CHAPTER 5

ADVERSE EVENTS REPORTING

5.1 INTRODUCTION

Alteplase® (t-PA) is licensed as an investigational new drug (IND) for use in the study Thrombolysis in Myocardial Ischemia (T3). Food and Drug Administration (FDA) regulations in the United States and Health Protectorate Branch (HPB) regulations in Canada, require prompt reporting of adverse reactions occurring in patients treated with investigational new drugs. A description of the reportable events, required documentation, procedures and materials for report submission, and report acknowledgement follow.

5.2 REPORTABLE EVENTS

Bleeding is the most frequent adverse effect of t-PA identified in the medical literature. Arterial thromboembolism and other serious treatment sequelae have been reported anecdotally but infrequently. Thrombolysis in Myocardial Ischemia investigators will be required to report each cerebrovascular accident (stroke, whether hemorrhagic or non-hemorrhagic), major bleeding during initial hospitalization (requiring transfusion and prolonging hospitalization) resulting from study drug treatment, all deaths within 70 days of study entry, and unexpected or severe adverse reaction to study drug treatment. Unexpected adverse reactions to study drug treatment would include but are not limited to allergic reactions, hypotension, arrhythmias, etc.

5.3 DOCUMENTATION

All reportable adverse experiences must be documented in the patient's hospital chart and on Thrombolysis in Myocardial Ischemia forms. Included at the end of this chapter is a copy of the FDA Form 1639 (7/86). This is the form used for reporting adverse reactions occurring with licensed pharmaceuticals (see Exhibit 5-1).

Adverse reaction reports should be submitted whenever an adverse drug effect is suspected. In all instances the study investigator should be prepared to provide additional information if necessary. A detailed narrative description should accompany FDA Form 1639, the adverse reaction report. This narrative description should include all relevant bedside observations as well as laboratory information. The Thrombolysis in Myocardial Ischemia investigator should include his/her assessment of the probability that the adverse reaction was related to: 1. the study treatment, 2. the patient's underlying disease, and 3. other circumstances affecting the patient.

5.4 ADVERSE REACTION REPORT SUBMISSION FOR ALL CLINICAL CENTERS

There are strict regulations concerning the prompt reporting of suspected adverse reactions. T3 Data Coordinating Center staff should be notified by telephone within one working day of the occurrence of any severe, alarming or life-threatening adverse reactions such as intracranial hemorrhage or hemorrhagic death. FDA Form 1639 (7/86) and the detailed narrative should be completed in a timely fashion (within three working days of any occurrence) and sent by overnight delivery to the Thrombolysis in Myocardial Ischemia Data Coordinating Center. The Canadian Health Protectorate Branch (HPB) has agreed to accept FDA Form 1639 to report adverse events and all deaths within 70 days of study entry for all Canadian patients participating in the Thrombolysis in Myocardial Ischemia (T3) Study.

Originals of adverse reaction reports should be sent to the Thrombolysis in Myocardial Ischemia Data Coordinating Center. At the same time a copy should be sent to the IND holder, Dr. Eugene Braunwald, in the Study Chairman's Office. If further important information is known to be in preparation (e.g., a surgical report), a preliminary report should still be sent within three working days. A follow-up report may be submitted whenever relevant information is available

(e.g., surgical reports, pathology reports, return visit examination or laboratory data, etc.).

The Data Coordinating Center staff will submit reports of deaths and adverse events to the FDA. The Data Coordinating Center staff will notify Dr. Eugene Braunwald, holder of the IND, each time material is sent to the FDA.

5.5 ADVERSE REACTION REPORT SUBMISSION FOR CANADIAN CENTERS

Canadian Clinical Center staff should submit the FDA Form 1639 along with other required information as outlined above for each death or adverse reaction to the T3 Data Coordinating Center. The Data Coordinating Center staff will submit reports from Canadian centers to both the FDA and the HPB. The Data Coordinating Center will notify Dr. Pierre Théroux, holder of the Canadian IND, each time material is sent to the HPB.

5.6 ACKNOWLEDGEMENT AND SUBMISSION OF ADVERSE REACTION REPORTS TO THE REGULATORY AGENCIES

Each shipment of adverse reaction reports sent by the Data Coordinating Center staff to the FDA must be identified by a serial number. The Data Coordinating Center staff will obtain the next sequential serial number from the Study Chairman's office at the time of shipment to the FDA. Data Coordinating Center staff will attach a completed FDA Investigational New Drug (IND) FDA Form 1571 with this serial number and treatment assignment information to the adverse reaction report and forward three sets of this information to the Food and Drug Administration by overnight carrier. A similar system is in place for submission of materials to the Canadian Health Protectorate Branch. Data Coordinating Center staff will send to the IND holders (Drs. Braunwald and Dr. Théroux), documents confirming the submission of the adverse reaction reports to the appropriate regulatory agency. Summaries of the adverse reaction reports will be prepared for the Safety and Data Monitoring Board as well as for the Food and Drug

Administration and the Health Protectorate Bureau at the regular required intervals.

T3 MANUAL OF OPERATIONS

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