Study Title: EMS Telehealth to Speed STEMI Reperfusion (THOR)

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Sponsor or funding source: Genentech

Background, Rationale and Context

STEMI is the most severe type of heart attack and carries a 30-day mortality of nearly 8%.[1] Reperfusion therapy is the mainstay of treatment for STEMI, either by percutaneous coronary intervention (PCI) or fibrinolytics.[2] Delays in reperfusion are associated with negative health outcomes. Specifically, each 30-minute delay in reperfusion corresponds to a 7.5% decrease in 1-year survival.[3] The current body of literature clearly shows that rural EMS agencies often have longer transport times, which makes the 90-minute first medical contact (FMC) to PCI time goal difficult to achieve.[4] Approximately 16% of Americans live more than an hour from a PCI-capable facility, reinforcing the need for timely therapies in rural prehospital settings to decrease heart muscle damage (disability) and mortality.[5-7] Recently, our team conducted an analysis of a large national EMS database, which showed that FMC to PCI times were longer for patients treated by rural EMS agencies even after these times were adjusted for distance to destination hospital.[8]In addition, our preliminary data for Cherokee Tribal EMS, who serves the Eastern Band of Cherokee Indians on the Qualla Boundary and its surrounding communities, show that **none of their patients who called 9-1-1 for a STEMI received reperfusion within the AHA time goal**. The American College of Cardiology and AHA support prehospital fibrinolytics when timely PCI cannot be performed.[9] Preliminary data from our HRSA project demonstrates the feasibility of using telehealth to guide care for a patient calling 9-1-1 for acute chest pain and suggests successful expansion to patients with acute STEMI. In Europe, telemedicine programs, which connect EMS providers with expert physicians to assist in EKG interpretation, have improved quality of care and decreased healthcare costs.[10] In addition, these European programs have demonstrated that telehealth can improve STEMI reperfusion times in rural settings.[11] However, STEMI telehealth programs have yet to be implemented and tested in the United States.

Current Therapies and Unmet Medical Need Related to STEMI Care

Rural Americans are much less likely than their urban counterparts to receive timely reperfusion. For example, since January 1, 2020 there were 37 patients with a STEMI cared for by Cherokee Tribal EMS (CTEMS), of which none (0% 0/37) received reperfusion within the American Heart Association recommended time goal. These delays in care are associated with excess mortality and high rates of

long-term morbidity from congestive heart failure and recurrent heart attacks. Eliminating this rural disparity is a top public health priority both nationally and locally. STEMI guidelines from the American College of Cardiology and American Heart Association (AHA) recommend reperfusion within 90 minutes of a patient's first-medical-contact (FMC) with emergency medical services (EMS). In most cases, reperfusion is accomplished with percutaneous coronary intervention (PCI; formerly known as angioplasty with stent) at tertiary care hospitals that offer this advanced capability. However, rural patients often live great distances from PCI centers and therefore have less than a $1/8^{th}$ odds of timely access to PCI compared to their urban counterparts. It has been estimated that at least 16% of Americans live in rural areas over an hour drive away from a PCI-center, which makes achieving PCI within 90-minutes very difficult. For those expected to have delayed PCI, guidelines recommend administration of fibrinolytics ("clot busting medication"). However, despite these recommendations and evidence suggesting fibrinolytic administration can reduce reperfusion times, few rural EMS agencies currently administer fibrinolytics. For example, over the past four years, Cherokee Tribal EMS has never given fibrinolytics.

The major barrier to fibrinolytic use in rural EMS systems is a lack of robust medical control to ensure the safe use of this medical reperfusion treatment. Due to bleeding risk, most community emergency physicians are hesitant to order fibrinolytics without being able to evaluate the patient. Although telehealth programs are gaining popularity across the United States and successfully connecting physicians with EMS systems, including one in Wilkes County, no EMS telehealth STEMI-specific programs have been initiated in rural America to our knowledge. To overcome the main barrier to fibrinolytic use and eliminate rural disparities in STEMI care, implementation of a sustainable and scalable EMS telehealth STEMI program is needed.

Our team at the Wake Forest University School of Medicine (WFUSM), led by Drs. Mahler and Stopyra, have experience implementing a collaborative cardiovascular rural EMS telehealth project to improve rural patient access to expert cardiovascular care with Health Resources and Services Administration (HRSA) funding. This telehealth service aims to improve the care of patients who call 9-1-1 for chest pain or shortness of breath, by assisting with early risk stratification to appropriately align patient risk and resource use. Thus, we have successfully established a telehealth workflow between a rural EMS service and a team of Wake Forest physicians. At the request of Cherokee Tribal EMS we now seek to expand our existing telehealth program to this service to improve STEMI care by facilitating timely reperfusion either through PCI or thrombolysis. Patients will be considered for thrombolytics if the patient meets clinical inclusion to receive the drug, the transport time is greater than 60 minutes, and the patient is transported by CTEMS via ambulance and not by helicopter transport. (See Screening Tool, Appendix 3) This proposal, which is supported by Duke Endowment and seeks drug from Genentech, is a clinical implementation and will become the local standard of care. We aim to collect data to evaluate the impact of implementation of this EMS Telehealth STEMI program on health outcomes.

Tenecteplase (TNKase→) is a modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin. In vitro studies demonstrated that in the presence of fibrin, tenecteplase conversion of plasminogen to plasmin is increased relative to its conversion in the absence of fibrin. This fibrin specificity decreases systemic activation of

plasminogen and the resulting degradation of circulating fibrinogen compared with a molecule lacking this property, which could potentially decrease the incidence of bleeding.

Refer to the Tenecteplase Investigator's Brochure for details on nonclinical and clinical studies.

Approved Indication

In the United States (US), TNKase→ (tenecteplase) is indicated to reduce the risk of death associated with acute ST elevation myocardial infarction (STEMI). In Canada, TNKase→ (tenecteplase) is indicated to reduce the mortality associated with acute myocardial infarction (AMI). Outside US and Canada, Metalyse→ (tenecteplase) is indicated in more than 90 countries for the thrombolytic treatment of AMI.

OVERVIEW OF CLINICAL DEVELOPMENT

Tenecteplase has been previously developed in other indications and has been approved for the treatment of AMI.

Completed and ongoing clinical studies of tenecteplase are summarized in the Tenecteplase Investigator's Brochure.

Acute Myocardial Infarction Clinical Development

Tenecteplase is indicated for use in the reduction of mortality associated with AMI and has been approved since 2000. Completed and ongoing clinical studies of tenecteplase are summarized in the Tenecteplase Investigator's Brochure.

Objectives

Objective 1: The primary aim is to assess the impact of implementation of an EMS STEMI telehealth program on patient reperfusion times.

We seek to improve consistent achievement of the reperfusion time goals from 0% to over 75% among STEMI patients in the Qualla Boundary. In Y1 we will begin measuring the project's impact on time from FMC to reperfusion. This will be measured using electronic health records from CTEMS and WFUSM and compared to the AHA time goal of reperfusion within 90 minutes. These times are routinely and reliably documented in the health records, and we have experience abstracting them in prior clinical trials. The baseline proportion of STEMI patients meeting the AHA reperfusion time goal in Qualla Boundary is 0%. In Y2 and Y3 we anticipate achieving the AHA time goal for reperfusion in at least 75% of STEMI encounters.

Objective 2: Assess program uptake/adoption by Cherokee Tribal EMS paramedics.

Our goal is to establish a successful telehealth connection in 90% of CTEMS STEMI calls. Telehealth communication will be conducted using Pulsara, a HIPAA compliant platform that can connect the EMS agency to a trained Physician 24/7/365 through a video, voice call, or chat. The EMS agency will be trained on the workflow after identification of patients and when to notify a physician for a further

patient evaluation and medication administration support. We will review electronic health records from CTEMS and WFUSM for STEMI calls and determine if a telehealth connection was made.

Methods and Measures

Design

We propose a pre-post evaluation of a planned clinical implementation of an EMS STEMI telehealth program. To Improve the care for STEMI patients, a tele-health program will be implemented to provide an additional resource for Paramedics. The administration of Fibrinolytics is in the EMS formulary and considered standard of care. We will collect data from patients to assess the impact of the program and perform quality assurance.

Setting

During this initial phase of this telehealth program implementation, participation will be limited to patients in Cherokee, NC who receive 9-1-1 care from Cherokee Tribal EMS, in the future this may be scaled to additional counties.

Subjects selection criteria

Project participants will receive standard/usual care and will be identified for participation in electronic quality surveillance retrospectively. For patients identified for participation in this project/quality surveillance, minimal risk is expected from participation beyond that encountered in daily clinical practice, as these participants will receive standard care.

- **Inclusion Criteria**
  All patients calling 9-1-1 in Qualla Boundary with possible STEMI as determined by the on scene paramedics will be included in the data.
- **Exclusion Criteria**
  As this is a Quality Surveillance study, subjects will not be excluded.
- **Sample Size**
  Within the Qualla Boundary we estimate 20-25 patients with EMS calls for possible STEMI will be accrued each year. Our estimated sample size that is treated with TNK is 35 total patients.

Interventions and Interactions

For quality assurance data collection, participants will be identified retrospectively and data will be collected electronically using the EHR (EMS records, and WFBH medical records).
A telehealth program will be implemented to support EMS in their care of patients with STEMIs including use of fibrinolytics if indicated. Fibrinolytics are in the North Carolina Office of EMS (NCOEMS) formulary and standard of care at Wilkes EMS.

Outcome Measure(s)

The primary outcome, FMC to reperfusion, will be measured using electronic health records from CTEMS and WFUSM. Patient reperfusion times will also be compared to the AHA time goal. Reperfusion times are routinely and reliably documented in both the EMS and hospital electronic health record. Our data team has ample experience collecting these measures in prior clinical trials.

For each STEMI patient in Qualla Boundary, we will obtain their FMC to reperfusion time and their sub-component times (e.g., FMC to EKG time, EKG to activation time, activation to reperfusion [by fibrinolytic or PCI] time) and these will be recorded in a study database. Data will be aggregated from patients before (baseline) and after EMS telehealth STEMI program implementation. FMC to reperfusion time will be reported as a mean with standard deviation and as a median with interquartile range.

- Qualla Boundary has a population greater than 5,000 with a local non-PCI hospital within its locality that serves locals and surrounding communities. Closest PCI centers utilized by CCTEMS are greater than 50 miles and 70 minutes away depending on dispatch location.
- The expected end of the study is defined as the completion of the project, year of 2025. In addition, the Investigator may decide to terminate the study at any time.
- The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 23 months.

Analytical Plan

Results will be analyzed initially using descriptive statistics. We anticipate time data to be non-normally distributed, therefore reperfusion times pre- and post-implementation will be compared using Wilcoxon Rank Sum tests. In addition, a linear regression model will be used to quantify the association between telehealth program implementation and FMC to reperfusion time while adjusting for the patient's demographics (sex, race, age, and ethnicity) and their distance from the tertiary care center. The proportion of patients meeting the AHA time goal will be reported in percentages with associated 95% confidence intervals before and after implementation. These proportions will be compared using a Chi-squared test. In addition, logistic regression models will assess association between telehealth program implementation and meeting AHA time goals while adjusting for potential confounders (as above).

Human Subjects Protection

Informed Consent

Written informed consent will not be obtained. This is a quality surveillance study and the risk of harm or discomfort that may occur as a result of taking part in this research study is not expected to be more than in daily life or from routine physical or psychological examinations or tests. The rights and welfare of study will be protected through the use of measures to maintain the confidentiality of study information. Study results will be presented or published in lieu of providing individual subjects additional information regarding the study. Patients will receive standard care (which following implementation in 2024 will include an EMS STEMI telehealth program). Data will be collected from paramedic records and the WFBH EMR. However, we are interested in publishing the findings of this implementation project. Therefore, this project meets the definition of human subjects' research.

Request of a waiver of consent:

1) *The research involves no more than minimal risk to participants.* The risk of harm or discomfort that may occur as a result of taking part in this research is not expected to be more than in daily life or from routine physical or psychological examinations or tests. Patients identified for participation in this study/quality surveillance will receive standard care. Administration of fibrinolytics is within the Scope of Practice and Protocols of Cherokee Tribal EMS. Therefore, the primary risk of participation is a breach in privacy and confidentiality.

2) *The waiver of informed consent will not adversely affect the rights and welfare of the participants*. The rights and welfare of participants will be protected through the use of measures to maintain the confidentiality of project information.

3) *The research could not practical ly be carried out without the waiver of informed consent.* To determine the effect of the telehealth program it must be utilized in a "real world" prehospital chest pain patient population. Performing informed consent would threaten the validity of this evaluation by introducing a significant selection bias. Furthermore, having paramedics obtain consent in the field is not practical or safe as this would prolong transport time and delay patient care, potentially leading to a worsening of clinical outcomes. In addition, ambulance transport for patients with acute chest pain is anxiety provoking. These patients are usually very concerned about having a heart attack and thus may not be in the appropriate frame of mind to ethically participate in informed consent during emergency transport.

4) *Participants will give verbal consent for both the conversation with the Physician and the use of the platform Pulsara.* Verbal consent for the use of the Pulsara platform will be obtained by the EMS provider. Once the physician is connected there will be a second verbal consent obtained for the conversation between the physician, EMS provider, and participant.

5) *Whenever appropriate, the subjects will be provided with additional information after participation.* Project results will be presented or published (if possible) in lieu of providing individual subjects additional information regarding the project.

<u>Confidentiality and Privacy</u>

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. Access to individually identifiable private information will be limited to those people required to access this information in order to conduct this project. This includes project team members, IRB, adjudication committee, and data monitors.

The project database will contain a limited amount of individually identifiable private information in the form of whole date elements and medical record numbers. Each participant

will be assigned a unique sequential project identifier that will be linked to the participant's research record and source documents through a log housed locally. Access to the entire project database will be limited to project team members at WFBMC who are involved in the trial management activities, including project team members, the institutional review board (IRB), adjudication committee, and data monitors.

The full electronic database will contain the participant's unique project identifier, full date elements, and medical record numbers, but will otherwise be clean of identifiers. A key will link the project identifier to participants' personal identifiers. This key will be housed in the project binder or electronically in a secure project folder behind the medical center firewall. Access to data containing personal identifiers will be restricted to the project team members, IRB, adjudication committee, and data monitors. Data entry will be performed by trained research staff with valid confidentiality agreements.

Our project team members have experience implementing an electronic process using a secure web-based data entry system for data collection and participant tracking. For this proposal, we will leverage forms and processes already in existence, along with our existing web infrastructure, REDCap.

The web-based system allows research personnel to interact with data using web forms. The website will be designed with input from the research staff so that the workflow follows the protocol and is in line with how the quality surveillance will be conducted. Website activity will be monitored and audited for security purposes. Users may view detailed tracking and management information for each participant and/or by assessment time point. Once logged in, research staff may run reports, enter data into forms, and review and edit data. As data are entered, validations rules are applied before data are saved. Inconsistencies are noted for staff to resolve. Research staff can resolve many queries immediately, comparing the screen to the source, often cleaning the entire database record on the spot. For queries not immediately resolvable, warnings are displayed whenever the data entry screen is recalled.
All access to the website will be logged and stored for auditing purposes.

Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Safety

The safety plan for patients in this study is based on clinical experience with tenecteplase in completed and ongoing studies. The anticipated important safety risks for tenecteplase are outlined below. Please refer to the Tenecteplase Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events are provided below.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of tenecteplase will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Risks Associated with Tenecteplase
Standard management of myocardial infarction should be implemented concomitantly with tenecteplase treatment.

Arterial and venous punctures should be minimized. Noncompressible arterial puncture must be avoided, and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the noncompressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately and treated appropriately. Heparin effects can be reversed by protamine.

Bleeding
The most common complication encountered during tenecteplase therapy is bleeding. This may be either superficial from punctures or damaged blood vessels or internal bleeding at any site or body cavity. Bleeding may result in life-threatening situations, permanent disability, or death.

- The incidence of intracranial hemorrhage, especially symptomatic intracranial hemorrhage (sICH), in patients with AIS is higher in alteplase-treated patients than placebo-treated patients in published studies (for detailed information, see the alteplase United States Package Insert [USPI])

The type of bleeding associated with thrombolytic therapy can be divided into two broad categories:

- Internal bleeding, involving intracranial and retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts
- Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures) or sites of recent surgical intervention

Management of Bleeding
Patients will be excluded for the presence of conditions related to risks of bleeding.

Should an arterial puncture be necessary during the first few hours following tenecteplase therapy, use an upper extremity vessel that is accessible to manual compression is preferable. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Each patient being considered for therapy with tenecteplase should be carefully evaluated and anticipated benefits weighed against potential risks associated with therapy.

Guidelines for management of patients who develop bleeding are provided in Table 1.

In addition, any intracranial hemorrhage events (symptomatic and/or asymptomatic), if not already reported as an SAE by the investigator, are considered non-serious adverse events of special interest for this study and should be reported and submitted to the Sponsor.

Arrhythmias
Coronary thrombolysis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia, etc.) are not different from those often seen in the ordinary course of AMI and may be managed with standard antiarrhythmic measures. It is recommended that anti-arrhythmic therapy for bradycardia and ventricular irritability be available when tenecteplase is administered.

Thromboembolism
The use of thrombolytics can increase the risk of thromboembolic events in patients with high likelihood of left heart thrombus, such as patients with mitral stenosis or atrial fibrillation.

Cholesterol Embolization
Cholesterol embolism has been reported rarely in patients treated with all types of thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures (e.g., cardiac catheterization, angiography, vascular surgery) and/or anticoagulant therapy. Clinical features of cholesterol embolism may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, retinal artery occlusion, bowel infarction, and rhabdomyolysis.

Use with Percutaneous Coronary Intervention
In patients with ST segment elevation myocardial infarction, physicians should choose either thrombolysis or percutaneous coronary intervention (PCI) as the primary treatment strategy for reperfusion. Rescue PCI if medically appropriate or subsequent elective PCI may be performed after administration of thrombolytic therapies; however, the optimal use of adjunctive antithrombotic and antiplatelet therapies in this setting is unknown.

Precautions

Standard management of acute ischemic stroke should be implemented concomitantly with tenecteplase treatment. Arterial and venous punctures should be minimized. Noncompressible arterial puncture must be avoided and internal jugular and subclavian venous punctures should be avoided to minimize bleeding from the noncompressible sites. In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately. Heparin effects can be reversed by protamine.

Re-administration

Readministration of plasminogen activators, including tenecteplase, to patients who have received prior plasminogen activator therapy has not been systematically studied. Three of 487 patients tested for antibody formation to tenecteplase had a positive antibody titer at 30 days. The data reflect the percentage of patients whose test results were considered positive for antibodies to tenecteplase in a radioimmunoprecipitation assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tenecteplase with the incidence of antibodies to other products may be misleading. Although sustained antibody formation in patients receiving one dose of tenecteplase has not been documented, readministration should be undertaken with caution.

Hypersensitivity

Hypersensitivity, including urticarial/anaphylactic reactions, have rarely (< 1%) been reported after administration of tenecteplase (e.g., anaphylaxis, angioedema, laryngeal edema, rash, and urticaria). Monitor patients treated with tenecteplase during and for several hours after infusion. If symptoms of hypersensitivity occur, appropriate therapy should be initiated.

Drug Interactions

Formal interaction studies of tenecteplase with other drugs have not been performed. Patients studied in clinical trials of tenecteplase were routinely treated with heparin and aspirin. Anticoagulants (such as direct oral anticoagulants, heparin and vitamin K antagonists) and drugs that alter platelet function (such as acetylsalicylic acid, dipyridamole, and GP IIb/IIIa inhibitors) may increase the risk of bleeding if administered prior to, during, or after tenecteplase therapy.

Drug/Laboratory Test Interactions

During tenecteplase therapy, results of coagulation tests and/or measures of fibrinolytic activity may be unreliable unless specific precautions are taken to prevent in vitro artifacts. Tenecteplase is an enzyme that, when present in blood in pharmacologic concentrations, remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis.

Management of Patients Who Experience Adverse Events

Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 1.

Table 1 Guidelines for Management of Patients Who Experience Bleeding

Event	Action to Be Taken
Bleeding	● In the event of serious bleeding, heparin and antiplatelet agents should be discontinued immediately and treated appropriately. Heparin effects can be reversed by protamine. ● Intramuscular injections and nonessential handling of the patient should be avoided for the first few hours following treatment with tenecteplase. ● Venipunctures should be performed and monitored carefully. ● Should an arterial puncture be necessary during the first few hours following tenecteplase therapy, it is preferable to use an upper extremity vessel that is accessible to manual compression. Pressure should be applied for at least 30 minutes, a pressure dressing applied, and the puncture site checked frequently for evidence of bleeding.

Refer to Sections 5.2−5.4 for details on safety reporting (e.g., adverse events) for this study.

SAFETY PARAMETERS AND DEFINITIONS

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death and any study-specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocolimposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with STEMI Care that were not present prior to the AE reporting period

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death)
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.)
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate. Expected adverse events in this project are limited to a potential loss of confidentiality. If a breach in confidentiality occurs, the event will be promptly reported to the IRB and other applicable regulatory agencies. The medical record will not be reviewed with the intent of detecting adverse events. In the event that an adverse event is identified during the chart review, the event will be recorded in the project records and IRB, sponsor, and other government agency event reporting criteria and guidelines will be followed.

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior tenecteplase exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable, including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech Patient Safety during the followup period.

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the tenecteplase (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the tenecteplase, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the tenecteplase or with similar treatments; and/or the AE abates or resolves upon discontinuation of the tenecteplase or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the tenecteplase (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to tenecteplase administration (e.g., cancer diagnosed 2 days after first dose of teneceteplase).

Expected adverse events are those adverse events that are listed or characterized in the package insert (PI) or current Investigator's Brochure (IB).

Unexpected adverse events are those not listed in the PI or current IB or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the PI or IB. For example, under this definition, hepatic necrosis would be unexpected if the PI or IB only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

ELICITING ADVERSE EVENT INFORMATION

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death.”

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 2Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE Grade Severity

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within90 days, a report should be completed and expeditiously submitted to Genentech, Inc. Pregnancies will be followed-up

until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
    - Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Other Special Situation Reports

The following other Special Situations Reports (referred hereinafter to as "Special Situation Reports) should be collected even in the absence of an Adverse Event and transmitted to Genentech:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors), off-label use, occupational health, lack of efficacy, unexpected beneficial effects and drug interaction

- Data related to a suspected transmission of an infectious agent via a studied product
- Cases of potential medicine-induced liver injury, as defined by Hy's Law
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population''

Product Complaints

A product complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

Exchange of Single Case Report with Genentech

Dr. Simon Mahler will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs) (related and not related to the product), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, Non-Serious AESIs, Product Complaints (with or without an AE) where the patient has been exposed to the Product

It is understood and agreed that **Dr. Simon Mahler** will perform adequate due diligence with regard to obtaining follow-up information on these events, if they are incomplete.

In addition, reasonable attempts must be made to obtain and submit the age or age group of the patient in order to be able to identify potential safety signals specific to a particular population.

The **Dr. Simon Mahler** agrees to allow requests for follow-up information from Genentech, for instance, in order to fulfill regulatory obligations, or where the requested information is not already routinely covered by standard follow-up activities (e.g. clarification of data discrepancies, or to request typical confirmatory laboratory data or batch numbers for biologics and other advanced therapies). Genentech will not contact the reporter directly for such data, but will route all such requests for follow-up to the provided **Dr. Simon Mahler** contact. It is understood and agreed that **Dr. Simon Mahler** will be responsible for the evaluation of all the case safety reports originating from the study.

Transmission of these reports (initial and follow-up) will be either electronically via email or by fax to the following email address/fax number:

Fax: 650-238-6067

Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be reported via:

PC Hotline Number: (800) 334-0290 (M-F: 5 am to 5 pm PST)

The MedWatch form should be sent to the Genentech contact specified above to report applicable events.

Reporting Timeline for Applicable Events

Transmission of the applicable event reports (initial and follow-up) will be sent within the timelines specified below:

Type of Report	**Timelines**
Serious Adverse Events (related and not related to the Product)	30 calendar days from awareness date
Special Situation Reports (With or without AE and pregnancy)	
Product Complaints (With or without AE)	
AESI	

Dr. Simon Mahler will send to will forward quarterly listings of non-serious AEs originating from the Study to Genentech.

Case Transmission Verification (CTV) of Single Case Reports

The Parties will verify that all Single Case Reports have been adequately received by Genentech/Roche, via **Dr. Simon Mahler** emailing Genentech/Roche a quarterly Line Listing that includes all fields detailed in Appendix 2: Content Required in the CTV Line Listing , documenting Single Case Report(s) sent by **Dr. Simon Mahler** to Genentech/Roche in the preceding quarter. The quarterly Line Listing will be exchanged within seven (7) Calendar Days of the end of the quarter. Following CTV, any Single Case Report which has not been received by Genentech/Roche must be forwarded by **Dr. Simon Mahler** to Genentech/Roche within five (5) Calendar Days from the request by Genentech/Roche.

At the end of the study a final cumulative case transmission verification report consisting of all the single case reports for the study will be sent to Genentech.

Quarterly line listings and cumulative/final CTV should be sent to ctvistsa@gene.com.

MedWatch 3500a Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

REPORTING TO REGULATORY AUTHORITIES

Genentech/Roche as the Marketing Authorisation Holder (MAH) will be responsible for the reporting of Individual Case Safety Reports (ICSRs) from the Study to the Regulatory Authority in compliance with applicable regulations.

Dr. Simon Mahler will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Dr. Simon Mahler will be responsible for the expedited reporting of safety reports originating from the Study to the Independent Ethics Committees/ Institutional Review Boards (IEC/IRB), where applicable.

REPORTING REQUIREMENTS FOR ADVERSE EVENTS ORIGINATING FROM PATIENT REPORTED OUTCOMES

Although sites are not expected to review the PRO data, if physician/study personnel become aware of a potential adverse event during site review of the PRO questionnaire data, he/she

will determine whether the criteria for an adverse event have been met and, if so, these must be reported per the reporting format agreed as above.

AGGREGATE REPORTS

Dr. Simon Mahler will be responsible for the distribution of safety information to Site IRB:

WFU Health Sciences IRB Office

Phone: (336)716-4542

Fax: (336)716-4480

For questions related to safety reporting, please contact Genentech Patient Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

All summary reports submitted by the Sponsor-investigator to any health authority should also be sent to Genentech. Copies of such reports, as described below, should be emailed to Genentech at: ctvistsa@gene.com

Dr. Simon Mahler will forward a copy of the Interim safety analysis

AND

Dr. Simon Mahler will forward a copy of the Publication to Genentech/Roche upon completion of the Study.

Study Close-Out

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Clinical Operations Contact Information Here: lytics-gsur@gene.com

And to Genentech Patient Safety CTV oversight mail box at: ctvistsa@gene.com.

Queries

Queries related to the Study will be answered by **Dr. Simon Mahler.** However, responses to all safety queries from regulatory authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. **Dr. Simon Mahler** agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that **Dr. Simon Mahler** as Sponsor of the Study, will be primarily responsible for assessment of the benefit-risk balance of the Study.

If **Dr. Simon Mahler** issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the Study and / or triggers any changes to the Study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist **Dr. Simon Mahler** with signal and risk management activities related to the Product within the Study.

Genentech will also provide **Dr. Simon Mahler** with any new relevant information that may modify or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

Compliance With Pharmacovigilance Agreement / Audit

The Parties shall follow their own procedures for adherence to single case reporting timelines. Each Party shall monitor and, as applicable, request feedback from the other Party regarding single case report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding single case reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute a regular joint meeting to address the issue. In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then discuss and agree in good faith upon the audit scope, agenda and execution of the audit. The requesting Party will bear the cost of the audit.

APPENDIX 1.

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

Genentech Supported Research

AE / SAE FAX No: 650-238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Patient Safety: (888) 835-2555

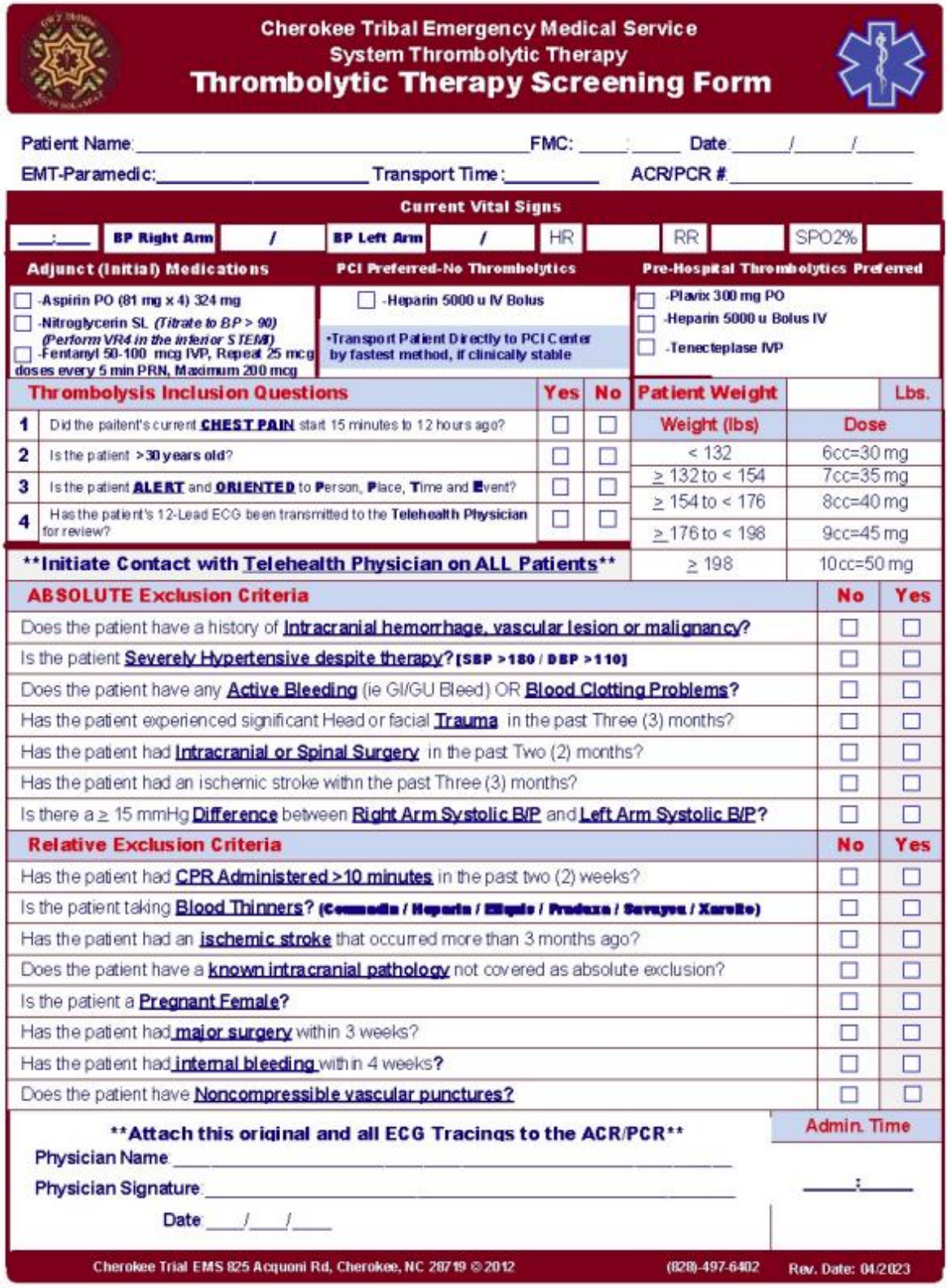
PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX 2: Content Required in the CTV Line Listing

The following fields must be populated by **Dr. Simon Mahler** in the CTV Line-Listing and sent to Genentech in an agreed format (e.g., Excel):

- CTV Period
- Product name
- Protocol/Program number (if applicable)
- Patient number/other identifier
- Sponsor reference number of case
- Submission date to Genentech
- Patient initials, as applicable

Appendix 3



Cherokee Tribal Emergency Medical Service
System Thrombolytic Therapy

Thrombolytic Therapy Screening Form

Patient Name:_____ FMC: ____:____ Date:____/____/____

EMT-Paramedic:_____ Transport Time:_____ ACR/PCR #:_____

Current Vital Signs

___:___	BP Right Arm	/	BP Left Arm	/	HR		RR		SPO2%	

Adjunct (Initial) Medications

- ☐ -Aspirin PO (81 mg x 4) 324 mg
- ☐ -Nitroglycerin SL *(Titrate to BP > 90)* *(Perform VR4 in the inferior STEMI)*
- ☐ -Fentanyl 50-100 mcg IVP, Repeat 25 mcg doses every 5 min PRN, Maximum 200 mcg

PCI Preferred-No Thrombolytics

- ☐ -Heparin 5000 u IV Bolus

•Transport Patient Directly to PCI Center by fastest method, if clinically stable

Pre-Hospital Thrombolytics Preferred

- ☐ -Plavix 300 mg PO
- ☐ -Heparin 5000 u Bolus IV
- ☐ -Tenecteplase IVP

Thrombolysis Inclusion Questions		Yes	No
1	Did the paitent's current **CHEST PAIN** start 15 minutes to 12 hours ago?	☐	☐
2	Is the patient **>30 years old**?	☐	☐
3	Is the patient **ALERT** and **ORIENTED** to **P**erson, **P**lace, **T**ime and **E**vent?	☐	☐
4	Has the patient's 12-Lead ECG been transmitted to the **Telehealth Physician** for review?	☐	☐

****Initiate Contact with Telehealth Physician on ALL Patients****

Patient Weight _____ Lbs.

Weight (lbs)	Dose
< 132	6cc=30 mg
≥ 132 to < 154	7cc=35 mg
≥ 154 to < 176	8cc=40 mg
≥ 176 to < 198	9cc=45 mg
≥ 198	10cc=50 mg

ABSOLUTE Exclusion Criteria	No	Yes
Does the patient have a history of Intracranial hemorrhage, vascular lesion or malignancy?	☐	☐
Is the patient Severely Hypertensive despite therapy? **[SBP >180 / DBP >110]**	☐	☐
Does the patient have any Active Bleeding (ie GI/GU Bleed) OR Blood Clotting Problems?	☐	☐
Has the patient experienced significant Head or facial Trauma in the past Three (3) months?	☐	☐
Has the patient had Intracranial or Spinal Surgery in the past Two (2) months?	☐	☐
Has the patient had an ischemic stroke withn the past Three (3) months?	☐	☐
Is there a ≥ 15 mmHg Difference between Right Arm Systolic B/P and Left Arm Systolic B/P?	☐	☐

Relative Exclusion Criteria	No	Yes
Has the patient had CPR Administered >10 minutes in the past two (2) weeks?	☐	☐
Is the patient taking Blood Thinners? **(Coumadin / Heparin / Eliquis / Pradaxa / Savaysa / Xarelto)**	☐	☐
Has the patient had an ischemic stroke that occurred more than 3 months ago?	☐	☐
Does the patient have a known intracranial pathology not covered as absolute exclusion?	☐	☐
Is the patient a Pregnant Female?	☐	☐
Has the patient had major surgery within 3 weeks?	☐	☐
Has the patient had internal bleeding within 4 weeks?	☐	☐
Does the patient have Noncompressible vascular punctures?	☐	☐

****Attach this original and all ECG Tracings to the ACR/PCR****

Admin. Time

Physician Name:_____

Physician Signature:_____ ____:____

Date ____/____/____

Cherokee Trial EMS 825 Acquoni Rd, Cherokee, NC 28719 © 2012 (828)-497-6402 Rev. Date: 04/2023

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