DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

0371 6 AUG 17 A9:58

IND 74,308

David E. Haines, M.D.
William Beaumont Hospital
Division of Cardiology
3601 West 13 Mile Road
Royal Oak, MI 48073

Dear Dr. Haines:

Please refer to your Investigational New Drug Application (IND) submitted February 6, 2006, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for intravenous metoprolol.

We note that your July 30, 2006 amendment responds to deficiencies in procedures/information required for use of exception from informed consent in emergency research as required under 21 CFR 50.24, which precluded the Agency from granting permission for you to conduct your proposed clinical investigation. These deficiencies were communicated to you in an Agency letter dated June 15, 2006.

We have completed our review of your amendment and, as communicated to Dr. William Merhi by Melissa Robb of this Division on August 9, 2006, have concluded that you may proceed with your proposed clinical investigation which provides for use of exception from informed consent in emergency research under 21 CFR 50.24.

We remind you that you must submit a copy of the information that was publicly disclosed both to this IND and to the Public Docket, Number 95S-0158, maintained by the Dockets Management Branch, HFA-305, 5630 Fishers Lane, Room 1061, Rockville, MD, 20857 as required by 21 CFR 312.54(a) ***

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road

19955-0158

RPT 19

Beltsville, MD 20705-1266

If you have any questions, please call Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Stockbridge
8/10/2006 11:12:38 AM

Treatment of Ventricular Tachyarrhythmias Refractory To **Shock** With Beta **Block**ers: "The **SHOCK** and **BLOCK** Trial"

INVESTIGATIONAL PLAN

Principal Investigators:

William Merhi DO
William Beaumont Hospital
Royal Oak, Michigan.

Rudolph Evonich MD
William Beaumont Hospital
Royal Oak, Michigan

David E. Haines MD
Director Heart Rhythm Center
William Beaumont Hospital
Royal Oak, Michigan

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1.0 **Introductory Statement**

Sudden cardiac death (SCD) is a catastrophic event and most commonly results from acute ventricular tachyarrhythmias. It is often triggered by acute coronary events, which may occur in persons without known cardiac disease or in association with structural heart disease. Advanced therapies such as thrombolytic agents, percutaneous coronary intervention, and implantable cardioverter defibrillators are of no value to thousands of victims who do not survive.[1] Many instances of SCD cannot be predicted and any intervention directed toward the general population would have to be applied to an estimated 1000 persons for every 1 person in whom SCD might be prevented.[2] Thus, it would be reasonable to develop new treatment strategies to improve response to resuscitative efforts.

Prompt electrical defibrillation is the treatment of choice in persons who develop SCD due to ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT). However, in up to 25% of all cardiac arrests, patients develop shock resistant VF, defined as VF persisting beyond three defibrillation attempts, and 87-97% of these patients die.[3] Medical therapy, including antiarrhythmic agents, sympathomimetic agents, and buffers have been relegated to a secondary role since there is little evidence that they are of benefit and there use is considered indeterminate or class IIB.[4-6] Furthermore, the "Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care" of the American Heart Association and the International Liaison Committee on Resuscitation recommend antiarrhythmic drugs as "acceptable" and "probably helpful" in the treatment of VF that persists after three or more external defibrillation shocks.[7] It has been previously reported that the survival rate of hospital patients suffering a cardiac

arrest in which epinephrine was required was only 6%.[8] Furthermore, Dorian et al reported a survival to hospital admission of 22.8% in patients suffering an out of hospital cardiac arrest and receiving amiodarone.[9] It is believed that the acute effects of amiodarone are due to the class II or beta blocking effects of the drug.

Resuscitation can only be considered successful if the survivor has no disabling cognitive function.[10] The American Heart Association/International Liaison Committee on Resuscitation guidelines state that with a duration of cardiac arrest of > 8 to 10 minutes, the frequency of significant, permanent neurologic damage becomes unacceptably high.[11] Newer treatment modalities are needed to improve patient outcomes.

Epinephrine has been used during cardiopulmonary resuscitation for more than 100 years yet its use has become controversial because it is associated with increased myocardial oxygen consumption, ventricular tachyarrhythmias, and myocardial dysfunction during the period after resuscitation.[12] The current International Guidelines on Emergency Cardiac Care cite both epinephrine and vasopressin as acceptable vasopressor drugs for treatment of refractory VF but neither drug is acknowledged to be of proven benefit.[13]

Beta blockers might improve patient outcomes by blunting the adverse affects of a hyperadrenergic state that occurs during a cardiac arrest and by improving the balance between myocardial oxygen supply and demand. Ditchey et al showed in an animal model that pretreatment with a beta blocker prior to cardiac arrest followed by standard epinephrine therapy results in reduced myocardial injury during CPR without compromising successful defibrillation or post resuscitation left ventricular function.[14]

The current research protocol was formulated in an attempt to develop new treatment options for patients who develop an in-hospital VF or pVT arrest refractory to electrical defibrillation with the specific goal of improving patient outcomes. The trial will utilize pre-filled, blinded syringes of Metoprolol in patients who develop an in-hospital cardiac arrest due to ventricular fibrillation or pulseless ventricular tachycardia (see study protocol).

2.0 Protocol Summary

Title	Treatment of Ventricular Tachyarrhythmias Refractory To Shock With Beta Blockers: The "SHOCK and BLOCK Trial"
Design	Prospective, single-center, randomized, blinded trial in 100 patients
Objective	To determine the effect of acute beta blocker therapy on outcome in patients who develop an in-hospital VF or pulseless VT arrest.
Enrollment	100 patients with in-hospital VF or Pulseless VT arrest.
Clinical Site	William Beaumont Hospital, Royal Oak
Time Course	August 2006 – August 2008
Primary Endpoint	Return of Spontaneous Circulation (ROSC)
Secondary Endpoint	Survival to hospital discharge; adverse effects; the number of precordial shocks required after the administration of lopressor or epinephrine; total duration of resuscitative efforts; need for additional anti-arrhythmic drugs.
Study Coordination	William Beaumont Hospital, Royal Oak

3.0 Background

Basis for the study/study rationale:

Sudden cardiac death (SCD) claims approximately 250,000 to 450,000 persons annually in the United States.[15-18] It is a term used to describe the sudden and unexpected death (due to cessation of cardiac function) within a short time period, typically ≤ to one hour.[16] More than 90% of SCD's occur in patients with known or previously unrecognized preexisting coronary heart disease or cardiomyopathies.[19] It is often the first manifestation of coronary heart disease. Despite advances in the treatment of heart disease, the outcome of patients experiencing SCD remains poor. Rea et al, noted that in patients with SCD, survival to hospital discharge for patients treated between 1998 and 2001 was not significantly better than those treated between 1977 and 1981 (15.7% versus 17.5%).[20] Furthermore, in approximately 5% of victims, there is no evidence of structural heart disease.

The mortality attributable to SCD is substantial, accounting for approximately 15% of the total mortality in the United States and other industrialized countries. The incidence of SCD increases with age and is 2-3 times more common in men than women.[18,21-22] The majority of SCD victims have no symptoms and are not identified as being at high risk before the event.[23] This emphasizes the importance of improving the outcome of resuscitation attempts. There is increasing awareness that major changes are necessary to reach that goal.[24] A short time frame after a cardiac arrest during which circulation has to be restored to prevent death or irreversible cerebral damage is essential.[25] Of the

different drugs that have been evaluated, only beta blockers and amiodarone have reduced the incidence of sudden death in the myocardial infarction survivor.[26]

Ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) appear to be responsible for 25-35% of all out of hospital episodes of sudden cardiac death.[27-28] Current American Heart Association (AHA) guidelines recommend prompt electrical defibrillation to reestablish organized electrical activity. Increasing duration of VF (i.e. "shock resistant VF") can result in two major adverse effects. First, an increased duration can reduce the ability to terminate the arrhythmia.[29] Second, if VF continues for more than four minutes, there is irreversible damage to the central nervous system and other organs.[30-31] Despite aggressive efforts, successful resuscitation from out-of-hospital cardiac arrest occurs in only one third of patients and only about 10% of all patients are ultimately discharged from the hospital, many of whom are neurologically impaired.[27,32-33] Also, the outcome of patients who suffer an in-hospital cardiac arrest is poor with reported survival to hospital discharge rates of 10-15%.[34-35] Thus, despite improvements and advances in the treatment of heart disease, the outcome of patients experiencing SCD remains poor.

Prompt and early defibrillation of VF or pVT has become the standard of care. Drug therapy for shock resistant VF or pVT has been relegated to a secondary role since there is little evidence that these agents are of benefit. As a result, their use is considered indeterminate or class IIB.[18-20] In addition, cardiac arrest and cardiopulmonary resuscitation are extreme forms of stress that lead to the highest catecholamine levels ever recorded in both human or experimental

animal models.[36-38] Endogenous catecholamine concentrations are high during ventricular fibrillation even in the absence of epinephrine administration. Currently, epinephrine is the vasopressor of choice for the treatment of cardiac arrest although vasopressin has been used as an alternative. Of note, vasopressin has been shown to be superior to epinephrine in patients with asystole however, its effects were similar to those of epinephrine in the management of VF or pulseless electrical activity.[12,39] Furthermore, previous studies have raised concern that epinephrine's beta adrenergic effect may increase the myocardial oxygen consumption/demand of the fibrillating heart, aggravate myocardial ischemia, predispose to post-defibrillation dysfunction and cardiac arrhythmias.[40-41] The mechanism of myocardial dysfunction after resuscitation is poorly understood however plasma catecholamines may have a direct cytotoxic effect on myocytes.[41]

Numerous animal studies have shown that beta adrenergic blockade reduces myocardial injury and improves survival.[14,41-44] Kudenchuk, et al undertook a study in patients with out of hospital cardiac arrest due to ventricular fibrillation. Patients were randomized to receive either amiodarone or placebo after three consecutive defibrillations and one dose of epinephrine.[15] The authors concluded that patients who received amiodarone had a higher rate of survival to hospital admission.[15] It is felt that the beneficial effects are related to the initial class II or beta blocking properties of amiodarone. Furthermore, Dorian, et al reported a higher rate of survival to hospital admission in patients who received amiodarone as compared to lidocaine for shock resistant out-of-hospital ventricular fibrillation.[9] Analysis from the European Myocardial Infarct Amiodarone Trial

and the Canadian Amiodarone Myocardial Infarction Trial revealed an interaction between beta-blockers and amiodarone, specifically, the combination group had a better survival and the interaction was statistically significant for arrhythmic death or resuscitated arrest.[45]

Ethical & Legal Considerations:

Research in the field of resuscitation presents unique ethical challenges. Specifically, patients cannot provide informed consent for participation. Surrogate permission, from family members when applicable, is rarely available.[46-47] Also, patient wishes at the time of the arrest are often unknown. In response to this dilemma, the 1995 Coalition Conference of Acute Resuscitation and Critical Care Researchers stated that research can and should be done in clinical circumstances where it is not feasible to obtain informed, prospective, or proxy consent for enrollment in a study protocol.[46-47] The coalition also endorsed a new risk category called "appropriate incremental risk" which refers to any potential risk associated with participation in the research study compared with the natural consequences of the medical condition. Although patients are at risk, they are also at risk of being denied beneficial therapy when no effective therapy currently exists.

The US Food and Drug Administration published an important "final rule" regarding exception to informed consent in certain emergency research circumstances. When implemented, these regulations should allow full resumption of clinical resuscitation even when informed consent is impossible.[17]

The circumstances under which exceptions to informed consent can be made must meet the following criteria:

1) The clinical trial addresses a life threatening condition that the individual to be enrolled has.
2) Currently available treatments are unproved or unsatisfactory.
3) The research cannot otherwise be carried out and is essential to determine the safety and effectiveness of the new treatment.
4) It is not feasible to obtain informed consent from the patient or a legal representative.
5) The risks of the experimental procedures are reasonable compared with those associated with the patient's medical condition and current standard therapy.

The current study fulfills all of the above criteria. All patients enrolled in the study will be randomized after suffering an in-hospital cardiac arrest which satisfies the first criteria. Furthermore, currently available drug therapies are unsatisfactory and survival to hospital discharge remains poor (fulfilling the second criteria). The entire basis of the study is to develop new therapies to improve patient outcomes after a VF or pulseless VT arrest and accordingly the research cannot be carried out and is essential to determine the safety and effectiveness of the new treatment (fulfilling the third criteria). It is impossible to predict which patients will develop an in-hospital VF or pulseless VT arrest and thus it is not feasible to obtain informed consent from the patient or legal representative due to the emergent and rapid nature of a cardiac arrest (fulfilling the fourth criteria). Given the overall poor prognosis of patients who develop shock resistant VF or pulseless VT, the risks of the experimental procedure are

reasonable compared with those associated with the patients medical condition considering that standard pharmacologic therapy is of indeterminate benefit and that beta blockers might actually improve survival and myocardial performance in the post-resuscitation phase (fulfilling the fifth criteria).

Therapeutic Window

The therapeutic window for treating cardiac arrest lasts only minutes. The chance for successful resuscitation is reduced 7-10% each minute. The study investigators commit to making all necessary efforts to contact the patient's legally authorized representative (LAR) at the earliest feasible opportunity and commit to notifying the LAR at the earliest feasible opportunity (within 48 hours) of the patient's inclusion in the study if consent cannot be obtained.

4.0 Study Design

4.1 Objective

The primary endpoint is the return of spontaneous circulation (ROSC). Specifically, the patient has a sufficiently stable and organized rhythm and blood pressure (with or without the use of pressors). Secondary endpoints include survival to hospital discharge, adverse effects, the number of precordial shocks required after the administration of metoprolol or epinephrine, the total duration of resuscitative efforts, and the need for additional antiarrhythmic drugs.

4.2 Design

This single-center, blinded, prospective, randomized study will enroll 100 patients who develop an in-hospital cardiac arrest due to VF or pVT. Intravenous metoprolol will be purchased from:

Watson Laboratories
311 Bonnie Circle Drive
Corona, CA 91720

IV metoprolol will be pre-loaded in blinded syringes with an identification number on the syringe. Only the research pharmacist will have the identification key to determine if study drug (i.e. metoprolol) is present. To ensure chemical stability and sterility over a 90 day period, the pre-formed syringes were sent to Analytical Research Labs (840 Research Parkway, Suite 546, Oklahoma City, OK 73104; Phone (405) 271-1144)-see attached report.

4.3 Patient Selection

A. Inclusion criteria

1. All patients age $\geq$ 18 years of age who develop an in-hospital VF or pVT arrest which persists after three or more precordial shocks.
2. Patients who develop an in-hospital cardiac arrest due to asystole or PEA which subsequently converts to VF or pVT will be included.

B. Exclusion criteria

1) Pediatric patients
2) Pregnancy
3) Age $\leq$ 18 years of age
4) Patients who develop VF or pVT in the emergency room, operating room or surgical intensive care unit.

4.4 Study Timeline

Enrollment in the study is expected to begin in August 2006 and continue until August 2008.

4.5 Endpoints

a. Primary Return of Spontaneous Circulation (ROSC)

b. Secondary Survival to hospital discharge, adverse effects, the number of precordial shocks required after the administration of metoprolol or epinephrine, total duration of resuscitative efforts, need for additional anti-arrhythmic drugs.

4.6 Plans for community consultation:

We participated in three meetings at approximately one month intervals to allow adequate time for public input. The first was at the Royal Oak Kiwanis Club, the second at the Birmingham Optimist club, and the third at the Boy's and Girls Club of Royal Oak (made up of adults/senior citizens). Members of our institutional review board were present at each meeting. Attendees were required to provide a signature which documented their attendance. Our research protocol was well received and many attendees were excited and eager for it to begin. All questions were answered and we provided contact information should questions or concerns arise. Furthermore, during our first meeting, we took a vote to determine the percentage of patients who were in favor of going forward with the trial and all attendees wanted to see the trial move forward and begin. Specific questions that came up during our community consultation include:

1) Why not obtain consent from every person who gets admitted to the hospital? Our response was that it would be logistically impossible due to the high volume of patients that present and are admitted to the hospital. Furthermore, this would create a statistical bias in that elderly patients and patients with terminal illnesses would be more likely to participate.
2) Are children going to be enrolled? No. Only patients 18 years of age or older will be enrolled.
3) What is the current standard of care? Electrical shocks. If patients don't improve with electrical shocks there are some medications which can be tried but their use has been delegated to a secondary role because even with their use, survival remains poor. Survival decreases 7-10% for each minute a person remains in a cardiac arrest.
4) Why don't you get consent during a cardiac arrest from a family member or spouse? It is impossible to predict who or when a person will suffer a cardiac arrest. Furthermore, during a cardiac arrest, trained hospital personal respond and have literally minutes to revive the patient. Survival decreases 7-10% for each minute a person remains during a cardiac arrest. It would be impossible to try and contact a family member or spouse during a cardiac arrest situation. Also, the initial shock and emotional trauma of the situation would make it difficult to discuss entry into a research protocol.
5) Will patients or family members be informed of their entry into a research protocol? Absolutely. Every effort will be made to inform the patient (if they survive) or their legal guardian of the patients entry into a research protocol (within 48 hours).
6) What if the patient has advanced directives and doesn't want to be resuscitated? They will not be eligible for enrollement into the study protocol.

7) Aren't patients supposed to expect research to be performed at resident affiliated hospitals and so you really don't need consent? It is not reasonable to assume patients knowingly present to certain hospitals with the idea that they will automatically be enrolled into a research protocol. We want to make sure that patients as well as their family or legally authorized representative understand that research is needed which may benefit society as a whole and that sometimes, during emergency situations, obtaining informed consent may not be possible. However, during such circumstances you can perform research if current treatment options are poor with the goal of developing new therapies that might save lives.
8) Will all patients receive standard of care? Yes. All patients will receive electrical shocks in addition to a powerful cardiac stimulant known as epinephrine (adrenaline).
9) Why don't you try it on animals first? It has been studied in animals and the data indicates that there is a benefit in the animal model. We need to determine if the same benefit would occur in humans.

4.7 Public Disclosure

Our intent to initiate the SHOCK and BLOCK trial at William Beaumont Hospital was relayed to the Mayor of the city of Royal Oak (James Ellison) and the Oakland County Executive (L. Brooks Patterson) via certified letter. We also plan on mailing fliers (sample attached) to various groups and city councils. We will be placing an announcement in the Detroit News, Beaumont Pipeline (in-hospital newsletter), and Beaumont Hospital Web site. We are in the process of producing a 5 minute presentation which will be shown on Beaumonts in-hospital closed circuit TV system which will allow patients the opportunity not to participate in the study. At the conclusion of the study, we plan on discussing our findings with the Kiwanis Club and Birmingham Optimist club as well as present our findings at the American Heart Association National Meeting. We will also send out fliers to area groups, city council's, Beaumont Hospital web site, and Newsletter ("Beaumont Pipeline").

4.8 Alternative Procedure

During the patients hospital stay, the in-hospital closed circuit TV system will Inform them of the trial and allow the patient the opportunity to not participate in the study by informing the nurse which would then be documented on the chart. Patients would then undergo standard CPR as per updated ACLS guidelines.

5.0 Conduct of the study

5.1 Pre-procedure evaluation and screening

All patients who develop an in hospital VF or pVT arrest will be eligible for enrollment. Also, patients who develop a cardiac arrest due to asystole or pulseless electrical activity which converts to VF or pVT will be eligible for enrollment.

5.2 Procedure

See study flow sheet. To summarize, patients who develop a pulseless arrest will immediately receive cardiopulmonary resuscitation (CPR) and oxygen. They will then be attached to a monitor/defibrillator. If the rhythm is shockable (i.e. VF or pVT), patients will receive one electrical shock at 120 to 200J utilizing a biphasic defibrillator or 360J utilizing a monophasic device followed by immediate resumption of CPR. After 5 cycles of CPR (compression to ventilation ratio of 30:2 or 2 minutes), patients will receive 1 electrical shock (200J with a biphasic device or 360J with a monophasic defibrillator) with immediate resumption of CPR. If VF or pVT remains, all patients will receive epinephrine 1 mg IVP during CPR. If after 5 cycles of CPR (or 2 minutes) VF or pVT persists, repeat electrical defibrillation will be performed followed by resumption of CPR. Patients will be randomized to epinephrine (1 mg IVP) versus metoprolol (5 mg IVP) which will be given during the CPR. If the rhythm remains shockable after 5 cycles of CPR (or 2 minutes), repeat defibrillation will be performed with immediate resumption of CPR during which patients will receive either epinephrine 1 mg IVP versus metoprolol (5 mg IVP). If VF or pVT remains, repeat electrical defibrillation will be performed followed by immediate resumption of CPR. Further drug therapy (i.e. amiodarone, lidocaine, or magnesium) will be at the discretion of the CPR captain.

Procedure details for Obtaining Consent:

1. If the patient is able to provide informed consent prior to administration of Metoprolol, they will be asked to do so by signing the consent form.
2. If the patient is unable to provide informed consent prior to the study and a legal representative or next-of-kin is immediately available, he or she will be asked to provide consent on the patients behalf. If the patients legal representative or next-of-kin objects to study participation, the patient will not be enrolled.
3. If the patients legal representative or next-of-kin is not immediately available, a family member that is immediately available will be provided the opportunity to object to the patients participation. Although some family members cannot provide consent for the patient, they can object to the patients participation. If a family member does object to study participation, the patient will not be enrolled.

4. If a legal representative, next-of-kin or other family member is not immediately available and a family member does not object, the patient will be enrolled into the study by a process referred to as "exception from informed consent requirements" and the patient will undergo the research treatment before informed consent is obtained.
5. At the earliest possible time, after the patient has received study treatment, the patient/legal representative/next-of-kin or family member will be informed of the patients inclusion in the study. If the patient remains incapacitated, your legally authorized representative, next-of-kin or other family member will be informed of your inclusion in this study.
6. At any time during the study, the patient/legal representative/next-of-kin, or other family member may discontinue the patients participation in the study.

5.3 Follow-up

Clinical follow-up, in the form of a telephone contact, including cerebral performance assessment, will be performed at discharge, 3 and 12 months following the cardiac arrest and if the patient survives.

6.0 **Data Management**

6.1 Data collection and analysis

Case report forms will be completed for all patients. All data will be entered and analyzed in a dedicated excel database.

6.2 Statistical analysis

Statistical analysis will be performed with the use of SAS® software (version 8.0, Cary, NC). Continuous variables will be presented as mean ± standard deviation.

7.0 **Investigators**

William Merhi DO, William Beaumont Hospital
Rudolph Evonich MD William Beaumont Hospital
David E. Haines MD, Director, Heart Rhythm Center, William Beaumont Hospital

Documentation: Attempt to Contact Legally Authorized Representative (LAR)

Date/Time	Print Name	Relation
_____/_____	_____	_____
_____/_____	_____	_____
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_____/_____	_____	_____
_____/_____	_____	_____

*Was a copy of the consent form mailed to the LAR? Yes or No
If yes, Date:_____

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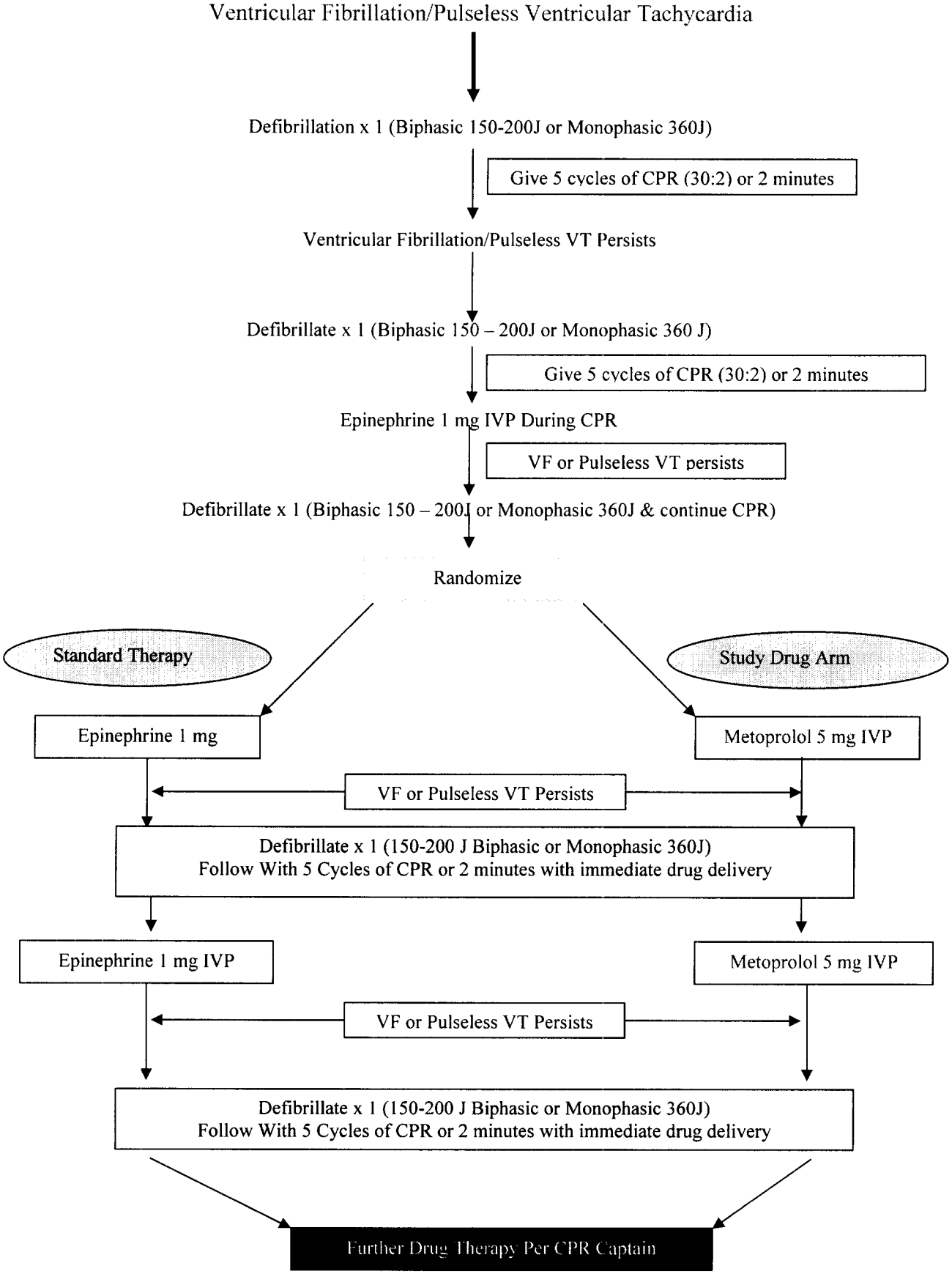
B. Study Flowchart:



CONSENT FORM AND AUTHORIZATION FOR DISCLOSURE OF PROTECTED HEALTH INFORMATION

William Merhi DO, Rudolph Evonich MD, and David Haines MD at William Beaumont Hospital are engaged in research to study new methods of improving survival in patients who develop an in-hospital cardiac arrest. This study will determine the safety and efficacy of the drug Metoprolol (a Beta Blocker) in patients who develop an in-hospital cardiac arrest. Current medical therapy is suboptimal and survival among patients who develop an in-hospital cardiac arrest is poor. This investigational study is known as:

Treatment of Ventricular Tachyarrhythmias Refractory To **SHOCK** With Beta **BLOCKERS**: "The **SHOCK** and **BLOCK** Trial"

This consent form is for use in a research study that may involve both subjects who do and do not have the legal capacity to consent to their participation. Accordingly, when the subject cannot legally consent to participate, the pronouns "you" and "your" should be read as referring to the subject rather than the legal representative or next-of-kin who is signing the form to give consent for the subject. If you are aware that the patient is pregnant, or has a "Do Not Resuscitate (DNR)" order, please let the study staff know. You may not participate in this study if you are currently enrolled in another related research study.

- **INTRODUCTION**

The purpose of clinical research is to look at the nature of disease and attempt to develop improved methods of diagnosis and treatment. Overall, survival is poor among patients who develop and in-hospital cardiac arrest. You have the right to know about the procedures that were performed during the study. This information is not meant to frighten or alarm you. It is to inform you of potential risks/benefits of study participation. Currently, research can be performed during emergency situations if current therapy is NOT satisfactory with the hope of developing new therapies which can potentially improve survival. Please read this information carefully and ask as many questions as you like.

- **DESCRIPTION OF THE STUDY**

The purpose of this research study is to evaluate the effectiveness of metoprolol, a "beta blocker," in treating patients in the hospital with a cardiac arrest. It will be given intravenously (given into a vein). The subjects who will take part in this study are 18 years of age or older, are experiencing a cardiac arrest in the hospital, and are in a life threatening situation. Patients who develop a cardiac arrest require prompt electrical defibrillation (electrical shocks) to restore the normal beating rhythm of the heart. In patients who do not respond to electrical defibrillation, current standard of care recommends the use of medications which have been shown to be of indeterminate benefit. Some people recover from a cardiac arrest, but many people do not. We want to learn whether giving metoprolol will improve survival of patients with a cardiac arrest. A total of 100 patients will be enrolled in the study. Patients will receive either the standard of care or the standard of care plus metoprolol. Which treatment you will receive will be completely random, similar to flipping a coin.

Although you meet the requirements for participation in this study, you may be unable to provide informed consent at the time of your enrollment. Therefore, you may be enrolled in this study by a

process referred to as "exception from informed consent requirements." This exception from informed consent is granted by the FDA under regulation 21 CFR 50.24. This regulation allows potential beneficial experimental emergency treatments to be conducted in life-threatening situations in which death may occur (cardiac arrest). To reiterate, you have already been enrolled into the study by the process of "exception from informed consent." This consent form is required for continued participation and follow by telephone.

Exception from informed consent requirements involves the following conditions:

1. If you are able to provide informed consent prior to entry into the research study, you will be asked to do so by signing this form.
2. If you are unable to provide informed consent prior to the study and a legal representative or next-of-kin is immediately available, he or she will be asked to provide consent on your behalf. If your legal representative or next-of-kin objects to your participation in the study, you will not be enrolled.
3. If your legal representative or next-of-kin is not immediately available, a family member that is immediately available will be provided the opportunity to object to your participation. Although some family members cannot provide consent for you, they can object to your participation. If a family member does object to your participation, you will not be enrolled.
4. If a legal representative, next-of-kin or other family member is not immediately available and a family member does not object, you will be enrolled into the study by a process referred to as "exception from informed consent requirements" and you will undergo the research treatment before informed consent is obtained.
5. At the earliest possible time, after you have received study treatment, you will be informed of your inclusion in the study. If you remain incapacitated (unable to read or understand this consent due to your medical condition), your legally authorized representative, next-of-kin or other family member will be informed of your inclusion in this study. The details of the study and other information contained in this informed consent document will be provided to him/her as soon as possible.
6. At any time during the study, you or your legal representative, next-of-kin, or other family member may discontinue your participation in the study.
7. You will not lose any benefits, normal care, and/or assistance as a result of your decision to discontinue participation in this study. You will receive the standard treatment normally provided to patients who have experienced a cardiac arrest.

Metoprolol is approved by the U.S. Food and Drug Administration (FDA) for patients with high blood pressure, congestive heart failure, angina pectoris (heart pain), myocardial infarction (heart attack), abnormal heart rhythms, and migraine headache. We are using metoprolol off-label for the management of patients in a cardiac arrest. The term "off-label" means the FDA has not approved its use for cardiac arrest. For the purpose of this study, we will be administering metoprolol "off-label" in the treatment of cardiac arrest.

When a patient is in a cardiac arrest, trained hospital staff and doctors must act very quickly. The patient receives cardiopulmonary resuscitation (CPR), electrical shocks, oxygen and a number of medications (including epinephrine). If you are receiving metoprolol, you will receive it up to two times intravenously (through the vein). The dose each time is 5 milligrams.

During your hospital stay, study staff will visit and examine you until you are discharged from the hospital. You will be assessed when you are discharged, and at 3 and 12 months you will be contacted by phone by a study staff member to see how you are doing. The phone call should take no longer than 5 minutes. The duration of your participation in this study will be 12 months.

Example for administration of a drug:
This study consists of administration of metoprolol (intravenously), a "beta-blocker" that may have some therapeutic effect on disease. These medications may cause adverse effects including allergic reaction.

- **RISKS, SIDE EFFECTS AND DISCOMFORTS:**

Side effects seen with the use of metoprolol, a generic equivalent form of the drug Metoprolol include:
Dizziness (1.8%); low blood pressure (1%); heart failure (1%); slow heart rate or heart block (1.5-5%); depression (5%); wheeze (1%); allergic reaction (5%).

Side effects seen with the use of Epinephrine include:
Palpitations (sensing a rapid heart beat or skipped beat), tachycardia (fast heart beat), sweating, Nausea, vomiting, breathing difficulty, pallor, dizziness, weakness, tremor, headache, apprehension, and anxiety.
Abnormal heart rhythms may follow administration of Epinephrine.

For administration of a medication:
There are unforeseen risks due to taking the drugs or participating in the study that have not been listed in this section.

- **BENEFITS:** The purpose of this study is to examine the safety and efficacy of metoprolol in patients who develop an in-hospital cardiac arrest and develop improved methods of care. However, you should understand that you may not benefit from participating in the study. You do not have to participate in this study to receive treatment for your medical condition. Alternatives are to receive the standard treatment routinely given to subjects with a cardiac arrest.

- **ECONOMIC CONSIDERATIONS:**

The cost of participation is covered by a research grant. There will be no additional charge to you. If routine care costs, normally covered by a third party payor, are <u>not</u> covered by your insurance, the costs will be your responsibility.

- **COMPENSATION:**

You should understand the possible effects or hazards that might occur during the course of the study as described in this consent form. Not all ill effects from use of the drug are known. Should inadvertent injury or damage result from your participation in this study, there are no designated funds provided for subsequent medical care or compensation by either the investigator or William Beaumont Hospital. However, you do not waive any legal rights by signing this consent form.

- **CONFIDENTIALITY, DISCLOSURE AND USE OF YOUR INFORMATION:**

Your medical and billing records of the study will remain confidential but may be disclosed or used by the following or their representatives: the investigators, William Beaumont Hospital, the Food and Drug

Administration, other governmental agencies, and Medtronics Emergency Response Systems. Your healthcare insurer including Medicare and Medicaid and their intermediaries (companies contracted to process claims) may also have access to your medical and billing records of the study. The purpose for this disclosure or use is, for example, to assure compliance with the study protocol, to evaluate the effectiveness of the study, or to provide protection to you as a study subject. The disclosure and use of your information will continue after your participation in the study, there is no expiration date for the use of your medical and billing records from the study.

Any information about you disclosed to the parties identified above may be re-disclosed by them; however, such re-disclosure is not under the protections of this Consent and Authorization.

- **STOPPING STUDY PARTICIPATION**

Your participation in this study is voluntary. After randomization should you or your next of kin decide on not participating you may withdraw from the study at any time without penalty or loss of benefits to which you are otherwise entitled, or without jeopardizing your medical care by your physician at William Beaumont Hospital. You may choose to stop being in this study at any time. Furthermore, you may also refuse to allow the researchers access to your health information. If you withdraw from the study, this will be documented in the chart.

Based on their judgment, the investigators in charge of the study can decide to remove you from this study without your consent for any appropriate reason, which will be explained to you.

- **CONTACTS:**

You may contact the Principal Investigator, William Merhi DO, of this study at (248)898-1682 to answer any questions you might have about your study participation or in case you think you may have any research related injuries. If you have any questions regarding your rights as a human research subject, you may contact the Institutional Review Board (Human Investigation Committee) Chairman at (248) 551-0662.

- **STATEMENT OF VOLUNTARY PARTICIPATION:**

I have read the above, have asked questions and have received answers about this study to my satisfaction. I understand what I have read and understand that participation in "**TREATMENT OF VENTRICULAR TACHYARRHYTHMIAS REFRACTORY TO SHOCK WITH BETA BLOCKERS: THE SHOCK and BLOCK TRIAL**" is voluntary. I understand that I will receive a copy of this document and will be promptly informed of any new findings regarding this study. I further authorize the use or disclosure of any health and personal information contained in records as described above.

Research Subject Name

Hospital Number

Research Subject Signature

Date Time

Alternative Signature
IF RESEARCH SUBJECT UNABLE TO SIGN

Name (please print)

Relationship to Subject

As the personal/legal representative of the study subject, please list the basis for your authority to sign this Consent and Authorization:

Court-appointed guardian ☐

Next of Kin ☐

Durable Power of Attorney ☐

Signature_____
Date/Time_____

(Please check the appropriate box)
Witness to Signature Only ☐ **OR**
Witness to Consent Process and Signature ☐

Witness Name (Please Print)

Witness Signature Date Time

- **INVESTIGATOR/AUTHORIZED CONSENT PROVIDER STATEMENT:**

I have explained this study and have offered the study subject an opportunity for any further discussion or clarification.

_____ _____

Name (please print) Phone Number

_____

Signature Date Time

Documentation: Attempt to Contact Legally Authorized Representative (LAR)

Date/Time	Print Name	Relation
_____/_____	_____	_____
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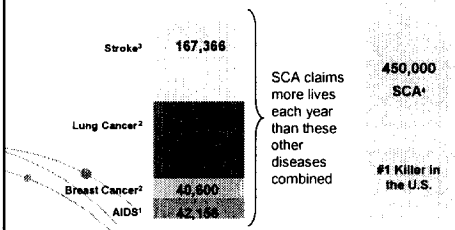
*Was a copy of the consent form mailed to the LAR? Yes or No
If yes, Date:_____

Treatment of Ventricular Tachyarrhythmias Refractory To Shock With Beta Blockers: The "SHOCK and BLOCK" Trial

New Treatment Options For Patients Developing a Cardiac Arrest Due to Lethal Heart Rhythms

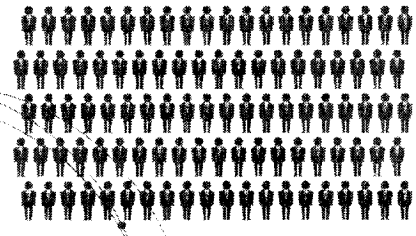
Magnitude of Sudden Cardiac Arrest (SCA) in the U.S.



[1] U.S. Census Bureau, *Statistical Abstract of the United States: 2001.*
[2] American Cancer Society, Inc., *Surveillance Research, Cancer Facts and Figures 2001.*
[3] *2002 Heart and Stroke Statistical Update*, American Heart Association.
[4] Zheng Z. *Circulation.* 2001;104:2158-2163.

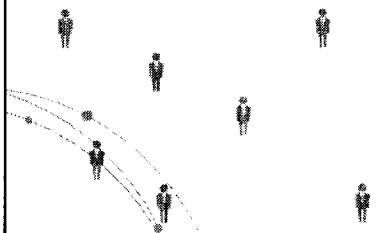
SCA Statistics

Consider 100 people with SCA



SCA Statistics

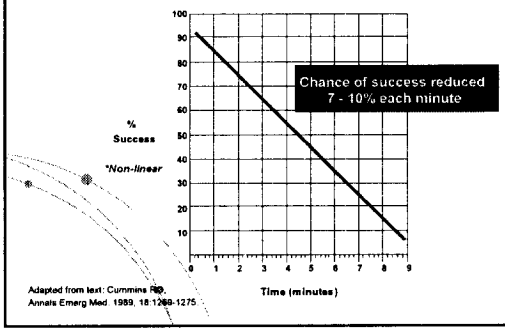
Survival Rate 7%



SCA Statistics

40% Recurrent SCA in 2 years

Resuscitation Success vs. Time*



Adapted from text: Cummins RO. Annals Emerg Med. 1989; 18:1269-1275.

Treatment of Ventricular Tachyarrhythmias Refractory to **Shock** with Beta **Block**ers:
"The **SHOCK** and **BLOCK** Trial"

- Objective:
  We want to learn whether giving Metoprolol (a "beta blocker") during CPR will improve survival in patients suffering a cardiac

Why are we doing this study?

- The vast majority of patients who suffer a cardiac arrest do not survive

Our ultimate goal is to develop improved methods of care and thus improve survival

What Is Metoprolol?

- Belongs to a class of drugs known as "Beta Blockers"
- Metoprolol is approved by the FDA for the treatment of:
  - High blood pressure
  - Congestive Heart Failure
  - Angina Pectoris (Heart Pain)
  - Myocardial Infarction (Heart Attack)
  - Abnormal Heart Rhythms
  - Migraine Headaches

Beta Blockers improve survival, and patients already on beta blockers have a lower incidence of Sudden Cardiac Death

What is Metoprolol?

- We will be using Metoprolol "off label" for the treatment of patients suffering an in-hospital cardiac arrest.
- "Off label" means the FDA has not approved the drug for the particular use (cardiac arrest).
- Numerous animal studies using Beta Blockers in cardiac arrest have shown a quicker return of a pulse and a longer survival time.
- Reports in the medical literature show patients receiving beta blockers have a lower number of recurrent cardiac arrests.

For the purpose of this study, we will be giving metoprolol "off-label" in the treatment of cardiac arrest

How Will the Study be Performed?

When a patient has an in-hospital cardiac arrest, trained hospital staff & doctors must act quickly.

- In this study, the patient will receive standard cardiopulmonary resuscitation (CPR).
- Electrical shocks, oxygen, and a number of medications will also be given.
- Patients will receive either the standard of care or the standard of care plus Metoprolol
- Which treatment the patient will receive will be completely random, similar to picking numbers out of a hat

Patients enrolled in the study will receive standard CPR. Some patients will also receive metoprolol up to two times through a vein, during CPR

What Are The Potential Risks/Benefits of The Trial

- Overall survival is poor following a cardiac arrest
- We want to develop improved methods of care
  - Patients enrolled in the study may benefit by improved survival
  - However, you should understand that patients may not benefit from participating in the study
  - As with any medication, not all of the possible hazzards or side effects are known and its effect on disease cannot be predicted

FDA Rules on Performing Research During an Emergency or Life Threatening Situation

It is not possible to obtain informed consent immediately prior to, or during a cardiac arrest.

The FDA allows Planned Emergency Research, designed to improve therapy, to occur under emergency circumstances, while doing everything possible to protect the rights and safety of the patient.

Ethical Considerations

The FDA's "Final Rule" regarding Exception to Informed Consent in Planned Emergency Research:

1) The research study addresses a life threatening condition.
2) Currently available treatments are unproved or unsatisfactory.
3) The research cannot otherwise be carried out & is essential to determine safety & effectiveness a new treatment.

JAMA 1995; 273: 1283-1287
Resuscitation 1997; 34: 151-183

Ethical Considerations

The FDA's "Final Rule" regarding Exception to Informed Consent in Planned Emergency Research:

4) It is not feasible to obtain informed consent from the patient or a legal representative.
5) The risks of the experimental procedures are reasonable compared with those associated with the patients medical condition and current standard therapy.

JAMA 1995; 273: 1283-1287
Resuscitation 1997; 34: 151-183

Opting Out of the Study

- During the patients hospital admission, the trial will be announced on William Beaumont Hospital's closed circuit TV system (which is available in every room)
- This will give the patient a chance to:
  - Learn about the study
  - Ask questions about the study
  - If desired, refuse to participate

Any patient admitted to the hospital can choose not to participate by informing the nurse.

Conclusion

- SCD remains a major public health problem
- Survival remains poor
- Continued efforts must be directed toward:
  - Primary prevention
  - Modifying coronary artery disease risk factors
  - Improving resuscitation services / therapies

Thank You!

Questions?

For More Information, Contact:
Dr. William Merhi
wmerhi@beaumont.edu
(248) 898-1682
Fax: (248) 898-4199

Script for Closed Circuit TV

Hello, my name is Dr. William Merhi and I'd like to tell you about a research protocol being performed by the division of cardiology here at Beaumont Hospital. The study involves patients who develop a cardiac arrest while in the hospital. When a person suffers a cardiac arrest, the heart does not beat normally and cannot support life. Some people recover from a cardiac arrest, but many people do not and overall survival is poor. We want to learn whether giving the drug metoprolol will improve survival in patients with a cardiac arrest. Metoprolol is FDA approved for the treatment of high blood pressure, abnormally fast heart rhythms, heart failure and heart attacks. A total of 100 patients will be enrolled in the study. Patients will receive either the standard of care or the standard of care plus metoprolol. The subjects who will take part in this study are 18 years of age or older, are experiencing a cardiac arrest in the hospital, and are in a life threatening situation. Unfortunately, the patients chance for survival decreases 7-10% for each minute the patient remains in a cardiac arrest. Because of the emergent nature of the situation it is impossible to predict who will suffer a cardiac arrest. Furthermore, it is impossible to obtain consent from the patient to participate in the study. The FDA allows research to be performed during emergency situations where obtaining consent is not immediately possible. This is known as exception to informed consent and the FDA allows this if current therapies are sub-optimal. As part of our public disclosure, we are required to inform you that the study is being performed here at William Beaumont Hospital. If you feel that you do not want to participate, please let your nurse know so that she can label your chart which will alert study personal not to enroll you into the study.

CPR RESEARCH STUDY
AD COPY

HIC #2006-008

Headline: Public Notification of CPR Study to be performed at William Beaumont Hospital (Royal Oak)

Copy:

On xxxxx, William Beaumont Hospital in Royal Oak, will initiate a research trial involving patients who develop an in-hospital cardiac arrest. The two-year study will evaluate the effectiveness of the drug Metoprolol (a beta blocker) to revive patients with sudden cardiac arrest.

Because of the medical circumstances surrounding this research, written consent to participate in this study cannot be obtained from participants.

For details on the risks and benefits, waiver of informed consent and other aspects of the study, visit wmerhi@beaumont.edu or call 248-898-1682.

Treatment of Ventricular Tachyarrhythmias Refractory To **SHOCK** With Beta **BLOCKERS**: "The **SHOCK** and **BLOCK** Trial"

William Beaumont Hospital
Division of Cardiology

May 8, 2006

William Beaumont Hospital will initiate a research trial in the field of Cardiac Resuscitation

Sudden cardiac arrest (SCA) is the leading cause of death in the U.S. Approximately 450,000 people die each year due to sudden death-surpassing AIDS, breast & lung cancer, and stroke combined. Only 10-15% of patients who suffer an in-hospital cardiac arrest survive. In an effort to improve the current poor outcomes of patients after a cardiac arrest, new treatment options are needed to improve survival.

Patients who develop a cardiac arrest require prompt electrical shocks to restore the normal beating rhythm of the heart. Some people recover from a cardiac arrest, but many people do not. We want to learn whether giving metoprolol (a "beta blocker') will improve survival in patients with a cardiac arrest. Metoprolol is FDA approved for the treatment of high blood pressure, angina (heart pain), congestive heart failure, abnormal heart rhythms, and heart attacks.

Since it is not possible to obtain consent from patients during a cardiac arrest the FDA has issued regulations to allow emergency research, with the goal of improving current therapy, to occur under emergency or life threatening circumstances in which obtaining informed consent is not feasible while doing everything possible to protect the rights and safety of the patient.

The planned emergency research study on in-hospital cardiac arrest fulfills the FDA requirements for waiver of informed consent. As part of that process, we are required to disclose to the public our intent to initiate the trial at William Beaumont Hospital to increase public awareness and address any questions.

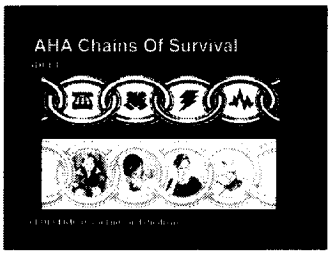
Public discussion/disclosure of the "SHOCK and BLOCK" trial will be held at:

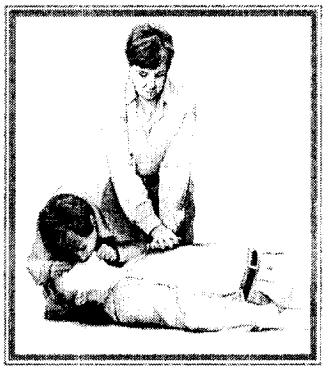
Kiwanis Club: May 11, 2006 at 12:10 pm at the First Congregational Church

Birmingham Optimist Club: May 25, 2006 at 8 AM at the Birmingham Community Club

Principle Investigators: David E. Haines, MD & William Merhi, DO

For more information: (248) 898-1682





Special points of interest:

- Sudden cardiac arrest is the leading cause of death in the U.S.
- Overall survival from SCA is poor
- New treatment options are needed to improve outcomes and survival

09/12/2005William Beaumont Hospital
Division of Cardiology
3601 West 13 Mile Road
Royal Oak, MI 48073

September 12, 2005

James Ellison
Royal Oak Mayor
211 S Williams Street
Royal Oak, MI 48067

Dear Mr. James Ellison:

As you know, William Beaumont Hospital is a leader in cardiovascular research. The purpose of this letter is to inform you of a potentially lifesaving clinical research trial scheduled to begin at William Beaumont Hospital. The trial was designed with the intent of developing new treatment strategies to improve outcomes in patients who develop an in-hospital cardiac arrest.

Sudden cardiac death is the leading cause of death in the United States surpassing lung & breast cancer, stroke, and AIDS combined. Despite aggressive resuscitation efforts, including electrical defibrillation and the use of potent cardiac medications, survival to hospital admission remains poor (~12-15%). Of those that survive to hospital admission, only 4% actually survive to hospital discharge and most have severe neurologic impairment. Patients with an in-hospital cardiac arrest experience a dismal prognosis as well with only 16% surviving to hospital discharge. In fact, survival from cardiac arrest remains poor despite the major reevaluation and publication of new CPR guidelines every 5-8 years for the past 30 years. Newer treatment strategies and therapies are needed to improve outcomes because it is impossible to predict who will develop a cardiac arrest.

The trial, known as "Beta Blockers for Resuscitation of In-Hospital Ventricular Fibrillation or Pulseless Ventricular Tachycardia: The SHOCK and BLOCK Trial," will randomly assign patients who develop an in-hospital cardiac arrest to either standard therapy or standard therapy plus study drug (i.e. beta blockers). Since it is impossible to predict who will develop a cardiac arrest, the Food & Drug Administration has established guidelines for performing research during an emergency situation in which obtaining consent is not possible. It is recommended that we disclose this information to community leaders and representatives prior to starting the research protocol.

As a leader in our community, we are contacting you to inform you of our intent to perform this trial at William Beaumont Hospital. We would respectfully request that you consider our proposal and provide us any feedback that you believe would be helpful to us. Please feel free to share this with any of the city's leadership, your constituents or your staff. You may contact us at any time with suggestions, questions or concerns. Thank you.

Respectfully,

William Merhi DO
Cardiology Fellow
William Beaumont Hospital

Division of Cardiology

3601 West 13 Mile Road
Royal Oak, MI 48073

Office (248)898-1682
Cell (248)992-0400

wmerhi@beaumont.edu

Respectfully,

David E. Haines, MD
Director, Heart Rhythm Center
William Beaumont Hospital

I acknowledge being informed of the trial: "Beta Blockers for Resuscitation of In-Hospital Ventricular Fibrillation or Pulseless Ventricular Tachycardia: The SHOCK and BLOCK Trial."

Print Name _____ Date _____ Signature _____

September 12, 2005

L. Brooks Patterson
Oakland County Executive
Executive Office Building
Building 34 East
1200 North Telegraph Road
Pontiac, MI 48341

Dear Mr. L. Brooks Patterson:

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Print Name _____ Date _____ Signature _____

CPR **Study Number**_____

DEMOGRAPHICS

1. Age: _____

2. Sex: ☐0 Female ☐1 Male

3. Height: _____cm: _____inches 4. Weight: _____kg : _____lbs

5. Race: (Check ONE only) ☐1 Afro-American ☐2 American Indian ☐3 Asian ☐4 Caucasian
☐5 Hispanic ☐6 Other _____

HISTORY PRIOR TO ADMISSION

YES	NO	UNK		YES	NO	UNK	
☐1	☐0	☐9	A. Hypertension	☐1	☐0	☐9	K. Prior Stroke
☐1	☐0	☐9	B. Diabetes (Insulin-dependent) Insulin dependent: ☐1 YES ☐0 NO	☐1	☐0	☐9	L. Prior intracranial or subarachoid hemorrhage
☐1	☐0	☐9	C. Peripheral Vascular Disease	☐1	☐0	☐9	M. Current Smoker (within past month)
☐1	☐0	☐9	D. Prior MI	☐1	☐0	☐9	N. Previous Smoker
☐1	☐0	☐9	E. Prior PTCA	☐1	☐0	☐9	O. Renal Insufficiency (Creatinine > 1.5)
☐1	☐0	☐9	F. Prior CABG	☐1	☐0	☐9	P. Malignancy (any kind)
☐1	☐0	☐9	G. COPD on Meds	☐1	☐0	☐9	Q. History of ICD
☐1	☐0	☐9	H. History of SCD	☐1	☐0	☐9	R. History of AF
☐1	☐0	☐9	I. History of VT	☐1	☐0	☐9	S. Other _____
☐1	☐0	☐9	J. History of VF				

CARDIAC ARREST DATA

1. Date and Time of arrest: __/__/__ __ __ __ __ (MO / DAY / 4-Digit YEAR) __ __:__ __ (Military time)

2. Was arrest witnessed? ☐1 YES ☐0 NO

3. Bystander CPR? ☐1 YES ☐0 NO (Before arrival of CPR team)

4. Amplitude of initial VF rhythm _____(mv)

5. Location of arrest? ☐1 RMF ☐2 Stepdown ☐3 MICU ☐4 CCU ☐5 Cath-lab ☐6 EP lab ☐7 Other _____

6. Suspected cause of arrrest
   ☐1 YES ☐0 NO A. Primary arrhythmia
   ☐1 YES ☐0 NO B. Pulmonary embolism
   ☐1 YES ☐0 NO C. Tamponade

7. TMS? ☐1 YES ☐0 NO

8. Initial cardiac rhythm
   ☐1 YES ☐0 NO A. VF
   ☐1 YES ☐0 NO B. Pulseless VT
   ☐1 YES ☐0 NO C. Asystole converting to VF
   ☐1 YES ☐0 NO D. PEA converting to VF

9. Rhythm at time of study drug:
   ☐1 YES ☐0 NO A. VF
   ☐1 YES ☐0 NO B. PVT
   ☐1 YES ☐0 NO C. Other pulseless rhythm
   ☐1 YES ☐0 NO D. Supraventricular rhythm

10. Additional treatments given during CPR

☐1 YES	☐0 NO	A. Sodium bicarbonate	☐1 YES	☐0 NO	I. Insulin
☐1 YES	☐0 NO	B. Atropine	☐1 YES	☐0 NO	J. Fibrinolysis
☐1 YES	☐0 NO	C. Lidocaine	☐1 YES	☐0 NO	K. Adenosine
☐1 YES	☐0 NO	D. Amiodarone	☐1 YES	☐0 NO	L. Cardizem/Verapamil
☐1 YES	☐0 NO	E. Procainamide	☐1 YES	☐0 NO	M. Dobutamine
☐1 YES	☐0 NO	F. Magnesium	☐1 YES	☐0 NO	N. Dopamine
☐1 YES	☐0 NO	G. Vasopressin	☐1 YES	☐0 NO	O. Norepinephrine
☐1 YES	☐0 NO	H. Calcium gluconate/chloride	☐1 YES	☐0 NO	P. Phenylephrine

DATES AND TIMES

1. Date and Time of 1st responder:	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
2. Date and Time of CPR team	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
3. Date and Time of onset of CPR	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
4. Date and Time of 1st Defibrillation	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	#Joules _____
5. Date and Time of 2nd Defibrillation	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	#Joules _____
6. Date and Time of 3rd Defibrillation	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	#Joules _____
7. Date and Time of 4th Defibrillation	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	#Joules _____
8. Date and Time of IV access	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
9. Date and Time of tracheal intubation	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
10. Date/Time of study drug administration	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
11. Date/Time of 2nd injection of study drug	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
12. Date and Time of Amiodarone admin	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	
13. Date and Time of Vasopressor admin	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR	__ __: __ __ (Military time)	

TREATMENT DATA

I. PRE STUDY DRUG

1. ☐1 YES ☐0 NO Transient return of spontaneous circulation
2. _____ Number of shocks
3. ☐1 YES ☐0 NO Treatment for Bradycardia
4. ☐1 YES ☐0 NO Antiarrhythmic drug treatment
   - A. ☐1 YES ☐0 NO Prophylactic
   - B. ☐1 YES ☐0 NO For VF or PVT
5. ☐1 YES ☐0 NO Pressor

II. POST STUDY DRUG

1. _____ Total duration of resuscitative effort (minutes)
2. Date/Time of 1st shock __ __/__ __/__ __ __ __ (MO / DAY / 4-Digit YEAR) __ __: __ __ (Military time)
3. Date/Time of 2nd shock __ __/__ __/__ __ __ __ (MO / DAY / 4-Digit YEAR) __ __: __ __ (Military time)
4. Date/Time of 3rd shock __ __/__ __/__ __ __ __ (MO / DAY / 4-Digit YEAR) __ __: __ __ (Military time)
5. _____ # of shocks until return of spontaneous circulation
6. ☐1 YES ☐0 NO Treatment for Bradycardia
7. ☐1 YES ☐0 NO Antiarrhythmic drug treatment
   - A. ☐1 YES ☐0 NO Prophylactic
   - B. ☐1 YES ☐0 NO For VF or PVT
8. ☐1 YES ☐0 NO Pressor
9. Blood pressure (mmHg) SBP _____/ DBP _____
10. Heart rate _____ beats/min
11. Rhythm
    - ☐1 YES ☐0 NO A. Supraventricular
    - ☐1 YES ☐0 NO B. Paced rhythm
    - ☐1 YES ☐0 NO C. Heart block
    - ☐1 YES ☐0 NO D. Wide complex ≤ 150 beats/min
    - ☐1 YES ☐0 NO E. Wide complex >150 beats/min
13. Spontaneous circulation restored with study drug? ☐1 YES ☐0 NO

CONCOMITANT MEDICATIONS

At Home	IH-Pre arrest	During CPR	IH- Post arrest	
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	1. ARB
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	2. ACE Inhibitors
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	3. ASA:
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	4. Beta blocker
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	5. Calcium channel blocker
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	6. Digoxin
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	7. Diuretics
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	8. Ticlid:
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	9. Plavix:
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	10. Cholesterol lowering agents, (Statin)
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	11. Nitrates (Oral)
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	12. Vasopressin
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	13. Amiodarone
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	14. Lidocaine
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	15. Sodium bicarbonate
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	16. Sotalol
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	17. Oral hypoglycemics
☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	☐0 NO ☐1 YES	18. Insulin

IN-HOSPITAL EVENTS OCCURRING SINCE ENROLLMENT

YES	NO		Date of first occurrence
☐1	☐0	1. Death	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	2. CVA If YES: ☐1 Stroke ☐0 TIA If STROKE, was it disabling? ☐1 YES ☐0 NO	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	3. Myocardial Infarction If YES: ☐1 Q-wave ☐0 Non q-wave	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	4. Cath	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	5. PCI/Stent	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	6. CABG	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR
☐1	☐0	7. Bleed. If YES: Was patient transfused? ☐1 YES ☐0 NO If YES: How many units _____ Hemoglobin _____	__ __/__ __/__ __ __ __ MO DAY 4-Digit YEAR

DISCHARGE INFORMATION

1. Date and time of **FINAL** hospital discharge __ __/__ __/__ __ __ __ (MO DAY 4-Digit YEAR) __ __: __ __ (Military time)

2. Total number of days in hospital? _____ (Total days = Final discharge date-admission date)

3. Total number of days in ICU? _____

4. Discharged to: ☐1 Home ☐2 Extended care facility ☐3 Died

5. Cerebral performance:

- ☐1 Good
- ☐2 Moderate
- ☐3 Severe
- ☐4 Coma or vegetative state
- ☐5 Brain Death

Cerebral Performance Categories (CPC Scale):

CPC 1: Good cerebral performance; conscious, alert, able to work, might have mild neurologic or psychologic deficit

CPC 2: Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment.

CPC 3: Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.

CPC 4: Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/wake cycles. Cerebral unresponsiveness.

CPC 5: Brain death: apnea, areflexia, EEG silence, etc.