Study Protocol

Protocol Title:
Investigator-Initiated, Pilot Study Evaluating the Efficacy of Etanercept in Acute Gout

ClinicalTrials.gov #: NCT03636373

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INTERVENTIONAL
RESEARCH PROTOCOL
(HRP-503a)

Title: **Investigator-Initiated, Pilot Study Evaluating the Efficacy of Etanercept in Acute Gout**

Study Sponsor: Rutgers, The State University of New Jersey
Responsible Party: Principal Investigator
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Principal Investigator (PI):
Naomi Schlesinger, MD
Professor and Chief, Division of Rheumatology Department of Medicine
Rutgers—Robert Wood Johnson Medical School
One Robert Wood Johnson Place, New Brunswick, NJ 08901
Office: 732-235-8378
schlesna@rwjms.rutgers.edu

Co-Investigators:
Robert Eisenstein, MD
Chair Department of Emergency Medicine
Rutgers—Robert Wood Johnson Medical School
One Robert Wood Johnson Place, New Brunswick, NJ 08901
eisensrm@rwjms.rutgers.edu

Amanda Borham, MD
Assistant Professor of Rheumatology
Rheumatology Center of New Jersey
56, Union Avenue, Somerville, NJ 08876
borhamam@rutgers.edu

Ahmed Abdel-Megid, MD
Rheumatology Center of New Jersey
56, Union Avenue, Somerville, NJ 08876
ahmedmegid@rhcnj.com

Vivien Hsu, MD
Rutgers—Robert Wood Johnson Medical School
Rm 458, Medical Education Building
125, Paterson Street, New Brunswick, NJ 08901
hsuvm@rwjms.rutgers.edu

Dirk F. Moore, Ph.D
Associate Professor
Rutgers School of Public Health, Room 215,
683 Hoes Lane West, Piscataway NJ 08854
mooredf@sph.rutgers.edu

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1.0 Research Introduction

1.1 Purpose/Specific Aims

The purpose of this pilot study is to investigate the safety and efficacy of etanercept (Enbrel™; Amgen) for the treatment of an acute gout attack. Etanercept is a chimeric protein containing the ligand-binding region of the tumor necrosis factor (TNF) receptor (TNFr), fused to the constant (Fc) region of a human IgG1 antibody.[1] Etanercept binds to TNFα, preventing its interaction with TNFr.

The study is designed to demonstrate that a single dose of etanercept 50 mg subcutaneously (SC), given at the onset of an acute gout attack, will be non-inferior to a single dose of triamcinolone acetonide 40 mg intramuscularly (IM), for relief of signs and symptoms, including pain.

A. Objectives

1. **Primary objective**—demonstrate that etanercept 50 mg SC is non-inferior to triamcinolone acetonide 40 mg IM, with respect to patient self-assessment of joint pain intensity in the most affected (target) baseline joint, at 72 hours post-dose.

2. **Secondary objectives**
   (a) Evaluate the efficacy of etanercept, compared to triamcinolone acetonide, with respect to the treatment of the signs and symptoms of an acute gout attack.
   (b) Compare the use of rescue medications in patients treated with etanercept or triamcinolone acetonide.
   (c) Compare the time to 100%, 80%, and 50% resolution of pain in etanercept- and triamcinolone acetonide-treated patients.
   (d) Evaluate the safety and tolerability of etanercept.

3. **Exploratory objectives**—compare etanercept and triamcinolone acetonide with respect to laboratory measures of acute inflammation and patient self-assessment of quality of life during an acute gout attack.

B. Hypotheses / Research Question(s)

Etanercept 50 mg SC, given at the onset of an acute gout attack, will be non-inferior to triamcinolone acetonide 40 mg IM, with respect to the relief of signs and symptoms, including pain.

1.2 Research Significance

Gout results from the crystallization of uric acid and deposition of monosodium urate (MSU) crystals in and around joints, and is the most common inflammatory arthritis in humans.[2] The 2007-2008 National Health and Nutrition Examination Survey (NHANES) gave a prevalence of 8.3 million adults with gout in the United States.[3] Important risk factors for hyperuricemia and gout include increasing age, male gender (4:1 male-to-female ratio prior to age 65, and 3:1 thereafter), obesity (prevalence doubles at BMI >30 kg/m^2), hypertension, chronic kidney disease (CKD), alcohol use, dietary fructose or animal purines, and the use of loop or thiazide diuretics.[4-6] Not surprisingly, clinically relevant comorbidities often complicate drug selection

and use in the gout population. The 2007-2008 NHANES survey of gout patients revealed hypertension in 74%, Stage 2 or greater chronic kidney disease (CKD) in 71%, obesity in 53%, diabetes in 26%, and heart failure in 11% of gout patients in the United States.[2,6,7]

The pathophysiology of acute gout is multifaceted, and involves a number of innate and adaptive immune cells, soluble inflammatory mediators, cytokines, and chemokines.[8] MSU crystals are directly cytotoxic to resident synoviocytes, inducing necroptosis (via the RIPK3-MLKL necrosome pathway).[8] Necrotic cells also release histones and related DAMPs, thereby activating resident macrophages via the NLRP3 inflammasome. The subsequent release of interleukin (IL)-1β triggers a cascade of events that stimulate the infiltration of neutrophils and monocytes into the affected joints. Monocytes differentiate into an M1 phenotype, and along with infiltrating neutrophils release a number of pro-inflammatory cytokines, including IL-6, IL-8, and TNFα. Under the influence of IL-8, TNFα, DAMPs, and MSU crystals themselves, neutrophils greatly amplify the inflammatory process through the formation of neutrophil extracellular traps (NETs), which contain lysosomal enzymes and reactive oxygen species (ROS). NET formation can also result in the destruction of infiltrating neutrophils, an event that may be involved in the resolution of inflammation.[8]

For reasons that are still incompletely understood, acute gout resolves spontaneously, even without treatment and the continuing presence of MSU crystals in the synovium, within approximately 7-10 days.[9-12] As with any inflammatory process, negative feedback mechanisms are critical for preventing run-away tissue damage and autoimmunity. Anti-inflammatory mediators identified in the synovial fluid of patients with acute gout include IL-10; IL-1 receptor antagonist (IL-1RA); transforming growth factor-beta1 (TGF-β1), which stimulates the release of IL-1RA; and soluble TNF receptors I and II (sTNFR-I/II).[9] In a murine model, the intraneural injection of neutralizing antibodies to both TNFα and IL-1β reduced neuropathic pain.[10] In contrast, in murine models of RA, such as collagen-induced arthritis, IL-1β blockade appears to be more effective than TNFα blockade in ameliorating the disease process.[13] One theory with respect to the resolution of inflammation involves the phagocytosis of necrotic neutrophils by macrophages.[9] As acute gout proceeds, infiltrating monocytes differentiate into a stronger M2 phenotype, associated with greater phagocytic capacity, and the secretion of TGF-β1.[9]

The role of TNFα in pain generation and propagation is best studied in inflammatory neuropathic pain.[14-19] TNFα is released by local Schwann cells, mast cells, fibroblasts, and endothelial cells in response to acute nerve injury, then amplifies the pain response via recruitment of circulating macrophages and neutrophils, which subsequently release IL-1β and other inflammatory cytokines. The specific role of TNFα in acute gout is not fully understood, but appears to involve the "priming" of neutrophils to secrete IL-1β in response to MSU crystal-induced cellular necrosis. IL-1β and IL-8 appear to play the central role in the subsequent recruitment and activation of inflammatory cells within the affected joint, including neutrophils, monocytes, and dendritic cells. Neutrophils greatly enhance the emerging inflammatory response via the release of additional inflammatory mediators, such as prostaglandin E2, nitric oxide, leukotriene B4 (LTB4), ROS, and the calcium-binding proteins S100A8 and S100A9. Crystal-induced activation of the classical complement cascade induces affected endothelial cells to release additional IL-8, along with the nociceptive stimulants bradykinin, substance P, and LTB4. This latter process helps to explain the sudden, intense pain associated with an acute gout attack.

The management of acute gout attacks has traditionally centered around the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and systemic or interarticular corticosteroids.[9,20,21] The ACP 2017 guidelines recommend that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout. Corticosteroids should be considered as first-line therapy in patients without contraindications because they are generally safer and a low-cost treatment option. [22]

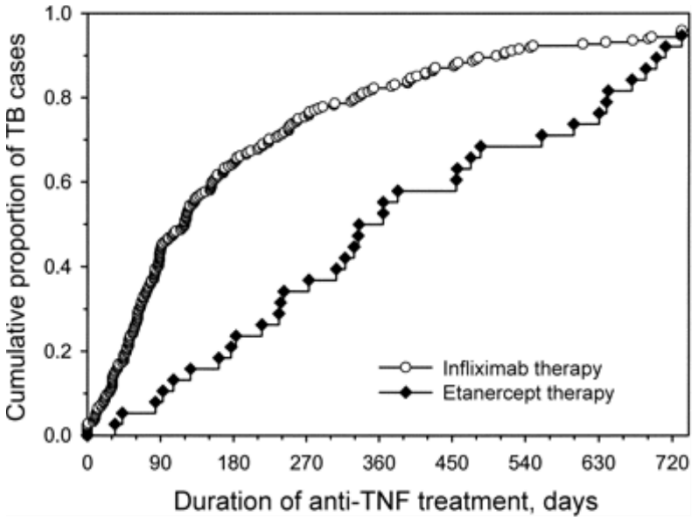
NSAIDs or colchicine should be used with caution in patients with renal or gastrointestinal disease, while corticosteroids can be problematic in patients with diabetes. Clinicians may be forced to choose a corticosteroid in patients with contraindications to NSAIDs and/or colchicine. Intramuscular (IM) triamcinolone acetonide (Kenalog®; Bristol-Myers Squibb) is a popular choice in patients that cannot receive oral therapy. A 2008 meta-analysis of three trials found IM triamcinolone acetonide to be equally effective to IM adrencorticotropic hormone, oral indomethacin, and oral prednisolone.[20] Triamcinolone acetonide IM 40 mg was chosen as the comparator in the large acute gout trials canakinumab studies comparing a single injection of canakinumab (10 to 150 mg) with a single 40 mg IM injection of triamcinolone acetonide. The studies were based on the experience of the investigators and the fact that in two countries in which the canakinumab trials[24-25] were performed, the 40 mg IM dose is labelled as the initial dose or usual dose and higher doses were not considered to be acceptable to investigators or the health authorities. Furthermore, according to a survey, 72% of prescriptions for triamcinolone acetonide in France, Germany and the UK in 2008 to 2009 were for the 40 mg dosage.[26]

A single 40 mg dose of IM triamcinolone acetonide is a popular treatment choice for an acute gout attack because it is effective, has a superior short-term safety profile compared to colchicine or NSAIDs, and offers the potential for effective treatment with single-dose drug administration.[21] In a study of 20 patients with acute gout exacerbation, patients were randomized to either oral indomethacin 50 mg three times daily for a minimum of 2 days, or IM triamcinolone acetonide as a single 60 mg dose.[23] Follow-up visits occurred at days 1-2, 3-4, 10-14, and 30. A second triamcinolone acetonide dose was allowed at the initial follow-up visit if symptoms had not improved by at least 50%. There was no difference in the mean time to total symptom resolution (8.3±4.3 versus 7.4±4.6 days, respectively, for indomethacin and triamcinolone acetonide; *P*=0.66). Respective mean clinical joint scores (0=complete resolution, 1=greater than 50% improvement, 2=less than 50% improvement, 3=no improvement, 4=worsening of symptoms or involvment of additional joints) at days 1-2, 3-4, and 10-14, were 1.5±0.85, 0.65±0.63, and 0.2±0.37 for indomethacin, compared to 1.0±0.72, 0.62±0.78, and 0.5±0.16 for triamcinolone acetonide (none of the differences between indomethacin and triamcinolone acetonide were significant). Only three out of ten patients randomized to triamcinolone acetonide required a second injection at the initial follow-up visit.[23] A separate study compared oral diclofenac 50 mg three times daily for 3 days, followed by 25 mg orally three times daily for 3 days (n=10), to single-dose IM betamethasone 7 mg (n=10) or intravenous (IV) methylprednisolone 125 mg (n=7) in 27 patients with acute gout attack.[27] Follow-up visits occurred at days 1, 3, 6, and 15, and no additional analgesic or antiinflammatory medications were allowed prior to the day 6 follow-up visit. The median patient self-assessment score for percentage improvement in symptoms at 24 hours was 75%, 75%, and 71% , respectively, for diclofenac, betamethasone, and methylprednisolone. At 72 hour follow-up, respective median scores were 85%, 90%, and 95%, compared to 100%, 100%, and 90% at study day 6. Overall, 67.7%, 90%, and 100% of patients, respectively, reported at least a 50% improvement in symptoms at 24 hours, compared to 100%, 90%, and 85.7% of patients, respectively, at both 72 hours and day 6.[27]

Newer biologic agents that target pro-inflammatory cytokines offer an alternative choice in patients unable to take first-line agents. Anti-IL-1β agents, such as anakinra (recombinant IL-1RA), canakinumab (human monoclonal anti-IL-1β), and rilonacept (soluble IL-1RA) have been studied for gout, but are not FDA-approved, although they are used off-label.[24,25,28] There is considerable evidence that TNFα inhibition is effective in the management of a range of human arthritides and musculoskeletal disorders, namely rheumatoid arthritis (RA), juvenile RA (JRA), ankylosing spondylitis, and psoriatic arthritis. Hence, in light of a major unmet need, a clinical study is warranted to further define the effect of TNFα blockade in patients with an acute gout attack.

For a number of reasons, the infection risk associated with etanercept is lower than that associated with the other approved TNFα blockers available in the United States (the monoclonal antibodies infliximab, adalimumab, certolizumab pegol, and golimumab:[29]

- Etanercept is a fully human fusion protein, in which the extracellular ligand-binding region of the TNF-alpha receptor is linked to the constant (Fc) fragment of an IgG1 antibody. Unlike the 4 monoclonal antibodies mentioned above, etanercept only binds to soluble TNF-alpha. Since it cannot bind membrane-bound receptor, the Fc region of etanercept does not initiate complement-mediated cell lysis (ie., in contrast to infliximab, activated T cells and macrophages expressing membrane-bound TNF-alpha receptors are not lysed by etanercept).[29,30]
- TNF-alpha (both soluble, and in particular membrane-bound) is essential for the formation of, and integrity of granulomas, and therefore for protection against tuberculosis (TB) and other granulomatous diseases.[31] In murine models of chronic TB, monoclonal antibody TNF-alpha receptor blockers penetrate granulomas more completely than etanercept, which may help to explain the lower TB risk associated with etanercept. In comparison to etanercept, the Odds Ratio (95% Confidence Interval) of TB with infliximab and adalimumab was 13.3 (2.6-69) and 17.1 (3.6-80.6), respectively.[31] Dixon WG et al reported a TB rate of 39/100,000 patient-years for etanercept, compared to 136/100,000 for infliximab (an incident ratio of 3.1 [1-9.5] versus etanercept), and 144/100,000 for adalimumab (incident ratio of 4.2 [1.4-12.4]).[32]
- The onset of TB tends to occur much later with etanercept than with the monoclonal antibodies, and may not involve the reactivation of latent TB, but rather spontaneous exposure/new infection.[33,34] The authors reported a TB infection rate of 28.3/100,000 patients treated with etanercept, versus 53.8/100,000 with infliximab (P<0.0001). With infliximab, 44% of infections occurred within the first 90 days of treatment, as opposed to only 10% with etanercept (P<0.001). The cumulative proportion of TB infections suggests an early cluster infections with infliximab, representing reactivation of latent TB, as opposed to a nearly linear pattern over time with etanercept (new infections as opposed to reactivation).[33,34]



- In the setting of hepatitis B (HBV) infection, TNF-alpha is essential for the production of HBV-specific cytotoxic T cells, which in turn destroy HBV-infected hepatocytes.[35] Most of the information regarding HBV reactivation in patients treated with TNF-alpha blockers is limited to case reports.[35] Cantini and colleagues reported a prevalence (95% confidence interval) of HBV reactivation of 4.6% (0.5-12.5%) with adalimumab, and 3.9% (1.1-8.4%) with etanercept.[36]
- In contrast to chronic HBV, the role of TNF-alpha in chronic hepatitis C (HCV) infection is not well established.[37] In theory, TNF-alpha blockade could permit increased viral replication, since it is involved in triggering apoptosis of HCV-infected hepatocytes. However, this is not supported by current observations. Pompili and colleagues reported on 216 chronic HCV patients treated with TNF-alpha blockers over a median period of 1.2 years and 260 cumulative patient-years of exposure, and observed only 3 cases of suspected HCV-related liver disease progression.[37] The authors concluded that the use of these agents in patients with chronic HCV infection appears to be safe in the short term, more evidence is required to assess long-term safety. The authors also questioned the value of HCV screening prior to initiation of TNF-alpha blocker therapy, as active HCV is not a treatment contraindication.[37]

1.3 Research Design and Methods

This is a 4-week, multi-center, double-blind, double-dummy, active-controlled clinical study designed to compare the safety and effectiveness of etanercept and triamcinolone acetonide in patients with acute attacks of gout.

A. There will be 4 visits to a study site and one follow up phone call. Visits will occur at either the adult Clinical Research Center (CRC) at RWJMS in New Brunswick, the Emergency Department at Robert Wood Johnson University Hospital (RWJUH) in New Brunswick, the office of Dr. Borham at 56 Union Avenue in Somerville, or the clinic of Dr. Schlesinger at RWJMS in New Brunswick.

Visit 1 (Day 1): Informed consent and screening (physical examination/medical history/urine pregnancy test, as indicated) will be completed. In subjects who qualify, baseline assessments will be completed and study drug administered.

Visits 2 (Day 4±1), 3 (Day 7±1), and 4 (Day 14±2): All study procedures listed on Table 2 will occur at each Visit. A second dose of study drug will be administered if the pain intensity is ≥5 at Visit 2.

Follow-up telephone call (Day 30±3): The study will end with the follow-up telephone call, designed to record adverse events, and learn whether there were recurrent gout attacks during treatment.

Table 1. Outline of study design

Screening and Baseline	Treatment Follow-up			End of Study
← Efficacy and Safety Assessments →				
Study Day 1 (Visit 1)	**Study Day 4±1 (Visit 2)**	**Study Day 7±1 (Visit 3)**	**Study Day 14±2 (Visit 4)**	**Study Day 30±3**
• Informed consent • Screening • Randomization • Dosing – Single dose of Etanercept 50 mg SC or – Single dose of Triamcinolone acetonide 40mg IM	72-hour re-dose if Pain Score ≥ 5	Follow-up	Follow-up	(Follow-up telephone interview)

Table 2. Study procedures

Visit	**Screening and Randomization**	**Baseline assessments**	**Treatment**			**Phone Call**
Study Day	**1**	**1**	**2**	**3**	**4**	
	1	**1**	**4±1**	**7±1**	**14±2**	**30±3**
Informed consent	X					
Inclusion/exclusion criteria	X					
Demographics		X				
Employment status		X				
Diagnosis of gout	X					
History of gout	X					
Medical history and current medical condition	X		X	X	X	
Concomitant medications	X		X	X	X	
Adverse events		X	X	X	X	X
Blood pressure and pulse		X	X	X	X	
Weight		X	X	X	X	
Height		X				
Physical examination		X	X	X	X	
Identification of the target joint of the current gout attack	X					
Record all affected joints of the current gout attack	X		X	X	X	
Pregnancy test (for women with childbearing potential)	X					
Hematology		X		X		
Blood chemistry		X		X		
Serum urate		X		X		
hSCRP		X		X		
Patient's assessment of gout pain in the target joint (Pain Score)	X*		X	X	X	

Visit Study Day	Screening and Randomization 1 1	Baseline assessments 1 1	Treatment 2 4±1	 3 7±1	 4 14±2	Phone Call 30±3
Patient's assessment of gout pain in the target joint (Likert)	X*		X	X	X	
Patient's global assessment of response to treatment (Likert)			X	X	X	
Physician's global assessment of response to treatment (Likert)			X	X	X	
Physician's assessment of Tenderness, Swelling and Erythema (Likert)	X*		X	X	X	
Physician's assessment of range of motion (Likert)	X*		X	X	X	
HAQ	X			X	X	
SF-36v2 ®	X				X	
Study drug administration		X	X**			
Dispense rescue medication diary		X	X	X		
Check use of rescue medication/ review diary			X	X	X	
Pain Score ≥ 5	X		X	X	X	
Patient-reported attack	X					

* Assessments will be done prior to dosing

** Second dose of study medication will be administered only if pain intensity still ≥ 5

B. Data Points collected including long-term follow-up

N/A. The study ends with the follow-up telephone call.

C. Duration of the Study and Length of Subject Participation

Dosing will occur at the conclusion of Visit 1 (Study Day 1), the Screening/Baseline visit. Visits 2-4 take place on Study Days 4±1, 7±1, and 14±2. The study will end with a follow-up telephone call on Study Day 30±3 designed to record adverse events (AEs), and learn whether there were recurrent gout attacks during treatment.

D. Primary and Secondary endpoints

i. Primary Outcome—pain intensity in the most affected baseline joint measured by the numeric 0-10 pain scale at 72 hours (Visit 2).

ii. Secondary Outcomes

[1] Patient's assessment of joint pain intensity in the most affected baseline joint on a 0-10 numeric pain scale, at Baseline and post-dose Visits 2, 3, and 4;

[2] Patient's assessment of joint pain intensity in the most affected baseline joint on a Likert scale, at Baseline and post-dose Visits 2, 3, and 4;

[3] Change in pain intensity from baseline to 72 hours

[4] Patient's global assessment of response to treatment, on a Likert scale at post-dose Visits 2, 3 and 4;

[5] Physician's assessment of Tenderness, Swelling and Erythema in the most affected joint, at post-dose Visits 2 and 3, using:

- — Tenderness on a 0-3 point scale ("no pain", "there is pain", "there is pain and patient winces", and "there is pain, patient winces, and then withdraws on palpation or passive movement of the affected study joint");
- — Swelling on a 0-3 point scale ("no swelling", "palpable", "visible", and "bulging beyond the joint margins";
- — Erythema ("present", "absent", or "not assessable"), and;

[6] Physician's assessment of range of motion on a Likert scale ("normal", "mildly restricted", "moderately restricted", "severely restricted", and "immobilized";
[7] Physician's global assessment of response to treatment, on a Likert scale, at post-dose Visits 2, 3 and 4.
[8] Compare the use of rescue medication in etanercept and triamcinolone acetonide patients:
(a) Time to first rescue medication intake;
(b) Total number of patients taking rescue medication, and;
(c) Total milligram dose of rescue medication taken.
[9] Time to complete 100%/80%/50% resolution of pain
[10] Safety and tolerability of etanercept

iii. **Exploratory objectives**:
[1] Quality of life, as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) and Medical Outcome Short Form (SF)-36v2™ Health Survey (acute version), and;
[2] Laboratory results at Baseline (Study Day 1) and Study Visit 3:
(a) Complete blood count (CBC) and differential;
(b) Comprehensive metabolic panel (CMP);
(c) High-sensitivity C-reactive protein (hSCRP), and;
(d) Serum urate.

1.4 Preliminary Data
None

1.5 Sample Size Justification
The sample size will be 20 patients per arm, for a total of 40 patients, based on a non-inferiority design. Details are given in Section 4.5.

1.6 Study Variables
A. Independent Variables, Interventions, or Predictor Variables
In randomized, double-blind, double-dummy fashion, subjects will receive a single dose of IM triamcinolone acetonide and SC placebo, or SC etanercept and IM placebo.

B. Dependent Variables or Outcome Measures
(1) Primary Outcome—joint pain intensity in the most affected baseline joint.
(2) Secondary Outcomes—see 1.3(D) above

1.7 Drugs/Devices/Biologics
At the completion of Visit 1 (Study Day 1), subjects will receive one SC injection and one IM injection. According to the study design and randomization schedule, each patient will be receiving either:

- Etanercept 50 mg SC and placebo IM, or;
- Triamcinolone acetonide 40 mg IM and placebo SC.

The Research Pharmacist at RWJMS is not blinded, and will be responsible for storage, inventory, preparation, and dispensing of all study medications:

- AMGEN will supply etanercept and its matching placebo in individual prefilled syringes. Thirty minutes before injection, prefilled syringes should be taken out from cold storage to equilibrate the injection solution with room temperature. The SC injection should be administered into the arm or thigh.
- Triamcinolone acetonide 40mg (1 mL) (or 1 mL of matching placebo) will be given as an IM injection. The vial should be shaken before use to ensure a uniform suspension. Prior to withdrawal, the suspension should be inspected for clumping or granular appearance (agglomeration). An agglomerated product results from exposure to freezing temperatures and should not be used. The matching placebo for triamcinolone acetonide will be 0.9% Normal Saline, supplied as 10 mL vials. One milliliter of 0.9% Normal Saline will be drawn up for the placebo injection. An amber colored tape will be placed on each syringe (active drug and placebo) to maintain blinding. The amber tape is see-through, it is tinted, to mask the color of the injection. The gradations on the syringe will still be visible. After withdrawal, the triamcinolone acetonide/matching placebo should be injected without delay to prevent settling in the syringe. IM injection should be made deeply into the gluteal muscle; for adults, a minimum needle length of 1½ inches is recommended.

Study drug dose adjustments and/or interruptions will not be permitted.

Rescue medications

Patients who have difficulty tolerating their pain, despite the treatment, are allowed to take acetaminophen (paracetamol) 500 mg orally as needed as rescue medication for pain. A maximum of 1 g/dose or 3 g/day of acetaminophen is allowed.

If there is insufficient pain relief, patients are allowed to take 20 mg of prednisone per day for up to 7 days.

A paper diary will be given to each patient in order to record time of intake of rescue medication and the amount taken. At the next visit or early discontinuation/termination the patient diary will be reviewed.

Concomitant treatment

Concomitant medications and/or non-drug therapy before the administration of study medication, and after start of study drug, will be collected, including medication name, dose, route of administration, and indication.

Prohibited medications or treatments not allowed after screening/randomization:

- any anti-inflammatory or analgesic treatment within the first 7 days after dosing for a gout attack, except rescue medication as defined above;
- any biologic agent other than etanercept, and;
- any live vaccination.

A. Drug/Device Accountability and Storage Methods

The Investigational Drug Service (IDS) of the Rutgers-Robert Wood Johnson Medical School is a cooperative service with the Department of Pharmacy of the Robert Wood Johnson University Hospital. The IDS is responsible for the storage, preparation and proper labeling of investigational drugs in use at the hospital and the medical school. The service is involved in creation of pharmacy portions of investigator-initiated protocols and in the acquisition of drug product for studies within the medical school community. In addition, the IDS provides the necessary information and education about investigational drugs to the pharmacy and nursing staffs in both institutions. The IDS is located on the 8th floor of the East Tower in the Clinical Research Center, Room ET-893.

The Research Pharmacy in the Clinical Research Center will control all of the IP and will supply the IP for the site in already prepared randomized kits in numerical order. An unblinded RN will be administering the injections at Dr.Borham's site. This person will pull the next numbered kit for each subject and monitor such things as supply usage to report back to the CRC pharmacy. Also, this person will record the daily temperature logs for both the entanercept or placebo (refrigerated), and triamcinolone or normal saline for placebo, ambient temperature.

1.8 Primary Specimen Collection

A. Blood and urine samples will be collected for blood chemistry, hematology, serum urate, hSCRP, and pregnancy testing at baseline. All except pregnancy testing will be repeated at visit 3. All specimens will be collected at the location of subject screening or follow-up visit. All samples collected at all sites will be processed by LabCorp. Clinical specimens will not be used for this study. The expenses for these lab tests will be covered by study funds.

1.9 Interviews, Focus Groups, or Surveys

N/A

1.10 Timetable/Schedule of Events

Please see Tables 1 and 2 in (1.3.A) above.

2.0 Project Management

2.1 Research Staff and Qualifications

Principal Investigator

Naomi Schlesinger, MD, Professor and Chief, Division of Rheumatology and Director, Rutgers Robert Wood Johnson Medical School- (RWJMS) Gout Center, Rutgers—RWJMS. Dr. Schlesinger is a previous President of the NJ Rheumatology Association and was the recipient of the 2015 *Rheumatologist of The Year* award by the Arthritis Foundation - New Jersey Chapter. She is a noted authority in the field of gout, having published many papers regarding the diagnosis, treatment, and pathogenesis. She is the author of over 200 scientific articles, abstracts, book chapters and reviews. Dr.Schlesinger is a co- Editor, with Dr.Lipsky of the soon to be published book "Gout', 1st Edition by

Elsevier and has written the chapter on 'Clinical features of gout" for the main text book in Rheumatology: "Rheumatology', published April, 2018.

Dr.Schlesinger's research has won recognition, including the work titled: Efficacy of canakinumab (ACZ885), a fully human anti-Interleukin (IL)-1beta monoclonal antibody, in the prevention of flares in gout patients initiating allopurinol therapy, which was selected as one of the 5 highest ranking abstracts that will likely shape our treatment paradigms for years to come in the 2010 ACR/ ARHP Annual Scientific Meeting and the work titled: Erectile dysfunction is common among gout patients, which was selected (one of 13) for inclusion in the official 2014 EULAR Press Conference from over 4000 abstracts. Other pioneering work includes treatment of gout with topical ice, seasonality of gout, diagnosing gout using ultrasound, understanding the pathogenesis of bone erosions in gout and the importance of anti-inflammatory treatment in gout. Dr. Schlesinger has been recognized among the world's top ten experts in gout research and treatment: PubMed, March 4, 2014 and Expertscape, March 10, 2014.

Dr. Schlesinger served as a scientific advisor, Consortium of Rheumatology Researchers of North America (CORRONA) gout registry, the Co-chair of the ACR- Crystal Study Group, as well as the Co-chair of the ACR abstract reviewer selection process: metabolic and crystal arthropathies. In addition, Dr. Schlesinger served on the newly formed American College of Rheumatology (ACR) Division Directors Special Committee (DDSC). She has a special interest in Evidence-Based Medicine and served as a Co-facilitator of the acute gout review group for the Cochrane International Collaboration as well as a member of the Outcome Measures in Rheumatology (OMERACT) gout special interest organizing group.

Dr.Schlesinger served as a leading International Consultant / PI (with Prof. Alexander So Lausanne, Switzerland) for the Novartis phases II and III Canakinumab gout trials 5/2007-6/2013. She serves as a consultant to pharmaceutical companies and contract research organizations (CROs) on gout drug development.

Co-Investigators

Robert Eisenstein, MD, Chair Department of Emergency Medicine, Rutgers—Robert Wood Johnson Medical School, New Brunswick, NJ

Amanda Borham, MD, Assistant Professor, Division of Rheumatology, Department of Medicine, Rutgers—Robert Wood Johnson Medical School, New Brunswick, NJ

Ahmed Abdel-Megid, MD, Volunteer Faculty, Division of Rheumatology, Department of Medicine, Rutgers—RWJMS. Dr. Abdel-Megid is an expert in the management of both localized and generalized pain and has specific training in the diagnosis and treatment of arthritis and rheumatism. He treats localized pain in the back, neck, shoulders and hands, including osteoarthritis, tendonitis and bursitis, as well as complex systemic pain caused by diseases like rheumatoid arthritis or systemic lupus. Dr. Abdel-Megid also treats clinical problems involving joints, soft tissues, autoimmune diseases, vasculitis, and heritable connective tissue disorders.

Vivien Hsu, MD, Professor, Division of Rheumatology, Department of Medicine, Rutgers—Robert Wood Johnson Medical School, New Brunswick, NJ

Dirk F. Moore, Ph.D, Rutgers School of Public Health and Rutgers Cancer Institute of New Jersey. Dr. Moore's expertise concerns the application of biostatistical methods to the study of human disease, including cancer. He has more than 90 peer-review publications. Dr. Moore uses case series and administrative databases to study factors associated with incidence and outcomes of breast and prostate cancer. He is experienced in the statistical analysis of proteomics and genetics data in human disease, having worked extensively with using biostatistical analyses to elucidate the effects of genes and proteins on disease.

2.2 Resources Available

The Clinical Research Center (CRC) will be supporting the study with regulatory, nursing, data management and operational support.

The CRC will work with Dr.Schlesinger and personnel at Dr. Borham's site to provide the training necessary for uniform data collection, protocol compliance, and data collection and entry. Major elements to be covered are inclusion and exclusion criteria, study procedures, randomization procedures, medication storage and dispensing, and data collection.

Initiation training will be conducted prior to first patient screened. The CRC will provide the following training to Dr. Borham's site.

CRC will coordinate and conduct the Site Initiation Visit with Dr. Schlesinger for both sites including:

a. Study specific aims
b. Background and significance
c. Patient population – Inclusion and Exclusion Criteria
d. Study drug review and specific dosing instruction
e. Recruitment of patients
f. Patient Consent
g. REDCap system orientation
h. Electronic Data Entry
i. Randomization

The CRC, with Dr. Schlesinger, will provide training of any amendments or modifications to the protocol or any study specific procedures as they occur to both sites.

2.3 Research Sites

Subjects will be seen at the CRC at RWJMS in New Brunswick, the clinic office of Dr. Schlesinger (her outpatient clinic at RWJMS in New Brunswick), the Emergency Department at RWJUH in New Brunswick, and the office of Dr. Borham (her office Rheumatology center of New Jersey at 56 Union Avenue in Somerville). These patients will be consented, screened, dosed, and evaluated for the duration of the study at these respective sites. The follow up visits for subjects enrolled in the Emergency Department and Dr. Schlesinger outpatient clinic will take place in the CRC.

3.0 Multi-Site Research Communication & Coordination

A. Document Consistency

The PI or PI's qualified designee will oversee both sites to ensure that both sites have the most current versions of study documents and HIPAA authorization.

B. Site Approvals

PI or PI's qualified designee will oversee all study sites to assure if the required approvals have been obtained and maintained as per institutional policy and FDA guidelines.

C. Modifications

PI or PI's qualified designee will oversee that the modifications have been communicated to all study sites, and the IRB of Record has approved the modification prior to implementation. On-going regular conference calls will be conducted with the coordinators at both sites to discuss issues that arise and data collections. Any modifications or changes to research will be communicated during the conference calls.

D. Data Security

PI or PI's qualified designee will oversee that the sites engaged in the study will safeguard data as required by FDA and local institutional security policies. REDCap Database is FDA CFR 21 Part 11 compliant. Data transmission will not include any personal health identifiers.

E. Legal Obligation

Local site investigators have completed CITI biomedical training required by the IRB of record and aware of federal regulations on conducting clinical research. They will also be trained on any applicable local laws required to conduct the research.

F. Adherence to Policy and Reporting of Non-Compliance

Study team will make all efforts to conduct the research as per the study protocol. Any non-compliance with the study protocol will be promptly reported to the proper authorities as required by institutional policy.

3.1 Outside Research

N/A

4.0 Research Data Source/s

4.1 Primary Data-Subjects and Specimens

4.2 Subject Selection and Enrollment Considerations

A. Recruitment Details

Subjects will be recruited from the practices of Dr. Schlesinger (her outpatient clinic at RWJMS Clinical Academic Building Suite 5200A, 125 Paterson Street, New Brunswick, NJ), Dr. Borham (her office at 56 Union Avenue in Somerville), and the Emergency Department at RWJUH in New Brunswick. Gout classification criteria ACR EULAR 2015 will be used for recruiting patients in the study. These patients will be consented, screened, dosed, and evaluated for the duration of the study at these respective sites. CITI certified site staff will be consenting the patients.

B. Source of Subjects

Please see 4.2A.

C. Method to Identify Potential Subjects

Please see 4.2A.

D. Subject Screening

Subjects will be screened for study eligibility by study staff at their respective locations listed above.

Inclusion Criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria:

1. Male or female patients age ≥18 to ≤85 year
2. History of established gout, as proposed by the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) provisional definition of gout (confirmed diagnosis of crystal-proven gout, and/or a score of ≥8 on the 2015 ACR/EULAR Gout Classification Criteria)[38];
3. Onset of current acute gout attack within 4 days prior to randomization (an acute attack in patients with established gout will be defined using modified 2015 ACR/EULAR criteria[38];
   (a) Presence of any warm joint;
   (b) Swollen joint;
   (c) Pain score at rest ≥5 on the 0-10 pain scale, and;[1]
   (d) Patient self-report of acute gout attack;
4. Baseline pain intensity ≥5 on a 0-10 pain scale;
5. Tender (≥1 on a 0-4-point Likert scale) and swollen (≥1 on a 0-4-point Likert scale) index joint;
6. Subject must be able to give informed consent, and must authorize release and use of collected health information;
7. If on urate-lowering therapy, a stable dose and regimen for at least 2 weeks prior to randomization, and expectance to remain on a stable dose and regimen for the duration of the double-blind treatment period, and;
8. Body mass index (BMI) ≤45 kg/m^2.

- **Exclusion Criteria**

Patients fulfilling any of the following criteria will not be eligible for inclusion in this study:

1. Use of intra-articular or IM corticosteroids within 14 days prior to screening;
2. Use of an IL-1 inhibitor, TNF inhibitor or other biologic or investigational drug within 30 days prior to screening;
3. History of a drug allergy to either study drug;
4. Diagnosis or history of:
   (a) rheumatoid arthritis (RA);
   (b) infectious/septic or other inflammatory arthritis;
   (c) alcoholic hepatitis or nonalcoholic steatohepatitis;
   (d) immunodeficiency syndromes, including Human Immunodeficiency Virus (HIV) infection;
   (e) Stage IIIb, IV, or V chronic kidney disease;
   (f) idiopathic thrombocytopenic purpura;
   (g) active, severe chronic pulmonary disease (eg, requiring oxygen therapy);
   (h) uncontrolled hypertension (≥ 200/105 mmHg);
   (i) symptomatic (New York Heart Association Class II, III, or IV) congestive heart failure;
   (j) uncontrolled diabetes Type I or II (recent blood glucose > 300 mg/dL);

[1]The 2015 ACR/EULAR provisional definition uses a pain score at rest of >3 on a 0-10 scale, along with criteria (a), (b), and (d). The combination of all 4 criteria provided 96% specificity and 85% sensitivity. The combination criteria (c) and (d) had the best diagnostic characteristics (sensitivity 83% and specificity 90%) (16).

(k) myocardial infarction, unstable cardiac arrhythmias or unstable symptomatic coronary ischemia, within the past 12 months before randomization;
(l) history of malignancy of any organ system within the past 5 years;
(m) multiple sclerosis or any other demyelinating disease, or;
(n) major chronic inflammatory disease or connective tissue disease other than RA or psoriatic arthritis (PsA), including but not limited to fibromyalgia or systemic lupus erythematosus (with the exception of secondary Sjögrens syndrome, etc.);

5. Contraindication to IM injection;
6. Donation or loss of ≥400 milliliters (mL) of blood in the 8 weeks before dosing;
7. Any live vaccination in the 3 months before the start of the study;
8. Active infection (including chronic or localized infections) for which anti-infectives were indicated within 4 weeks before screening;
9. Any serious infection, defined as requiring hospitalization or intravenous anti-infectives, within 8 weeks before first dose of investigational product;
10. Prosthetic joint infection within 5 years of screening, or native joint infection within 1 year of screening;
11. Known alcohol addiction or dependency, daily alcohol use, or current substance use or abuse;
12. Positive medical history for hepatitis B or C (subjects with a history of hepatitis B vaccination without history of hepatitis B infection are allowed to enroll);
13. History of active tuberculosis;
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive pregnancy test (guide regarding pregnancy attached), or;
15. Female patients who are physiologically capable of becoming pregnant must use an acceptable method of contraception with a Pearl Index (PI) failure rate <1 throughout the study, and for 4 weeks after study drug discontinuation: the following female patients are excluded from using contraception:
    (a) female patients whose career, lifestyle, or sexual orientation precludes intercourse with a male partner, and;
    (b) female patients whose male partners have been sterilized by vasectomy or other means.

E. Recruitment Materials

A "flyer" or paper advertisement (attached) will be posted in the waiting rooms of Drs. Schlesinger and Borham.

F. Lead Site Recruitment Methods

N/A

4.3 Subject Randomization

Treatments will be assigned using permuted blocks and stratified by enrollment site. The randomization tables will be provided by the Rutgers Department of Biostatistics. Research pharmacist at Clinical Research Center will supply the study medication for the site in already prepared randomized kits in numerical order. The subjects will be identified by the PI in her clinic at RWJMS and the Co-Investigator or Sub-investigator at Emergency Department in the RWJUH and

Rheumatology center of NJ (RHCNJ). The subjects will be administered the study medication in numerical order.

4.4 Secondary Subjects

N/A

4.5 Number of Subjects

The primary aim of this study is to show that Etanercept is an effective therapy for gouty arthritis, by which we mean that it is at least as effective as Tiamconolone acetonide at reducing pain at the 72 hour (visit 2) time point. Thus, the study is powered to determine non-inferiority of the Etanercept arm. To this end, we will compute a 95% Students t confidence interval for the difference in VAS scores at 72 hours. If the lower limit of this confidence interval is above a specified non-inferiority limit, we will concluded that Etanercept is as effective as Triamcinolone acetonide. Of course, if the lower limit of this confidence interval were to exceed zero, then Etanercept would be shown to be superior, which would be an even stronger outcome.[39]

Based on a 2012 study of gout (Schlesinger et al. 2012)[24], the mean VAS pain scores at 72 hours were found to be 25.0 and 35.7 in the Canakinumab and Triamcinolone acetonide arms, respectively, for a difference of -10.7. The standard deviation in each group was approximately 12.5. This information is based on Table 1 and Figure 2C of Schlesinger et al. 2012). For the current study, pain will be assessed and reported on a 10-point scale rather than the 100-poing scale typically used for VAS pain indication. Hence, we scale down these measures by a factor of 10 to adapt them to this study.

Using this information, we have the following information for 80% power for a non-inferiority outcome for three plausible values of the standard deviation:

Non-inferiority limit	Standard Deviation	Power
-1.04	1.15	80%
-1.07	1.20	80%
-1.11	1.25	80%

For example, if the standard deviation is found to be 1.20, and if the true VAS scores for the two arms are the same, we will have 80% power to find that the lower limit of the 95% confidence interval for VAS scores exceeds -1.07, on the 10-point scale we use in this study.

We will follow up this analysis with a linear regression analysis of the change in pain scores at 72 hours and at other time points at which numeric scores are collected, adjusted for clinical and patient characteristics. Changes in pain score with successive visits will be modelled using standard longitudinal data analysis methods in order to provide a comparison of the full profile of pain measurements.

A. Total Number of Subjects

40

B. Total Number of Subjects If Multicenter Study
40

C. Required Number of Subjects to Complete Research
All 40 subjects enrolled will be followed with intent to treat analysis.

D. Feasibility of Recruiting
Clinical practices of Dr. Schlesinger and Borham see approximately 140 patients annually with an acute gout attack. Emergency Department see approximately 40 subjects annually with an acute gout attack. We expect recruitment to require approximately 16 months.

4.6 Consent Procedures

A. Consent

- **Documenting Consent**
  A written Informed Consent Document will be used.
- **Waiver of Documentation Of Consent**
  N/A
- **Waiver or Alteration of Consent Process**
  N/A

B. Consent Process

Dr. Borham's site study coordinator and study staff will be provided with training in obtaining informed consent for research purposes. The CRC staff will reference GCP guidelines and the CRC SOP for Obtaining Informed Consent and provide a copy of the SOP for filing and reference on site. Since the Study Coordinator is new to Clinical Trials, the CRC nurse manager, or experienced designee, will provide oversight of the first informed consent process to ensure the process is in accordance with the SOP and GCP guidelines. Observations and oversight will be provided until the study coordinator and the CRC Nurse Manager have ensured these process guidelines are adhered to. As detailed in the CRC SOP, the site coordinator will be trained to emphasize that consent is voluntary and that the medical care the patient receives will not be influenced by his or her decision and that, should the patient agree to participate, he or she is free to withdraw from the study at any time.

Dr. Eisenstein and CRC study nurse will introduce the study to potential subjects enrolled in the Emergency department. Study nurse will complete the Department of Emergency Medicine Consent Checklist to determine that the potential subject is able to voluntarily reason, understand and appreciate the nature and consequences of the research interventions. Potential subjects will be allowed as much time as needed to adequately read and consider the consent form and to decide whether or not to enroll in the study. The consent form will be reviewed with the subject in a private room prior to signing the form. If any subject is determined to be under the influence of pain medications that would affect their ability to consent, that subject will not be approached by the study staff.

- **Location of Consent Process**
  Consent process will take place on the adult Clinical Research Center (CRC) or the office of Dr. Schlesinger (her outpatient clinic at RWJMS Clinical Academic Building Suite 5200A, 125 Paterson Street, New Brunswick, NJ), or in the Emergency Department of RWJUH, or the

office of Dr. Borham (her office at 56 Union Avenue in Somerville, NJ), depending on the location of the patient.

- **Ongoing Consent**
  Subjects will be informed of any new findings or information that arise, after the consent process that may affect their willingness to continue study participation.
- **Individual Roles for Researchers Involved in Consent**

1. Consent Discussion Duration
On a case-by-case basis, adequate time to ensure subject comprehension.
2. Coercion or Undue Influence
The discussion will take place in a private examination room. Subjects will be informed that the decision to participate is purely voluntary, and in no way influences his/her treatment.
3. Subject Understanding
The investigator obtaining consent will go through the consent form line by line, making certain the subject fully comprehends any potential risks or benefits associated with study participation.

4.7 Special Consent/Populations

N/A

4.8 Economic Burden and/or Compensation for Subjects

A. Expenses

None. There is no cost to the study subject.

B. Compensation/Incentives

Subjects may earn a total of $220 for study participation. Compensation will be based on the amount of completed study visits: $70 for the screening (Visit 1), $30 for Visit 2, $30 for Visit 3, $70 for Visit 4, and $20 for the follow-up telephone call.

4.9 Risks to Subjects

A. Description of Subject Risk

Etanercept

- **Very common adverse effects** (approximately 10% or greater):
  a. Injection site reactions—erythema, tenderness, pain, bruising, warmth, swelling, itching and/or infection at the injection site. These reactions are most common during the first month following injection, and disappear despite continued etanercept treatment.
  b. Infections—can include viral, bacterial (including tuberculosis), and fungal infections. Serious infections have been rare (approximately 0.1-1%).
- **Common adverse effects** (approximately 1-10% of patients):
  a. Allergic reactions—may include headache, flushing, shortness of breath, itching and rash, hives, or more severe reactions such as dizziness, difficulty breathing, hypotension, or angioedema.

b. Development of autoantibodies—some patients do develop autoantibodies. Rarely (approximately 0.1-1% of patients), these autoantibodies may be associated with a lupus-like syndrome.
c. Other common side effects include fever.

– **Uncommon adverse effects** (approximately 0.1-1% of patients):

a. **Non-melanoma skin cancer**—Non-melanoma skin cancers are cancers that form in squamous cells (the top layer of skin cells) or basal cells (the round cells just under the squamous cells). Symptoms of non-melanoma skin cancers may include a change in the appearance of your skin, such as a new growth or a sore that will not heal.
Non-melanoma skin cancers have been reported with etanercept use and are more common in patients with psoriasis. These skin cancers rarely spread to other parts of the body. In clinical studies, patients with psoriasis treated with etanercept, were at a higher risk of getting squamous cell and basal cell skin cancers. Non-melanoma skin cancers have also been reported uncommonly in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis and psoriatic arthritis.

- **Non-cancer side effects**

a. Psoriasis—may include new or worsening of psoriasis.
b. Eye disease
   i. Uveitis (a type of eye inflammation) has been reported with etanercept use. Symptoms may include: in one or both eyes, blurred or cloudy vision, eye redness and/or eye pain especially when looking at bright lights.
   ii. Scleritis, a type of eye inflammation affecting the white outer coating of the eye (known as the sclera), can occur in association with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis and has been reported with etanercept use. Symptoms may include: in one or both eyes, blurred or cloudy vision, redness in the whites of the eye, eye pain, sensitivity to light and irreversible damage to the eye.
c. Blood problems—low blood counts have been reported with etanercept use. Reports have included low white blood cells, low platelets, and low red blood cells. Symptoms of a low blood count may include fever that does not go away, bruising, bleeding, or very pale skin.
d. Heart failure—congestive heart failure (CHF) and worsening of CHF in patients who already have it, occurred in patients treated with etanercept. In a clinical trial to treat CHF with etanercept, the results suggested a possible chance that etanercept worsened CHF. Symptoms of heart failure may include shortness of breath and ankle swelling.
e. Systemic and Cutaneous vasculitis—systemic vasculitis (inflammation of blood vessels in the body) and cutaneous vasculitis (inflammation of blood vessels in the skin) have been reported with etanercept use. Symptoms of vasculitis may include fever, loss of appetite, weight loss, feeling tired, general aches and pains. Systemic vasculitis is uncommon (which may affect between 1 and 10 people in every 1,000). Cutaneous vasculitis is rare (which may affect between 1 and 10 people in every 10,000).
f. **Elevated liver enzymes**—elevated liver enzymes on blood tests have been reported with etanercept use

- **Rare side effects** (which may affect between 1 and 10 people in every 10,000):
  a. **Cancer**—There have been reports of cancer in adults, adolescents, and children following etanercept use. It is possible that etanercept may increase the risk of getting lymphoma (cancer of the lymph nodes), leukemia (cancer of the blood) or other cancers. It is unknown if etanercept might influence the development and course of cancer (spreading, the effect of treatment of the cancer, or the cancer coming back after treatment). There have been cases of unusual cancers in children and teenage patients who started using TNF-blocking agents at less than 18 years of age.
  Overall cancers occurred in about 1% (1 in 100) of patients with rheumatoid arthritis treated with etanercept in clinical studies for up to 5 years. This is similar to the rate of cancer that would be expected for rheumatoid arthritis or psoriasis patients if they were not receiving etanercept.

  Lymphoma
  It is known that subjects with rheumatoid arthritis and psoriasis, whether on etanercept or other treatments, are at a higher risk (up to several times higher) compared with the general population of developing lymphoma (a type of cancer of the lymph nodes). It is also known that those with more active (worse) disease have the highest risk. In rheumatoid arthritis clinical studies, patients treated with etanercept were three times more likely to develop lymphoma than people in general (without rheumatoid arthritis). They were no more likely to develop lymphoma, however, than moderate to severe rheumatoid arthritis patients overall. The role of etanercept and other TNF-blocking therapies in the development of lymphoma is not known.

  Leukemia
  Cases of leukemia have been reported in association with TNF-blocker use. Even in the absence of TNF-blocker therapy, patients with rheumatoid arthritis may have approximately twice the risk of developing leukemia than people without rheumatoid arthritis.

  b. **Melanoma skin cancer**—melanoma (an aggressive form of skin cancer) has been reported in patients taking etanercept. Melanoma develops in the cells that produce melanin which is the pigment that gives skin its color. The first melanoma symptoms often are a change in an existing mole and/or the development of a new, unusual-looking growth on skin.
  c. **Non-cancer side effects**
     — **Opportunistic infections**—opportunistic infections are unusual infections that occur most commonly when immune system is weakened.
     — **Serious skin reactions**—severe skin reactions that can be life-threatening rarely occur. These reactions can cause rashes, blistering (on skin, inside the mouth, nose or other areas), and shedding of the skin.
     — **Nervous system problems**—Nervous system events, including multiple sclerosis, convulsions and inflammation of the nerve in the eye, Guillain-

Barré syndrome (inflammation of the peripheral nerve in your arms and legs) and inflammation of the spinal cord have been reported in patients taking etanercept. You may experience numbness or tingling, dizziness, weakness in your arms and/or legs, or problems with your vision if you are having a neurologic problem

- **Sarcoidosis**—sarcoidosis is a disease that causes inflammation in the lungs and other tissues, and has been reported with etanercept use.
- **Other rare side effects**—other rare side effects include swelling of the lymph nodes, diarrhea, chest pain, fever, interstitial lung disease (lung scarring), and liver problems such as hepatitis (injury of the liver).

- **Very Rare side effects** (which may affect less than 1 person in 10,000):
  a. **Blood problems**—aplastic anemia (the body stops producing all blood cells) have been reported with etanercept use. Some of the patients with aplastic anemia died. Symptoms of a low blood count may include fever that does not go away, bruising, bleeding, or very pale skin.

- **Other Risks**
  a. **Inflammatory bowel disease (IBD)**—inflammatory bowel disease (is the name of a group of disorders in which the intestines [small and large intestines or bowels] become inflamed, causing redness) has been reported in patients taking etanercept. Symptoms of IBD may include pain in the belly, diarrhea (may be bloody), unexplained weight loss, loss of appetite, bleeding from the rectum, and fever.
  b. **Hepatitis B Virus (HBV) Reactivation**—reactivation (to make active again) of hepatitis B virus in patients who have had prior hepatitis B virus infection and worsening of chronic hepatitis, have been reported with etanercept use. Reactivation can occur spontaneously (without warning), but more often is triggered when using other medications that suppress (stop) the immune system.
  c. **Merkel cell skin cancer**—Merkel cell skin cancer (an aggressive type of non-melanoma skin cancer) has been reported in patients taking etanercept. Merkel cell cancer affects touch sensitive cells deep in the skin, and often spreads if it is not caught early.

1. **What are the risks of using etanercept in combination with other drugs?**
   While we do not know the side effects of using etanercept in combination with all drugs, we do know the following drugs may affect how etanercept works or that etanercept may affect how they work.

   a. Live vaccines should not be given while subjects are taking etanercept.
   b. Subjects with rheumatoid arthritis taking a drug called sulfasalazine with etanercept commonly (which may affect between 1 and 10 people in every 100) had lower numbers of white blood cells (white blood cells help to fight infection). Using these two drugs together could increase risk of an infection.
   c. Hypoglycemia (low blood sugar levels) has been reported rarely (which may affect between 1 and 10 people in every 10,000) in patients who start taking etanercept and are on medicine for diabetes.

d. Using a drug called anakinra with etanercept can increase your risk of getting an infection and lower numbers of white blood cells (cells that help to fight infection).
e. Using a drug called abatacept with etanercept can increase your risk of getting an infection.

2. What are the risks of taking the other drugs required by this study?

Triamcinolone acetonide is a corticosteroid, and can cause any of the following side effects:

1. High blood pressure, salt and water retention, weight gain, and potassium deficiency.
2. High blood sugar (glucose).
3. Adrenal gland suppression.
4. Viral, bacterial, fungal, protozoan or helminthic (intestinal worm) infections.
5. Reactivation or worsening of infections such as Candida, Cryptococcus, Mycobacterium (TB), Nocardia, Pneumocystis, or Toxoplasma.
6. Development or worsening of cataracts and/or glaucoma.
7. Worsening (including a tear in the stomach or intestine) of peptic ulcers, diverticulitis, or ulcerative colitis.
8. Aseptic necrosis (cell death and loss) of bone, muscle weakness and loss, osteoporosis (including bone fracture and spine compression), and tendon rupture.
9. Seizures, depression, giddiness, headache, trouble sleeping, mood swings, tingling or numbness in fingers, toes, and/or extremities, personality changes, psychiatric disorders, and dizziness.

B. Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects

Etanercept has been reported to cross (the placenta) from a pregnant mother into the unborn baby. The effects of this on the baby are unknown; however, infants may be at an increased risk of infection. Therefore, the administration of live vaccines to infants for 16 weeks after the pregnant mother's last dose of etanercept is generally not recommended.

Etanercept has been reported to be transferred into breast milk. Babies should not be fed breast milk produced during treatment with etanercept and for an additional 4 weeks after the end of the mother's treatment with etanercept.

Triamcinolone acetonide should only be used during pregnancy when the possible benefits are greater than the risk. There is no evidence in humans that the drug harms the unborn fetus. However, in animal studies corticosteroids have been shown to cause birth defects.

Since the effect of etanercept in not known, and triamcinolone acetonide is known to cause birth defects in some animals, it is possible that these drugs may cause birth defects in people. For this reason, no one can be in this study who is pregnant or who could get pregnant while taking the study drug. Women of childbearing age who are sexually active, must use an acceptable method of effective birth control as listed below:

- Hormonal method (tablets, implants placed under the skin by a health care provider, injections, or transdermal patches)
- Intrauterine device (IUD)
- Intrauterine hormonal-releasing system (IUS)
- Surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)

- Male partner has had a vasectomy and testing shows there is no sperm in the semen
- Sexual abstinence (not having sex)
- Two barrier methods (male partner must use a condom, and the female must use a diaphragm, cervical cap, or contraceptive sponge); the female partner must also use spermicide in addition to a barrier method

C. Risks to Non-Subjects

N/A

D. Assessment of Social Behavior Considerations

N/A

E. Minimizing Risks

Subjects will be given sufficient time to read the consent form and understand study procedures prior to signing the consent. Study personnel will spend the time needed to thoroughly explain and respond to questions potential subjects may have about the study.

Study personnel will be educated and trained on study procedures to minimize any discomforts or inconveniences to the subjects. No vulnerable populations will be enrolled in this study. Both study sites are located within 5 minutes from major hospitals, which will help to provide subjects with prompt medical care in the event of an emergency.

Study data will never be stored on mobile computers or flash drives. Staff is well trained on protecting the privacy and confidentiality of study subject health information. PHI will not be collected as data or transmitted via email. Data collected will be limited to that necessary to conduct the research.

F. Certificate of Confidentiality

N/A

G. Potential Benefits to Subjects

Subjects may or may not experience acute pain relief if receiving etanercept. Triamcinolone acetonide is approved for use in this patient population.

H. Provisions to Protect the Privacy Interests of Subjects

To keep subject participation in this study confidential, all study records will be stored in a secure location. The institutions where the information is collected will be listed in the consent form. Sharing of information will be limited as required by law or as required to conduct the research. The data will be de-identified and coded with a study ID to minimize subject identification.

I. Research Team Access to Subject Data

Research team will have access to study files and research data. Access will be limited to research personnel through password protection. User authentication will be enforced in REDCap system to limit access to the minimum required to perform the tasks. No data with personal identifies will be captured by the system.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.

N/A

4.11 Chart/Record Review Selection
The study personnel at each site will have access to their subject medical records and will enter all relevant data into the REDCap database.

4.12 Secondary Specimen Collection
N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)
The database does not capture any PHI. A unique Study ID will be assigned to the subject and this will be used to identify the subject in the study. All efforts will be made to protect collected data. Only the study personnel at the local site will have access to study data for the subjects that are enrolled at that site. However, PHI will be collected in order to complete phone call on day 30.

Study coordinators will collect the Name, Address and Telephone number of each subject for the purpose of communication with the subject during study participation.

5.2 Family Educational Rights and Privacy Act (FERPA)
N/A

5.3 NJ Access to Medical Research Act
N/A

5.4 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)
N/A

6.0 Research Data Protection and Reporting

6.1 Data Management and Confidentiality

A. We will calculate the mean (and 95 percent confidence interval) difference in Pain scores for etancercept compared to triamcinolone acetonide. If the upper limit of the confidence interval is less than zero, then we will have demonstrated superiority. If the upper limit is greater than zero, but less than 20% above zero, then etanercept will have been shown to be non-inferior to triamcinolone acetonide.

B. The primary objective of the study is to determine if etanercept is non-inferior to the current standard of care (triamcinolone acetonide) at reducing the pain associated with an acute gout attack, as measured by the Pain scale. Based on a 2012 study of gout compazring canakinumab vs triamcinolone acetonide, the mean difference in pain scores at 72 hours was 10.7, with a standard deviation of 36.21. Assuming a Type I error rate of 5%, 20 patients per cohort would give us 80% power to detect a reduction in pain scores of 32.92, which we consider to be a clinically significant reduction in pain (6).

C. The database will be created and maintained in REDCap electronic data capture (EDC) system hosted at Rutgers Robert Wood Johnson Medical School. REDCap is a secure web application for building and managing online surveys and databases which is US FDA 21 CFR Part 11 compliant, specifically geared to support online or offline data capture for research studies and operations. Procedures for securing the data include password protection, limited access to study computers, encryption, authorization of access based on user roles.

Study personnel will be provided with adequate training on how to use the system and secure data. The study personnel will maintain all study records according to ICH GCP guidelines.

Patient contact information will be maintained by the study team and will be stored in a secure location. Only study team members will have access to the subject study files.

D. The investigators or their qualified designee will ensure that the source documents and subject study files are legible and complete. The investigators will be responsible for the regular review of the conduct of the study, for verifying adherence to the protocol and for confirming completeness, consistency and accuracy of all documented data and accuracy of source documentation verification.

E. Data Handling:

- **Data**
  Data will be collected on subject demographics, employment status, history of gout, medical history including medication, assessments of gout pain, current medical conditions, physical examination, AEs, vital signs, laboratory tests, study drug administration, questionnaires, etc.

- **Data Storage**
  The data will be collected at the 2 sites listed above by the study personnel. Study data will be collected at the study visits and entered into the REDCap system by study personnel. All research related data will be stored for 10 years from study closure in Rutgers University Records Center in Livingston Campus located at 7 Kilmer Road, Edison, NJ. Subject binders/folders at Dr. Schlesinger's site will be stored in the study coordinator's office, RM ET-876, 8th floor East Tower, Clinical Research Center and Dr.Borham's site will be stored in Rheumatology center of NJ, 56 Union Ave, Somerville.

- **Data Access**
  Study team will have access to the data until the day of the data lock, which will occur at the end of data collection and entry, and after addressing all open queries and thereafter the data will be analyzed by the Statistician and archived.

- **Data Transmission**
  Data will be entered by study personnel directly into the REDCap database. Data will not be transmitted or received via email or any other application other that the database created to collect data. RWJMS will collect the Study files from Dr. Borham's site after completion of the study for archiving.

- **Data Transporting and Sharing**

Sites will have access to the same REDCap database. In addition, the statistician will have access to the REDCap database. PHI and patient information from Dr.Borham's site will not be transferred. Any remaining PHI will be removed from the study materials prior to transfer.

6.2 Data Security

Refer to 6.1.C above

6.3 Data and Safety Monitoring

A. Periodic Data Evaluation

There will be no interim data analysis for this study. Safety and efficacy data will be analyzed at the end of the study, *during* statistical analysis. Potential adverse events, will be reviewed in real-time by the PI and other study personnel, as indicated.

B. Type of Data Evaluated

All post randomization data will be reviewed for safety and efficacy.

C. Collection of Safety Information

Nature of adverse events:

- Severity: The intensity of an adverse event and is categorized as 1) Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated 2) Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate activities of daily living 3) Severe; medically significant but not immediately life threatening
- Relationship: The extent to which an adverse event is considered to be related to the intervention of study procedures. An adverse event is considered suspected if there is a reasonable possibility that the event may have been caused by the procedure. Suspected also means possible, probably or definitely related to the intervention or the study procedure. Not- suspected means the adverse event is clearly due to an extraneous event.

Serious Adverse events will be classified as follows:

- A SAE is defined as any untoward medical occurrence that meets any of the following criteria:
  - Results in death
  - Is life-threatening
  - Requires inpatient hospitalization or prolongation of existing hospitalization
  - Is a congenital anomaly or birth defect
  - Is an important medical event

Study Safety data will be reported to the Amgen Inc. and the IRB as mandated by the law and as stated in executed research agreement.

D. Frequency of Data Collection

Please see section 1.3, Research Design and Methods

E. Reviewer of Data
Please see section 6.3.A above

F. Schedule of Review of Cumulative Data
Please see section 1.3, Research Design and Methods

G. Tests for Safety Data
Please see section 1.3, Research Design and Methods

H. Suspension of Research
Serious adverse events that occur during the study period will be reported according to IRB guidelines. Study procedures may be stopped if the investigators believe the safety of study subjects is threatened.

6.4 Reporting Results

A. Sharing of Results with Subjects
There are no plans to share study results with study participants, beyond the reporting to individual subjects of any signs of therapeutic response or possible adverse event.

B. Individual Results
Subjects will be informed of any signs of therapeutic response or possible adverse event.

C. Aggregate Results
Please see section 6.4.A above

D. Professional Reporting
Study results will be presented at scientific meetings as research poster or platform presentations. The investigators plan to publish the results of the study in the scientific literature.

E. ClinicalTrials.Gov Registration and Data Reporting
The trial has been registered on ClinicalTrials.gov, as required by U.S. law.

6.5 Data Sharing
N/A

7.0 Data and/or Specimen Banking
N/A

8.0 Other Approvals/Authorizations
N/A

9.0 Bibliography
1. ENBREL® (etanercept) injection, for subcutaneous use Package Insert. Amgen. Manufactured by Immunex Corp., revised 11/2017.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum* 2011;63(10):3136-41.

3. Roddy E, Choi H. Epidemiology of gout. *Rheumatology Clinics of North America* 2014;40(2):155-75.
4. Doherty M. New trends into the epidemiology of gout. *Rheumatology* 2009;48:ii2-8.
5. Singh JA. Racial and gender disparities in patients with gout. *Curr Rheumatol Rep* 2013;15(2):307.doi:10.1007/s11926-012-0307-x.
6. Stamp LK, Chapman PT. Gout and its comorbidities: implications for therapy. *Rheumatology* 2013;52:34-44.
7. Richette P, Clerson P, Perissin L, et al. Revisiting comorbidities in gout: a cluster analysis. *Ann Rheum Dis* 2015;74:142-7.
8. Desai J, Steiger S, Anders H-J. Molecular Pathophysiology of Gout. *Trends in Molecular Medicine* 2017;23(8):756–68.
9. Abhishek A, Roddy E, Doherty M. Gout—a guide for the general and acute physicians. *Clinical Medicine* 2017;17(1):54-9.
10. Schafers M, Brinkhoff J, Neukirchen S, Marziniak M, Sommer C. Combined epineurial therapy with neutralizing antibodies to tumor necrosis factor-alpha and interleukin-1 receptor has an additive effect in reducing neuropathic pain in mice. *Neuroscience Letters* 2001;310:113-16.
11. Chen YH, Hsieh SQ, Chen WY, et al. Spontaneous resolution of acute gouty arthritis is associated with rapid induction of the anti-inflammatory factors TGFβ1, IL-10 and soluble TNF receptors and the intracellular cytokine negative regulators CIS and SOCS3. Ann Rheum Dis 2011;70:1655-1663.
12. Gaffo AL, Schumacher HR, Saag KG, Taylor WJ, Dinnella J, Outman R, Chen L, et al. Developing a provisional definition of flare in patients with established gout. Arthritis Rheum 2012;64(5):1508-17.
13. Zelenka M, Schafers M, Claudia Sommer C. Intraneural injection of interleukin-1β and tumor necrosis factor-alpha into rat Sciatic nerve at physiological doses induces signs of neuropathic pain. *Pain* 2005;116:257-63.
14. Myers RR, Campana WM, Shubayev VI. The role of neuroinflammation in neuropathic pain: mechanisms and therapeutic targets. *Drug Discovery Today* 2006;11(1/2):8-20.
15. YokoseK, SatoS, AsanoT, YashiroM, KobayashiH, Watanabe H, et al. TNF-α potentiates uric acid-induced interleukin-1β (IL-1β) secretion in human neutrophils. *Modern Rheumatology* 2017[Online];Available: http://dx.doi.org/10.1080/14397595.2017.1369924 (Accessed 12 Sep 2017).
16. Locksley RM, Heinzel FP, Shepard HM, et al. Tumor necrosis factors alpha and beta differ in their capacities to generate interleukin 1 release from human endothelial cells. *J Immunol* 1987;139(6):1891-5;10
17. Chapman PT, Yarwood H, Harrison AA, et al. Endothelial activation in monosodium urate monohydrate crystal-induced inflammation: in vitro and in vivo studies on the roles of tumor necrosis factor alpha and interleukin-1. Arthritis Rheum 1997;40:955-965.
18. Tonussi CR, Ferreira SH. Tumour necrosis factor-alpha mediates carrageenin-induced knee-joint incapacitation and also triggers overt nociception in previously inflamed rat knee-joints. Pain 1999;82(1):81-7.
19. Williams RO, Marinova-Mutafchieva L, Feldmann M, Maini RN. Evaluation of TNF-alpha and IL-1 blockade in collagen-induced arthritis and comparison with combined anti-TNF-alpha/anti-CD4 therapy. J IMmunol 2000;165(12):7240-5.
20. Lucassen JHJ, Van de Laar FA, Van de Lisdonk EH. Systemic corticosteroids for acute gout. *Cochrane Database of Systematic Reviews* 2008; Issue 2. Art. No.:CD005521.
21. Cronstein BN, Terkeltaub R. The inflammatory process of gout and its treatment. *Arthritis Research & Therapy* 2006;8(Suppl 1):S3(DOI:10.1186/ar1908)
22. Qaseem A, Harris RP, Forciea MA, for the Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. Ann Intern Med 2017;166:58–68

23. Alloway JA, Moriarty MJ, Hoogland YT, et al. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheumatol 1993;20:111-3.
24. Schlesinger N, Mysler E, Lin HY, et al. Canakinumab reduces the risk of acute gouty arthritis attacks during initiation of allopurinol therapy: results of a double-blind, randomised study. Ann Rheum Dis 2011;70(7):1264-71;11.
25. Schlesinger N, Alten R, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with lIMited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their extensions. Ann Rheum Dis 2012;71:1839-1848.
26. IMS Disease Analyser: Prescriptions of triamcinolone acetonide in France, and Germany for August 2009 to August 2010 and in the UK for December 2008 to December 2009, personal communication.
27. Werlen D, Vischer TL. Corticosteroid therapy for the treatment of acute attacks of crystal-induced arthritis: an effective alternative to nonsteroidal antiinflammatory drugs. *Rev Rhum* 1996;63(4):248-54.
28. Cavagna L, Taylor WJ. The emerging role of biotechnological drugs in the treatment of gout. Biomed Res Int. 2014;2014:264859.
29. Goffe B, Cather JC. Etanercept: an overview. *J Am Acad Dermatol* 2003;49(2):S105-11.
30. Conner V. Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immunosuppression. *Rheum Int* 2009;31(3):327-37.
31. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is mhigher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: the three-year prospective French Research Axed on Tolerance of Biotherapies registry. *Arthritis Rheum* 2009;60(7):1884-94.
32. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis* 2010;69:522-8.
33. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associuated with tumnor necrosis factor antagonists. *CID* 2004;38:1261-5.
34. Wallis RS, Broder M, Wong J, et al. Granulomatous infectionsdue to tumor necrosis factor blockade: correction. *CID* 2004;39:1254-5.
35. Mori S, Fujiyama S. Hepatitis B virus reactivation associated wityh antirheumatic therapy: risk and prophylaxis recommendationsx. *World J Gastroenterol* 2015;21(36):10274-89.
36. Cantini F, Boccia S, Goletti D, etal. HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int J Rheum* 2014;(ID 926836).
37. Pompili M, Biolato M, Miele L, et al. *World J Gastroenterol* 2013; 19(44): 7867-73.
38. Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2015; 67(10):2557-68.
39. Little RJA,Rubin DB (2016) Statistical Analysis with Missing Data, 3rd ed. Wiley Series in Probability and Statistics, New York.

APPENDIX A: ACR/EULAR 2015 Gout Classification Criteria

SUBJECT ID: _____ DATE: __ __/__ __ __/__ __

ACR-EULAR GOUT CLASSIFICATION CRITERIA#

Entry Criterion (Only apply criteria below to those meeting this entry criterion)		**At least one episode of swelling, pain, or tenderness in a peripheral joint or bursa**	■Y ■N
Sufficient Criterion (If met, can classify as gout without applying criteria below)		**Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus**	■Y ■N
Criteria (to be used if Sufficient Criterion not met): *Score ≥8 required for classification as gout*		**Categories**	**Score**
CLINICAL	**Pattern of joint/bursa involvement during symptomatic* episode(s) ever**	Joint(s) or bursa(e) other than ankle, midfoot or 1st MTP (or their involvement only as part of a polyarticular presentation)	0
		Ankle OR midfoot (as part of monoarticular or oligoarticular episode without MTP1 involvement)	1
		MTP1 (as part of monoarticular or oligoarticular episode)	2
	Characteristics of symptomatic episode(s) ever: i) Erythema overlying affected joint (patient-reported or physician-observed) ii) can't bear touch or pressure to affected joint iii) great difficulty with walking or inability to use affected joint	No characteristics	0
		One characteristic	1
		Two characteristics	2
		Three characteristics	3
	Time-course of episode(s) ever: Presence (ever) of ≥2, irrespective of anti-inflammatory treatment: i) Time to maximal pain <24 hours ii) Resolution of symptoms in ≤14 days iii) Complete resolution (to baseline level) between symptomatic episodes	No typical episodes	0
		One typical episode	1
		Recurrent typical episodes	2
	Clinical evidence of tophus: Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles).	Absent	0
		Present	4
LAB	**Serum urate:** Measured by uricase method. Ideally should be scored at a time when the patient was not taking urate-lowering treatment and patient was beyond 4 weeks of the start of an episode (i.e., during intercritical period); *if* practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4mg/dL [<0.24mM] †	-4
		4-<6mg/dL [0.24-<0.36mM]	0
		6-<8mg/dL [0.36-<0.48mM]	2
		8-<10mg/dL [0.48-<0.60mM]	3
		≥10mg/dL [≥0.60mM]	4
	Synovial fluid analysis of a symptomatic (ever) joint or bursa:** Should be assessed by a trained observer.	Not done	0
		MSU negative	-2
IMAGING‡	**Imaging evidence of urate deposition in symptomatic (ever) joint or bursa:** Ultrasound evidence of double-contour sign¶ *or* DECT demonstrating urate deposition§.	Absent OR Not done	0
		Present (either modality)	4
	Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrate at least one erosion.††	Absent OR Not done	0
		Present	4
		TOTAL SCORE	
		CLASSIFY AS GOUT? (If met sufficient criterion or total score ≥8)	■Y ■N

* Symptomatic episodes are periods of symptoms that include any of swelling, pain, or tenderness in a peripheral joint or bursa.
† If serum urate <4mg/dL (0.24mmol/L), **take away 4 points**; if serum urate ≥4-<6mg/dL (≥0.24mmol/L - <0.36mmol/L), score this item as 0
If polarizing microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show MSU crystals, **take away 2 points. If synovial fluid was not assessed (not done), score this item as 0.
‡ If imaging not available, score these items 0.
¶ Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false positive DCS (artifact) may appear at the cartilage surface that should disappear with a change in the insonation angle of the probe).[31,32]
§Presence of colour-coded urate at articular or peri-articular sites. Images should be acquired using a dual energy computed tomography scanner, with data acquired at 80 and 140 kV and analysed using gout-specific software with a two material decomposition algorithm which colour-codes urate.[33] A positive scan is defined as the presence of colour-coded urate at articular or peri-articular sites. Nailbed, submillimeter, skin, motion, beam hardening and vascular artefacts should not be interpreted as evidence of DECT urate deposition.[34]
††Erosion is defined as a cortical break with sclerotic margin and overhanging edge; excluding DIP joints and gull wing appearance.

#Neogi, et al. *Arthritis & Rheumatology*. 2015;67(10):2557-2568.
Neogi, et al. *Annals of the Rheumatic Diseases*. 2015;74(10):1789-1798.

Presence of MSU crystals in symptomatic joint/bursa or tophus sufficient criterion for gout diagnosis (no further scoring needed).