIMI progress reports and minutes, reports for the Safety and Data Monitoring Committee meetings, monitoring end point results, preparing data bank study analyses, and ensuring the quality and accuracy of data collection. The CC staff will also assist in training of Clinical Center staff.

11.2.3 Radionuclide Core Laboratory

The TIMI Radionuclide Core Laboratory is located at Yale University School of Medicine in New Haven, Connecticut. This central laboratory is responsible for insuring that each Clinical Center and in some cases affiliated satellite hospitals are able to obtain radionuclide studies which are reproducible and

of high quality. In addition, this laboratory is also responsible for receipt, review and analysis of all TIMI radionuclide test data on all enrolled patients from each of the TIMI Clinical Centers and transmission of results to the Coordinating Center in a timely manner. Monitoring of the quality, completeness, and timeliness of TIMI radionuclide test procedures conducted at the Clinical Centers is performed by this laboratory on a regular basis.

11.2.4 Radiographic Core Laboratory

The TIMI Radiographic Core Laboratory is located at the University of Washington in Seattle, Washington. This central laboratory is responsible for insuring that each Clinical Center is able to obtain radiographic studies which are reproducible and of high quality. This laboratory is also responsible for receipt, review and analysis of all TIMI radiographic test data including assessment of PTCA performance and success on all enrolled patients from each of the TIMI Clinical Centers and transmission of results to the Coordinating Center in a timely manner. In addition, this laboratory is responsible for monitoring the quality, completeness, and timeliness of the TIMI radiographic test procedures conducted at the Clinical Centers on a regular basis.

11.2.5 NHLBI Program Office

The NHLBI Program Office in the Cardiac Diseases Branch of the Division of Heart and Vascular Diseases is responsible for the overall direction and administration of TIMI. The Program Office provides general organizational and scientific guidance for the study and monitors the study's progress for the Institute. Statistical guidance is provided by representatives from the NHLBI's Biostatistics Research Branch.

11.2.6 Drug Distribution Center

The Drug Distribution Center (DDC) is responsible for packaging, labeling, and shipping study drugs to the Clinical Centers, and acting along with the NHLBI Program Office as liaison to the pharmaceutical companies. The center assures the quality of the drugs, monitors the drug usage, and recalls and disposes of unused drugs. In addition, the center assists the Coordinating Center in monitoring drug related problems and prepares and ships blood collection tubes to the Clinical Centers. The Drug Distribution Center is located at the Veterans Administration Medical Center in Albuquerque, New Mexico.

11.2.7 Pathology Core Laboratory

The Pathology Core Laboratory for the TIMI trial was established to investigate the pathophysiologic effects of thrombolytic therapy. This laboratory will provide for standardized pathological analysis of the coronary arteries and other portions of the heart. The Pathology Core Laboratory is located at the National Heart, Lung, and Blood Institute, National Institutes of Health.

11.2.8 Coagulation Core Laboratory

A Coagulation Core Laboratory was established to provide central analysis of levels of plasminogen, fibrinogen, fibrin degradation products and tPA levels at specified intervals according to the TIMI protocol for all patients enrolled in the TIMI Phase II. The Coagulation Core Laboratory is located at the University of Vermont in Burlington, Vermont.

11.2.9 ECG Reading Center

The ECG Reading Center was established to provide standardized measurement of electrocardiograms, and to verify that qualifying ECGs meet eligibility criteria. The ECG Reading Center is located at George Washington University in Washington, D.C.

11.2.10 PTCA Quality Control Laboratory

The PTCA Quality Control Laboratory was established at Brown University in Providence, Rhode Island to provide independent review of PTCA films. Problems encountered are brought to the attention of the PTCA Subcommittee. Angioplasty operators applying for certification after Phase II randomization has begun at their Clinical Center must submit complete coronary cine angiograms to the PTCA Quality Control Laboratory for their most recent five successfully treated patients.

11.3 STUDY ADMINISTRATION

11.3.1 Study Chairman

The Study Chairman, appointed by the NHLBI Director, has major responsibility for the scientific direction and administration of TIMI. The Study Chairman:

1. Advises the NHLBI Program Office on data monitoring and other issues of importance to the overall conduct of the study;

2. Develops and maintains, with advice from other study participants, an internal organizational structure that meets the needs of the study and the NHLBI;

3. Is informed on all aspects of study operations and, using the study organization developed, formulates study policy and takes action as necessary to insure the smooth operation of the study;

4. Appoints study participants to appropriate positions and committees as needed;

5. Serves as Chairman of the TIMI Executive Committee, Steering Committee and Operations Committee; and

6. Serves as an ex-officio member of the Safety and Data Monitoring Committee.

The Study Chairman has been appointed to serve for the duration of the study unless other arrangements are made by mutual agreement between the Chairman and the NHLBI Director. In the event that the Study Chairman is unable to serve because of resignation, death, or serious illness, the NHLBI Director will appoint a new Chairman.

11.3.2 Safety and Data Monitoring Committee

The Safety and Data Monitoring Committee is composed of an independent group of experts which includes senior scientists, cardiologists, a biostatistician and an ethicist. The Study Chairman, and the Principal Investigator from the Coordinating Center, and representatives from the NHLBI Program Office also participate as non-voting members. The Safety and Data Monitoring Committee meets at least twice a year. Its primary role is to advise the National Heart, Lung, and Blood Institute on all policy matters relating to the TIMI trial. The Committee has responsibility for protecting the scientific conduct and integrity of the TIMI trial. Its functions include:

1. Review of the TIMI Protocol;

2. Review of any changes in the design or operation of TIMI which are recommended by the Steering Committee;

3. Reviewing the study's performance, progress and findings at regular intervals; and

4. Formulating recommendations for the continuation or termination of the study based on evidence of beneficial or adverse effects of therapy or the enrollment of a sufficient number of patients.

Recommendations made by the Committee must be approved by NHLBI prior to implementation.

11.3.3 Steering Committee

The Steering Committee is composed of the Study Chairman and Principal Investigators from each TIMI Clinical Center, the Core Laboratories, Coordinating Center and NHLBI Program Office. This committee provides the scientific direction for the study and meets periodically to assess progress. The Steering Committee is responsible for developing the final protocol in Phase II and for carrying out the protocol. The Study Chairman will represent the Steering Committee by serving as an ex-officio member of the TIMI Safety and Data Monitoring Committee. Recommendations made by the Steering Committee are subject to approval by NHLBI.

The following six technical subcommittees have been established: PTCA, Concomitant Therapy, Entrance Criteria, Forms, Non-Invasive Testing, and Non-Fatal End Points. These subcommittees were charged with responsibility for developing specific areas of the TIMI protocol.

11.3.4 Executive Committee

The Executive Committee is the operational arm of the Steering Committee and is composed of appointed members representing all components of the TIMI trial. The Executive Committee addresses policy issues as well as operational aspects of the trial and makes recommendations to the Steering Committee.

11.3.5 Operations Committee

The Operations Committee is the operational arm of the Executive Committee and is composed of the Study Chairman, the Director of the Coordinating Center and representatives from the NHLBI Program Office. This committee participates in weekly conference calls.

11.3.6 Mortality and Morbidity Classification Committee

The Mortality and Morbidity Classification Committee (MMCC) is responsible for the development of standardized procedures to classify each TIMI death by cause and each TIMI nonfatal myocardial infarction by amount of evidence for the diagnosis. This committee will be composed of members who are not investigators treating patients at TIMI Clinical Centers. Members are blinded to the identity of the experimental treatment received by study patients. The MMCC is also responsible for developing standard definitions and classification of mechanical revascularization, and other nonfatal cardiac events.

11.3.7 Hemorrhagic Event Review Committee

The Hemorrhagic Event Review Committee (HERC) is responsible for the development of standardized procedures to classify each TIMI hemorrhagic event.

EXHIBIT 11-1

TIMI ADMINISTRATIVE STRUCTURE

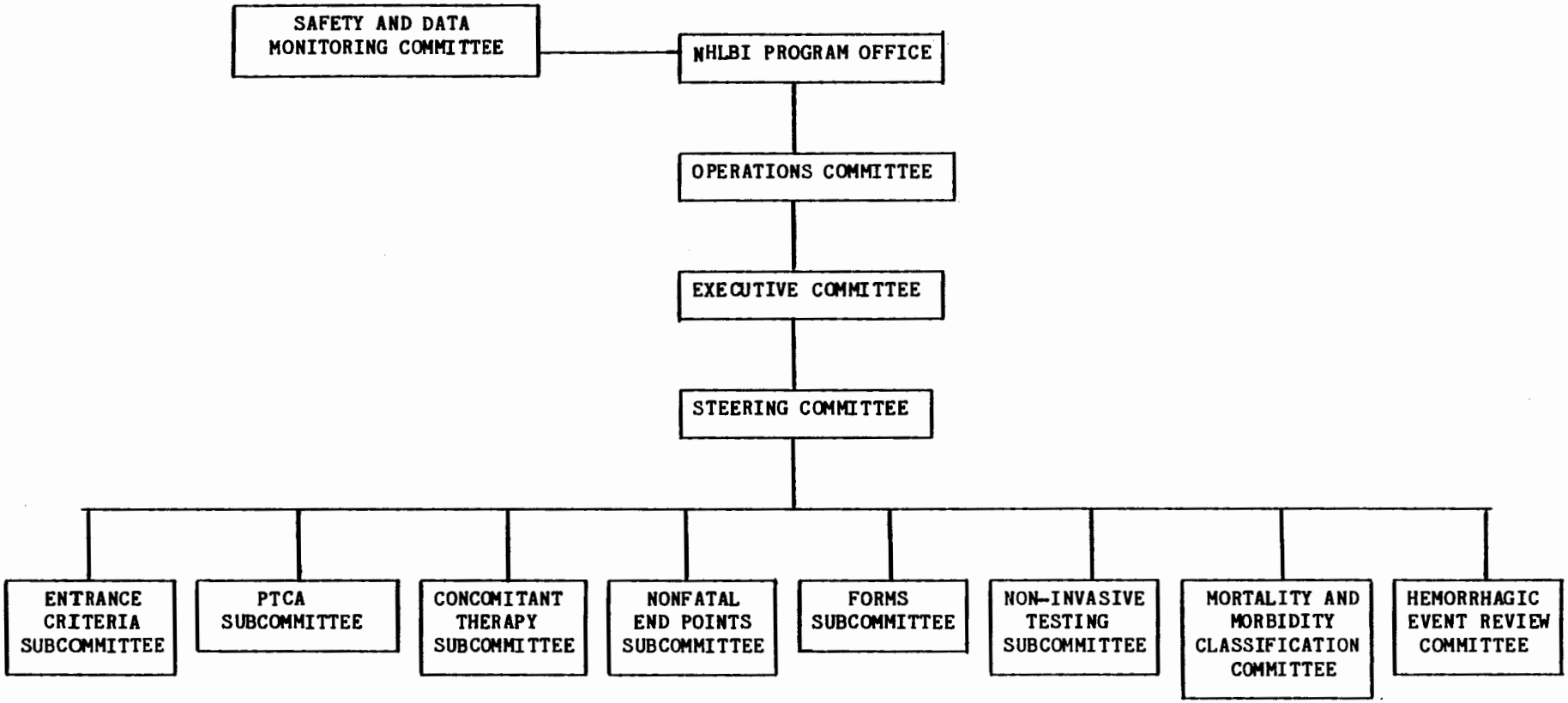


EXHIBIT 11-2

PHASE II TIMI CLINICAL CENTERS

1.	Albert Einstein College of Medicine	New York, New York
	a. Montefiore Hospital	
	b. North Central Bronx Hospital	
	c. Englewood Hospital	
	d. New Rochelle Hospital	
	e. Nyack Hospital	
2.	Baylor College of Medicine	Houston, Texas
	a. Ben Taub General Hospital	
	b. Methodist Hospital	
	c. Houston Veterans Administration Hospital	
3.	Boston University	Boston, Massachusetts
	a. Boston University Hospital	
	b. Boston City Hospital	
	c. Brockton Hospital	
	d. Norwood Hospital	
4.	Brown University	Providence, Rhode Island
	a. Rhode Island Hospital	
5.	Columbia University	New York, New York
	a. Columbia Presbyterian Medical Center	
	b. Harlem Hospital	
6.	Cornell Medical Center	New York, New York
	a. New York Hospital	
7.	George Washington University	Washington, D.C.
	a. George Washington University Hospital	
	b. Mt. Vernon Hospital	
8.	Harvard University	Boston, Massachusetts
	a. Beth Israel Hospital	
	b. Emerson Hospital	
9.	Mayo Foundation	Rochester, Minnesota
	a. St. Mary's Hospital	
	b. Rochester Methodist Hospital	
10.	University of Massachusetts Medical School	Worcester, Massachusetts
	a. University of Massachusetts Medical Hospital	
11.	University of Texas Health Science Center	Dallas, Texas
	a. Parkland Memorial Hospital	
	b. Humana Hospital Medical City Dallas	
12.	Washington University	St. Louis, Missouri
	a. Barnes Hospital	

EXHIBIT 11-2 (Continued)

PHASE II TIMI CLINICAL CENTERS

13.	Yale University	New Haven, Connecticut
	a. Yale New Haven Hospital	
	b. Danbury Hospital	
14.	Baystate Medical Center	Springfield, Massachusetts
15.	Bridgeport Hospital	Bridgeport, Connecticut
16.	Maine Medical Center	Portland, Maine
17.	New York Medical College	Valhalla, New York
	a. Westchester County Medical Center	
	b. Northern Westchester Hospital	
	c. United Hospital	
	d. Phelps Memorial Hospital	
	e. St. Joseph's Medical Center	
18.	New York University	New York, New York
	a. New York University Medical Center	
	b. Bellevue Hospital	
	c. Beekman Downtown Hospital	
19.	North Shore University	Manhasset, New York
	a. North Shore University Hospital	
20.	Northwestern University	Chicago, Illinois
	a. Northwestern University Medical Center	
	b. Evanston Hospital	
	c. Glenbrook Hospital	
21.	St. Louis University	St. Louis, Missouri
	a. St. Louis University Medical Center	
	b. St. John's Mercy Hospital	
	c. St. Joseph Hospital	
22.	University of Alabama at Birmingham	Birmingham, Alabama
	a. University of Alabama Hospital	
	b. Carraway Methodist Medical Center	
	c. VA Hospital	
23.	University of Minnesota	Minneapolis, Minnesota
	a. Hennepin County Medical Center	
	b. Fairview Southdale Hospital	
	c. St. Paul Ramsey Hospital	
	d. Abbott Northwestern Hospital	
24.	William Beaumont Hospital	Royal Oak, Michigan

CHAPTER 12

CONDUCT OF THE TRIAL

12.1 INTRODUCTION

To achieve the objectives of this large-scale multicenter trial, will require the collaboration of many different people (patients, Clinical Center personnel, consultants, etc.). The investigators will have to be trained in all aspects of the protocol, the study data will have to be closely monitored by the Coordinating Center, periodic data reports will have to be reviewed by special committees, and various ongoing quality control procedures will have to be established.

12.2 TRAINING AND CERTIFICATION

Before the start of the study, training sessions will be organized for Clinical Center personnel. The protocol, manual of operations and organizational structure of the study will be clearly explained. The training session will cover procedures for collecting patient data, procedures for completing examination forms and instructions in the mechanics of edit procedures. With the assistance of Core Laboratory personnel, procedures for collecting and processing other study materials will also be reviewed. If new personnel join the study in progress, a special training session could be scheduled at the Coordinating Center or in conjunction with a site visit to the Clinical Center.

Each Clinical Center hospital participating in TIMI Phase II is required to have one or more individuals on the staff certified to perform the tasks of nurse-coordinator, physician performing PTCA, radiographic technician and radionuclide technician. Training and/or experience in addition to completion of specified assignments is required for each individual to become certified.

The Radiographic Core Laboratory will organize a separate training session to provide instruction in radiographic procedures. Final evaluation of each Clinical Center's capability to perform radiographic studies in the manner required for analysis, and certification, will be performed after examination of sample cineangiograms obtained utilizing the specified procedures and submitted from each center. Comparable training and certification session will be provided by the Radionuclide Core Laboratory. The PTCA Subcommittee will review the experience of each PTCA operator and based on the review will designate individuals as certified to perform PTCA in TIMI II A or II B. Provisional certification will be based on review by Radiographic Core Laboratory staff of cine angiograms documenting successful PTCA. Final certification of PTCA operators will be based on review of cine angiograms for consecutive cases assigned to either two-hour or 18 to 48-hour PTCA. This review will be performed by the PTCA Subcommittee.

12.3 DATA EDITING AND MANAGEMENT

The completed and keyed study forms will be edited by computer for several kinds of deficiencies and errors.

1. Unanswered or illegible items.

2. Values of quantitative variables which are outside some preset range.

3. Values of qualitative responses which are not permissible (usually due to data entry errors).

4. Inconsistencies among items within a form.

5. Gross inconsistencies among forms from different visits for specific variables.

6. Patient identification, follow-up visit number, and follow-up visit date errors or inconsistencies.

For each detected error a correction procedure will be initiated. The Clinical Center staff will have to complete correction forms and send them promptly to the Coordinating Center in order to correct the computer data file.

A computer inventory of all forms received at the Coordinating Center for each patient will be developed and maintained. This inventory will make it possible to generate a list of study forms which are past due and to send such lists to the investigators. Another computer file will contain the keyed data from all of the study forms received from the Clinical Centers and Core Laboratories. This file will be structured to allow easy addition of new follow-up forms for each patient and will be designed so that all of the forms for a given patient can be linked together to facilitate analysis.

At the time the Coordinating Center receives a form indicating that a patient has been enrolled into the trial, it will generate an Appointment Schedule listing the expected dates and permissible time windows around these dates for completion of the follow-up visits. These schedules will be sent to the Clinical Centers to aid in scheduling patient follow-up visits.

All fatal events as well as nonfatal cardiovascular events and other morbid events will be reported on special study forms completed by the study investigators and submitted to the Coordinating Center. In addition, at the request of the Principal Investigator of a Clinical Center, the Coordinating Center will attempt to locate patients who have been lost to follow-up to determine their vital status.

The study forms on which the fatal and nonfatal events are recorded will become a part of the computer files. Each reported event will be monitored to make sure that it is validated by the Mortality and Morbidity Classification Committee.

A physician responsible for processing the event reports will be appointed at the Coordinating Center and will receive copies of all forms on which these events are reported as well as any accompanying documentation of the events, such as ECGs, X rays, hospital summaries, autopsy reports, death certificates, etc. When all the required information has been collected for a particular event, the records (with all information on study treatment deleted) will be sent to the Mortality and Morbidity Classification Committee which will either make a final judgment upon it or ask for more information. The evaluation of the Committee will be added to the computer files.

Periodically, selected items of data in the computer file will be listed in a compact but readable form -- one or two pages per patient -- and sent to the appropriate Clinical Center. Staff at that site will be asked to check whether the data recorded in the Coordinating Center's electronic file correspond to the data in the Clinical Center records. In addition, some investigators will find these lists helpful for patient management purposes.

12.4 QUALITY CONTROL PROCEDURES

12.4.1 Monitoring the Clinical Centers

One aspect of quality control will consist of management reports generated by computer about the study forms and their data. Such reports will include:

1. Patient enrollment, by Clinical Center.
2. Number and percentage of forms with detected errors, by Clinical Center.
3. Number of delinquent forms, by Clinical Center.
4. Number of missed examinations, by Clinical Center.
5. Number of delinquent radiographic studies, by Clinical Center.
6. Quality of radiographic and radionuclide studies.
7. Assessment of PTCA performance.
8. Qualifying ECGs which do not meet required ECG eligibility criteria, by Clinical Center.

Other indicators of work progress and adherence to protocol will be summarized periodically.

Site visits to participating Centers to resolve problems may be scheduled at the discretion of the Executive and Steering Committees and/or Safety and Data Monitoring Committee.

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

Only angioplasty operations who are certified to have the expertise meeting the stringent TIMI criteria will be permitted to perform PTCA in study patients. The results of angiography and angioplasty will be reviewed by the Radiography Core Laboratory staff. The PTCA Subcommittee will work with the Radiographic Core Laboratory and PTCA Quality Control 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.

12.4.2 Site Visits

Staff of the Coordinating Center and the NHLBI Program Office will site visit the Centers routinely and when indicated on the basis of the Center's performance. The objectives of the site visits are to make sure training has been effective for TIMI personnel, to make sure equipment is in line with TIMI specifications, to further train TIMI personnel as needed in fine points of data collection procedures and to trouble-shoot time/motion problems in transporting patients. Transport must proceed rapidly enough so candidate identification, informed consent, eligibility ascertainment, randomization and treatment can all be completed within the narrow time window allowed. Demonstrations, drills and walk-through exercises may be appropriate.

Later in the study, return site visits will focus on verfication of procedures and data. Data in the Coordinating Center will be verified against TIMI patient charts; and study personnel will be recertified.

Experience in other cooperative studies suggests that such visits are useful for identifying and solving special problems in patient management and data collection. These visits also allow members of the Clinical Center staff an opportunity to meet other members of the study and discuss study problems with them. Face-to-face contact has a beneficial effect on study personnel morale.

12.4.3 Monitoring the Core Laboratories

Reliable central coding and reporting procedures and appropriate internal and external monitoring procedures for the TIMI Core Laboratories will be developed. Quality control reports on the performance of the Core Laboratories will be prepared periodically for review by the Steering Committee, Safety and Data Monitoring Committee, NHLBI and any other appropriate groups.

12.5 DATA ANALYSIS

During TIMI Phase II, the specific primary and secondary end points as well as other information concerning the effects of thrombolytic therapy will be reviewed by the Safety and Data Monitoring Committee at six-month intervals.

Because interim looks at the data are planned prior to the end of data collection for Phase II, monitoring bounds or other analytic approaches will be established for the primary end point. Monitoring boundaries will set upper and lower limits for treatment differences with respect to the primary end point. These monitoring bounds, when examined in conjunction with other

end points, especially side effects, provide useful guidelines for possible early stopping.

The data reports prepared at the Coordinating Center 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, including analysis for subgroups of patients defined by baseline findings (e.g., high risk vs. low risk; patients treated within two hours of onset of symptoms versus those treated 2-4 hours after onset; patients with and without Q wave abnormalities on the qualifying ECG; patients with and without chest pain at the time of entry), and reports on overall study and individual Clinical Center performance with regard to patient intake and follow-up.

The incidence of the combined end point total mortality and definite nonfatal myocardial infarction, death (all causes), coronary death, sudden coronary death, nonfatal MI, and total cardiac events will be computed and the results for the treatment groups compared using the simple test for two proportions as well as life table analysis. The latter analysis makes maximum use of the available data and accounts for the various times of entry and termination of follow-up. This analysis takes account of the actual length of follow-up for each individual and by plotting the survival curves for each treatment strategy, one can examine the difference in survival among the groups for any length of follow-up.

The treatment groups will be compared with regard to demographic characteristics, clinical history, clinical characteristics, biochemical and hematologic determinations, and ECG findings, for the period before admission to hospital, and at entry (baseline data). Specifically, the following variables will be considered in evaluating comparability of the treatment groups: age, sex, height, and weight; history of smoking, and physical activity; history of diabetes, hyperlipidemia, hypertension, stroke, previous myocardial infarction, intermittent claudication, and other relevant clinical conditions; history of previous treatment, particularly with beta-blockers, diuretics, antiarrhythmics, antihypertensives, oral hypoglycemic agents, and digitalis; presence of azotemia and hyperglycemia; criteria for diagnosis of the qualifying event, including history of the attack, ECG findings, enzyme levels, and number of hours between onset of chest pain and entry into the trial. For the period between admission to hospital and entry, comparison will also be made between the treatment groups with regard to heart rate, blood pressure, and presence or onset of heart failure, shock, conduction defect or arrhythmia, medication used in the coronary care unit, and presence of chest pain at initiation of treatment.

Among these baseline data, special attention will be paid to known or presumed secondary risk factors (i.e., location of infarct, number of previous infarcts, cardiac failure, dysrhythmia, blood pressure, smoking habits) in evaluating treatment group comparability. During the conduct of the study, this list may change as a result of study of risk factors.

The baseline factors listed in the previous paragraph, along with other factors found to be related to patency and mortality and/or found to have somewhat different baseline distributions among the treatment groups, will

be included as concomitant variables in the evaluation of treatment effects with respect to the major end points.

To account for the correlation of various baseline variables with the outcome variable and possible differences among the treatment groups with respect to these variables, the techniques of stratification, multiple linear regression and multiple logistic regression will be employed. The Cox life table regression model will also be used to compute and compare the event curves for the treatment groups after adjustment for various baseline characteristics.

The large data base to be obtained in TIMI Phase II will provide the opportunity to observe the degree of correlation between objective measurements and clinical outcome. For example, the degree of correlation between global and regional left ventricular function by contrast radiography and mortality may be determined and the influence of covariates evaluated.

CHAPTER 13

POLICY MATTERS

13.1 INTRODUCTION

The Steering Committee will have primary responsibility for all end point, data bank, and ancillary studies (defined below), and for all publications and presentations evolving from TIMI Study research.

Principal investigators at all TIMI sites, including the Coordinating Center, and the NHLBI Program Office, have equal status with regard to developing protocols, participating in such studies as are approved by the Steering Committee, and collaborating in the development and publication of research papers based on TIMI material. With the approval of the Principal Investigators, associate investigators at the various sites are also encouraged to participate in this process. TIMI investigators proposing studies which require the collaboration of one or more of the TIMI Central Units (Core Laboratories or Coordinating Center) should contact the appropriate individuals prior to submission of a given proposal. The appropriate staff in the Central Unit should participate in drafting the proposal, indicate willingness to participate, and identify sources of funding to support the level of effort required for the project.

The Coordinating Center should be consulted in the development and analysis of protocols which require review of data accumulated from the different sites and deposited at the Coordinating Center. The biomathematical services of the members of the Coordinating Center will be available to the fullest extent in the design and carrying out of all TIMI research.

13.1.1 Purpose of Procedural Guidelines

The procedures for end point, data bank, and ancillary studies (defined below), and for publication of TIMI research results will be given in detail in the Manual of Operations. They will be based on those used in other cooperative clinical trials. These procedures are intended to protect the interests of all participants in the trial, namely, to assure that study data conform to the requirements of study design, are accurately presented, authorship is appropriately acknowledged, and the text of all publications is well written.

13.2 TYPES OF TIMI RESEARCH

TIMI research and the resulting presentations and publications may be grouped into the following study categories:

1. End point studies
2. Data bank studies
3. Ancillary studies

The distinctions among these types of studies as well as of independent studies will be given in detail in the Manual of Operations. Research other than end point studies may be conducted prior to the end of the TIMI investigation and is encouraged so that TIMI may gain greater visibility in the scientific community and the end point test techniques may be refined in preparation for later final analyses.

13.2.1 End Point Studies

An end point study is a study pertaining to the fundamental goals of the project (namely, the evaluation of the efficacy of thrombolytic therapy and thrombolytic therapy followed by angioplasty in the treatment of acute myocardial infarction) or which involves data, such as treatment assignment, thrombolytic success rates, differences in ventricular function by treatment assignment, or mortality rates, which cannot be released prior to the end of the study. These studies will summarize the study's findings based on the entire study population, and will be written at the conclusion of the project.

13.2.2 Data Bank Studies

A data bank study is a study which uses data, specimens or recordings, routinely collected on patients when they are logged, screened or randomized into TIMI and analyzes these to answer some scientific question. Data used in this research are not directly related to the fundamental goals of the study (i.e., the efficacy of TIMI experimental therapies). In general, such studies are conducted with the idea of producing a scientific paper for publication based on the results.

13.2.3 Ancillary Studies

An ancillary study is a study which uses supplementary data collected on patients who are logged, screened or randomized into TIMI, over and above the data collection required by the TIMI Protocol. Such studies are restricted to consideration of a specific test technique or involve only supplemental data collected on TIMI patients. Ancillary studies must be reviewed and approved by the Executive Committee and ratified by the Steering Committee prior to initiation.

13.3 INDEPENDENT STUDIES

It is understood that each Clinical Center has the right to conduct studies which are independent of the TIMI study in patients with acute myocardial infarction who do not meet criteria for randomization into TIMI. TIMI participants agree not to use thrombolytic therapy outside of TIMI nor to conduct an independent study of the efficacy of a thrombolytic agent or angioplasty under investigation by TIMI in eligible patients with acute myocardial infarction during the period of active recruitment by TIMI.

APPENDIX I

LIST OF DATA COLLECTION FORMS

1. Informed Consent Form: Used to collect each patient's written informed consent to participate in the study. Each Principal Investigator may revise it for local use in his/her clinic. Information may be added but not deleted from the model form.

2. Screening Form: Completed to determine the patient's eligibility.

3. Admission Form: Used to record the status of the eligible patient at the time of admission with regard to medical history, results of medical and physical examination, laboratory findings, etc.

4. Treatment Assignment Form: Completed to document opening the Treatment Allocation Mailer and evaluation of thrombolytic therapy at 24 hours.

5. Patient Information Sheet: Completed and kept at the Clinical Center to aid in locating the patient, if necessary, during the course of the study or afterwards.

6. PTCA Form: Completed to document percutaneous transluminal coronary angioplasty (PTCA).

7. Cardiac Catheterization Forms: Used to record data needed for the quantitative analysis of coronary and left ventricular angiograms and to report results of these procedures. (Quantitative angiographic reading and ventriculogram interpretation transmitted electronically).

8. Radionuclide Ventriculography Forms: Used to record data needed in the quantitative analysis of radionuclide studies and to report results of these procedures.

9. Clinical Data Worksheet: Completed daily and kept at the Clinical Center to document the patient's hospital stay.

10. Hospital Discharge Form: Completed at time of discharge of patient from hospital to record medical history since treatment initiation, including adverse effects of treatment and prescription of other drugs.

11. Follow-up Visit Form: Used to collect patient data at the scheduled follow-up visits with regard to medical history since the last visit and results of physical examinations.

12. Missed Visit Form: Used to document that a follow-up visit will not be completed. May be a subset of the follow-up visit form.

13. Telephone Contact Form: Used to collect patient data at the scheduled telephone contacts with regard to vital status, hospitalization and serious illness.

APPENDIX I (Continued)

LIST OF DATA COLLECTION FORMS

14. Subsequent Hospitalization Form: Completed when the patient is re-hospitalized. Used to record diagnosis, treatment and cause of hospitalization.

15. Death Notification Form: Completed and forwarded to the Coordinating Center as soon as it is learned a patient has died.

16. Cause of Death Form: Used to document cause of death.

17. Event Assessment Forms: Completed by the Mortality and Morbidity Classification Committee for each event reviewed (myocardial infarction, cardiac surgery, death) or by the Hemorrhagic Event Review Committee for hemorrhagic events.

18. ECG Reading Form: Used to record the electrocardiographic analysis of the central ECG readings. (Transmitted by tape.)

19. Laboratory Data Form: Completed to document CK and APTT levels and medication taken from baseline until hospital discharge.

20. Coagulation Core Laboratory Blood Samples Forms: Completed to document all blood samples drawn for submission to the Coagulation Core Laboratory and to record analysis of blood specimens. (Transmitted electronically.)

21. Myocardial Infarction Event Form: Completed to document a coronary thrombosis or myocardial infarction event.

22. Hemorrhagic Event Form: Completed to document a hemorrhagic event.

23. Transfusion Record Form: Completed to document any transfusion of blood products.

24. Cardiac Surgery Form: Completed to document coronary artery by-pass graft surgery (CABG).

25. Exercise Test Form: Completed to record evaluation of exercise capacity and myocardial ischemia by means of standardized maximal ETT.

26. Preliminary Report Forms: Items contained on Preliminary Report Forms are a subset of items from the forms completed at the Clinical Centers.

    A. Treatment Assignment.

    B. Cardiac catheterization and PTCA performed during initial hospitalization.

    C. Hospital Discharge.