81st MEDICAL GROUP
PROPOSAL FOR CLINICAL INVESTIGATION
(Human Study)
Federalwide Assurance (FWA) # FWA00004447 / DoD Assurance of Compliance # 50003

1. Protocol Number: FKE20140029H

(Assigned by the Clinical Research Laboratory (CRL) Protocol Office staff.)

2. Title of Protocol: "Short-Term Application of Tocilizumab following Myocardial Infarction (STAT-MI)"

Include target disease(s), study type (e.g., Phase I, Phase II, Phase III, pilot), investigational drugs or procedures, and if study is multi-institutional.

3. Date Approved by Institutional Review Board (IRB):

(Entered by the CRL Protocol Administrator).

4. Signature Section:

4.1. Principal Investigator

I am aware that I am not authorized to accept any funds or other form of compensation for conducting this research. All subjects will be treated in compliance with all applicable organizational, service, DoD, and Federal regulations, and all applicable FDA and HHS guidelines. I have read, understand, and signed the Certificate of Compliance. I understand I must submit a review of this protocol in the form of a progress report at least once annually to obtain continuation approval and a final report when the study is completed. I will notify the Clinical Research Laboratory's Protocol Coordinator prior to any PCS or separation actions.

_____ _____

MATTHEW B. CARROLL, Col, USAF, MC, FACP, FACR **Date**
81 MDOS/SGOMJ

4.2. PI's Squadron/Flight Commander

I have reviewed this proposal and conducted an appropriate peer scientific review and found this study to be consistent with good scientific research practice. I approve my flight's personnel support requirements. I understand that I will be the point of contact for correction of deficiencies should the Principal Investigator fail to meet the compliance requirements. I find this proposal to have sufficient scientific merit for consideration by the Institutional Review Board.

_____ _____

CHERRI' L. SHIREMAN, Col, USAF, NC **Date**
81 MDOS/CC

4.3. Statistical Review: As a person knowledgeable in statistics I have reviewed and approved the study design of this proposal IAW DoD Assurance of Compliance #50003.

_____ _____

SUIZHAO WANG, GS-13, MD, PhD **Date**
CRL Biostatistician

4.4. Medical Monitor: I understand and agree to fulfill the responsibilities of a Medical Monitor IAW AFI 40-402 and the guidance I have received from the IRB. I also agree to complete the required website training. *(Requirement for all Greater Than Minimal Risk proposals)*

_____ _____

CHRISTOPHER TESSIER, Maj, USAF, MC **Date**
81 MDOS/SGOMM

4.5. Primary Reviewer: I have conducted an appropriate human subject protection review of this proposal and found it to be in compliance with AFI 40-402, and applicable FDA and HHS guidelines.

_____ _____

DAWN HIGGINS, Maj, USAF, NC **Date**
81 MDSS/SGSX

4.6. IRB Chairperson: This proposal was reviewed and approved by the 81st Medical Group Institutional Review Board.

_____ _____

DAWN HIGGINS, Maj, USAF, NC **Date**
Acting Chairperson, 81 MDG IRB

5. Personnel: *(Nothing goes on this line. Fill out items below)*

5.1. Principal Investigator: *State first and last name, grade, service branch, corps, specialty, squadron/office symbol, phone, beeper number, and email.*

Matthew B. Carroll, Col, USAF, MC, FACP, FACR, Staff Rheumatologist, 81st MDOS/ SGOM, Phone 376-3829, Pager 382-8316, Email: Matthew.carroll.1@us.af.mil

5.1.1. Date Principal Investigator Completed Website Training: 20 June 2013

5.2. Associate Investigator(s): *State first and last name, grade, service branch, corps, specialty, squadron/office symbol, e-mail, phone, and beeper number.*

Charles Haller, Captain, USAF, MC, 81st MDOS/SGOM, Internal Medicine Resident, Phone: 376-0400, Pager 228-382-8321, email: Charles.Haller.1@us.af.mil

Christopher D. Smith, Captain, USAF, MC, 81st MDOS/SGOM, Internal Medicine Resident, Phone: 376-0400, Pager 228-257-7254, email: Christopher.Smith.305@us.af.mil

Rishawn Carriere-Ducre, Contractor, USAF, Clinical Research Coordinator, 81st MDSS/ SGSE, Phone 228-376-4376, Email: rishawn.carriere-ducre.ctr@us.af.mill

Audrey D. Greenwell, Contractor, USAF, Clinical Research Coordinator, 81 MDSS/ SGSE; Phone 228-376-4352, Email: audrey.greenwell.ctr@us.af.mil

Contractors with The McConnell Group, Inc. are covered by Federalwide Assurance #FW00018069, Addendum # F50492, and a DoD IAIR with the 81st Medical Group. They have completed the required investigator website training.

5.2.1. Date Associate Investigator(s) Completed Website Training:

Capt Haller – 9 June 2014
Capt Smith – 17 March 2014
Ms. Carriere-Ducre – 15 November 2013
Ms. Greenwell – 14 April 2014

5.3. Collaborative Investigator(s): None

5.4. Medical Monitor: *For studies that are classified as Greater Than Minimal Risk human subjects, provide the first and last name, grade, service branch, corps, specialty, department, office symbol, e-mail, phone, fax, beeper number, curriculum vitae, and website training date of individual who agrees to serve as the Medical Monitor for this study. This person cannot be an investigator on this study. The CRL Protocol Coordinator will provide a copy of the Medical Monitor responsibilities. (For Cooperative Oncology Group studies, a Medical Monitor is not needed if a data safety monitoring board is overseeing the study. For FDA regulated studies, the sponsor appointed monitor may satisfy this requirement.)*

Christopher Tessier, Major, USAF, MC, Staff Endocrinologist, 81st MDOS/SGOMM, Phone: (228) 376-3629, Email: Christopher.tessier@us.af.mil

5.4.1. Date Medical Monitor Completed Website Training: 10 July 2014

5.5. Medical Facility Commander: Thomas W. Harrell, Col, USAF, MC, CFS, Commander, 81st Medical Group
(Change accordingly if submitting from institution other than 81st Medical Group)

6. Study Classification:

6.1. Level of Risk: Greater Than Minimal Risk

Choose the most appropriate and delete the other. ***The IRB will ultimately determine the level of risk.***
Definition: *Minimal Risk exists when the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*

6.2. Research Focus Area: TREATMENT, DIAGNOSIS, OR OTHER (TDO). These would be proposals that evaluate diagnostic procedures or acute interventions that treat a current medical condition. In addition, some proposals may address questions that do not fall into the other categories (ex: materials testing, experiments in cell biology, analytical chemistry, etc.)

6.3. Medical Research Area: Internal Medicine, Cardiology

7. Abstract:

Provide a brief description (< 250 words) of the proposed study. This is a stand-alone description of the study that will be added to the IRB agenda and meeting minutes, and should include the aims/objectives of the study, including the hypotheses or research questions; and the research design, sample, data collections methods, and statistical analysis. It is suggested that this section be written after sections 6-11 have been written.

Introduction: Interleukin 6 (IL-6) is a cytokine that has a pro-inflammatory effect on the immune system. In acute MI IL-6 levels rapidly increase in response to ischemia and inflammation. Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). The use of tocilizumab within the first 24 hours of admission for acute MI could reduce 30 day mortality.

Methods: This randomized, placebo controlled trial will assign subjects within 24 hours of admission to treatment with either 162 mg of tocilizumab subcutaneously once or placebo in addition to usual pharmacologic and interventional standard of care for acute MI (ST segment elevation MI or non-ST segment elevation MI).

Outcomes: The primary outcome is difference in 30 day (plus/minus 5 days) occurrence of major adverse cardiac events (as defined later in this protocol) between placebo and Tocilizumab treated groups. Secondary outcomes to be assessed include length of hospitalization, readmission rates by day 30, CRP levels at 0 hours, 24 hours, 48 hours, and 30 days following treatment, and safety of Tocilizumab with focus on rates of known side effects.

8. Research Proposal: *(Nothing goes on this line. Fill out the items below.) These sections below should be concisely written for the proposal users (i.e., clinical associates, nurse practitioners, research nurses), yet include sufficient information to allow for a critical review by the Scientific Reviewer and the IRB members.*

8.1. Purpose and Significance: *State the problem or question under study (e.g., describe the disease and current limitations of knowledge or therapy). State concisely the importance and health relevance of the research described by relating the specific aims to the broad, long-term objectives. State the practical application(s). Significance is often demonstrated using numbers affected, cost of care, impact on quality of life, etc.*

Interleukin 6 (IL-6) is a cytokine that has a pro-inflammatory effect on the immune system. Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling - they are released by cells and affect the behavior of other cells, and sometimes the releasing cell itself. IL-6 is an important mediator of fever and of the acute phase response. IL-6 is responsible for stimulating acute phase protein synthesis as well as the production of neutrophils in the bone marrow. The acute-phase response is the detectable change in acute phase proteins, a class of proteins whose plasma concentrations increase or decrease in response to inflammation. IL-6 is secreted by T cells and macrophages to stimulate the immune response during infection and after trauma, especially burns or other tissue damage leading to inflammation. Smooth muscle cells in the tunica media of many blood vessels also produce IL-6 as a pro-inflammatory cytokine. IL-6 is capable of crossing the blood-brain barrier [Banks WA, et al 1994] and triggering production of Prostaglandin E2 in the hypothalamus, thereby changing the body's temperature set point. In muscle and fatty tissue, IL-6 stimulates energy mobilization that leads to increased body temperature. IL-6 can be secreted by macrophages in response to specific microbial molecules, referred to as pathogen-associated molecular patterns (PAMPs). IL-6 is also produced by adipocytes and is thought to be a reason why obese individuals have higher endogenous levels of CRP.[Bastard J, et al 1999] IL-6 signals through a cell-surface type I cytokine receptor complex consisting of the ligand-binding IL-6Rα chain (CD126) and the signal-transducing component gp130 (also called CD130). CD130 is the common signal transducer for several cytokines but the expression of CD126 is restricted to certain tissues. As IL-6 interacts with its receptor, it triggers the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through certain transcription factors.[Heinrich PC, et al 1998]

Acute Myocardial Infarction (MI) occurs when myocardial ischemia, a diminished blood supply to the heart muscle, exceeds a critical threshold and overwhelms myocardial cellular repair mechanisms designed to maintain normal function. Ischemia at this critical threshold level for an extended period results in irreversible myocardial cell damage or death. A common clinical diagnostic classification scheme is based on electrocardiographic findings as a means of distinguishing between two types of acute MI, one that is marked by ST elevation (STEMI) and one that is not (NSTEMI). In acute MI IL-6 levels rapidly increase in response to ischemia and inflammation. In one study, plasma IL-6 levels were increased at all sampling points from admission to discharge in patients with acute MI as compared with IL-6 levels in controls.[Miyao Y, et al 1993] Cardiac catheterization did not influence plasma IL-6 levels.[Miyao Y, et al 1993] In another study, patients with acute MI demonstrated a peak in IL-6 levels on days 1 and 2 which then declined rapidly to lower, although not normalized, levels during hospitalization and at 6 and 12 weeks.[Gabriel AS, et al 2004] It has also been demonstrated that elevated levels of IL-6 are associated with worse outcomes in acute MI. In one study elevated IL-6 levels at day 1 and day 30 were independent predictors of adverse events.[Lopez-Cuenca, A et al 2013] In another study, on univariante analyses, baseline IL-6 was related to death but not recurrent

non-fatal acute coronary syndromes.[Zamani P, et al 2013] Another study demonstrated significant correlations between increased IL-6 levels and impaired left ventricle systolic and diastolic function supportive of a role of IL-6 in post-infarction cardiac damage.[Karpinski L, et al 2008] This same group also demonstrated that an increased level of IL-6 in acute MI was an independent predictor of left ventricle systolic and diastolic dysfunction 6 months after MI.[Karpinski L, et al 2008]

Tocilizumab is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). The drug is administered as either a monthly intravenous infusions or as a weekly subcutaneous injection. The dose of the monthly infusion can vary between 4 mg/kg and 8 mg/kg but the once a week injection is 162 mg subcutaneously. The medication is currently FDA approved for the treatment of Rheumatoid Arthritis. In patients with rheumatoid arthritis IL-6 is overproduced in the body, causing fatigue, anemia, inflammation and damage to bones, cartilage and tissue. Tocilizumab blocks the action of IL-6 and reduces these effects. The most common adverse effects of tocilizumab in clinical studies were respiratory tract infections, headaches, hypertension, and elevations in liver tests suggesting liver injury. Injection site reactions (rash, redness, swelling, itching) may also occur. Use of tocilizumab has been associated with serious infections such as tuberculosis, sepsis, and fungal infections. Individuals with active infections should not be treated with tocilizumab. Tocilizumab may worsen or cause new diseases of the nervous system. Other side effects include reduced levels of white blood cells or platelets, reactivation of herpes zoster infection (shingles), and hypersensitivity (allergic) reactions. In studies, gastrointestinal perforation was observed in patients with diverticulitis.

Based on the known elevation and persistence of this elevation as well as the pathophysiologic effects that IL-6 has on the heart in acute MI, we hypothesize that the administration of a single dose of tocilizumab, 162 mg subcutaneously once within 24 hours of admission for treatment of a patient's acute MI, will be beneficial in lowering 30 day (plus/minus 5 days) MACE (as defined in Section 8.3) in addition to ALL the routine, standard of care medications and interventions normally provided for NSTEMI or STEMI.

Secondary endpoints that will be studied include length of hospitalization, readmission within 30 days, CRP levels at 0 hours, 24 hours, 48 hours, and 30 days (plus/minus 5 days) following injection, symptoms and quality of life as described in questionnaire at 30 day phone follow up, and safety of Tocilizumab throughout 30 day period.

A trial was found on www.clinicaltrials.gov in mid July 2014 which looked at the effective of a single intravenous dose on the primary outcome of change in high sensitivity C-reactive protein area under the curve (AUC) [www.clinicaltrials.gov trial NCT01491074]. Secondary outcomes assessed by this trial were mainly non-clinical in nature (coronary flow reserve, endothelial function, left ventricular function and size, and infarct size). This trial will differ from this study in that clinically relevant outcomes will be assessed and a single subcutaneous dose of tocilizumab will be administered.

8.2. Hypotheses/Research Questions:

State the specific hypotheses or research questions you wish to test.

H_o: The use of a single subcutaneous injection of tocilizumab (Actemra) within 24 hours of admission for a myocardial infarction (STEMI or NSTEMI) does NOT affect the 30 day rate of major adverse cardiac events.

H_a: The use of a single subcutaneous injection of tocilizumab (Actemra) within 24 hours of admission for an acute myocardial infarction (STEMI or NSTEMI) does lower the 30 day (plus/minus 5 days) rate of major adverse cardiac events.

8.3. Study Objectives: *State in bullet form the primary and secondary study objectives. Specific endpoints such as survival, response, or change in surrogate markers should be defined.*

Primary Outcome: 30 day rate of major adverse cardiac events (MACE) following administration of Tocilizumab IV single dose within 24 hours of NSTEMI or STEMI as compared to administration of placebo. This data will be gathered by telephone interview at day 30 (plus/minus 5 days)* to after receipt of either the active medication (tocilizumab) or placebo.

*-We request a window of plus/minus 5 days around the day 30 follow-up phone interview to allow for delays in reaching subject due to holidays, "down" Fridays, or difficulty reaching the subject.

**Major adverse cardiac events will be defined as death, repeat STEMI, repeat NSTEMI, new arrhythmia, septal/valvular rupture, dissection, pericarditis, tamponade, and any other significant changes in the subjects health that may have developed.

Secondary Outcomes:

- Length of initial hospitalization
- Readmission within 30 day study period
- CRP at 0 hours, 24 hours following injection, 48 hours following injection, and at 30 days
- Symptoms and quality of life as described by patient at 30 day telephone follow up. Specific questions detailed in attached Questionnaire.
- Safety of Tocilizumab to include known side effects noted during admission and at 30 day telephone follow-up. These include serious infections, GI perforations, and anaphylaxis.

The secondary outcomes will be collected at day 30 in the same fashion as the primary outcome (phone interview) although the subject will be requested to present to the Keesler Medical Center lab for a repeat CRP.

8.4. Background and Rationale:
Provide relevant scientific background: experimental and clinical rationale, description of supportive clinical studies including toxicities of drugs or procedures, justification for specific study design, and description of alternative treatment approaches (i.e., both standard care and state of the art). Include key references, but not a complete literature review.

The Keesler Medical Center Cardiology Service is the busiest Cardiology service in the AFMS. Well over 1000 cardiac catheterizations are performed annually. About 60 – 70% of these catheterizations are performed on an elective basis (i.e. subject is

clinically stable, has no active chest pain, but has symptoms concerning for occlusive coronary artery disease that may benefit from placement of a stent). The other 30 – 40% are performed for patients that experience symptoms consistent with an acute myocardial infarction (chest pain, elevation in cardiac biomarkers, with or without EKG changes). Thus, there are at least 200 subjects annually that could potentially be eligible for this study. After applying the exclusion criteria listed, there should still be at least 125 – 150 subjects annually that would be eligible for this study. With our statistical analysis supporting the need to enroll 98 patients, assuming a 25% drop out rate, we anticipate that 125 subjects will potentially need to be enrolled to reach a meaningful statistical assessment of the primary outcome.

As explained in Section 8.1 above, the reason for studying the primary endpoint is that this is a typical endpoint of pharmacologic interventions when assessing their effectiveness in treating acute MI (NSTEMI or STEMI).

Length of Admission: A significant change in length of admission between groups may represent a significant cost related factor in the absence of difference in primary outcome.

Readmission: A significant change in readmission would potentially influence both healthcare cost and patient morbidity.

Recurrence/Complications: This outcome would assess cardiac morbidity between study groups and represents a typical endpoint of pharmacologic intervention when assessing their efficacy in treating acute MI.

CRP: Assessment of CRP at discharge and 30 days may offer insight into the impact of single dose therapy these biomarkers. This data may be used for adjustment of dosing to optimize outcome in follow up trials.

Symptoms and Quality of Life: Will be assessed using a teleconsult standardized questionnaire. These outcomes carry significance to overall patient wellbeing.

Safety of Tocilizumab: As a new medication in the treatment of a common condition the secondary endpoint of safety is always important to assess as a new therapy may be effective but if it has a high rate of adverse or serious adverse events then the number needed to treat may be more than the number needed to harm.

At the current time it is not known what impact tocilizumab will have on the secondary endpoints of this trial. It is anticipated that by blocking IL-6 very early in the pathologic process of myocardial infarction (as this protocol proposes), jeopardized myocardial will heal faster, thus subjects will hopefully feel better faster (improved quality of life and resolution of symptoms), the amount of time they spend in the hospital will be shorter, and they will not have another heart attack soon after the one they were admitted for. It is also anticipated that one injection of tocilizumab will not have any adverse effects.

At the time of this protocol, the mortality rate for NSTEMI and STEMI within 30 days of admission is 2% and 3 – 5% respectively.[Roe 2010] The rate of rehospitalization for recurrence, heart failure, or other changes within 30 days for either NSTEMI or STEMI is 17 – 25%.[Joynt 2011] It has been shown that mortality and recurrence/readmission have been steadily decreasing over the last decade or so. The reason for the decline has been earlier aggressive pharmacologic treatment, institution of new medications to treat NSTEMI/STEMI (such as statins and blood thinners such as Lovenox®), and opening blocked arteries with coronary artery stenting.

9. Study Design:

Describe research study design. State in detail how the research is designed to answer the hypotheses/research questions, and how the research is to be conducted. Provide an estimate of the length of time the proposal will be open. Identify any distinct phase points (subject accrual, treatment phase, follow-up, data analysis, etc). Include, if applicable, any or all of the following:

Within 24 hours of admission for acute MI (STEMI or NSTEMI), subjects eligible for the study will be interviewed to verify accuracy of the diagnosis and presence of exclusion criteria which would make the subject ineligible to participate. Once a subject has been found to be eligible to participate in the study and then signs the written consent, the subject will be randomized to receive either tocilizumab 162 mg subcutaneously once or matching placebo once. No additional doses of tocilizumab will be administered.

As part of this protocol, ALL subjects will receive the usual/standard of care pharmacologic and other interventions currently used for the treatment of acute MI. These interventions include but are not limited to administration of aspirin, clopidogrel, a statin (typically atorvastatin), beta-blocker medications, nitroglycerin, Heparin or low-molecular weight heparin medications, Glycoprotein IIb/IIIa medications, and interventions such as cardiac catheterization with stent placement or referral for bypass. The study will NOT affect the treating provider's decision about which and when these various standard of care interventions would be used.

- Drug Administration (if applicable)

Describe fully and clearly how all drugs specified in the proposal are prepared and administered, including special precautions. Clinical associates who write the orders and nurses who administer the therapy must be able to clearly understand this section.

Within 24 hours of admission, all patients with an acute MI (STEMI or NSTEMI) will be interviewed and if they are eligible for this study will be randomized to receive either one subcutaneous injection of tocilizumab 162 mg once or placebo once. The study medication will be ordered through our Inpatient Pharmacy (which supports Inpatient operations and is thus available 24 hours a day, 7 days a week) and administered by a Registered Nurse on the inpatient ward. It will be administered in the usual fashion as when patients with Rheumatoid Arthritis administer it for their arthritic condition.

- Treatment Modifications (if applicable)

Describe fully the criteria for dose modifications and/or other modifications of the treatment regimen made in response to toxicity, pharmacokinetics, tissue studies, etc.

There are no study medication treatment modifications that will be permitted during this trial.

- Pharmacokinetic Studies (if applicable)

Describe dose(s) to be monitored, sampling time points and sample handling procedures. Include type of specimen tubes, minimum blood volume, and person responsible for blood collection and transport. Include pharmacokinetic worksheet in an appendix.

N/A

- On Study Evaluation (if applicable)

In checklist format, describe required on study evaluations and include a schema in an appendix. Include all necessary evaluations as outlined above in the section on Pre-Treatment Evaluation. Provide nursing guidelines for monitoring vital signs if these parameters are used in the study.

- Consent the patient
- Verify patient meets inclusion and has no exclusion criteria as detailed below.
- Collect sample from unblinded pharmacy.
- Treat patient with sample within 24 hours of admission.
- Check CRP at 0 hours, 24 hours, 48 hours, and 30 days (plus/minus 5 days) following treatment
- Telephone follow-up with patient or family of patient 30 days (plus/minus 5 days) following treatment utilizing questions from questionnaire.

We request a window of plus/minus 5 days around the day 30 follow-up phone interview and repeat lab (CRP) to allow for delays in reaching subjects due to holidays, "down" Fridays, weekends, travel delays the subject may experience, or difficulty reaching the subject.

- Concurrent Therapies (if applicable)

Provide guidelines for concurrent therapy such as PCP prophylaxis in HIV-infected patients, and list contraindicated therapies (describe drug interactions if known).

As part of this protocol, ALL subjects will receive the usual/standard of care pharmacologic and other interventions currently in place for the treatment of acute MI. These interventions include but are not limited to administration of aspirin, clopidogrel, a statin (typically atorvastatin), beta-blocker medications, nitroglycerin, Heparin or low-molecular weight heparin medications, Glycoprotein IIb/IIIa medications, and interventions such as cardiac catheterization with stent placement or referral for bypass. The study will not affect the treating providers decision about which and when these various standard of care interventions should be used.

~~Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and~~

~~CYP3A4. Its effects on CYP2C8 or transporters are unknown. *In vivo* studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of tocilizumab, respectively.~~
(request removal of paragraph above)

- Surgical Guidelines (if applicable)

There are NO surgical interventions that will be part of this protocol

- Radiation Therapy Guidelines (if applicable)

There are NO radiation therapies offered as part of this protocol.

- Off Study Criteria (if applicable)

Describe criteria which will result in a subject being taken off-study. Include voluntary patient withdrawal, disease progression or resolution, significant organ toxicity, and non-compliance. Describe any testing to be performed if a subject is taken off-study (i.e. final evaluation).

Patients may voluntarily withdrawal from the study at any time without penalty and without affecting the standard of care for the ongoing treatment of their acute MI that they would normally receive (care received either as an inpatient or outpatient. No other off study criteria exist.

- Post-Study Evaluation (if applicable)

In checklist format, describe post-study evaluations (include frequency and tests) and include a schema in an appendix.

- Patient telephone numbers as well as alternate contact numbers for next of kin will be obtained during his or her hospital stay. Patients will be contacted 30 days (plus/minus 5 days) after injection with Tocilizumab and will be asked a series of questions regarding their recovery from their MI, any events, complications or new cardiac diagnoses that developed during that time (attached). Patients will be asked to have a CRP level drawn 30 days (plus/minus 5 days) following treatment at the Keesler Medical Center Laboratory. In the event that a patient cannot be reached by telephone, his or her alternate contact information will be used to gather data regarding possible events.

We request a window of plus/minus 5 days around the day 30 follow-up phone interview and repeat lab (CRP) to allow for delays in reaching subjects due to holidays, “down” Fridays, weekends, travel delays the subject may experience, or difficulty reaching the subject.

10. Sample:

10.1. Number of subjects:

Clearly delineate statistically how the sample size (number of subjects) was determined. For comparative trials, the number of subjects per arm is derived from the expected response rates or other outcome measures, the difference to

be detected, and the power to detect the difference. Background data supporting the predicted response rates and expected difference should be included. Identify the desired difference to be detected, level of significance (α), power of the study (1-β) and sample size. For descriptive studies, tables and formulae are available. Discuss any plans or provisions for verification of assumptions or validation of sample size.

Indicate the number of subjects to be enrolled, and the approximate distribution and stratification (i.e. 150 Total Subjects; 100 Treatment Arm, 50 Placebo Arm). If the proposal will be enrolling subjects at more than one facility, indicate anticipated enrollment by location.

You must contact Dr. Wang, the CRL Biostatistician, for guidance and input in this section before submitting your completed proposal for review. He can be contacted at (228) 376-4358.

Statistical hypotheses:

Primary hypothesis $H_0 1$ – The prevalence of major adverse cardiac events is equal to 0.50

Secondary hypothesis $H_0 2$ – The major adverse cardiac events are equal among Tocilizumab group and Placebo group.

For hypothesis $H_0 1$, in a prevalence study the sample size is determined by how accurately to determine the prevalence. Accuracy is defined by the size of an interval (d or the "margin of error") around the mean of a random variable with the probability (c or the statistical confidence) the random variable takes on values within that interval. As the prevalence of MACE is unknown, convention calls to use an estimated prevalence, p, of 0.50. Using the method by Lwanga and Lemeshow[1], sample size was estimated with *IBM SPSS SamplePower 3* for prevalence at a 95% confidence level with margin error of 10%. Result indicated it will require a sample of 98 subjects to detect a prevalence of 0.50 ± 0.10 at a 95% confidence level. Assume 10% missing, 108 subjects will be required. For primary subjective, we will enroll total 108 patients from 81st Medical Center.

Power for hypothesis $H_0 2$ was assessed using *G*Power Version 3.1.3*[2] for χ^2 - Goodness-of-fit tests. As there is no available data to calculate the effect size, we assume to detect the medium effect size 0.30. The result indicates total 98 subjects will be required to achieve a power of approximately 0.84 to detect a moderate effect size of 0.30 at α = 0.05. As discussed earlier, we will request 125 subjects assuming a potential 25% drop out rate.

χ^2 tests - Goodness-of-fit tests: Contingency tables
Analysis: Post hoc: Compute achieved power

Input:	Effect size w	= 0.3
	α err prob	= 0.05
	Total sample size	= 98
	Df	= 1
Output:	Noncentrality parameter λ	= 8.8200000

[1] Lwanga SK and Lemeshow S. *Sample Size Determination in Health Studies: A Practical Manual*. WHO. 1991, pg 2.

[2] Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007; 39 (2): 175-191.

Critical χ^2 = 3.8414588
Power (1-β err prob) = 0.8437251

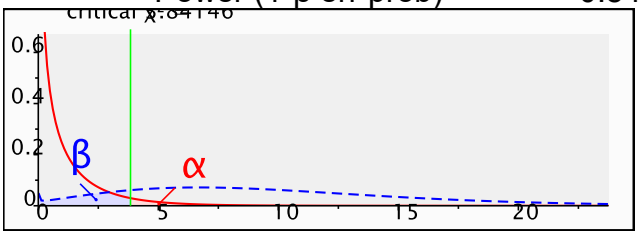

Fig. 1. χ^2 tests - Goodness-of-fit tests: 98 subjects will detect moderate effect size 0.3 with power of .84 at α level .05

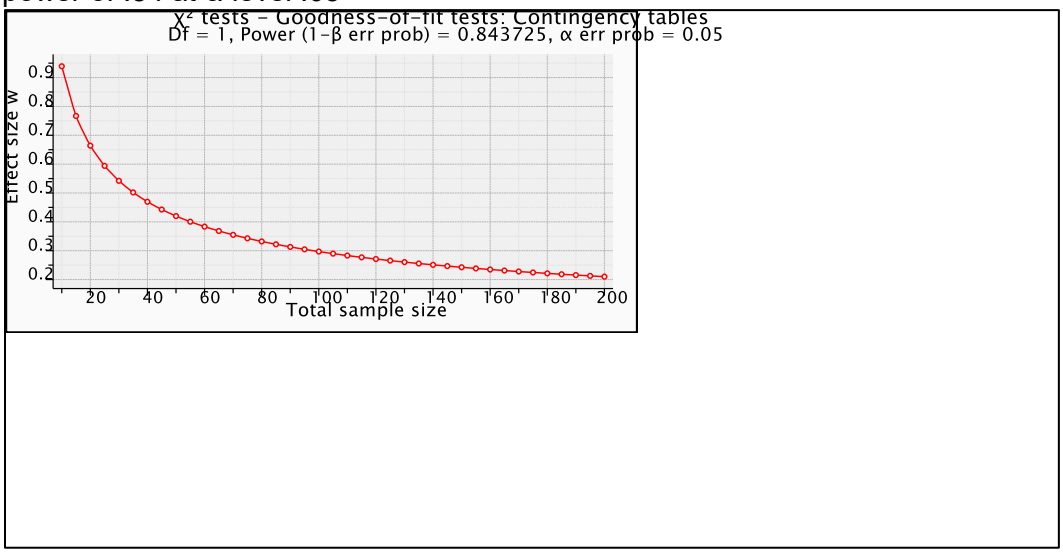

Fig. 2. χ^2 tests - Goodness-of-fit tests: Relationship between effect size and sample size

10.2. Inclusion criteria:

List, in bullet format, inclusion criteria. Define patient population: e.g. age range, disease or disease subtype, stage and risk group. Diagnostic criteria and laboratory parameters which define the disease, stage and/or risk group should be included.

- Subjects over the age of 18 years old
- Subjects who present to Keesler Medical Center with clinical, physical examination, serologic, and electrocardiographic evidence of an acute MI (NSTEMI or STEMI), as determined by the treating physician.

10.3. Exclusion criteria:

List, in bullet format, exclusion criteria which are not directly related to the underlying disease: e.g. organ dysfunction, specific prior therapy, HIV +, pregnant or lactating women, underlying medical conditions such as diabetes, psychiatric disorders (describe assessment procedures and provide justification for exclusion), social situation interfering with study compliance, hypersensitivity to study drugs, and concurrent therapy. Avoid overlap between inclusion and exclusion sections (e.g., inclusion - free of opportunistic infections; exclusion - presence of an opportunistic infection).

- Subjects with clinical, physical examination, or radiographic evidence suspicious for active Tuberculosis (TB)
- Subjects with a known history of Hepatitis B or Hepatitis C infection
    - This exclusion refers specific subjects who are actively being treated with medications for Hepatitis B or C or who have known virologic evidence on ongoing infection with Hepatitis B or C
- Subjects who are immune compromised including transplant recipients, patients with HIV, etc.
- Subjects with evidence of Tuberculosis infection on chest xray
- Subjects with known allergic reaction to tocilizumab or other IL-6 inhibitors
- Subjects with clinical, physical examination, serologic, or radiographic evidence of active infection
- Subjects receiving therapy for malignancy—this will ***not exclude*** subjects receiving therapy for non-melanoma skin cancer such as basal cell carcinoma or squamous cell carcinoma of the skin
- Female subjects who are pregnant or breast-feeding
- Subjects with existing cognitive impairment such as known moderate to severe dementia or subjects who present with new onset delirium

Women of childbearing age will be offered participation in this trial after they have received a pregnancy test which is negative. Women who have had a hysterectomy or who are post-menopausal will not have a pregnancy test prior to enrollment but this will be documented in the medical record.
While live vaccines are not administered to patients with acute MI, subjects will be educated to not receive any live vaccines for 30 days after receiving the tocilizumab injection.

As the current medical literature supports a rapid rise of IL-6 within the first 1 – 2 days of acute MI this would preclude the time it takes to have a PPD or Quantiferon TB test performed (results take at least 2 – 3 days). To have the most effect tocilizumab will need to be administered within the first 24 hours of admission.

Screening for active TB in this trial will be clinical and radiographic. To screen for active TB patients will undergo a routine admission history and physical examination to look for symptoms and signs related to their acute MI but also to look for other active medical conditions. Universally, at the time of admission, patients have an extensive battery of serologic, radiographic, and electrocardiographic studies to help assess the severity of the patient's acute MI but also to characterize the type (STEMI vs. NSTEMI) and to screen for other illnesses such as infection, bleeding disorders, etc. A Chest X-Ray is universally performed as part of the work-up for acute MI to look for additional disorders such as aortic dissection, pneumonia, etc.

At a minimum Chest X-Ray must be performed for all acute MI as interventions such as cardiac catheterization would be contraindicated in someone with aortic dissection. It is important to noted that ALL of the investigations noted (from the history and physical

exam to the blood tests, X-rays, etc.) are standard of care and NOT requested to be performed as part of this study. It is with near 100% certainty that all of these tests will have been performed, again as they are standard of care. With all of this information already available, a sufficient screen for active TB can be made. It has been demonstrated that Chest X-Ray and combinations of Chest X-Ray and symptoms were more sensitive and more accurate screening strategies for identifying TB cases than symptom screening alone.[van't Hoog AN, et al 2012]

Performing sputum microscopy on all participants in this study did not yield additional suspects.[van't Hoog AN, et al 2012] Integrating the obtained clinical history, the physical examination performed at admission, and the results of the Chest X-Ray, subjects will be excluded if they have signs or symptoms suspicious for infection. They will also be excluded if they have abnormalities on Chest X-Ray that could be consistent with neoplasia, infection (such as pneumonia), aortic dissection, vasculitis (cavitation), or active TB. Essentially, subjects with a normal Chest X-Ray or evidence of heart failure will be considered for enrollment in this trial, otherwise any other changes on Chest X-Ray would preclude enrollment.

For latent TB we do not feel that the one-time administration of a biologic response modifier such as tocilizumab will meaningfully increase the risk of reactivation of TB. Keane et al in 2001 documented a median number of doses to reactivation of TB was 3.[Keane J, et al 2001] This early study suggested that chimeric monoclonal antibodies like infliximab was associated with an increased risk of TB reactivation as compared to the humanized extracellular portion of the tumor necrosis factor receptor.[Keane J, et al 2001] The risk of TB reactivation appears to be low for tocilizumab.[De Keyser F 2011]

As of 2011 no cases of tuberculosis reactivation under tocilizumab treatment were reported despite the fact that most clinical trials with tocilizumab did not perform TB screening and TB was an exclusion criterion in only two trials. It has been considered that this significantly decreased risk is due to the well-established role of IFN-γ production in the antituberculosis immune response. I*n vitro* findings that tocilizumab, in contrast with infliximab and etanercept, does not impair IFN-γ production in response to mycobacterial antigen exposure and Mycobacterium tuberculosis-induced interleukin 6 inhibits the responsiveness of macrophages towards IFN-γ, may suggest a low risk for TB reactivation during tocilizumab therapy.[De Keyser 2011]

As noted earlier the role of a single dose of tocilizumab has been studied in a different trial (www.clinicaltrials.gov trial NCT01491074). This trial did NOT exclude subjects with risk factors for TB and did not actively screen subjects for TB prior to the subject receiving a larger dose of this medication. This trial adds additional insight that tocilizumab can reasonably safely be given as a one-time dose without the need for aggressive TB screening.
[http://www.clinicaltrials.gov/ct2/show/NCT01491074?term=tocilizumab+and+myocardial&rank=1]

10.4. Rationale for subject selection:

Explain why you have restricted subject enrollment to those subjects meeting your inclusion criteria. The proposal must include (a) a rationale for research subject selection based on a review of gender/ethnic/race categories at risk for the disease/condition being studied; (b) strategies/procedures for recruitment (including advertising, if applicable); and (c) justification for exclusions, if any. If the proposal involves subject enrollment at multiple sites, describe plans for ensuring appropriate IRB review and approval at each site. Explain the rationale for the involvement of special classes of subjects, if any, such as fetuses, pregnant women, children, cognitively impaired individuals, prisoners or other institutionalized individuals, or others who are likely to be vulnerable. Reference the appropriate Clinical Center Medical Administrative Series or Federal Regulations Subparts as necessary when discussing the research involvement of these subjects. Discuss what, if any, procedures or practices will be used in the proposal to minimize their susceptibility to undue influences and unnecessary risks (physical, psychological, etc.) as research subjects.

Subjects under the age of 18 will be excluded as they do not fall under the scope of care or training for internal medicine physicians. Subjects with known active or latent tuberculosis or with evidence of tuberculosis found on chest x-ray will be excluded as biologic response modifier medications should not be administered to subjects with active infection. This exclusion also holds true for subjects with any active infection—they will be excluded as biologic response modifiers such as tocilizumab could worsen an active infection. Patients with known allergic reaction to IL-6 inhibitors will be excluded to avoid causing harm through such reactions.

Regardless of which arm a subject is randomized to all subjects presenting to Keesler Medical Center and enrolled in this study will be treated with the standard of medical care regardless of their inclusion of exclusion status for this study.

Any subject who is pregnant will be excluded due to unknown effects of tocilizumab on the fetus. Subjects of reproductive potential will have a pregnancy test obtained prior to enrollment and administration of the medication in this study.

10.5. Randomization Process (if applicable):

If applicable, describe the study arms, the randomization points (i.e. at study entry or later), and the criteria for patient stratification. Describe the procedure to assign patients to a treatment arm and the name and phone number of the person performing randomization. A flowsheet is highly recommended. Patients should be analyzed according to treatment assigned, not by treatment actually received.

Placebo will be obtained from the pharmaceutical company that will be prepared to appear identical to Tocilizumab. Upon enrollment of a subject into the study an order will be placed in the inpatient electronic medical record (Eccentris) by one of the study investigators so that the inpatient pharmacy will receive the order to prepare the injection and provide it to the subject's inpatient registered nurse who will then administer it. Randomization will be performed in blocks generated by the program www.random.org

11. Human Subject Protection:

All subjects will be treated in compliance with AFI 40-402, and applicable FDA and HHS guidelines. *(Required sentence – do not delete)*

11.1. Evaluation of Benefits and Risks/Discomforts:

Describe the potential benefits to subjects or to others that may reasonably be expected from the research. If volunteers are involved, specify compensation, if

applicable. Describe any potential risks (physical, psychological, social, legal or other) and assess their likelihood and seriousness. Where appropriate, describe alternative treatment and procedures that might be advantageous to the subjects. Describe the procedures for protecting against or minimizing any potential risks, such as violations of confidentiality, and assess their likely effectiveness. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects (data safety and monitoring board). Discuss why the risks to subjects are reasonable in relation to the anticipated benefits in relation to the importance of the knowledge that may reasonably be expected to results.

Particularly for pediatric patients, the Principal Investigator must carefully consider the risk and benefit of the treatment. A study that poses greater than minimal risk without prospect for direct benefit cannot be approved by the IRB. Describe and classify the risks to pediatric subjects (minimal risk, greater than minimal risk). Describe the benefits (therapeutic intent?). State whether the study meets federal guidelines (ref. 45 CFR 46 Subpart D) as an approvable category of research in children (e.g., "Therefore, this proposal involves greater than minimal risk to children, but presents the prospect of direct benefit to individual subjects.").

For cognitively or physically impaired patients, provide justification for inclusion of such patients in the study, how informed consent will be obtained, and information on supportive services. If cognitive impairment is caused by the disease (e.g., brain tumors or HIV infection), or is a side effect of the therapy (e.g., high-dose IL-2), special provisions for surrogate consent may be required.

The potential benefit to subjects enrolled in this trial is that if they receive the active medication (tocilizumab) and if there is a decrease in the primary outcome, another medication will be available for patients presenting with acute MI. This is how medications such as low molecular weight heparins (i.e. enoxaparin), statins, clopidogrel, and others have garnered FDA approval and now are standard of care.

The potential risks to subjects enrolled in this trial is increased mortality through an unknown mechanism or effect. Subjects may also be at increased risk of infection if they receive this medication, to include a risk of developing TB. Other side effects associated with use of tocilizumab are likely to have less impact on the general health of subjects enrolled in this trial but nonetheless could be associated with untoward harm.

11.2. Consent and Assent Processes, and Documents: *Describe the consent procedures to be followed, including the circumstances in which consent will be sought and obtained, where and who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. Also include a statement that the investigator(s) will annotate in the participant's electronic medical record (AHLTA) that he/she is participating in a research study.*

The proposed informed consent document must be attached. It should be written in the second person and in language understandable to someone who has not completed high school. Children are generally not empowered to give consent, but depending on their age, they may have the ability to give assent ("assent" means a child's affirmative agreement to participate in research). Every proposal involving children (those individuals under age 18) should include a discussion of how assent will be obtained for the particular study.

Patients admitted to the inpatient units at Keesler Medical Center receiving care for an acute MI will be recruited. They will be interviewed by one of the investigators. If they meet the inclusion/exclusion criteria the investigator will explain the study and give the patient an informed consent document to read. If they agree to participate in the study and after any questions have been adequately answered then written consent will be obtained. Subjects will be consented at the patient's bedside either on the unit, in the Emergency Room, or in the catheterization lab and will receive a signed copy of the

consent. The investigator will also make a note in the subjects electronic medical record (AHLTA) stating he/she is participating in a research study.

12. Data Collection and Measurement:

12.1. Data Collection:

Describe data to be collected, data collection procedures, and any required data collection forms. Describe how the data obtained will be stored. Describe procedures for safeguarding confidential subject information.
(All data collection instruments/forms/surveys must be provided electronically and hard copy with proposal.)

The data to be collected include those noted below:

- Patient demographics to include age, gender, race, and BMI. This data will be gathered from the inpatient electronic medical record (Essentris, AHLTA, T-Systems, and/or CHCS)
- Log of those treated with placebo and those treated with Tocilizumab
- CRP at 0 hours, 24 hours, 48 hours, and 30 days following treatment. The first two labs will be drawn while the patient is inpatient if possible. The 30 day lab will be scheduled to be drawn as an outpatient. It will be drawn at the Keesler Medical Center Laboratory.
- Questionnaire answers will be collected via telephone follow up with the patient or family member 30 days following treatment.

The data gathered above will be stored in an Excel spreadsheet stored on the H:/ drive of the investigator's CAC enabled access computer. The questionnaire will be stored by the research assistants at the CRL and stored in a secure cabinet in their section.

12.2. Response Criteria (if applicable): *List the tests and observations needed to evaluate response and provide time intervals for assessing response.*

The effect of the medication tocilizumab on the primary and secondary outcomes will be collected 30 days after the subject has been enrolled and has received either the study medication or placebo. Response criteria are noted below:

MACE (major adverse cardiac events) defined as death, recurrence of STEMI, NSTEMI, new arrhythmias, septal/valvular rupture, coronary dissection, pericarditis, cardiac tamponade, and other outcomes will be collected by record review and subject phone interview.

Secondary outcomes noted earlier will also be collected by record review and subject phone interview.

Changes in CRP will be measures using standard lab assay at the time points noted.

13. Data Analysis: *Describe data analysis strategy including the statistical tests or procedures to be used with each variable or group of variables, and/or each hypothesis/research question. Identify and discuss any assumptions made (variability of instrumentation, analytical detectable limits, etc).*

Discuss any plans for interim analyses and criteria for early termination of the study (i.e. agent under study is clearly not effective).

Identify who will be responsible for final data analysis.

You must contact Dr. Wang, the CRL Biostatistician, for guidance and input in this section before submitting your completed proposal for review. He can be contacted at (228) 376-4358.

Descriptive statistics:

Sample means and standard deviations of continuous demographic variables of the subjects in the Tocilizumab treatment and placebo groups will be calculated.

Frequency distributions of nominal demographic variables for each group will be calculated and graphed.

Homogeneity of the groups will be tested by two-sided t-tests or with contingency tables using chi-square or Fisher's exact test if the expected frequencies are less than five.

Hypothesis Testing:

Null hypotheses $H_0 1$ will be assessed with binomial test. Also, the binomial confidence interval for the prevalence of major adverse cardiac events at a 95% confidence level will be calculated. As "n" is small, the binomial confidence interval will be estimated using the Wilson interval[3,4].

Null hypotheses $H_0 2$ will be tested with contingency tables using Chi-square or Fisher's exact test if the expected frequencies are less than five.

The difference of hospitalization length and CRP levels will be analyzed with two-tail student t-test.

The readmission rates will be evaluated with contingency tables using Chi-square or Fisher's exact test if the expected frequencies are less than five.

Middle point monitoring: We will perform the safety analysis at middle point (or 54 subjects enrolled). If there is statistical significant difference, we will stop the trial at that point otherwise continue trial till all required subjects enrolled.

Analysis Tools: We will apply IBM SPSS Statistics to analyze all data.

14. Pharmaceutical and Investigational Device Information: From the Tocilizumab package insert--

DRUG NAME (Trade and Generic)	Tocilizumab (Actemra)
COMMERCIAL ~~OR INVESTIGATIONAL~~ (CIRCLE ONE)	

[3] Newcombe RG. Two-side confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine, 1998; 17:857-872

[4] Wilson EB. Probable inference, the law of succession, and statistical inference. J of American Statistical Assoc, 1972; 22: 209-212

FORMULATION	162 mg pre-filled syringe
SIDE EFFECTS	Tocilizumab subcutaneous data in rheumatoid arthritis (RA) included 2 double-blind, controlled, multicenter studies. Over 1700 patients were enrolled. All patients in both studies received background non-biologic DMARDs. The safety observed for tocilizumab administered subcutaneously was consistent with the known safety profile of intravenous tocilizumab, with the exception of injection site reactions, which were more common with subcutaneous tocilizumab. *Injection Site Reactions* The frequency of injection site reactions was 2.4 - 10.1%. These injection site reactions (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation. *Immunogenicity* In the 6-month control period in SC-I, 0.8-1.6% developed anti-tocilizumab antibodies; of these, all developed neutralizing antibodies. No correlation of antibody development to adverse events or loss of clinical response was observed. *Laboratory Abnormalities* *Neutropenia* During routine laboratory monitoring a decrease in neutrophil count below 1 × 109/L occurred in 2.9-3.7%. There was no clear relationship between decreases in neutrophils below 1 x 109/L and the occurrence of serious infections. *Elevated Liver Enzymes* During routine laboratory monitoring, elevation in ALT or AST ≥3 x ULN occurred in 1.4-6.5% receiving tocilizumab. *Lipids* During routine laboratory monitoring 19% experienced sustained elevations in total cholesterol > 6.2 mmol/l (240 mg/dL). **Serious Infections** Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported . Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections. Do not administer in patients with an active infection, including localized infections. ***Tuberculosis*** Evaluate patients for tuberculosis risk factors and test for latent infection. Consider anti-tuberculosis therapy prior to initiation of tocilizumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is

	recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy. It is recommended that patients be screened for latent tuberculosis infection prior to starting tocilizumab. The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy. ***Viral Reactivation*** Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded. **5.2 Gastrointestinal Perforations** Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. Use tocilizumab with caution in patients who may be at increased risk for gastrointestinal perforation.
IND/IDE Number:	None
IND/IDE Holder:	None
STABILITY AND STORAGE	Do not use beyond expiration date on the container, package or prefilled syringe. Tocilizumab must be refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect syringes from light by storage in the original package until time of use, and keep syringes dry. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If visibly opaque particles, discoloration or other foreign particles are observed, the medication should not be administered.
ADMINISTRATION PROCEDURES	Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use tocilizumab prefilled syringes (PFS) exhibiting particulate matter, cloudiness, or discoloration. Tocilizumab for subcutaneous administration should be clear and colorless to pale yellow. Do not use if any part of the PFS appears to be damaged. Subjects receiving tocilizumab for subcutaneous administration will receive the full amount in the syringe (0.9 mL), which provides 162 mg.
INCOMPATIBILITIES	

No dose adjustment is required in patients with mild renal impairment but tocilizumab has not been studied in patients with moderate to severe renal impairment.

15. Support Required: *(Nothing goes on this line.) Fill out the items below where support is required for your proposal that is to be provided by someone outside of your immediate control. Investigators are required to submit a "Request of Support" letter signed by the responsible authority of the required area. Put "N/A" after each item where no support is needed and delete graph.*

15.1. CRL Support: Dr Suizhao Wang, CRL Biostatistician, will provide data analysis.

15.2. Keesler Main Lab or Radiology Support: *List all tests/tasks you would like to have performed at the Keesler Clinical/Pathology Flight or the Keesler Radiology Flight.*

Description of Test Name	Type of Test/Specimen	Number of Tests/Specimens
C-Reactive Protein	Blood	4 (one at time of injection, 24 hours after injection, 48 hours after injection, and 30 days after injection)

15.3. Pharmacy Support: *List any support that you require from the Keesler Pharmacy. Include drugs being used for research (whether on formulary or not), compounding, storage, etc. Indicate the quantity, storage, and preparations.*

We will request support from Pharmacy to obtain and supply the study medication tocilizumab and a placebo.

15.4. Radioisotopes: N/A

15.5. Nursing Support: *Describe what you will be asking the nursing staff to do in support of your research (e.g., administering an experimental drug, distributing questionnaires)*

Inpatient nursing will administer tocilizumab or placebo after an order for the medication has been written in the inpatient electronic medical record (Eccentris). Administration of a subcutaneous medication is within the scope of their practice and requires no special training.

15.6. Other Support: N/A

16. Funding Requirements:

Provide estimated funding requirements for this proposal. Please use the following excel chart, which is designed for a three-year period. For those proposals that require funding for less than three years, please complete only those years applicable. You will only need to fill in the blue boxes. The table will self-add. ***If no funding support is required put "N/A" and delete the chart.***

Fiscal Year	20__		20__		20__	
SGO and External Funds	SGO	External	SGO	External	SGO	External
Equipment	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Supplies	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Other (Specify below)	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Sub-Total	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00
Total SGO Funds						$0.00
Total External Funds						$0.00
Total Funding						$0.00

16.1. Itemized List of Purchases by Fiscal Year: *List all equipment, supplies and contracts needed for the entire study, listed by Fiscal Year. Please delete years not needed. Please list items and fill in blue boxes. Tables will self add.* ***If none of these are needed put "N/A" after each item and delete the chart(s).***

Equipment: N/A

Supplies:

First Year:

Item	Unit Cost	Number Required	Total
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
		Subtotal	$0.00
		5% surcharge	$0.00
		Total	$0.00

Second Year:

Item	Unit Cost	Number Required	Total
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
	$0.00	0	$0.00
		Subtotal	$0.00
		5% surcharge	$0.00
		Total	$0.00

Contract Services: N/A

16.2. External Resources N/A
16.2.1. Drugs to be provided by a Non-DoD Source: N/A
16.2.2. Consumable Supplies to be provided by a Non-DoD Source: N/A
16.2.3. Loaned Equipment: N/A
16.2.4. Items to be Proffered: N/A
16.2.5. Grant: No grant money is requested or will be pursued.

17. Bibliography: *Conduct a search of the scientific literature for related studies and list the major publications in the field of the investigation below.*

Banks WA, Kastin AJ, Gutierrez EG (September 1994). "Penetration of interleukin-6 across the murine blood–brain barrier". *Neurosci. Lett.* 179 (1–2): 53–6. doi:10.1016/0304-3940(94)90933-4. PMID 7845624.

Bastard J, Jardel C, Delattre J, Hainque B *et al.* (1999). "Evidence for a Link Between Adipose Tissue Interleukin-6 Content and Serum C-Reactive Protein Concentrations in Obese Subjects". *Circulation* 99 (16): 2219–2222. doi:10.1161/01.CIR.99.16.2219.c.

Heinrich PC, Behrmann, I, Müller-Newen G, Schaper F, Graeve L (1998). "Interleukin-6 type cytokine signalling through the gp130(Jak/STAT pathway". *Biochem. J.* 334 (Pt 2): 297–314. PMC 1219691. PMID 9716487.

Miyao Y, Yasue H, Ogawa H, Misumi I, Masuda T, Sakamoto T, Morita E. Elevated plasma interleukin-6 levels in patients with acute myocardial infarction. Am Heart J. 1993 Dec;126(6):1299-304. PubMed PMID: 8249785.

Gabriel AS, Martinsson A, Wretlind B, Ahnve S. IL-6 levels in acute and post myocardial infarction: their relation to CRP levels, infarction size, left ventricular systolic function, and heart failure. Eur J Intern Med. 2004 Dec;15(8):523-528. PubMed PMID: 15668089.

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van't Hoog AH, Meme HK, Laserson KF, Agaya JA, Muchiri BG, et al. (2012) Screening Strategies for Tuberculosis Prevalence Surveys: The Value of Chest Radiography and Symptoms. PLoS ONE 7(7): e38691. doi:10.1371/journal.pone.0038691

Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104. PubMed PMID: 11596589.

Tocilizumab Package Insert; http://www.gene.com/download/pdf/actemra_prescribing.pdf; accessed 5 July 2014.

http://www.clinicaltrials.gov/ct2/show/NCT01491074?term=tocilizumab+and+myocardial&rank=1

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ATTACHMENTS: (Include with Proposal)

1. Informed Consent Document
2. HIPAA Authorization Form
3. Certificate of Compliance
4. Curriculum Vitae of Principle Investigator
5. Data collection instruments/tools/checklist(s) (if applicable)
6. Request for Support Letter(s) (if applicable)
7. Request for Funding Letter (if applicable)
8. Curriculum Vitae of Medical Monitor (if applicable)
9. Copy of poster or flyer advertising research study (if applicable)